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Research article

Comparative analysis of two-hour creatinine clearance and the C-G formula for renal function assessment in critically ill patients

Congyou Liu [a], Xingyun Zhu [b], Xinzhu Guo [a], Yingyan Wang [a], Ying Bai [a], Hao Wang [a,*]

[a] Department of Intensive Care Unit, Beijing Jishuitan Hospital, Capital Medical University, 31 East Xinjiekou Street, Xicheng District, Beijing, 100035, China
[b] Department of Endocrinology and Metabolism, Beijing Jishuitan Hospital, Capital Medical University, Beijing, China

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ABSTRACT

Objective and rationale: To investigate if the 2-h creatinine clearance (Ccr_2) provides a more precise and timely assessment of renal function in critically ill patients compared to the Cockcroft-Gault formula ($Cr_{C\text{-}G}$).

Materials and methods: This cohort study incorporated 74 patients who were hospitalized for more than 48 h in the Intensive Care Unit over 6 months. A 24-h urine collection protocol was observed, and concurrently, 316 2-h urine specimens were obtained. Then calculated and analyzed the correlation and consistency between Ccr_2, $Cr_{C\text{-}G}$, and 24-h creatinine clearance (Ccr_{24}) values. The rates of change in $Ccr_2(\Delta Ccr_2)$ and $Cr_{C\text{-}G}(\Delta Cr_{C\text{-}G})$ were compared over two consecutive samples.

Results: The R-values of Ccr_2 and Ccr_{24} in the early, middle and late 24 h were 0.640, 0.886 and 0.854 ($P < 0.001$), with biases of −2.1, 1.7, and 6.3 ml/min/1.73 m^2, respectively. Meanwhile, the R-values for $Cr_{C\text{-}G}$ and Ccr_{24} at these time points were 0.618, 0.822, and 0.828($P < 0.001$), with biases of −14.0, −5.2, and −1.8 ml/min/1.73 m^2, respectively. For patients with $Ccr_{24} \geq 60$ ml/min/1.73 m^2, the R-value of Ccr_2 and Ccr_{24} during the middle 2 h was 0.852($P < 0.001$), while the R-values for $Cr_{C\text{-}G}$ and Ccr_{24} were 0.763($P < 0.001$), with biases of −2.3 ml/min/1.73 m^2 and -14.2 ml/min/1.73 m^2 respectively. For the group with $Ccr_{24} \geq 120$ ml/min/1.73 m^2 ($n = 72$), both Ccr_2 and Ccr_{24} displayed a statistically significant elevation compared to $Cr_{C\text{-}G}$ ($P < 0.001$), yet no significant difference was observed between Ccr_2 and Ccr_{24} ($P = 0.289$). Out of 50 patients, 46(92 %) experienced a $\Delta Ccr_2 \geq 20$ % at least once, compared to 20(40 %) with a $\Delta Cr_{C\text{-}G} \geq 20$ %($P < 0.001$). 25(50 %) with a $\Delta Ccr_2 \geq 50$ %, compared to 3(6 %) with a $\Delta Cr_{C\text{-}G} \geq 50$ %($P < 0.001$).

Conclusion: Ccr_2 demonstrates a more accurate and more timely indicator of renal function in critically ill patients than $Cr_{C\text{-}G}$.

1. Introduction

For critically ill patients, timely and accurate renal function assessment is imperative. The glomerular filtration rate (GFR) serves as

* Corresponding author.
E-mail address: wanghaojst@163.com (H. Wang).

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a direct indicator of kidney function. Approximately 35–40 % of critically ill patients experience notable daily variations in renal function, rendering them in a precarious state of instability [1]. In intensive care units (ICU), the prevalence of augmented renal clearance (ARC) approaches 50 % [2–5], precipitating suboptimal dosing of medications primarily excreted by the kidneys, such as β-lactams, glycopeptides, and aminoglycoside antibiotics [6]. Consequently, this inadequacy in dosing contributes to treatment ineffectiveness, the emergence of drug resistance, and potentially elevated mortality rates. Hence, precise assessment of renal function becomes paramount in identifying ARC-afflicted patients and promptly adjusting medication dosages based on creatinine clearance, thereby optimizing clinical treatment outcomes. Furthermore, acute kidney injury (AKI) represents a prevalent complication in ICU, with an incidence ranging from 12.9 % to 53.2 %, constituting a threefold higher risk compared to non-critically ill patients [7–10]. Even instances of mild, reversible AKI are strongly correlated with unfavorable prognoses, including heightened mortality risks [11]. Consequently, early and accurate evaluation of renal function serves as a pivotal tool in detecting AKI onset and facilitating the implementation of corresponding preventative and therapeutic interventions. Such measures not only mitigate the frequency of AKI occurrences but also attenuate the mortality associated with renal replacement therapy. Currently, estimations of GFR primarily utilize serum creatinine measurements, urine output, or various creatinine-based mathematical models [12–15].

