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Original article

[Translated article] Assessment of serum creatinine-based equations for estimating glomerular filtration rate in critically ill patients with or without augmented renal clearance

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ABSTRACT

Background: Serum creatinine-based equations are commonly used to estimate glomerular filtration rate (eGFR) in critically ill patients, despite not having been specifically developed for this population. This study aimed to assess and compare the performance of three widely used serum creatinine-based equations in this setting.
Methods: Observational retrospective study conducted in four intensive care units of a tertiary university hospital. The most commonly used serum creatinine-based equations, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD-4), and Cockcroft-Gault (CG) equations were compared to the creatinine clearance from 24-hour urine collection ($CrCl_{24h}$), used as the reference method. Bland and Altman plots, bias and precision were performed to contrast $CrCl_{24h}$ values with estimated GFR. Bias and its 95% confidence interval were calculated as the mean difference between the eGFR estimated by each equation and the measured $CrCl_{24h}$. Precision was reported as one standard deviation of the bias.
Results: A total of 261 patients were included. In patients with $CrCl_{24h}$ between 0–129 mL/min, no significant differences were observed between equations. However, in patients with augmented renal clearance (15.7%), with a mean $CrCl_{24h}$ of 180 mL/min, there was a statistically significant bias between the CKD-EPI equation (66.4 mL/min/1,73m^2) and both the CG and MDRD-4 equations (24.8 mL/min/m^2 and 29.3 mL/min/1,73 m^2, respectively; $p < 0.01$).
Conclusions: This study highlights that the most commonly used equations to estimate glomerular filtration rate in critically ill patients have remarkable limitations compared to creatinine clearance from 24-hour urine collection. In critically ill patients with $CrCl_{24h}$ between 0-129 mL/min, no significant differences were found between the CG, MDRD-4, and CKD-EPI equations. However, for patients with augmented renal clearance, the CG and MDRD-4 equations performed statistically better than the CKD-EPI equation.
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Evaluación de ecuaciones basadas en creatinina sérica para estimar la tasa de filtración glomerular en pacientes críticos con y sin aclaramiento renal aumentado

Palabras clave:
Creatinina
Estado crítico
Tratamiento farmacológico
Tasa de filtración glomerular
Eliminación renal

RESUMEN

Objetivo: las ecuaciones basadas en creatinina sérica se utilizan de forma rutinaria para estimar la tasa de filtración glomerular (TFGe) en pacientes ingresados en unidades de cuidados intensivos, a pesar de que no fueron específicamente desarrolladas para dicha población. El objetivo de este estudio fue evaluar y comparar las 3 ecuaciones basadas en creatinina sérica habitualmente empleadas en este contexto.
Métodos: estudio observacional retrospectivo realizado en 4 unidades de cuidados intensivos de un hospital universitario de tercer nivel. Se compararon las ecuaciones basadas en creatinina más utilizadas: la *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI), la *Modification of Diet in Renal Disease* (MDRD-4) y la ecuación de *Cockcroft-Gault* (CG) con el aclaramiento urinario de creatinina en 24 horas (CrCl24h) como método de referencia. Se realizaron gráficos de Bland-Altman, así como análisis de sesgo y precisión, para comparar los

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valores de CrCl24h con la TFGe. El sesgo y su intervalo de confianza del 95% se calcularon como la diferencia media entre la TFGe estimada por cada ecuación y el CrCl24h medido. La precisión se estimó como la desviación estándar del sesgo.
Resultados: se incluyeron 261 pacientes. En aquellos pacientes que presentaban un CrCl24h entre 0 y 129 ml/min/1,73 m² no se observaron diferencias significativas en sesgo y precisión entre las ecuaciones. CKD-EPI presentó el sesgo más bajo (−13,9 ml/min/1,73 m^2) en este grupo de pacientes. Sin embargo, en los pacientes con un aclaramiento renal aumentado (15,7%), donde la media de CrCl24h fue 180 ml/min, se observaron diferencias estadísticamente significativas entre la ecuación de CKD-EPI (66,4 ml/min/1,73 m^2) y las ecuaciones de CG y de MDRD-4 (24,8 ml/min/m^2 y 29,3 ml/min/1,73 m^2, respectivamente; $p < 0,01$) en cuanto al sesgo.
Conclusiones: este estudio evidencia que las ecuaciones habitualmente utilizadas para estimar el filtrado glomerular en pacientes críticos presentan limitaciones importantes en comparación con el aclaramiento de creatinina en orina de 24 horas. En el subgrupo de pacientes con un CrCl24h entre 0 y 129 ml/min/1,73 m² no se observaron diferencias significativas en el sesgo y la precisión entre las ecuaciones CG, MDRD-4 y CKD-EPI. En cambio, entre los pacientes con aclaramiento renal aumentado, las ecuaciones CG y MDRD-4 mostraron un desempeño estadísticamente superior al de CKD-EPI.
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Introduction

