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A retrospective observational study on the discordance rate of antibiotic dosing among critically ill patients: Considerations for using KDIGO guideline

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ABSTRACT

Optimizing antibiotic dosing in critically ill patients is challenging. This study evaluated the discordance rate of antibiotic dosing between the Cockcroft-gault (CG) and chronic kidney disease-epidemiology collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) equations in medical intensive care units (MICUs) patients. We also assessed the concordance analysis of estimated kidney function and stage of dosing for each antibiotic agent between equations. A retrospective study was conducted on patients in MICUs who received commonly used antibiotic agents between August 2020 and July 2023. The agreement was assessed using a weighted kappa statistic. A total of 171 patients with 266 cystatin C sampling points were included. The mean age and median sarcopenia index were 67.23 years and 0.45, respectively. The CKD-EPI eGFRcys 2012 equation showed the highest discordance in antibiotic dosing. Discordance rate of antibiotic dosing based on CG and CKD-EPI eGFR based on creatinine ranged from 10% to 30%. Compared with cystatin C-based equations, Piperacillin/tazobactam had the highest negative discordance rates, while ertapenem had the lowest. The acute kidney injury group exhibited a reduced correlation and an increased discordance rate of antibiotic agents between creatinine-based and cystatin C-based equations. Various equations for estimating renal clearance from the Kidney Disease: Improving Global Outcomes guideline result in different antibiotic dosages. Further research is required for appropriate dose adjustment.

1. INTRODUCTION

Critically ill patients often have conditions such as sepsis and multi-organ dysfunction. These conditions impact pharmacokinetics and lead to over-therapeutic or subtherapeutic drug levels [1]. Previous research identified that the dose selection (37.1%) was the leading cause of antibiotic-related problems in intensive care unit (ICU) settings [2]. Therefore, optimizing antibiotic dosing in critically ill patients is crucial for improving outcomes.

Since 1998, the US Food and Drug Administration (FDA) has recommended the Cockcroft-Gault (CG) equation for assessing drug pharmacokinetics in patients with renal impairment [3]. This results in manufacturers recommending antibiotic dosing based on the CG equation. When only serum creatinine is available, the CG equation can be used to estimate creatinine clearance for commonly used antibiotics approved by the FDA in earlier years [4–7]. Conversely, the

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2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends using estimated glomerular filtration rate (eGFR) equations with serum creatinine for drug dosing and switching to combined creatinine and cystatin C equations when estimated glomerular filtration rate based on creatinine (eGFRcr) is unreliable [8,9], aligning with the US FDA's 2024 recommendation for pharmacokinetic studies [10]. Serum creatinine is not a reliable measure for estimating glomerular filtration rate in critically ill patients. Previous studies show that cystatin C-based eGFR equations and the chronic kidney disease-epidemiology collaboration (CKD-EPI) eGFRcr-cys had the highest accuracy, least bias, and more precision compared to other methods in critically ill patients when we compared these equations with measured GFR (mGFR) [11]. Cystatin C is a newer endogenous biomarker that can provide a more accurate estimate of GFR. However, in Thailand, the use of cystatin C is limited due to its higher cost compared to serum creatinine. As a result, the creatinine-based equation remains the most commonly used method for adjusting antibiotic doses in clinical practice. A more accurate estimation of GFR could enhance appropriate antibiotic dosing, leading to improved clinical outcomes and reduced adverse drug reactions. While some studies showed the improved accuracy of the CKD-EPI eGFR equation by combining creatinine and cystatin C to assess kidney function, there are limited data on using this equation for antibiotic dose adjustment, especially in critically ill patients [12,13].

A survey study of pharmacists on the current practice of estimating kidney function for antimicrobial dosing shows that 86% who routinely estimate kidney function utilized the CG equation [14]. According to recommendations from KDIGO and the US FDA, this approach could influence our decision-making when selecting the eGFR equation for antibiotic dosing [8,10]. Estimating renal clearance with different equations can result in varying antibiotic dosages, potentially compromising patient safety. In addition, data on this issue is limited for critically ill patients using antibiotics. In this study, we aimed to evaluate the discordance rate of antibiotic dosing between the CG and KDIGO guideline (CKD-EPI eGFRcr 2021, CKD-EPI eGFRcys 2012, and CKD-EPI eGFRcr-cys 2021) in critically ill patients. We also compared the concordance of estimated renal clearance and stage of dosing (SOD) using the CG equation with CKD-EPI eGFR equations for commonly used antibiotics in medical intensive care units (MICUs).

2. MATERIALS AND METHODS

2.1. Study design, setting, and participants

This retrospective observational study was conducted at King Chulalongkorn Memorial Hospital in Thailand. The inclusion criteria were as follows: (i) patients aged ≥18 years admitted to MICUs between August 2020 and July 2023; (ii) patients who received antibiotics, including meropenem, imipenem/cilastatin, ertapenem, piperacillin/tazobactam, cefoperazone/sulbactam, ampicillin/sulbactam, sulbactam, colistin, fosfomycin, amikacin, gentamicin, and vancomycin during MICU admission. We aimed to compare estimated renal clearance and SOD using the CG equation and CKD-EPI eGFR equations, so we included patients with serum cystatin C and creatinine levels measured on the same day during their MICU admission. We excluded patients receiving extracorporeal circuit treatments (e.g., Extracorporeal Membrane Oxygenation or Renal Replacement Therapy), patients who died within 24 hours post-MICU admission, and pregnant. Patients with incomplete baseline characteristic data were excluded from the study. This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB No. 0848/66). All data were fully anonymized before we accessed them. The IRB waived the requirement for patients' informed consent.

2.2. Data collection

Data were collected from the e-PHIS-CUH program and medical charts to gather demographic information, including actual body weight, serum albumin levels, APACHE II scores, and the presence of septic shock within 24 hours of cystatin C measurement. The use of a standardized electronic medical record system ensures consistent data collection. The data were collected retrospectively from a complete hospital database, which minimized potential recall bias. We also recorded corticosteroid exposure within 14 days prior to cystatin C measurement. Kidney function was assessed at the time of each concurrent cystatin C and creatinine measurement, utilizing these results to calculate eGFR with the CKD-EPI eGFRcr 2021, CKD-EPI eGFRcys 2012, and CKD-EPI eGFRcr-cys 2021 equations (Supplementary Table 1). Acute kidney injury (AKI) was evaluated based on the serum creatinine criteria from the KDIGO [15].

Some patients receiving care in the MICU exhibited fluctuations in serum creatinine and cystatin C levels. All collected serum creatinine and cystatin C were used for discordance and concordance analyses. We used the CG equation to estimate creatinine clearance (CrCl) for comparison with eGFR equations, particularly the CKD-EPI from the latest KDIGO guidelines [8,9]. We selected these specific eGFR equations because they represent the most commonly used and updated methods for assessing kidney function in clinical practice, including in critically ill patients [3,13]. The CG equation, despite its limitations and lack of standardization for predicting kidney function, is commonly used for antibiotic dosing. This widespread use makes it the most relevant comparator for evaluating the real-world impact of alternative eGFR equations, particularly in this patient population [16–18].

2.3. Definitions

Discordance rate was defined as the percentage of occurrences where there was a discrepancy in drug dosing for at least one antibiotic agent when comparing the CG equation to the eGFR equations. Positive discordance indicated that higher doses were suggested by eGFR, while negative discordance suggested lower doses. Intra-individual difference referred to the numerical difference between CG and eGFR, with thresholds (15 ml/min, 30 ml/min, 20%, and 30%) based on previous studies to categorize the extent of discrepancy [17,19,20]. The percent of absolute difference between equations was calculated as [(CG-eGFR)/CG] × 100. Stage of dosing (SOD) was defined as the recommended drug dosing stage according to the Uptodate and Lexi-drug application or simulation studies

used in our setting [21–27] (Supplementary Tables 2–10). We utilized the results of renal clearance from the CG equation and other eGFR equations to guide the SOD. The AKI group was defined as patients who met KDIGO's creatinine criteria for AKI diagnosis at each occurrence of cystatin C and creatinine measurement. In addition, we assessed the serum creatinine to cystatin C ratio with a cutoff value of 0.8 as a potential biomarker for sarcopenia in critically ill patients [28].