Alterations in serum creatinine levels consistently exhibit a delay in response to changes in GFR, typically manifesting 48–72 h subsequent to GFR decline [16]. Consequently, serum creatinine and assorted formulas predominantly serve as diagnostic tools in individuals with normal renal function or those with chronic renal insufficiency, offering a more reliable depiction of GFR in patients with stable renal function. However, in critically ill patients, the accuracy of serum creatinine as a renal function assessment tool is significantly compromised due to factors such as poor nutritional status, diminished muscle mass, elevated metabolic states, and the renal tubules' minor creatinine secretion [17]. Consequently, the utility of other filtration markers such as cystatin C and estimation methodologies reliant on cystatin C in delineating renal function in critically ill patients is notably compromised [5]. Presently, it is posited that for such patients, calculating creatinine clearance from a 24-h urine collection offers a more precise GFR measurement, aside from using exogenous markers [17,18]. Nevertheless, this method's complexity and inability to rapidly reflect renal function changes in critically ill patients are notable drawbacks. Consequently, shorter urine collection periods for creatinine clearance calculations may more effectively represent real-time renal function alterations [19]. This study investigates the correlation and consistency between 2-h (Ccr_2) and 24-h (Ccr_{24}) creatinine clearance in critically ill patients, assessing their ability to depict rapid renal function changes and their viability as renal function indicators.

2. Material and methods

2.1. Ethical approval statement

The study was carried out by declaration of Helsinki and approved by the Ethics Committee of Beijing Jishuitan Hospital (approval date: 2023 June 9). Approval No. of Ethics Committee: 积伦[K2023]第[155]号-00. Informed consent was obtained from all individual participants included in the study.

2.2. Study design and setting

This prospective cohort study was conducted in the 34-bed comprehensive ICU of Beijing Jishuitan Hospital. The study included both postoperative and non-surgical patients admitted to the ICU between July and November 2023, meeting the following criteria: hospitalization duration of ≥48 h, age ≥18 years, an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≥10 points, and presence of a urinary catheter. Exclusion criteria included regular dialysis for chronic renal insufficiency, urine output <0.5 ml/kg/h for over 6 h, skeletal muscle atrophy, absence of enteral or parenteral nutrition, severe hypotension requiring high-dose vasopressors, usage of cimetidine and ranitidine, and non-catheterized patients.

2.3. Data collection

Upon patient enrollment, standard ICU diagnostic and treatment procedures were followed. Collected data included patient demographics (age, height, admission weight, APACHE II score), medical history (past and current illnesses, surgical records), vital signs (heart rate, blood pressure), and usage of vasoactive drugs, diuretics, and other medications.

2.4. Specimen collection and analysis

Urine samples were collected over 24 h starting from 6am on the second day post-ICU admission. Total urine volume was recorded, and 15 ml was reserved for creatinine testing. Urine output between 6am and 8am and 6pm–8pm was separately recorded, and 15 ml was preserved for creatinine testing. Blood creatinine levels were drawn at 6am and 6pm. Beginning from the third day, collect urine samples daily between 6am and 8am, record the volume of urine, and simultaneously retain samples for urinary creatinine and serum creatinine tests. Continue this collection for three consecutive days. Ccr_2 and Ccr_{24} intervals were calculated, alongside the Cockcroft-Gault formula ($Cr_{C\text{-}G}$) for GFR evaluation. Results were adjusted for body surface area (BSA). Based on Ccr_{24} values, patients were categorized into three groups: ≤60, 60–120, and >120 ml/min/1.73 m^2 for paired T-test analysis. ARC is defined as Ccr_{24} exceeding 120 ml/min/1.73 m^2.

The following formulas were employed.

1. $Ccr_2\left(\text{ml}/\text{min}/1.73\text{m}^2\right) = \frac{\text{Urinary Creatinine Concentration}(\mu\text{mol/L})\times\text{Urine Volume(ml)}}{\text{Plasma Creatinine Concentration}(\mu\text{mol/L})\times 120(\text{min})} \times \frac{1.73\left(m^2\right)}{\text{BSA}(m^2)}$.
2. $Ccr_{24}\left(\text{ml}/\text{min}/1.73\text{m}^2\right) = \frac{\text{Urinary Creatinine Concentration}(\mu\text{mol/L})\times\text{Urine Volume(ml)}}{\text{Plasma Creatinine Concentration}(\mu\text{mol/L})\times 1440(\text{min})} \times \frac{1.73\left(m^2\right).}{\text{BSA}(m^2)}$.
3. $Cr_{C-G}\left(\text{ml}/\text{min}/1.73\text{m}^2\right) = \frac{(140-\text{age})\times\text{weight(kg)}}{(0.818\times\text{Plasma Creatinine Concentration}(\mu\text{mol/L}))} \times \frac{1.73\left(m^2\right)}{\text{BSA}(m^2)}$. For female patients, this value is further adjusted by multiplying by 0.85.
4. $BSA\left(\text{m}^2\right) = \text{weight(kg)}^{0.425} \times \text{height(cm)}^{0.725} \times \frac{71.84}{10000}$.