Critically ill patients admitted to intensive care units (ICUs) exhibit pathophysiological changes that can significantly alter drug kinetics, thereby complicating dose optimisation.[1] The accurate assessment of renal function is crucial for drugs eliminated primarily via the kidneys. To date, glomerular filtration rate (GFR) remains the reference standard for assessing renal function.[2] It is ideally measured using exogenous markers, such as inulin or radiopharmaceuticals, including technetium-99 m-labelled diethylenetriaminepentaacetic acid, which are freely filtered by the glomerulus and neither reabsorbed nor secreted. However, these techniques are costly and difficult to implement in ICU clinical practice.[3]

Twenty-four-hour urinary creatinine clearance ($CrCl_{24h}$) has been proposed to measure GFR; however, its accuracy is also limited by variability in urine collection and in creatinine production during hospitalisation.[4] Consequently, serumcreatinine-based equations incorporating anthropometric data are widely used in clinical practice to estimate GFR (eGFR). The most commonly used equations are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease (MDRD-4) equation, and the Cockcroft-Gault (CG) equation.[5–7]

As these equations were not originally developed for critically ill patients, their validity in this clinical setting remains a matter of debate. Incorrect estimation of renal function, whether overestimation or underestimation, can result in inappropriate drug dosing, compromising therapeutic efficacy and increasing the risk of toxicity. This issue is particularly relevant in critically ill patients, since their renal function fluctuates frequently and conventional estimation methods are significantly limited.

The literature indicates that these equations show a modest correlation with GFR, but lack sufficient accuracy in critically ill patients, exhibiting clinically relevant bias and error, particularly in renal failure and augmented renal clearance (ARC).[8–10] Augmented renal clearance, defined as an eGFR ≥ 130 mL/min[11] as measured by 24-h urine collection, is of particular relevance for antimicrobial therapy, as suboptimal exposure is associated with an increased risk of treatment failure. Thus, accurate estimation of GFR is essential in this population.[12]

This study aimed to assess the performance and accuracy of 3 serum creatinine-based equations for estimating GFR in critically ill patients with and without ARC, using $CrCl_{24h}$ measured in ICU patients as the reference method.

Materials and methods

Study population

This observational, retrospective, single-centre study was conducted in 4 ICUs at Hospital Clínic de Barcelona (Spain) between January and September 2020. Inclusion criteria: patients aged 18 years or over with a urinary catheter and at least one $CrCl_{24h}$ measurement during ICU stay, since this parameter is routinely determined twice weekly in these units at our institution. Exclusion criteria: patients requiring renal replacement therapy or presenting with anuria. The study received approval from the hospital ethics committee (HCB/2022/1012).

Data collection

Demographic, clinical, and laboratory variables were extracted from the electronic medical record, including sex, age, weight, and height. Body surface area was calculated using the DuBois and DuBois formula. $CrCl_{24h}$ was calculated from 24-h urine output, with concurrent measurement of serum and urinary creatinine concentrations. In patients with multiple measurements, only the first $CrCl_{24h}$ measurement was included. Table 1 shows the equations used to estimate eGFR. Actual body weight at ICU admission was used for the CG equation. For a more comprehensive analysis of the subpopulation of patients with

Table 1
Equations for estimating GFR based on serum creatinine.