2.4. Statistical analysis

Descriptive statistics were used to analyze the discordance rate. The Wilcoxon signed-rank test was used to compare estimated kidney function between the CG and eGFR equations. To evaluate the agreement of kidney function between the CG and the various CKD-EPI eGFR equations, we utilized the concordance correlation coefficient (CCC) and Bland-Altman plots. Subgroup analyses were conducted for AKI and non-AKI patients to evaluate discordance and concordance in antibiotic dosing and renal clearance within these groups. Regarding missing data, we performed a complete case analysis, where patients with any incomplete baseline data were excluded from the study.

Our sample size was determined based on previous findings, which reported a 32.00% difference in SOD for meropenem between the CG and CKD-EPI eGFRcr-cys equations, with a CCC range of 0.568–0.830 and a weighted kappa of 0.651 (95% CI: 0.590–0.712) [16]. Our pilot study revealed a difference of 49.30% [29]. Therefore, we set K1 at 0.50 and K2 at 0.70, requiring a minimum of 98 serum creatinine and cystatin C sampling points to achieve 90% power with an alpha of 0.05 [30]. The agreement of SOD between eGFR equations was assessed using the weighted kappa statistic with Cicchetti–Allison weights. The interpretation of the CCC and weighted kappa statistics is shown in Table 1 [31,32]. All analyses were conducted using STATA (Version 18.0).

Table 1. Interpretation of the CCC and weighted kappa statistics.

CCC		Weighted kappa statistic	
Value	**Interpretation**	**Value**	**Interpretation**
>0.80	Excellent	0.81–1.00	Almost perfect
0.20–0.80	Acceptable	0.61–0.80	Substantial
<0.20	Poor	0.41–0.60	Moderate
		0.21–0.40	Fair
		0.00–0.20	Slight
		<0.00	Poor

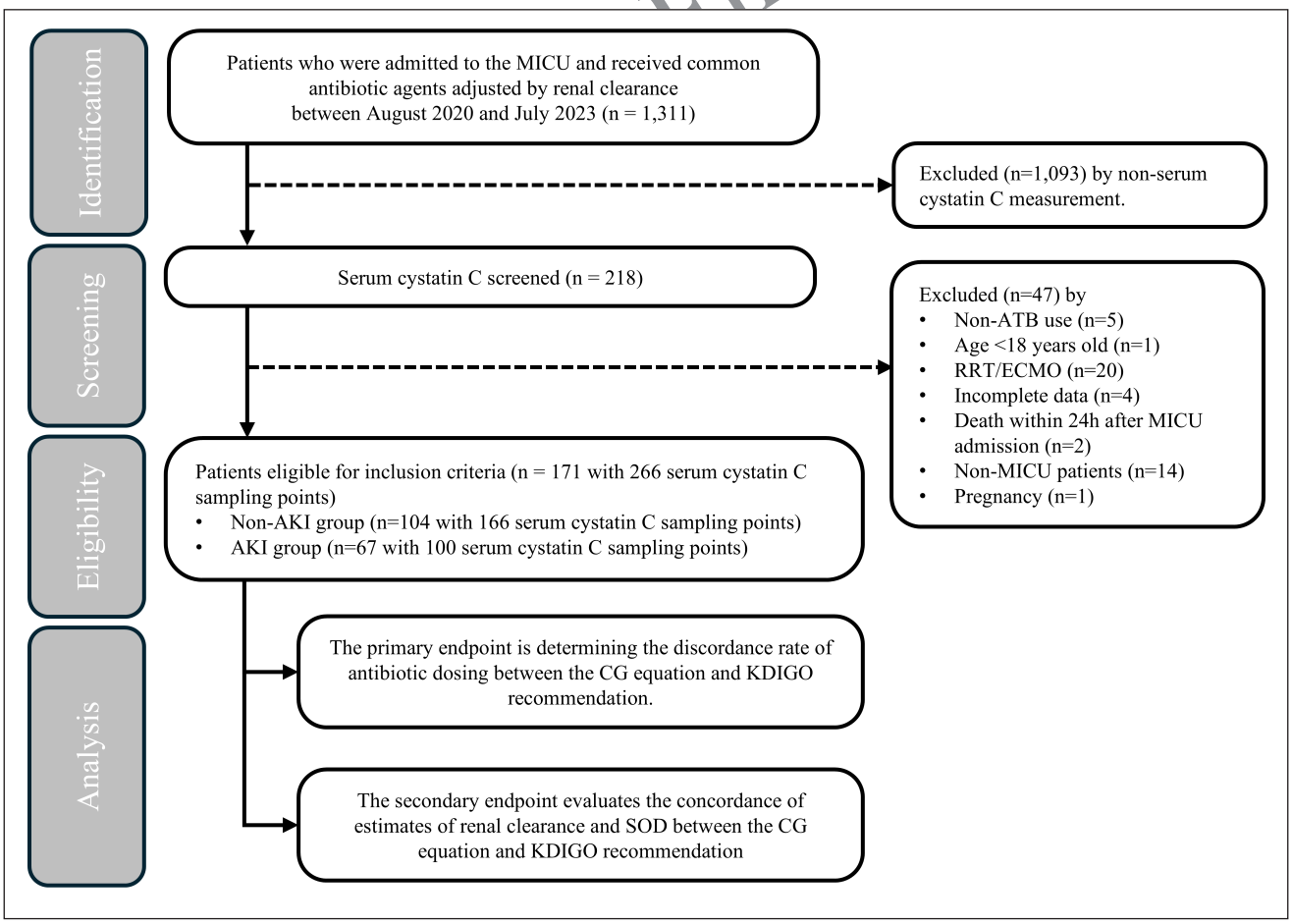

Figure 1. Flowchart of inclusion and exclusion criteria.

Table 2. Baseline characteristics ($N = 171$).