For the initial assessment, the first results of Ccr_2 and $Cr_{C\text{-}G}$ obtained in succession served as the baseline. Subsequently, calculated the change rate of Ccr_2 and $Cr_{C\text{-}G}$ for two consecutive times for each patient. These were denoted as ΔCcr_2 and $\Delta Cr_{C\text{-}G}$, respectively, and were computed using the formulas:

$$\Delta Ccr_2(\%) = 100 \times \frac{(\text{Ccr}_{2\text{baseline}} - \text{Ccr}_2)}{\text{Ccr}_{2\text{baseline}}}$$

$$\Delta Ccr_{C-G}(\%) = 100 \times \frac{(\text{Ccr}_{\text{C-Gbaseline}} - \text{Ccr}_{\text{C-G}})}{\text{Ccr}_{\text{C-Gbaseline}}}$$

These calculations were performed for all patients, taking into account their weight and height at the time of admission.

2.5. Statistical analysis

SPSS 26.0 software was utilized for database creation and statistical analysis. Continuous data were presented as mean ± standard deviation and analyzed using paired t-tests or ANOVA. Categorical data were expressed as percentages and analyzed using the $\chi 2$ test. The intraclass correlation coefficient (ICC) was calculated to compare consistency between different creatinine clearance methods. Bland-Altman analysis was used to assess biases between Ccr_2, $Cr_{C\text{-}G}$, and Ccr_{24}. A *P*-value <0.05 was considered statistically significant. For multiple sample groups, a corrected *P*-value <0.017 indicated statistical significance. PASS 15 software calculated the sample size based on the difference test of the ICC, aiming to test whether the ICC was higher than 0.80 with $\alpha = 0.05$ and $\beta = 0.10$. Considering a 10 % dropout rate, the required sample size was determined to be 70 cases.

3. Results

3.1. Patient demographics

The study included 74 patients, yielding 316 2-h urine samples. The average age was 64.0 ± 15.7 years, with a gender distribution of 49 males and 25 females. Average weight and body mass index (BMI) were 67.5 ± 14.3 kg and 24.1 ± 4.4 kg/m^2, respectively. Among them, 34 patients (45.9 %) experienced shock, 32 patients (43.2 %) had hypertension, and 22 patients (29.7 %) had diabetes. During specimen collection, 40.5 % of the patients were treated with at least 20 mg of furosemide. Reasons for ICU admission varied: trauma (25.7 %), post-major surgery (20.3 %), cardiovascular diseases (10.8 %), severe pneumonia (5.4 %), other severe infections (17.6 %), and miscellaneous causes (16.2 %) (Table 1).

Table 1
Demographic data and basic characteristics.

Variables(n = 74)	
Age(years)	64.0 ± 15.7
Sex (Male/Female)	49/25
Weight(kg)	67.5 ± 14.3
BMI (kg/m^2)	24.1 ± 4.4
APACHE II score	17.6 ± 6.2
Prevalence of shock (%)	45.9
History of hypertension (%)	43.2
History of diabetes (%)	29.7
Use of diuretics (%)	40.5
Use of mannitol (%)	6.0
Reasons for ICU admission (%)	
Trauma	35.1
Post-major surgery	20.3
Cardiovascular diseases	10.8
Severe infections	17.6
Severe pneumonia	5.4
Others	16.2

BMI, Body Mass Index, ICU, Intensive Care Unit.