$\boldsymbol{CrCl_{CKD-EPI}}$ =
Woman: $144 \times [(CrS/0.7)^{-0.329}] \times 0.993^{Age}$ (if CrS ≤0.7 mg/dL); $144 \times [(CrS/0.7)^{-1.209}] \times 0.993^{Age}$ (if CrS >0.7 mg/dL)
Man: $141 \times [(CrS/0.9)^{-0.411}] \times 0.993^{Age}$ (if CrS ≤0.9 mg/dL); $141 \times [(CrS/0.9)^{-1.209}] \times 0.993^{Age}$ (if CrS >0.9 mg/dL)
$\boldsymbol{CrCl_{MDRD-4}}$= $175 \times (CrS)^{-1.154} \times (Age)^{-0.203} \times 0.742$ if woman $\times$ 1.210 if Black
$\boldsymbol{CrCl_{CG}}$ = [(140-age) × actual weight in kg]/(72 × CrS en mg/dL) × 0.85 if woman × BSA

BSA, Body surface area (m^2); CrS, serum creatinine.

ARC, the cohort was stratified into patients with $CrCl_{24h}$ between 0 and 129 mL/min and patients with ARC.

Statistical analysis

Continuous variables are expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR), and categorical variables are expressed as absolute numbers and percentages. The Shapiro–Wilk test was used to assess the normality of the distribution of continuous variables. Spearman correlation coefficients (rS) were used to analyse correlations between $CrCl_{24h}$ and the CKD-EPI, MDRD-4, and CG equations. Bland–Altman plots were used to analyse the agreement between $CrCl_{24h}$ values and eGFR values. Bias was calculated as the difference between the mean $CrCl_{24h}$ and the mean of each eGFR equation, with a 95% confidence interval (95% CI). Accuracy was determined using the standard deviation of the bias. The 95% limits of agreement were also calculated to assess the differences between $CrCl_{24h}$ and eGFR.

An ANOVA test was performed to assess statistically significant differences between the equations. A p-value of <0.05 was used as a cutoff for statistical significance. Statistical analysis was carried out using Stata software v. 16.1 (StataCorp LP, College Station, TX).

Results

The study included 261 patients; 60.2% were men, with a median age of 64 years (IQR 54–73). Table 2 shows the demographic and clinical data of the study population. The median $CrCl_{24h}$ value for the entire cohort was 63 mL/min (IQR 32–107). The medians of eGFR using CKD-EPI, MDRD-4, and CG were 83.8 mL/min (IQR 43.2–104.7), 80.3 mL/min (IQR 42.5–123.2), and 75.9 mL/min (IQR 43.2–121.6), respectively. The prevalence of ARC was 15.7% (41 patients), using a cutoff point of ≥130 mL/min.

Table 3 shows a direct comparison between $CrCl_{24h}$ and each GFR estimating equation. Spearman coefficients for patients with a $CrCl_{24h}$ between 0 and 129 mL/min showed a moderate correlation for all GFR estimating equations ($p < 0.01$). The strongest correlation with measured $CrCl_{24h}$ was observed for the CG equation (rS = 0.76), followed by the CKD-EPI equation (rS = 0.75), and the MDRD-4 equation (rS = 0.74). For patients with ARC, the correlation between the eGFR equations and $CrCl_{24h}$ was weak (rS ≤0.3). The CG equation showed a slightly higher correlation (rS = 0.30), followed by the MDRD-4 equation (rS = 0.18), and the CKD-EPI equation (rS = 0.14).

Figs. 1 and 2 show Bland–Altman plots for the full and stratified cohorts, respectively. For patients with eGFR between 0 and 129 mL/min, the CKD-EPI equation showed the lowest bias (−13.9 mL/min/1.73 m^2; 95% CI: −17.3 to −10.6 mL/min/1.73 m^2) and the highest accuracy (±25.6 mL/min/1.73 m^2). In contrast, the CG and MDRD-4 equations showed greater bias (−22.0 mL/min/m^2; 95% CI: −26.9 to −17.1 mL/min/m^2 and −23.5 mL/min/1.73 m^2; 95% CI: −29.0 to −18.0 mL/min/1.73 m^2, respectively) and lower accuracy, reflected by wider variability (±36.7 mL/min/m^2 for CG and ± 41.5 mL/min/1.73 m^2 for MDRD-4). No significant differences were found between the equations in terms of bias and accuracy in this subgroup of patients.