Baseline characteristics	Overall ($n = 171$)	Non-AKI group ($n = 104$)	AKI group ($n = 67$)
Age (year), mean (SD)	67.23 (17.45)	68.72 (16.17)	64.91 (19.16)
Female sex, *n* (%)	86 (50.29)	53 (50.96)	33 (49.25)
Weight (kg), mean (SD)	58.15 (13.28)	57.15 (13.85)	59.70 (12.27)
Body mass index (kg/m^2), mean (SD)	22.71 (4.58)	22.44 (4.79)	23.13 (4.25)
Body surface area (m^2), mean (SD)	1.60 (0.21)	1.58 (0.21)	1.62 (0.19)
Sarcopenia index (SI), median (IQR)	0.45 (0.26)	0.41 (0.19)	0.53 (0.30)
Underlying disease, *n* (%)	150 (87.72)	93 (89.42)	57 (85.07)
Cardiovascular disease	97 (56.73)	62 (59.62)	35 (52.24)
Endocrinologic disease	57 (33.33)	36 (34.62)	21 (31.34)
Thyroid dysfunction	10 (5.85)	6 (5.77)	4 (5.97)
Oncologic disease	48 (28.07)	26 (25.00)	22 (32.84)
Solid tumors	35 (20.47)	18 (17.31)	17 (25.37)
Hematologic malignancies	13 (7.60)	8 (7.69)	5 (7.46)
Neurological disease	33 (19.30)	23 (22.12)	10 (14.93)
Pulmonary disease	29 (16.96)	18 (17.31)	11 (16.42)
Gastrointestinal disease	26 (15.20)	18 (17.31)	8 (11.94)
Renal disease	16 (9.36)	7 (6.73)	9 (13.43)
Transplantation	5 (2.92)	3 (2.88)	2 (2.99)
Current smoker, *n* (%)	15 (8.77)	8 (7.69)	7 (10.45)
Past corticosteroid use within 14 days, *n* (%)	121 (70.76)	75 (72.12)	46 (68.66)
Immunocompromised[a], *n* (%)	47 (27.49)	30 (28.85)	17 (25.37)
Immunosuppressive agents use[b], *n* (%)	13 (7.60)	9 (8.65)	4 (5.97)
Serum albumin[c] (gm/dl), mean (SD)	2.90 (0.54)	2.91 (0.57)	2.88 (0.49)
Septic shock[c], *n* (%)	57 (33.33)	30 (28.85)	27 (40.30)
APACHE II Score[c], mean (SD)	20.85 (5.26)	20.67 (5.22)	21.13 (5.35)
Charlson comorbidity index, mean (SD)	3.19 (2.86)	3.19 (2.92)	3.19 (2.78)
Site of infection, *n* (%)			
Respiratory tract	104 (60.82)	64 (61.54)	40 (59.70)
Unknown sources	28 (16.37)	19 (18.27)	9 (13.43)
Bloodstream	24 (14.04)	15 (14.42)	9 (13.43)
Intra-abdominal	12 (7.02)	7 (6.73)	5 (7.46)
Urinary tract	5 (2.92)	2 (1.92)	3 (4.48)
Skin and soft tissue	3 (1.75)	2 (1.92)	1 (1.49)
Bone and joint	3 (1.75)	2 (1.92)	1 (1.49)
Antibiotic use, *n* (%)			
Meropenem	129 (75.44)	82 (78.85)	47 (70.15)
Colistin	54 (31.58)	34 (32.69)	20 (29.85)
Vancomycin	51 (29.82)	31 (29.81)	20 (29.85)
Piperacillin/tazobactam	38 (22.22)	21 (20.19)	17 (25.37)
Sulbactam (including ampicillin/sulbactam cefoperazone/sulbactam[d], and sulbactam)	30 (17.54)	16 (15.38)	14 (20.90)
Fosfomycin	19 (11.11)	12 (11.54)	7 (10.45)
Amikacin	10 (5.85)	6 (5.77)	4 (5.97)
Imipenem/cilastatin	3 (1.75)	2 (1.92)	1 (1.49)

[a]Immunocompromised patients, including innate immune deficiency, oncological disease with chemotherapy, hematologic stem cell transplant, solid organ transplant, acquired immunodeficiency syndrome, immunosuppressive agents use, current corticosteroid use (equivalent ≥ 20 mg of prednisolone at least three weeks or cumulative dose ≥ 600 mg of prednisolone).
[b]Immunosuppressive agents, including selective immunosuppressant [anti-thymocyte globulin, baricitinib, leflunomide, mycophenolate mofetil (MMF), sirolimus, teriflunomide, tofacitinib, and vedolizumab], TNF-alpha inhibitors, calcineurin inhibitors, interleukin inhibitor, and azathioprine.
[c]Septic shock, APACHE II score, serum albumin, and serum creatinine were recorded on the day of cystatin C sampling, and past corticosteroid use was recorded 14 days before cystatin C sampling.
[d]Cefoperazone/sulbactam was administered to 14 patients (8.19%).

3. RESULT

3.1. Characteristics of the study population

A total of 171 patients with 266 serum cystatin C sampling points met the inclusion criteria (Fig. 1). Of these, 57 patients (33.33%) have multiple serum cystatin C and serum creatinine measured in MICUs, 104 patients with 166 serum cystatin C sampling points were in the non-AKI group, and 67 patients with 100 serum cystatin C sampling points were in the AKI group. The mean ± SD age was 67.23 ± 17.45 years. The mean ± SD of BMI and BSA was 22.71 ± 4.58 kg/m^2 and 1.60 ± 0.21 m^2, respectively. The sarcopenia index (SI) exhibited a median [interquartile range (IQR)] of 0.45 (0.26). Meropenem was the most frequently administered antibiotic (75.44%), followed by colistin (31.58%) and vancomycin (29.82%). The baseline characteristics are presented in Table 2.

Two hundred sixty-six sampling points of serum creatinine and cystatin C were included for primary and secondary analysis. The median (IQR) serum creatinine was 0.90 (0.89) mg/dl, while the mean ± SD serum cystatin C was 2.40 ± 1.19 mg/l. The AKI staging, according to KDIGO, was as follows: Stage I, 69.00%; Stage II, 22.00%; and Stage III, 9.00%. The mean intra-individual differences for the eGFR were as follows: CKD-EPI eGFRcr 2021, CKD-EPI eGFRcys 2012, and CKD-EPI eGFRcr-cys 2021 had a difference of 10.62 ± 58.30 ml/min, 51.12 ± 70.98 ml/min, and 36.56 ± 64.22 ml/min,

Table 3. Baseline biomarker and kidney function ($N = 266$).

Parameters	Overall ($n = 266$)	Non-AKI group ($n = 166$)	AKI group ($n = 100$)
Serum creatinine (mg/dl), median (IQR)	0.90 (0.89)	0.63 (0.55)	1.38 (1.09)
Serum cystatin C (mg/l), mean (SD)	2.40 (1.19)	1.75 (1.34)	3.14 (1.60)
Cockcroft–Gault, CrCl (ml/min), median (IQR)	59.97 (65.26)	78.10 (78.32)	44.20 (33.92)
CKD-EPI eGFRcr 2021 (ml/min/1.73 m²), mean (SD)	79.19 (37.38)	93.11 (34.23)	56.09 (30.37)
CKD-EPI eGFRcys (ml/min/1.73 m²), median (IQR)	25.23 (29.83)	34.95 (40.89)	16.90 (15.23)
CKD-EPI eGFRcr-cys 2021 (ml/min/1.73 m²), median (IQR)	40.44 (42.32)	58.21 (52.41)	26.62 (19.07)

CKD-EPI eGFR, chronic kidney disease-epidemiology collaborative estimated glomerular filtration rate calculated using serum cystatin C and/or creatinine; cr, serum creatinine; cys, serum cystatin C; IQR, interquartile range; mg/dl, milligram per deciliter; SD, standard deviation; ml/min/1.73m², milliliters per minute per 1.73 square meters of body surface area.

respectively, among overall patients. In the non-AKI group, the differences were 19.82 ± 71.97 ml/min for CKD-EPI eGFRcr 2021, 64.92 ± 85.24 ml/min for CKD-EPI eGFRcys 2012, and 47.36 ± 78.20 ml/min for CKD-EPI eGFRcr-cys 2021. The Wilcoxon signed-rank test indicated significant differences in kidney function estimates from CKD-EPI eGFRcr 2021, CKD-EPI eGFRcys 2012, and CKD-EPI eGFRcr-cys 2021compared to the CG equation, with all p-values < 0.05. The baseline biomarker and kidney function are shown in Table 3.

3.2. Agreement of kidney function between creatinine clearance and estimated glomerular filtration rate

The CKD-EPI eGFR equation, based on creatinine, cystatin C, or combined, demonstrated acceptable agreement with the CG equation in all groups except the CKD-EPI eGFRcr 2021 shows excellent agreement in AKI group. The CCC in both AKI and non-AKI groups is shown in Table 4. The Bland–Altman plot illustrates the differences between the CG and eGFR equations (Fig. 2). Both eGFR equations based on cystatin C or combined creatinine and cystatin C exhibited significant bias and a higher mean difference than creatinine alone (95% CI of mean difference for CKD-EPI eGFRcr 2021 −2.99 to 11.23, CKD-EPI eGFRcys 39.42 to 56.64, and CKD-EPI eGFRcr-cys 2021 24.25 to 39.88). The limits of agreement were wide in all eGFR equations. Although the mean difference between the non-AKI and AKI groups was similar to that of the overall patient population, the AKI group had a lower mean difference than the non-AKI group (Supplementary Fig. 1).