3.2. Correlation and Consistency Analysis

The correlation coefficients (R values) for Ccr_2 and Ccr_{24} at 6am–8am and 6pm–8pm on the second day, and 6am–8am on the third day were 0.640, 0.886, and 0.854, respectively, all with a statistical significance of $P < 0.001$. Similarly, the R values for $Cr_{C\text{-}G}$ and Ccr_{24} at these time points were 0.618, 0.822, and 0.828, respectively, also with $P < 0.001$. The biases identified in the comparisons of Ccr_2 and Ccr_{24} were −2.1, 1.7, and 6.3 ml/min/1.73 m^2, respectively. In the comparisons between $Cr_{C\text{-}G}$ and Ccr_{24}, the biases were found to be −14.0, −5.2, and −1.8 ml/min/1.73 m^2. Further analysis was conducted on patients with $Ccr_{24} \geq 60$ ml/min/1.73 m^2 (n = 53). The R values for the correlation of Ccr_2 and Ccr_{24} at 6pm–8pm on the second day were 0.852 with a significance of $P < 0.001$. For $Cr_{C\text{-}G}$ and Ccr_{24}, the R values were 0.763 with $P < 0.001$. The Bland-Altman analysis for this subset of patients revealed a bias of −2.3 ml/min/1.73 m^2 between Ccr_2 and Ccr_{24}, and a bias of −14.2 ml/min/1.73 m^2 between $Cr_{C\text{-}G}$ and Ccr_{24} (Figs. 1 and 2). We divided the patients into two groups based on whether a diuretic agent was administered during the consistency test. Of the 74 patients, 30 were administered furosemide intravenously, with an average dosage of 35.0 ± 26.0 mg. The clinical characteristics of the two groups of patients were shown in Additional file 5. For these patients, the R values for Ccr_2 and Ccr_{24} were 0.847 and 0.843 respectively, with biases of 8.2 and 12.4 ml/min/1.73 m^2 at 6pm–8pm on the second day and 6am–8am on the third day. $P < 0.001$ for these results. The R values for $Cr_{C\text{-}G}$ and Ccr_{24} were 0.767 and 0.775 respectively, with biases of −1.2 and −0.5 ml/min/1.73 m^2. In the group of 44 patients who did not receive diuretics, the R values for Ccr_2 and Ccr_{24} at 6pm–8pm on the second day were 0.881 and 0.834 respectively, with biases of −2.6 and 2.3 ml/min/1.73 m^2. The R values for $Cr_{C\text{-}G}$ and Ccr_{24} were 0.799 and 0.804 respectively, with biases of −7.9 and 2.6 ml/min/1.73 m^2. The P value for these results was also less than 0.001.

3.3. Paired t-tests of Ccr_2 and $Cr_{C\text{-}G}$

In this segment of the study, 221 paired 2-h urine and corresponding blood samples were analyzed. The mean values of Ccr_2 and $Cr_{C\text{-}G}$ were calculated to be 108.5 ± 81.2 ml/min/1.73 m^2 and 96.0 ± 60.6 ml/min/1.73 m^2, respectively, while the average Ccr_{24} was determined to be 106.5 ± 77.3 ml/min/1.73 m^2. Statistical analysis revealed that the differences between Ccr_2 and Ccr_{24} were not significant ($P = 0.565$). However, $Cr_{C\text{-}G}$ demonstrated a significant reduction compared to both Ccr_2 and Ccr_{24} ($P < 0.001$ and $P = 0.001$, respectively). Subsequently, the Ccr_{24} values were categorized into three distinct groups based on their ranges: ≤60, 60–120, and >120 ml/min/1.73 m^2. In the group with $Ccr_{24} \leq 60$ ml/min/1.73 m^2 (n = 62), no statistically significant disparity was evident between Ccr_2 and $Cr_{C\text{-}G}$ values ($P = 0.830$). Nevertheless, both Ccr_2 and $Cr_{C\text{-}G}$ measurements demonstrated a notable elevation compared to Ccr_{24} levels ($P = 0.003$ and 0.008, respectively). In the group with Ccr_{24} ranging from 60 to 120 ml/min/1.73 m^2 (n = 87), no statistically significant distinction was observed between Ccr_2 and $Cr_{C\text{-}G}$ values ($P = 0.357$), and neither exhibited significant deviation from Ccr_{24} levels ($P = 0.035$ and 0.282, respectively).For the group with $Ccr_{24} \geq 120$ ml/min/1.73 m^2 (n = 72), Both Ccr_2 and Ccr_{24} displayed a statistically significant elevation compared to $Cr_{C\text{-}G}$ ($P < 0.001$), yet no significant variance was observed between Ccr_2 and Ccr_{24} ($P = 0.289$) (Table 2 and) Fig. 3). The incidence of Ccr_{24}>120 ml/min/1.73 m^2 stands at 32.6 % upon analysis of 221 paired 2-h urine samples. Within the cohort of 74 patients, 41 individuals exhibited a Ccr_2>120 ml/min/1.73 m^2 at least once, constituting 55.4 % of the total patient population.