For patients with ARC, the CKD-EPI equation showed the greatest bias (66.4 mL/min/1.73 m^2; 95% CI: 54.5 to 78.2 mL/min/1.73 m^2)

Table 3
Analysis of the correlation between estimated GFR derived from serum creatinine-based equations and $CrCl_{24h}$, and evaluation of estimation accuracy and precision.

	CKD-EPI	MDRD-4	CG
$CrCl_{24h}$ < 130 mL/min			
Spearman coefficient	0.75	0.74	0.76
Bias	−13.9	−23.5	−22.0
[95% CI]	[−17.3;−10.6]	[−29.0;−18.0]	[−26.9;−17.2]
Accuracy	±25.6	±41.5	±36.7
Upper limit of agreement	36.2	57.9	49.8
Lower limit of agreement	−64.0	−104.9	−93.8
Limits of agreement range	100.2	162.8	143.7
$CrCl_{24h}$ ≥ 130 mL/min			
Spearman coefficient	0.14	0.18	0.30
Bias	66.4*	29.3*	24.8*
[95% CI]	[54.5–78.2]	[9.9–48.7]	[5.7–43.9]
Accuracy	±38.7	±63.5	±62.4
Upper limit of agreement	142.2	153.7	147.0
Lower limit of agreement	−9.5	−95.2	−97.5
Limits of agreement range	151.7	248.9	244.5

Bias [95% CI], accuracy, limits of agreement, and limits of agreement range are expressed in mL/min/m^2 for CG and in mL/min/1.73^2 for CKD-EPI and MDRD-4.
* $p < 0.01$.

Table 2
Demographic and clinical data stratified by glomerular filtration rate.

	$CrCl_{24h}$ < 130 mL/min (n = 220)	$CrCl_{24h}$ ≥ 130 mL/min (n = 41)	Full cohort (n = 261)
Male, % (n)	59.5% (131)	63.4% (26)	60.2% (157)
*Age, y**	65** [55–74]	65** [43–65]	64 [54–73]
Weight, kg*	73.9 [63.9–84.3]	80.0 [70–90]	75.0 [65–85]
Body surface area, m^{2}*	1.84 [1.67–1.96]	1.94 [1.77–2.09]	1.84 [1.69–1.98]
Serum creatinine, mg/dL*	1.03 [0.68–1.64]	0.54 [0.42–0.7]	0.89 [0.59–1.5]
Reason for admission			
Medical, % (n)	76.8 (169)	75.6 (31)	76.6 (200)
Cardiovascular	6.4 (14)	2.4 (1)	5.7 (15)
Respiratory	13.2 (29)	9.8 (4)	12.6 (33)
Trauma	6.8 (15)	14.6 (6)	8.0 (21)
Neurological	16.4 (36)	34.1 (14)	19.2 (50)
Infectious	19.5 (43)	9.8 (4)	18.0 (47)
Hepatobiliary	10.9 (24)	2.4 (1)	9.6 (25)
Other	3.6 (8)	2.4 (1)	3.4 (9)
Surgical, % (n)	23.2 (51)	24.4 (10)	3.4 (61)
APACHE II – mean (SD)	15.4 (6.5)	13.0 (7.3)	15.0 (6.7)
SOFA, day 1 – mean (SD)	6.0 (3.6)	5.8 (4.5)	5.9 (3.7)

APACHE-II, Acute Physiology and Chronic Health Evaluation; SD, Standard deviation; SOFA, Sequential Organ Failure Assessment.
* Age, weight, body surface area, and serum creatinine are expressed as medians [lower quartile–upper quartile].
** < 0.01.