3.3. Discordance rate of antibiotic dosing based on absolute difference of estimates renal clearance between equations

The highest discordance rate for antibiotic dosing was observed (89.10%) when the absolute difference in

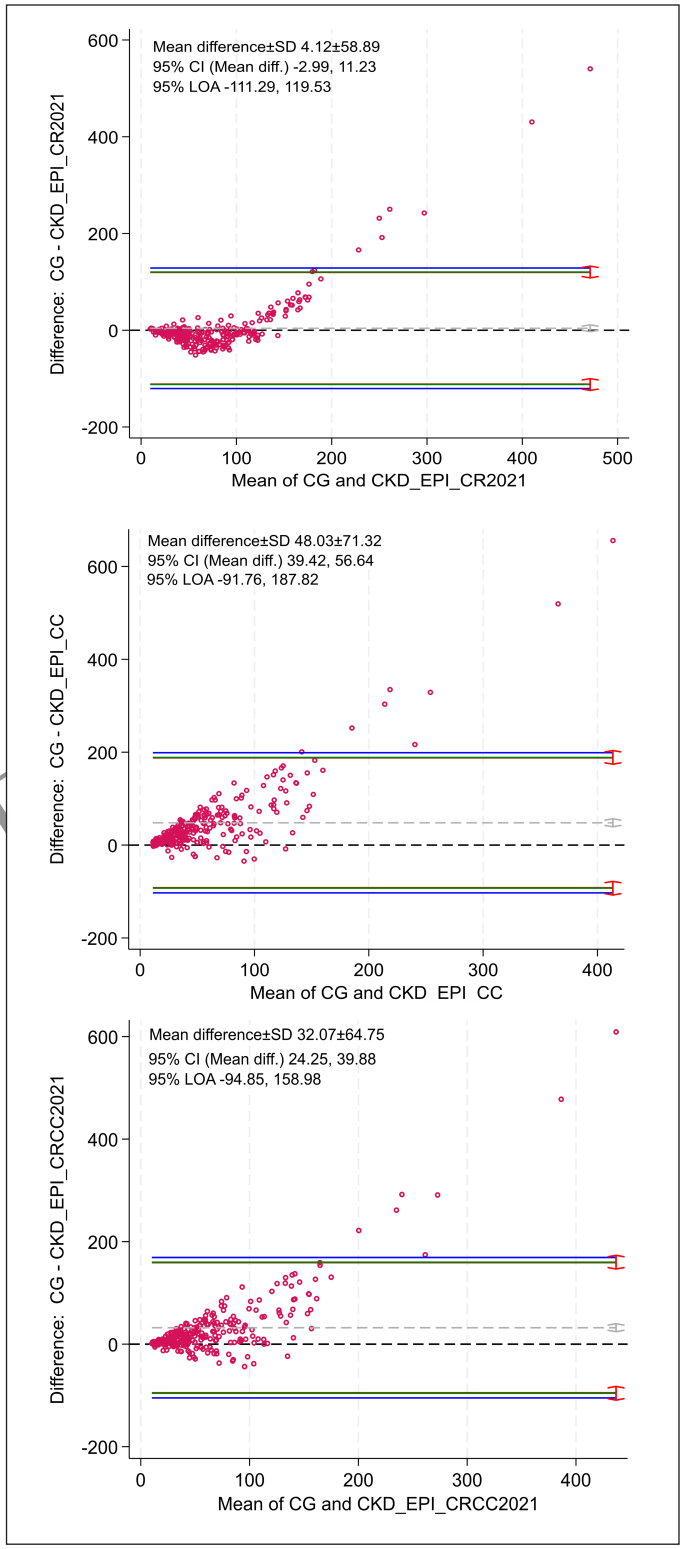

Figure 2. Bland–Altman analysis of 266 cystatin C sampling points. Grey dashed lines represent bias and 95% CI. Red lines represent 95% Limits of Agreement (LoA) and 95% CI for the upper and lower LoA

renal clearance was 20% or more between the CG and CKD-EPI eGFRcys equation, followed by CKD-EPI eGFRcr-cys 2021 (71.05%) and CKD-EPI eGFRcr 2021 (50.75%). The discordance rate on the absolute difference in renal clearance

Table 4. CCC between creatinine clearance and estimates glomerular filtration rate (n = 266).

eGFR equation	CCC for Cockcroft–Gault and eGFR equations*					
	Overall (n = 266)		Non-AKI group (n = 166)		AKI group (n = 100)	
	CCC	95% CI	CCC	95% CI	CCC	95% CI
CKD-EPI eGFRcr 2021	0.583	0.537, 0.629	0.496	0.445, 0.546	0.850	0.798, 0.901
CKD-EPI eGFRcys	0.257	0.208, 0.305	0.207	0.149, 0.265	0.212	0.132, 0.293
CKD-EPI eGFRcr-cys 2021	0.420	0.368, 0.472	0.349	0.285, 0.413	0.514	0.415, 0.613

*All comparisons between the CG equation and eGFR equations were significant; AKI, acute kidney injury; CCC, concordance correlation coefficient; CG, Cockcroft–Gault equation; CKD-EPI eGFR, chronic kidney disease-epidemiology collaborative estimated glomerular filtration rate calculated with serum creatinine and/or cystatin C; Cr, serum creatinine; Cys, serum cystatin C; 95% CI, 95% confidence interval.

Table 5. The rate of discordance in antibiotic dosing based on the absolute difference between creatinine clearance and estimates glomerular filtration rate.

Discordance rate	Overall (n = 266)	Non-AKI group (n = 166)	AKI group (n = 100)
Cockcroft–Gault and CKD-EPI eGFRcr 2021			
Absolute difference ≥15 ml/min, *n* (%)	98 (36.84)	83 (50.00)	15 (15.00)
Absolute difference ≥30 ml/min, *n* (%)	40 (15.04)	38 (22.89)	2 (2.00)
Absolute difference ≥20 %, *n* (%)	135 (50.75)	97 (58.43)	38 (38.00)
Absolute difference ≥30 %, *n* (%)	79 (29.70)	62 (37.35)	17 (17.00)
Cockcroft–Gault and CKD-EPI eGFRcys			
Absolute difference ≥15 ml/min, *n* (%)	192 (72.18)	126 (75.90)	66 (66.00)
Absolute difference ≥30 ml/min, *n* (%)	134 (50.38)	93 (56.02)	41 (41.00)
Absolute difference ≥20 %, *n* (%)	237 (89.10)	149 (89.76)	88 (88.00)
Absolute difference ≥30 %, *n* (%)	223 (83.83)	138 (83.13)	85 (85.00)
Cockcroft–Gault and CKD-EPI eGFRcr-cys 2021			
Absolute difference ≥15 ml/min, *n* (%)	140 (52.63)	86 (51.81)	54 (54.00)
Absolute difference ≥30 ml/min, *n* (%)	78 (29.32)	58 (34.94)	20 (20.00)
Absolute difference ≥20 %, *n* (%)	189 (71.05)	111 (66.87)	78 (78.00)
Absolute difference ≥30 %, *n* (%)	146 (54.89)	81 (48.80)	65 (65.00)

CKD-EPI eGFR, chronic kidney disease-epidemiology collaborative estimated glomerular filtration rate calculated using serum cystatin C and/or creatinine; cr, serum creatinine; cys, serum cystatin C; ml/min, milliliters per minute.

of 15 ml/min or more between the CG and CKD-EPI eGFRcr 2021 was observed at 36.84% for overall patients, 50.00% for the non-AKI group, and 15.00% for the AKI group. This outcome was consistent across both non-AKI and AKI groups. The discordance rate of antibiotic dosing is shown in Table 5.