3.4. Daily renal function variability

Among the 74 patients, 50 completed the collection of blood and urine samples from 6am to 8am for 5 consecutive days. Analysis of

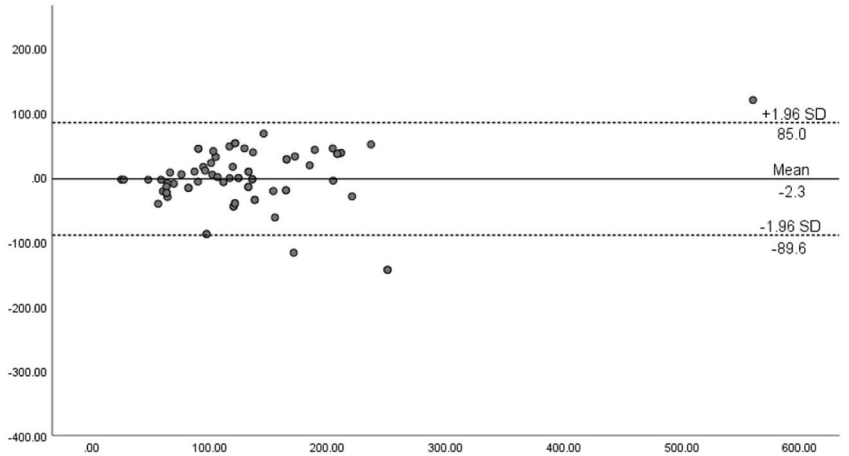

Fig. 1. Consistency Analysis of 2-h creatinine clearance (Ccr_2) and 24-h Creatinine Clearance (Ccr_{24}) in Patients with $Ccr_{24} \geq 60$ ml/min/1.73 m^2 on the Evening of the Second Day.The horizontal axis represents the mean values (ml/min/1.73 m^2) of Cr_2 and Ccr_{24}. The vertical axis indicates the difference (ml/min/1.73 m^2) between Cr_2 and Ccr_{24}. The solid line on the y-axis marks the bias (mean of the differences). The upper and lower dashed lines represent the upper and lower limits of agreement, calculated as bias ±1.96 times the standard deviation of the bias.

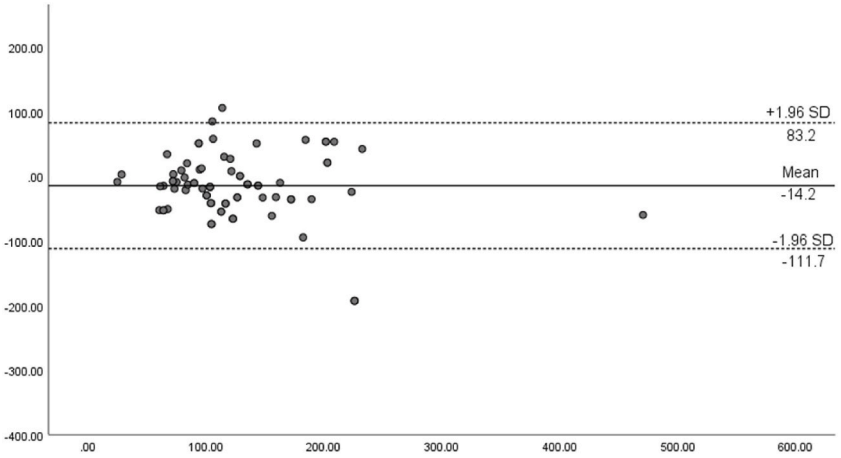

Fig. 2. Consistency Analysis of Cockcroft-Gault formula for glomerular filtration rate assessment ($Cr_{C\text{-}G}$) and 24-h Creatinine Clearance (Ccr_{24}) in Patients with $Ccr_{24} \geq 60$ ml/min/1.73 m^2 on the Evening of the Second Day. The horizontal axis represents the mean values (ml/min/1.73 m^2) of$Cr_{C\text{-}G}$ and Ccr_{24}. The vertical axis indicates the difference (ml/min/1.73 m^2) between $Cr_{C\text{-}G}$ and Ccr_{24}. The solid line on the y-axis marks the bias (mean of the differences). The upper and lower dashed lines represent the upper and lower limits of agreement, calculated as bias ±1.96 times the standard deviation of the bias.

Table 2
Paired *t*-test Comparing Ccr_2 and $Cr_{C\text{-}G}$.