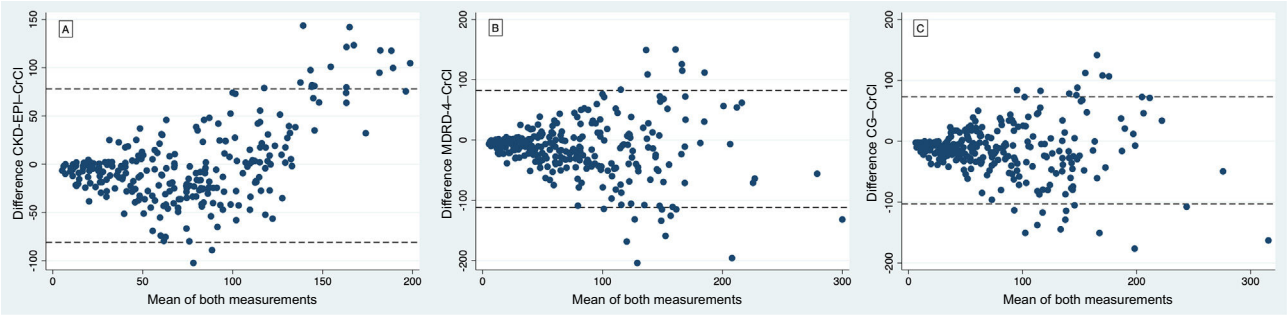

Figure 1. Bland–Altman plots for the full cohort. The Y-axis represents the difference between measured $CrCl_{24h}$ and the eGFR equation; the X-axis represents the mean of both measurements. A) CKD-EPI equation, B) MDRD-4 equation, and C) CG equation.

compared with the CG eq. (24.8 mL/min/m^2; 95% CI: 5.7 to 43.9 mL/min/m^2) and the MDRD-4 eq. (29.3 mL/min/1.73 m^2; 95% CI: 9.9 to 48.7 mL/min/1.73 m^2), with statistically significant differences between the CKD-EPI equation and the CG and MDRD-4 equations ($p < 0.01$). Conversely, no significant differences in accuracy were observed among the 3 GFR estimating equations in this cohort, with values of ± 38.7 mL/min/1.73 m^2 for the CKD-EPI equation, ± 62.4 mL/min/m^2 for the CG equation, and ± 63.5 mL/min/1.73 m^2 for the MDRD-4 equation. Table 3 shows the limits of agreement, and Fig. 3 shows the estimated bias.

Discussion

Our study shows that the accuracy and clinical utility of GFR estimating equations can vary significantly with patient profile. In the studied cohort, no serum creatinine-based equation proved superior to the others in critically ill patients with a $CrCl_{24h}$ between 0 and 129 mL/min. The 3 evaluated equations (CKD-EPI, MDRD-4 and CG) showed a moderate correlation with $CrCl_{24h}$ (rS = 0.74–0.76; $p <$ 0.01) and all exhibited moderate bias and wide limits of agreement. In line with previous studies,[13–15] our findings also suggest that the equations tend to overestimate eGFR; the median eGFR values calculated using CKD-EPI, MDRD-4, and CG were 20.8, 17.3, and 13.0 mL/min higher than the median $CrCl_{24h}$ value, respectively.

The use of equations to estimate eGFR in critically ill patients remains a matter of debate, as these equations are commonly used to adjust drug dosages in clinical practice, despite not being validated for this patient group.[16] Patients in intensive care may experience significant physiological changes, including an increased volume of distribution, increased cardiac output, hypoalbuminaemia, a high incidence of acute kidney injury, and frequent use of extracorporeal systems. These factors can significantly impact the pharmacokinetics and pharmacodynamics of many drugs, particularly those primarily eliminated via the kidneys.[9,17,18] Furthermore, prolonged hospital stays and catabolic states can alter creatinine production, making serum creatinine an unreliable biomarker for renal function assessment because of its high variability.[19]

Several studies have evaluated the performance of serum creatinine-based equations in intensive care settings. However, the results have