3.4. Comparison of antibiotic dosing stages between creatinine clearance and estimates glomerular filtration rate

Continuous GFR from 266 serum creatinine and cystatin C were matched with the SOD of each antibiotic agent for weighted kappa analysis. The CKD-EPI eGFRcr 2021 equation found substantial agreement and positive discordance of antibiotic dosing with the CG equation for all antibiotic agents. The CKD-EPI eGFRcys 2012 equation showed fair agreement and negative discordance with the CG equation. CKD-EPI eGFRcr-cys 2021 demonstrated moderate agreement and negative discordance with the CG equation for all antibiotic agents except sulbactam, which shows substantial agreement.

Table 6. Discordance rate of SOD for each antibiotic agent between creatinine clearance and estimates glomerular filtration rate.

Antibiotic agents		Weighted k (95% CI)	Discordance rate (n, %)	
			Negative discordance	Positive discordance
		Meropenem		
CKD-EPI eGFRcr	Overall[a]	0.643 (0.620–0.675)	6 (2.26)	55 (20.68)
	Non-AKI[b]	0.540 (0.489–0.599)	1 (0.60)	31 (18.67)
	AKI[c]	0.650 (0.612–0.694)	5 (5.00)	24 (24.00)
CKD-EPI eGFRcys	Overall[a]	0.251 (0.235–0.282)	164 (61.65)	5 (1.88)
	Non-AKI[b]	0.242 (0.222–0.269)	95 (57.23)	2 (1.20)
	AKI[c]	0.128 (0.097–0.170)	69 (69.00)	3 (3.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.536 (0.477–0.554)	87 (32.71)	10 (3.76)
	Non-AKI[b]	0.577 (0.542–0.632)	38 (22.89)	5 (3.01)
	AKI[c]	0.360 (0.199–0.470)	49 (49.00)	5 (5.00)

Continued

Antibiotic agents		Weighted *k* (95% CI)	Discordance rate (n, %)	
			Negative discordance	Positive discordance
		Imipenem		
CKD-EPI eGFRcr	Overall[a]	0.645 (0.623–0.662)	4 (1.50)	69 (25.94)
	Non-AKI[b]	0.526 (0.511–0.593)	1 (0.60)	38 (22.89)
	AKI[c]	0.665 (0.632–0.760)	3 (3.00)	31 (31.00)
CKD-EPI eGFRcys	Overall[a]	0.266 (0.253–0.283)	174 (65.41)	4 (1.50)
	Non-AKI[b]	0.245 (0.136–0.301)	101 (60.84)	3 (1.81)
	AKI[c]	0.150 (0.095–0.188)	73 (73.00)	1 (1.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.541 (0.492–0.585)	98 (36.84)	16 (6.02)
	Non-AKI[b]	0.515 (0.450–0.614)	48 (28.92)	11 (6.63)
	AKI[c]	0.435 (0.382–0.471)	50 (50.00)	5 (5.00)
		Ertapenem		
CKD-EPI eGFRcr	Overall[a]	0.643 (0.515–0.772)	2 (0.75)	22 (8.27)
	Non-AKI[b]	0.257 (0.011–0.503)	1 (0.60)	14 (8.43)
	AKI[c]	0.780 (0.646–0.915)	1 (1.00)	8 (8.00)
CKD-EPI eGFRcys	Overall[a]	0.255 (0.179–0.330)	107 (40.23)	2 (0.75)
	Non-AKI[b]	0.227 (0.121–0.333)	57 (34.34)	1 (0.60)
	AKI[c]	0.166 (0.067–0.265)	50 (50.00)	1 (1.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.557 (0.450–0.665)	42 (15.79)	4 (1.50)
	Non-AKI[b]	0.584 (0.403–0.765)	13 (7.83)	3 (1.81)
	AKI[c]	0.440 (0.297–0.584)	29 (29.00)	1 (1.00)
		Piperacillin/tazobactam		
CKD-EPI eGFRcr	Overall[a]	0.720 (0.654–0.739)	6 (2.26)	62 (23.31)
	Non-AKI[b]	0.675 (0.616–0.705)	3 (1.81)	39 (23.49)
	AKI[c]	0.705 (0.672–0.719)	3 (3.00)	23 (23.00)
CKD-EPI eGFRcys	Overall[a]	0.212 (0.176–0.218)	192 (72.18)	8 (3.01)
	Non-AKI[b]	0.181 (0.156–0.209)	119 (71.69)	5 (3.01)
	AKI[c]	0.130 (0.075–0.162)	73 (73.00)	3 (3.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.451 (0.342–0.490)	123 (46.24)	17 (6.39)
	Non-AKI[b]	0.412 (0.398–0.418)	70 (42.17)	13 (7.83)
	AKI[c]	0.361 (0.260–0.406)	53 (53.00)	4 (4.00)
		Sulbactam		
CKD-EPI eGFRcr	Overall[a]	0.750 (0.716–0.774)	3 (1.13)	30 (11.28)
	Non-AKI[b]	0.596 (0.499–0.646)	0	21 (12.65)
	AKI[c]	0.834 (0.775–0.866)	3 (3.00)	9 (9.00)
CKD-EPI eGFRcys	Overall[a]	0.375 (0.347–0.413)	133 (50.00)	2 (0.75)
	Non-AKI[b]	0.352 (0.274–0.357)	76 (45.78)	0
	AKI[c]	0.352 (0.333–0.376)	57 (57.00)	2 (2.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.637 (0.580–0.657)	61 (22.93)	4 (1.50)
	Non-AKI[b]	0.645 (0.505–0.677)	26 (15.66)	3 (1.81)
	AKI[c]	0.585 (0.483–0.623)	35 (35.00)	1 (1.00)
		Colistin		
CKD-EPI eGFRcr	Overall[a]	0.663 (0.616–0.672)	3 (1.13)	42 (15.79)
	Non-AKI[b]	0.462 (0.401–0.652)	1 (0.60)	25 (15.06)
	AKI[c]	0.744 (0.695–0.813)	2 (2.00)	17 (17.00)
CKD-EPI eGFRcys	Overall[a]	0.229 (0.176–0.282)	154 (57.89)	6 (2.26)
	Non-AKI[b]	0.207 (0.193–0.208)	84 (50.60)	3 (1.81)
	AKI[c]	0.136 (0.113–0.138)	70 (70.00)	3 (3.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.479 (0.369–0.576)	83 (31.20)	12 (4.51)
	Non-AKI[b]	0.463 (0.367–0.510)	34 (20.48)	8 (4.82)
	AKI[c]	0.381 (0.315–0.411)	49 (49.00)	4 (4.00)
		Aminoglycosides		
CKD-EPI eGFRcr	Overall[a]	0.656 (0.637–0.679)	5 (1.88)	74 (27.82)
	Non-AKI[b]	0.546 (0.456–0.594)	1 (0.60)	44 (26.51)
	AKI[c]	0.683 (0.617–0.710)	4 (4.00)	30 (30.00)
CKD-EPI eGFRcys	Overall[a]	0.259 (0.231–0.281)	176 (66.17)	8 (3.01)
	Non-AKI[b]	0.253 (0.215–0.309)	99 (59.64)	5 (3.01)
	AKI[c]	0.111 (0.093–0.139)	77 (77.00)	3 (3.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.494 (0.474–0.521)	109 (40.98)	20 (7.52)
	Non-AKI[b]	0.483 (0.414–0.594)	52 (31.33)	14 (8.43)
	AKI[c]	0.352 (0.297–0.422)	57 (57.00)	6 (6.00)
		Vancomycin		
CKD-EPI eGFRcr	Overall[a]	0.675 (0.643–0.719)	7 (2.63)	77 (28.95)
	Non-AKI[b]	0.618 (0.563–0.670)	2 (1.20)	52 (31.33)
	AKI[c]	0.636 (0.586–0.741)	5 (5.00)	25 (25.00)
CKD-EPI eGFRcys	Overall[a]	0.235 (0.222–0.261)	178 (66.92)	7 (2.63)
	Non-AKI[b]	0.199 (0.176–0.237)	112 (67.47)	5 (3.01)
	AKI[c]	0.157 (0.103–0.162)	66 (66.00)	2 (2.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.509 (0.459–0.560)	102 (38.35)	14 (5.26)
	Non-AKI[b]	0.480 (0.447–0.536)	65 (39.16)	10 (6.02)
	AKI[c]	0.389 (0.336–0.430)	37 (37.00)	4 (4.00)
		Fosfomycin		
CKD-EPI eGFRcr	Overall[a]	0.640 (0.566–0.655)	6 (2.26)	43 (16.17)
	Non-AKI[b]	0.432 (0.368–0.473)	0	29 (17.47)
	AKI[c]	0.729 (0.697–0.845)	6 (6.00)	14 (14.00)
CKD-EPI eGFRcys	Overall[a]	0.223 (0.202–0.263)	146 (54.89)	7 (2.63)
	Non-AKI[b]	0.245 (0.195–0.293)	80 (48.19)	3 (1.81)
	AKI[c]	0.090 (0.028–0.117)	66 (66.00)	4 (4.00)
CKD-EPI eGFRcr-cys	Overall[a]	0.461 (0.429–0.576)	87 (32.71)	13 (4.89)
	Non-AKI[b]	0.477 (0.434–0.542)	37 (22.29)	10 (6.02)
	AKI[c]	0.336 (0.292–0.360)	50 (50.00)	3 (3.00)