Ccr_{24} group (ml/min/1.73m^2) (n = 221)	Mean values(x ± s)(ml/min/1.73m^2)		
	Ccr_2	$Cr_{C\text{-}G}$	Ccr_{24}
All (n = 221)	108.5 ± 81.2	96.0 ± 60.6*	106.5 ± 77.3†
≤60 (n = 62)	43.3 ± 27.6	42.7 ± 24.0	35.2 ± 15.8†‡
60-120(n = 87)	95.6 ± 35.6	92.1 ± 31.1	88.3 ± 16.8
≥120(n = 72)	180.1 ± 95.5	146.6 ± 68.1*	189.9 ± 78.0†

Ccr_2, 2-h creatinine clearance, $Cr_{C\text{-}G}$, Cockcroft-Gault formula for glomerular filtration rate assessment, Ccr_{24}, 24-h creatinine clearance, *Comparison between Ccr_2 and $Cr_{C\text{-}G}$, statistically significant ($P < 0.017$), †Comparison between $Cr_{C\text{-}G}$ and Ccr_{24}, statistically significant ($P < 0.017$);‡Comparison between Ccr_2 and Ccr_{24}, statistically significant ($P < 0.017$). For multiple sample groups, a corrected *P*-value <0.017 indicated statistical significance.

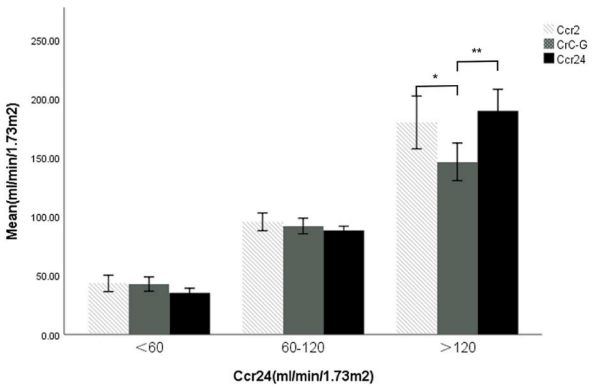

Fig. 3. Paired *t*-test comparing $Cr_{C\text{-}G}$, Ccr_2 and Ccr_{24}. *Comparison between Ccr_2 and $Cr_{C\text{-}G}$, statistically significant ($P < 0.001$), **Comparison between Ccr_{24} and $Cr_{C\text{-}G}$, statistically significant ($P < 0.001$). Ccr_2, 2-h creatinine clearance, $Cr_{C\text{-}G}$, Cockcroft-Gault formula for glomerular filtration rate assessment, Ccr_{24}, 24-h creatinine clearance.

these samples revealed that the mean fluctuation in ΔCcr_2 ranged between 21 % and 51 %. Simultaneously, the average variation in $\Delta Cr_{C\text{-}G}$ was observed to be between 9 % and 17 %. Within this subset of 50 participants, 46 patients (92 %) had $\Delta Ccr_2 \geq 20$ % at least once, while 20 patients (40 %) had $\Delta Cr_{C\text{-}G} \geq 20$ %. The difference was statistically significant ($P < 0.001$). Furthermore, there were 25 patients (50 %) with $\Delta Ccr_2 \geq 50$ %, and 3 patients (6 %) with $\Delta Cr_{C\text{-}G} \geq 50$ %, the difference was statistically significant ($P < 0.001$).

4. Discussion

This study revealed that for critically ill patients such as trauma, major surgery, severe infections, and shock, Ccr_2 exhibits superior consistency and reduced bias when juxtaposed with Ccr_{24} in comparison with $Cr_{C\text{-}G}$, and for ARC patients, $Cr_{C\text{-}G}$ significantly underestimates the GFR, whereas Ccr_2 provides a more accurate estimation. Consequently, Ccr_2 emerges as a more reliable indicator for the assessment of renal function in critically ill patients when compared to $Cr_{C\text{-}G}$. Given the propensity for renal function to exhibit significant fluctuations in critically ill patients, the utility of Ccr_2 becomes evident. Instances where ΔCcr_2 exceeds 20 % and 50 % at least once demonstrate a substantial elevation compared to $\Delta Cr_{C\text{-}G}$. This signifies that Ccr_2 can serve as a real-time bedside metric, offering a more timely reflection of alterations in patients' renal function.