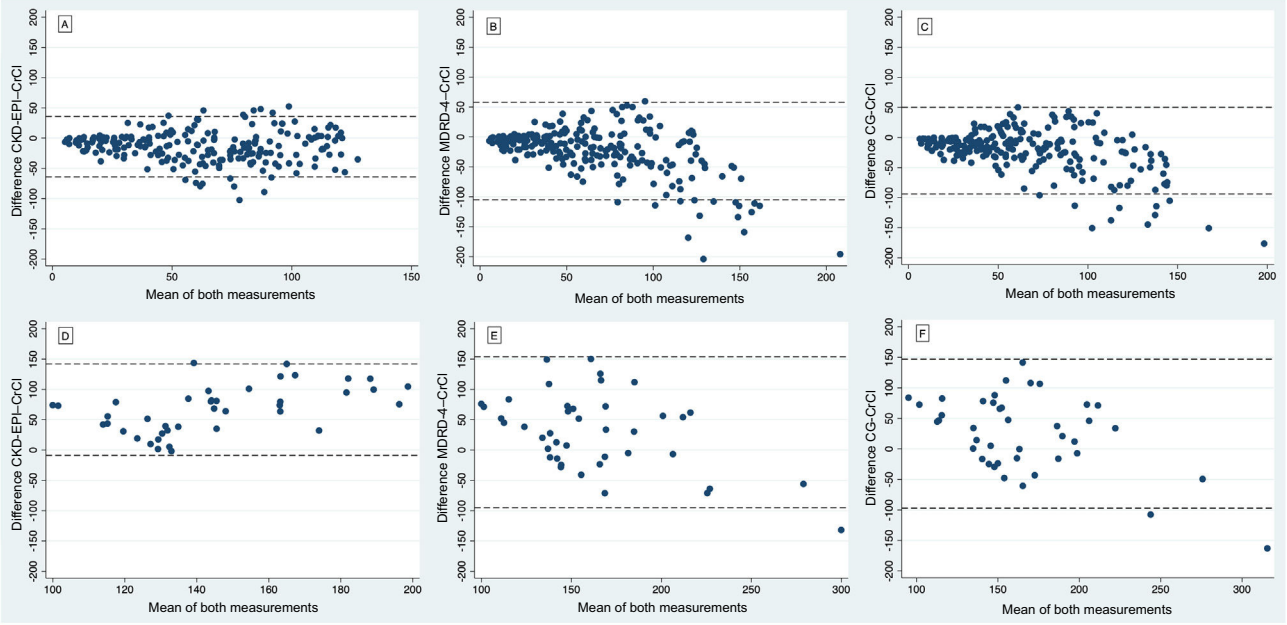

Figure 2. Bland–Altman plots using a cut-off point of ≥130 mL/min for ARC. The Y-axis represents the difference between the measured $CrCl_{24h}$ and the eGFR equation; the X-axis represents the mean of both measurements. Patients with $CrCl_{24h}$ between 0 and 129 mL/min are shown in the upper plots: A) CKD-EPI, B) MDRD-4, and C) CG. Patients with ARC are shown in the lower plots: D) CKD-EPI, E) MDRD-4, E) and F) CG. ARC, augmented renal clearance; GFR, Glomerular filtration rate.

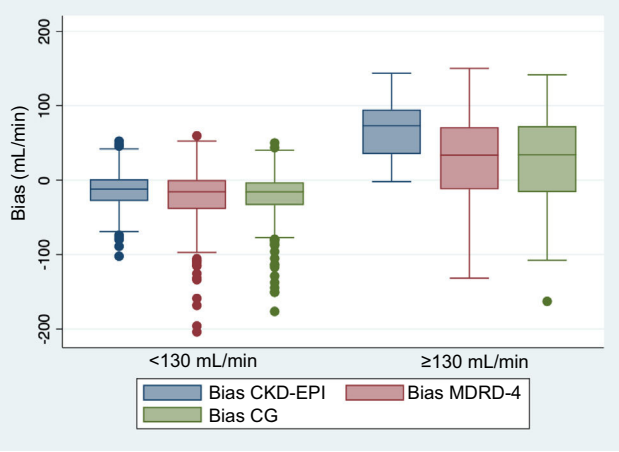

Figure 3. Estimated bias in eGFR using different creatinine-based equations in patients with CrCl24 < 130 mL/min and in patients with ARC.