[a]Overall instance of serum creatinine and cystatin C included 266 sampling points from 171 critically ill patients.
[b]Non-AKI patients included 166 sampling points from 104 critically ill patients.
[c]AKI patients included 100 sampling points from 67 critically ill patients.
CG, Cockcroft–Gault equation; eGFR, estimated glomerular filtration rate; CKD-EPI eGFR, chronic kidney disease-epidemiology collaborative estimated glomerular filtration rate calculated with serum creatinine and/or cystatin C; cr, serum creatinine; cys, serum cystatin C; 95% CI, 95% confidence interval.

The CKD-EPI eGFRcys 2012 equation showed highest discordance in determining SOD compared to the CG equation, with negative discordance rates of 71.69% for piperacillin/tazobactam (weighted *k* 0.181: 95% CI 0.156–0.209), 67.47% for vancomycin (weighted *k* 0.199: 95% CI 0.176–0.237), and 60.84% for imipenem (weighted *k* 0.245: 95% CI 0.136–0.301) in the non-AKI group. The differences in SOD between CG and CKD-EPI eGFRcr-cys 2021 exhibited negative discordance for 42.17% (weighted *k* 0.412: 95% CI 0.398–0.418), 39.16% (weighted *k* 0.480: 95% CI 0.447–0.536), and 31.33% (weighted *k* 0.483: 95% CI 0.414–0.594) of cases for piperacillin/tazobactam, vancomycin, and aminoglycosides, respectively, in the non-AKI group. The positive discordance between the CKD-EPI eGFRcr 2021 and the CG equation ranged from 10% to 30%. The AKI group showed a decreased concordance with eGFR based on cystatin C or combined (Table 6).

4. DISCUSSION

Cystatin C is considered to be a more effective marker than serum creatinine for estimating GFR because it is not influenced by factors such as age, sex, or muscle mass [33,34]. However, several studies have indicated that hypothyroidism decreases serum cystatin C levels, while factors such as corticosteroid use, smoking, chronic inflammation, obesity, and hyperthyroidism increase these levels [3,33–35]. Serum cystatin C is becoming increasingly recognized as an alternative marker for predicting kidney function. However, its measurement in Thailand has only recently commenced. Few critically ill patients have had their cystatin C levels measured. Our study found that serum cystatin C measurements are frequently used for elderly patients with sarcopenia and malnutrition, in accordance with the KDIGO 2024 recommendation to accurately predict kidney function [8]. This finding may explain why our results showed higher renal clearance in creatinine-based equations compared to those based on Cystatin C.

Our study showed that various eGFR equations differ from the CG equation. Equation based on combined biomarkers performed moderately in agreement with the CG. In a previous study that excluded AKI patients, the CCC ranged from 0.568 to 0.830, with a mean deviation of −6 to −16.20 ml/min between CKD-EPI eGFR and the CG equation [16]. Compared to previous studies [19,34,36], our study identified higher bias and lower CCC with 95% CI of 0.496 (0.445–0.546), 0.207 (0.149–0.265), and 0.349 (0.285–0.413) for CKD-EPI eGFRcr 2021, CKD-EPI eGFRcys 2012, and CKD-EPI eGFRcr-cys 2021, respectively, in non-AKI group. Our study revealed significant discordance between eGFR equations and the CG equation. Using the KDIGO suggestion for drug dosing in this specific group of patients can lead to variation of dosing [8]. This discordance has important clinical implications, as relying on a single eGFR equation may lead to inappropriate antibiotic dosing in critically ill patients. Systematic differences in eGFR between equations result from variations in GFR measurement methods and non-GFR determinants, leading to bias and imprecision [7]. Previous research has shown that creatinine is less accurate in elderly patients due to low muscle mass and malnutrition, which can lead to an overestimation of eGFR and an increased risk of drug toxicity [37]. A recent study involving critically ill patients found a mean age of 58.7 ± 14.9 years, a median BMI of 27.3 (22–35.3) kg/m^2, and a mean (SD) albumin of 2.8 (0.6) g/dl [17]. This group was younger and had a higher body weight compared to our research. Critically ill patients exhibit several non-GFR determinants, such as muscle wasting, inactivity, hypoalbuminemia, and elevated levels of serum C-reactive protein (CRP) or tumor necrosis factor (TNF), affecting GFR estimates, contributing to discordance between the equations [7,11]. Our findings support the theory of systematic differences, as we observed larger differences in CCC than those reported in previous studies [11,16,38]. These differences can be attributed to variations in physiological and clinical variables, including elderly age, body weight, muscle wasting, hypoalbuminemia, AKI, and critical illness. Our findings show that numerous non-GFR determinants affect both serum creatinine and cystatin C levels in critically ill patients. This leads to the observed discordance. Even though the equations suggested by KDIGO are generally more reliable, they still have difficulty dealing with these complex factors in the intensive care unit [8]. Therefore, selecting the appropriate equations to optimize dosage regimens for critically ill patients requires a careful evaluation of the risks and benefits.