The application of 24-h creatinine clearance is complex and cannot reflect the rapid fluctuations in renal function in critically ill patients. Hence, a shorter duration of urine collection for creatinine clearance calculation may offer a more real-time responsive measure of renal function changes [19]. This study meticulously chose urine samples from the initial 2 h, the mid-2 hours, and the final 2 h of a 24-h urine collection period, aligning the collection of hourly urine with concurrent blood creatinine sampling, and observed that the correlation and bias between Ccr_2 and Ccr_{24} during these three time periods were superior to those of $Cr_{C\text{-}G}$. Of note, the correlation between Ccr_2 and Ccr_{24} during the 6pm–8pm interval on day 2 exhibited the strongest correlation and the least bias. This observation may be attributed to the fact that both Ccr_2 and Ccr_{24} were calculated using the same serum creatinine results. Additionally, the collection of urine samples during these 2 h falls within the midpoint of the 24-h period, suggesting that it may be most closely related to the average GFR over this 24-h duration. Therefore, the investigation further distinguished a time point (6pm–8pm on the second day) for deeper analysis in patients with normal renal function ($Ccr_{24} \geq 60$ ml/min/1.73 m^2). The findings indicated a strong correlation between Ccr_2 and Ccr_{24} ($R = 0.852$, $P < 0.001$) and a relatively weaker, yet significant correlation between $Cr_{C\text{-}G}$ and Ccr_{24} ($R = 0.763$, $P < 0.001$), with biases of −2.3 ml/min/1.73 m^2 and -14.2 ml/min/1.73 m^2, respectively. Consequently, Ccr_2 emerges as a more reliable indicator of renal function in critically ill patients, as opposed to $Cr_{C\text{-}G}$, which is less correlated and more biased. In contrast to prior research, the studies posit that for healthy volunteers, a shortened urine collection period spanning 1–3 h, utilized to calculate creatinine clearance, can effectively substitute the traditional 24-h urine collection method in assessing GFR [20,21]. While Cherry et al. highlighted that short-term urine collections (2 and 6 h) correlate poorly with 24-h creatinine clearance, other studies have suggested that a 2-h urine collection may suffice for assessing renal function in critical patients, albeit with inconsistent results due to factors like small sample sizes and varied patient demographics [19,22–25]. This study's results endorse Ccr_2 as a more accurate proxy for Ccr_{24} in critically ill patients with diverse primary diseases and unstable hemodynamic and metabolic statuses. Through an analysis of the subgroups categorized by diuretic and non-diuretic use, the consistency between Ccr_2 and Ccr_{24} in both diuretic group and non-diuretic group of patients was better than that between $Cr_{C\text{-}G}$ and Ccr_{24}. However, in the diuretic group, despite the high consistency of Ccr_2 and Ccr_{24}, the bias was larger compared to the non-diuretic group. This issue should be carefully considered in clinical settings, particularly for critically ill patients receiving diuretics.

Additionally, the study found no significant difference between Ccr_2 and Ccr_{24} in paired t-tests, while $Cr_{C\text{-}G}$ was notably lower than both Ccr_2 and Ccr_{24}. Further stratification of patients based on Ccr_{24} values revealed that in cases of $Ccr_{24} \leq 60$ ml/min/1.73 m^2, both Ccr_2 and $Cr_{C\text{-}G}$ tended to overestimate GFR, whereas in patients with $Ccr_{24} \geq 120$ ml/min/1.73 m^2, Ccr_2 more accurately estimated GFR, and $Cr_{C\text{-}G}$ significantly underestimated it. This aligns with findings from prior research studies [3,26,27]. Previous investigations have demonstrated that in severe cases of AKI, both the CG formula and the Modification of Diet in Renal Disease (MDRD) formula tend to overestimate the GFR [3]. French researchers utilized iohexol clearance as the reference standard to evaluate static and dynamic GFR estimation methods in patients with shock within a 12-h timeframe, including the CG formula, MDRD formula, and the Cooperative Institute for Chronic Kidney Disease Epidemiology (CKD-EPI) formula, as well as various dynamic mathematical formulas (Jelliffe, Chen, Chiou and Hsu, Moran and Myers, Yashiro, Seelhammer, and Brater) [28]. The findings indicated that none of the mathematical formulas provided accurate GFR estimates and generally exhibited a tendency to overestimate GFR. Moreover, in critically ill patients with ARC, both the CG formula and MDRD formula tend to underestimate GFR when compared to 8-h or 24-h creatinine clearance [3]. Baptista elucidated in the most recent review that, for critically ill patients, the estimated GFR derived from formulas exhibits a tenuous correlation with measured GFR, emphasizing the superior accuracy of utilizing measured GFR within the ICU context [29].

In this study, the prevalence of ARC stands at 32.6 % across the 221 paired 2-h urine samples. Among the 74 patients included in the analysis, 41 individuals exhibited at least one instance of $Ccr_2 > 120$ ml/min/1.73 m^2, representing 55.4 % of the total patient cohort. Specifically, among these patients, there were 21 trauma patients and 8 patients each with major surgery and severe infection (Additional file 4). The incidence of ARC is notably high, predominantly manifesting in patients experiencing trauma, severe infection, or major surgery, consistent with findings from prior investigations. Earlier research has demonstrated ARC incidence rates ranging from 22.1 % to 65.1 %, with identified risk factors encompassing age, male gender, trauma, severe infection, and vasopressor usage [29]. Notably, in Udy's study, GFR was estimated using 8-h creatinine clearance. Within seven days of ICU admission, 65.1 % of patients developed ARC, with trauma patients constituting the majority of cases.[30].