been inconsistent. Ruiz et al. reported that the CKD-EPI and CG equations were slightly more accurate than the MDRD equation, with biases of −11.3 mL/min/1.73 m^2, −18.8 mL/min/1.73 m^2, and −22.5 mL/min/1.73 m^2, respectively. These results are consistent with those obtained in our study.[20] A study in Australia by Tsai et al. reported that, although the GFR equation adjusted for total body weight had a low bias (−8.2 mL/min/1.73 m^2), the CKD-EPI equation showed the narrowest limits of agreement (115.9 mL/min/1.73 m^2) in the non-Indigenous subpopulation.[21] In our study, the CKD-EPI equation showed the lowest bias and narrowest limits of agreement (100.2 mL/min/1.73 m^2) in patients with a $CrCl_{24h}$ between 0 and 129 mL/min.

In contrast, Wongpraphairot et al. found limited validity of eGFR equations in 49 critically ill patients; the CG equation showed the best performance, with a bias of −8.6 mL/min/1.73 m^2 compared with the CKD-EPI and MDRD-4 equations, which showed biases of −19.0 mL/min/1.73 m^2 and −32.0 mL/min/1.73 m^2, respectively.[8] These findings contrast with those of our study: among patients with $CrCl_{24h}$ between 0 and 129 mL/min, the CKD-EPI equation showed the lowest bias (−13.9 mL/min/1.73 m^2), followed by the CG equation (−22.0 mL/-min/m^2), and the MDRD-4 equation (−23.5 mL/min/1.73 m^2). These differences could arise from the lower incidence of ARC in the study by Wongpraphairot et al. than in our study and the previously mentioned studies. This lower incidence may reflect a population with characteristics associated with a lower ARC risk: older age, a lower proportion of male patients, and fewer cases of traumatic and surgical aetiology, in contrast to our cohort and those of Ruiz et al. and Tsai et al.

Several studies have shown that young age, trauma as the cause of ICU admission, and male sex are independent factors that increase the risk of ARC.[18,22] Identifying patients with ARC is of vital importance to avoid underdosing of drugs eliminated via the kidneys. Although data on the performance of eGFR equations in critically ill patients with ARC remain limited, several studies have highlighted the importance of dose adjustment in this population, particularly for hydrophilic antibiotics, where appropriate dosing is essential to prevent treatment failure and the emergence of resistance due to suboptimal serum drug concentrations.[9,17]

The incidence of ARC described in the literature ranges from 30% to 65%.[23] We observed a lower incidence of ARC, which could be partly attributed to the heterogeneity of the ICUs included (2 general ICUs, 1 respiratory ICU, and 1 surgical ICU). Among the subgroup of patients with ARC, all eGFR equations evaluated showed a modest correlation (rS ≤0.3; $p > 0.05$) and high bias values relative to $CrCl_{24h}$, consistent with international studies indicating the low accuracy of these equations in the context of renal hyperfiltration.[8,20,21] The CG equation showed the lowest bias (24.8 mL/min/m^2), followed by the MDRD-4 eq. (29.3 mL/min/1.73 m^2) and the CKD-EPI eq. (66.4 mL/min/1.73 m^2), although all significantly underestimated renal function in patients with ARC (148.7 mL/min/m^2; 136 mL/min/1.73 m^2 and 114 mL/min/1.73 m^2, respectively). It is worth noting that significant differences in bias were observed between the CKD-EPI equation and the other 2 equations ($p < 0.01$).