Discordance in at least one antibiotic agent was frequently observed in patients with an absolute difference of 20% or more in their eGFR. A recent study indicated a discordance rate of 30% or more, with an absolute difference of 15 ml/min or more between the CG and CKD-EPI eGFRcr-cys 2021 equations, reported at 52.20% and 58.20%, respectively [17]. In our study, we found discordance rates of 52.63% and 54.89%, which are similar to these previous findings. We observed negative discordance between the CG and cystatin C-based equations. In contrast, the CKD-EPI eGFRcr 2021 demonstrated positive discordance, indicating that lower doses are recommended with cystatin C-based equations and higher doses with the creatinine-based equation. In comparing CG with CKD-EPI eGFRcys 2012, we observed the most significant negative discordance at up to 72.18%, and with CKD-EPI eGFRcr-cys 2021, the discordance reached up to 46.24%. This finding, while seemingly suggesting reduced dosing, requires careful interpretation, as creatinine-based eGFR, particularly CG, can overestimate actual renal function in critically ill patients with reduced muscle mass due to sarcopenia, malnutrition, and prolonged immobilization. The recent critically ill study shows the total discordance rate of meropenem at 45.00%, piperacillin/tazobactam at 11.60%, and sulbactam at 9.10% [17]. Another study that included 56.00% of ICU patients found a negative discordance of 38.00% for CKD-EPI eGFRcys and 24.00% for CKD-EPI eGFRcr-cys 2012 in meropenem dosing. Our findings have a higher discordance rate in overall patients when compared with previous studies [16,17]. Several factors affect the pharmacokinetics of critically ill patients, aside from renal clearance [1]. This negative discordance carries a substantial clinical risk of antibiotic underdosing, especially in critically ill patients with leaky capillaries or hypoalbuminemia [1]. Relying solely on renal clearance by CKD-EPI eGFRcys for dose adjustment can result in insufficient drug levels. Therapeutic drug monitoring (TDM) is essential for maintaining appropriate drug levels and reducing potential risks. However,

several studies indicate that cystatin C-guided dosing, while not significantly affecting overall clinical outcomes, reduces the risk of adverse drug events [20,39,40].

According to the KDIGO 2024 recommendation, the CKD-EPI eGFR based on creatinine is preferred for drug dosing in patients with renal impairment [8]. This study demonstrated that antibiotic dosing based on the CKD-EPI eGFRcr 2021 showed substantial agreement with the CG equation, as well as higher dosing up to 28.95% for all antibiotics. This is concerning for drugs with a narrow therapeutic index, as small dosage variations may lead to toxicity. Antibiotic dosing using the CKD-EPI eGFRcys and CKD-EPI eGFRcr-cys 2021 equations showed fair and moderate agreement with the CG equation, respectively, and often results in lower dosing up to 71.69%. In these cases, a lower dose suggested by a cystatin C-based or combined eGFR equation—less affected by muscle mass—may accurately reflect the patient's true GFR. This can enable optimal antibiotic dosing, helping to prevent harmful overdoses and toxicities that may arise from relying on an inflated creatinine-based GFR. However, applying these equations uniformly without considering equation-specific biases or the patient's clinical status can lead to inappropriate dosing. This highlights the importance of careful monitoring for both efficacy and safety when making antibiotic dose adjustments according to the KDIGO 2024 recommendations [8]. Currently, there is no definitive conclusion regarding the most effective equation for adjusting antibiotic dosing in critically ill patients with renal impairment. Future research should evaluate the association between renal clearance estimation equations and clinical outcomes to determine the best equation for antibiotic dosing in this patient population.

The differences in dose adjustment breakpoints and stages in research led to varying discordance rates for each antibiotic agent across studies [16,17]. Our findings demonstrated the varying discordance rates among different antibiotics depending on their dose adjustment breakpoints and stages. For instance, some antibiotics require a narrow range of GFR with higher dose adjustment breakpoints or multiple dosing stages. For example, piperacillin/tazobactam requires dose adjustments at a CrCl breakpoint of 100 ml/min with four stages of dosing, whereas the ertapenem dose adjustments at a CrCl breakpoint is 30 ml/min with two stages of dosing. These findings indicate a greater discordance rate for piperacillin/tazobactam than ertapenem. Although the mean intra-individual differences of eGFR were high between equations, less effect on drugs with lower dose adjustment breakpoints and a low number of dosing stages. The AKI group had lower intra-individual differences in eGFR. This study indicates that poor kidney function is associated with a higher discordance rate for each antibiotic agent. This contrasts with previous studies that suggested patients with poorer kidney function experienced less discordance compared to those with intact kidney function [17].

Prior research has discussed drug-specific models for eGFR assessment and individualized dosing, supported by studies showing varied correlations between eGFR and drug clearance [38,41–43]. Previous studies evaluated the clinical outcomes in patients who received antibiotic dose adjustment by cystatin C. For cefepime, Cystatin C-based dosing results in a reduced risk of morbidities, including AKI and encephalopathy [39]. Furthermore, when comparing CKD-EPI eGFRcr 2021 with CKD-EPI eGFRcys 2012, most ADEs related to antibiotics occurred in patients whose eGFRcys were >30% lower than their eGFRcr [20]. Cystatin C-based dosing tends to impact antibiotic dose optimization. Although our study cannot determine which equation is the best for estimating renal clearance in antibiotic dose adjustment to improve patient clinical outcomes, we recognize concerns regarding variations in dosage when using different equations. Therefore, our results can serve as a basis for future research. Future research should evaluate the pharmacokinetics of antibiotics and clinical outcomes using cystatin C-based equations for antibiotic dose adjustment in critically ill patients.

The generalizability of this study is limited due to its single-center design, retrospective nature, and focus on a specific population of patients in MICUs. In addition, we did not investigate the patients' clinical outcomes. Our findings indicate that changing the renal dose adjustment from the estimated renal clearance calculated using the CG formula to the equation suggested by the 2024 KDIGO guidelines may result in different dosage regimens [8]. This is particularly relevant for antibiotics with narrow therapeutic ranges and those with higher dose adjustment breakpoints or multiple dosing stages. Future research should focus on the relationship between different equations for estimating renal clearance and clinical outcomes in critically ill patients, to determine the most suitable equation for this population.

4.1. Strengths and limitations

Our study had some strengths and limitations. This study was the first to compare the discordance rate between eGFR equations for common antibiotics used in critically ill patients with infections. Following KDIGO 2024 recommendations, we examined the discordance among newer CKD-EPI eGFR equations, which may influence the staging of antibiotic dosing in clinical settings. Moreover, we explored discordance in both the AKI and non-AKI groups, which are common challenges for drug dose optimization in these patients. Our study has limitations. First, patients with incomplete data were excluded; only four patients (2.34%) were removed from the study, resulting in minimal impact on the outcomes. Second, we did not evaluate the association between renal clearance estimation equations and clinical outcomes. While previous studies have asserted the superior accuracy of cystatin C-based eGFR equations compared to creatinine-based equations in critically ill patients [11,13], our study did not directly validate these equations against mGFR. Third, we only measured serum cystatin C and creatinine once during MICU stay, potentially missing fluctuations in biomarker levels over time. Fourth, fifty-seven (33.33%) patients had multiple orders of biomarkers during MICU admission, potentially impacting discordance and concordance analysis. Fifth, the estimates of GFR equations were not adjusted by BSA because most patients in this study had an average weight. Their BSA was lower than 1.73 m^2, which may have had less impact on the dosing stage in our patients. Sixth, some variables, such as serum CRP and TNF levels, were not collected, which may have influenced serum cystatin C levels. Seventh TDM, particularly for colistin and beta-lactams, was limited in our setting, which could have helped confirm drug-specific models and optimize dosing. Finally, the small sample size of our study to the routine

use of creatinine-based dosing may have impacted the evaluation of discordance and concordance analysis. Future research is needed for a prospective multi-center study to enhance data completeness and increase the sample size. In addition, studies examining the relationship between renal clearance estimation equations and clinical outcomes are essential, as this information is crucial for clinical practice.

5. CONCLUSION

The discordance of antibiotic dosing in critically ill patients was significant, especially in cystatin C-based equations. However, the CKD-EPI eGFRcr equation shows the lowest discordance.

Our findings suggest being cautious with antibiotic dose adjustments for medications with higher dose adjustment breakpoints or multiple dosing stages, such as piperacillin/tazobactam. Currently, there is no absolute equation to guide the adjustment of antibiotic doses in critically ill patients with renal impairment. Antibiotics with narrow therapeutic windows require careful risk-benefit assessments and, when possible, TDM. Future research should focus on identifying optimal equations for adjusting antibiotic doses based on renal function to enhance treatment outcomes.