The unstable state of renal function leads to increased uncertainty in the efficacy of clinical drug treatment in critically ill patients. Cherry et al.'s research delineates a weak correlation between short-term (2 h, 6 h) creatinine clearance and the 24-h creatinine clearance measurements. This discrepancy is attributed to the myriad factors that more profoundly influence renal function in critically ill patients compared to those with milder conditions [25]. These patients undergo continuous and dynamic changes in renal function. Hence, urine collection over brief intervals (less than 8 h) fails to accurately represent the true renal function level. Recent studies further indicate that approximately 35–40 % of critically ill patients experience notable daily variations in renal function, underscoring its unstable nature [1]. Consequently, identifying real-time, reliable indicators of renal function changes in this patient group is imperative. Serum creatinine, a traditionally used indicator, significant elevations are not observed until the GFR falls below

55 ml/min/1.73 m^2 [31]. As a result, serum creatinine levels typically lag behind GFR changes, with notable increases occurring 48–72 h post-GFR decline [16]. This delay renders the CG formula, which estimates GFR based on serum creatinine, ineffective for real-time monitoring of renal function alterations. An alternative approach involves simultaneous blood and urine creatinine measurements to calculate the ΔCcr_2, thereby circumventing this limitation and providing a timelier reflection of renal function fluctuations. This study analyzed the rate of change of Ccr_2 and $Cr_{C\text{-}G}$ over two consecutive measurements. Findings reveal that using ΔCcr_2 for evaluating renal function changes in critically ill patients showed average fluctuation ranges of 21%–51 %, while the $\Delta Cr_{C\text{-}G}$ method yielded a 9%–17 % fluctuation range. Among 50 patients who underwent specimen collection over five consecutive days, 46 (92 %) exhibited a $\Delta Ccr_2 \geq 20$ % at least once, compared to only 20 patients (40 %) with a $\Delta Cr_{C\text{-}G} \geq 20$ %. Furthermore, 25 patients (50 %) had a $\Delta Ccr_2 \geq 50$ %, in contrast to only 3 patients (6 %) for $\Delta Cr_{C\text{-}G}$, with these differences being statistically significant ($P < 0.001$). These results highlight the substantial daily dynamic changes and considerable fluctuations in the renal function of critically ill patients. Depending on the assessment method, these fluctuations range approximately between 9% and 51 %, with ΔCcr_2 demonstrating a significantly larger range than $\Delta Cr_{C\text{-}G}$. This suggests that ΔCcr_2 is a more sensitive indicator for detecting renal function fluctuations in critically ill patients, aligning with recent research findings [1].

However, this study's limitations include its single-center design and small sample size, suggesting that multi-center studies with larger cohorts might enhance the robustness of these findings. Additionally, while Ccr_{24} is used as the gold standard for GFR measurement, the minor secretion function of renal tubules for creatinine might impact the results.

5. Conclusions

In conclusion, the Ccr_2 emerges as a superior indicator compared to $Cr_{C\text{-}G}$ for assessing renal function in critically ill patients. Particularly in patients exhibiting ARC, the $Cr_{C\text{-}G}$ tends to underestimate the GFR. The renal function in critically ill patients is subject to daily instability. Relative to the $Cr_{C\text{-}G}$, the Ccr_2 more effectively captures the rapid and significant fluctuations of renal function as a real-time bedside indicator in critically ill patients.

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Financial interests

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Ethics approval

The study was carried out by declaration of Helsinki and approved by the Ethics Committee of Beijing Jishuitan Hospital (approval date: 2023 June 9).

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Data availability statement

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

CRediT authorship contribution statement

Congyou Liu: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xingyun Zhu:** Methodology. **Xinzhu Guo:** Data curation. **Yingyan Wang:** Data curation. **Ying Bai:** Supervision. **Hao Wang:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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List of abbreviations

GFR Glomerular filtration rate
ICU Intensive Care Unit
ARC Augmented renal clearance
AKI Acute kidney injury
Ccr_2 2-h creatinine clearance
Ccr_{24} 24-h creatinine clearance
APACHE II score Acute Physiology and Chronic Health Evaluation II score
$Cr_{C\text{-}G}$ Cockcroft-Gault formula for glomerular filtration rate assessment
BSA Body surface area
ΔCcr_2 The rates of change in Ccr_2
$\Delta Cr_{C\text{-}G}$ The rates of change in $Cr_{C\text{-}G}$
ICC Intraclass correlation coefficient
BMI Body mass index
MDRD formula Modification of Diet in Renal Disease formula
CKD-EPI formula:Cooperative Institute for Chronic Kidney Disease Epidemiology formula

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31500.

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