Our results in patients with ARC are consistent with the current literature. Baptista et al. demonstrated, in a cohort of 86 patients with ARC, that eGFR equations are inadequate for estimating eGFR in these patients. In their study, Spearman correlation coefficients were 0.26 for the CG equation and 0.22 for the MDRD-4 equation, with a greater bias for the latter (48 mL/min/1.73 m^2) compared with the CG eq. (39 mL/min/1.73 m^2).[24] These findings are consistent with a previous study that evaluated the performance of the CG and MDRD-4 equations in patients with ARC, reporting Spearman coefficients of 0.34 and 0.29, and biases of 11.2 mL/min/1.73 m^2 and 19.9 mL/min/1.73 m^2, respectively.[25] Subsequent studies included the CKD-EPI equation in the analysis. For example, Ruiz et al. obtained results consistent with those of our study in terms of bias, observing that the CG equation exhibited the lowest bias (35.7 mL/min/1.73 m^2), followed by the MDRD-4 eq. (40.9 mL/min/1.73 m^2), and the CKD-EPI eq. (57.9 mL/min/1.73 m^2).[21] Similarly, Al-Dorzi et al., in a cohort of patients with ARC, reported the best Spearman correlation coefficient for the adjusted CG equation (rS = 0.38), followed by the MDRD-4 and CKD-EPI equations (rS = 0.27 and rS = 0.22, respectively), with biases of 0.7 mL/min, 29.2 mL/min/1.73 m^2 and 44.0 mL/min/1.73 m^2, respectively.[26] Taken together, our results and the literature suggest that the CKD-EPI equation may not be suitable for patients with ARC, given its poor performance, as evidenced by a low Spearman correlation coefficient (rS = 0.14) and a high bias (66.4 mL/min). Therefore, in patients with ARC, eGFR should be estimated using the CG or MDRD-4 equations.

The results of this study should be interpreted with caution, taking into account both its strengths and limitations. Its strengths include the large sample size of critically ill patients and the evaluation of 3 different eGFR equations commonly used in routine clinical practice. Its limitations include the heterogeneity of the study cohort, as patients were recruited from 4 different hospital ICUs. The retrospective nature of the study also limits the ability to ensure the accuracy of the 24-h urine measurements, as undetected errors may have occurred during collection. Another limitation is the use of $CrCl_{24h}$ as the reference standard rather than substrates that are exclusively filtered, such as inulin. However, our objective was to evaluate methods commonly used in daily clinical practice. Furthermore, cystatin C-based equations were not included, as this parameter is not routinely measured in patients admitted to the ICUs at our institution. We also assumed a steady-state condition to estimate GFR, although it is recognised that critically ill patients may experience fluctuations in creatinine production during their ICU stay. Finally, this study is limited by the lack of analysis of the impact of using different GFR estimating equations on drug dosing in patients with ARC. Future studies could also focus on assessing systemic exposure for drugs where therapeutic concentration monitoring is available as a tool for dose optimisation.

This study highlights that the equations commonly used to estimate glomerular filtration rate in critically ill patients have significant limitations compared with $CrCl_{24h}$. Clinicians should be aware of this limitation when using serum creatinine-based equations to assess renal function in patients admitted to ICUs. No significant differences in bias and accuracy were observed between the CG, MDRD-4, and CKD-EPI equations in patients with a $CrCl_{24h}$ between 0 and 129 mL/min. However, in patients with ARC, the CG and MDRD-4 equations performed

better than the CKD-EPI equation, suggesting that the latter should not be used in this clinical context.

Contribution to the scientific literature

Equations for estimating glomerular filtration rate are routinely used in critically ill patients, despite not being validated in this population. This study expands the available knowledge on the performance of 3 creatinine-based equations for estimating glomerular filtration rate commonly used in this clinical setting. The results are particularly relevant for the subpopulation of patients with augmented renal clearance (≥130 mL/min), as they have an increased risk of underexposure to predominantly renally eliminated antimicrobials, which could lead to treatment failure and impact mortality.

In this setting, the data may raise awareness among clinicians and pharmacists of the limitations of these equations, thereby supporting appropriate dosing of renally eliminated drugs.

Ethical responsibilities

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the hospital's ethics committee (registration reference HCB/2022/1012). Exemption from informed consent was requested as the study design was retrospective and non-interventional.

CRediT authorship contribution statement

Joan Ramon Roma: Writing – review & editing; Writing – original draft; Methodology; Investigation; Formal analysis; Data curation; Conceptualisation. **Natàlia Arranz-Pasqual**: Writing – review & editing; Investigation; Data curation. **Carla Bastida:** Writing – review & editing; Writing – original draft; Supervision; Project administration; Methodology; Conceptualisation; Validation. **Dolors Soy:** Writing – review & editing; Supervision; Methodology; Conceptualisation; Validation.

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Conflict of interest

None declared.

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