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7. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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9. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

10. ETHICAL APPROVAL

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB No. 0848/66). All data were fully anonymized before we accessed them. The IRB waived the requirement for patients' informed consent.

11. DATA AVAILABILITY

The datasets that were used and analyzed during this study are not publicly available due to confidentiality reasons. This restriction is imposed by the Med Chula Institutional Review Board. Data requests can be sent to the corresponding author.

12. PUBLISHER'S NOTE

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13. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Cotta MO, Roberts JA, Lipman J. Antibiotic dose optimization in critically ill patients. Med Intens. 2015;39(9):563–72. doi: https://doi.org/10.1016/j.medin.2015.07.009
2. Li XX, Zheng SQ, Gu JH, Huang T, Liu F, Ge QG, *et al*. Drug-related problems identified during pharmacy intervention and consultation: implementation of an intensive care unit pharmaceutical care model. Front Pharmacol. 2020;11:571906. doi: https://doi.org/10.3389/fphar.2020.571906
3. Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: core curriculum 2021. Am J Kidney Dis. 2021;78(5):736–49. doi: https://doi.org/10.1053/j.ajkd.2021.04.016
4. FDA. Label: MERREM IV (meropenem for injection): United States Food and Drug Administration (US. FDA); 2016 [updated 12/2016]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050706s037lbl.pdf
5. FDA/CDER. Vancomycin hydrochloride for injection: United States Food and Drug Administration (US. FDA) and The Center for Drug Evaluation and Research (CDER); 2018 [updated 7/2018]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209481s000lbl.pdf
6. FDA. Coly-Mycin M parenteral (Colistimethate for Injection, USP): United States Food and Drug Administration (US. FDA); 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050108s033lbl.pdf
7. St. Peter WL, Bzowyckyj AS, Anderson-Haag T, Awdishu L, Blackman M, Bland A, *et al*. Moving forward from Cockcroft-Gault creatinine clearance to race-free estimated glomerular filtration rate to improve medication-related decision-making in adults across healthcare settings: a consensus of the National Kidney Foundation Workgroup for implementation of race-free eGFR-based medication-related decisions. Am J Health Syst Pharm. 2025;82(12):644–59. doi: https://doi.org/10.1093/ajhp/zxae317
8. Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4S):S117–314. doi: https://doi.org/10.1016/j.kint.2023.10.018
9. Awdishu L, Maxson R, Gratt C, Rubenzik T, Battistella M. KDIGO 2024 clinical practice guideline on evaluation and management of chronic kidney disease: a primer on what pharmacists need to know. Am J Health Syst Pharm. 2025;82(12):660–71. doi: https://doi.org/10.1093/ajhp/zxaf044
10. Center for Drug Evaluation and Research. Pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing: United States Food and Drug Administration (US. FDA); 2024 [Clinical – Pharmacology]. Available from:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing
11. Carlier M, Dumoulin A, Janssen A, Picavet S, Vanthuyne S, Van Eynde R, *et al*. Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med. 2015;41(3):427–35. doi: https://doi.org/10.1007/s00134-014-3641-9
12. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, *et al*. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49. doi: https://doi.org/10.1056/NEJMoa2102953
13. Eiamcharoenying J, Kulvichit W, Lumlertgul N, Chaiwatanarat T, Peerapornratana S, Srisawat N. The role of serum cystatin C in estimation of renal function in survivors of critical illness. J Crit Care. 2020;59:201–6. doi: https://doi.org/10.1016/j.jcrc.2020.07.005
14. Jodlowski TZ, Sym D, Marziliano A, LaPan-Dennis G, Ashby CR, Jr., Ruhe JJ. A survey of pharmacists in academia on the current practice of estimation of kidney function for antimicrobial dosing in adults. J Pharm Pract. 2016;29(4):382–5. doi: https://doi.org/10.1177/0897190014566310
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–84. doi: https://doi.org/10.1159/000339789
16. Peters BJ, Rule AD, Kashani KB, Lieske JC, Mara KC, Dierkhising RA, *et al*. Impact of serum cystatin C-based glomerular filtration rate estimates on drug dose selection in hospitalized patients. Pharmacotherapy. 2018;38(10):1068–73. doi: https://doi.org/10.1002/phar.2175
17. Williams VL, Gerlach AT. Establishing discordance rate of estimated glomerular filtration rate between serum creatinine-based calculations and cystatin-C-based calculations in critically ill patients. Pharmacotherapy. 2025;45(3):161–8. doi: https://doi.org/10.1002/phar.70000
18. Khader NA, Kamath VG, Kamath SU, Rao IR, Prabhu AR. Kidney function estimation equations: a narrative review. Ir J Med Sci. 2025;194(2):725–43. doi: https://doi.org/10.1007/s11845-025-03874-y
19. Wang Y, Adingwupu OM, Shlipak MG, Doria A, Estrella MM, Froissart M, *et al*. Discordance Between creatinine-based and cystatin C-based estimated GFR: interpretation according to performance compared to measured GFR. Kidney Med. 2023;5(10):100710. doi: https://doi.org/10.1016/j.xkme.2023.100710
20. Hanna PE, Wang Q, Strohbehn IA, Moreno D, Harden D, Ouyang T, *et al*. Medication-related adverse events and discordancies in cystatin C-based vs serum creatinine-based estimated glomerular filtration rate in patients with cancer. JAMA Netw Open. 2023;6(7):e2321715. doi: https://doi.org/10.1001/jamanetworkopen.2023.21715
21. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, *et al*. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835–64. doi: https://doi.org/10.1093/ajhp/zxaa036
22. Jaruratanasirikul S, Nitchot W, Wongpoowarak W, Samaeng M, Nawakitrangsan M. Population pharmacokinetics and Monte Carlo simulations of sulbactam to optimize dosage regimens in patients with ventilator-associated pneumonia caused by *Acinetobacter baumannii*. Eur J Pharm Sci. 2019;136:104940. doi: https://doi.org/10.1016/j.ejps.2019.05.018
23. Kanchanasurakit S, Santimaleeworagun W, McPherson CE, Piriyachananusorn N, Boonsong B, Katwilat P, *et al*. Fosfomycin dosing regimens based on Monte Carlo simulation for treated carbapenem-resistant enterobacteriaceae infection. Infect Chemother. 2020;52(4):516–29. doi: https://doi.org/10.3947/ic.2020.52.4.516
24. Saelim W, Changpradub D, Thunyaharn S, Juntanawiwat P, Nulsopapon P, Santimaleeworagun W. Colistin plus sulbactam or fosfomycin against carbapenem-resistant *Acinetobacter baumannii*: improved efficacy or decreased risk of nephrotoxicity? Infect Chemother. 2021;53(1):128–40. doi: https://doi.org/10.3947/ic.2021.0007
25. Santimaleeworagun W, Leelasupasri S, Sitaruno S. Optimization of fosfomycin doses for treating pseudomonas aeruginosa infection in critically Ill patients by using Monte Carlo simulation. Thai J Pharm Prac. 2019;11(4):869–78.
26. Asuphon O, Montakantikul P, Houngsaitong J, Kiratisin P, Sonthisombat P. Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of Pseudomonas aeruginosa infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation. Int J Infect Dis. 2016;50:23–9. doi: https://doi.org/10.1016/j.ijid.2016.06.017
27. Leelawattanachai P, Wattanavijitkul T, Paiboonvong T, Plongla R, Chatsuwan T, Usayaporn S, *et al*. Evaluation of intravenous fosfomycin disodium dosing regimens in critically ill patients for treatment of carbapenem-resistant enterobacterales infections using Monte Carlo simulation. Antibiotics (Basel). 2020;9(9):615. doi: https://doi.org/10.3390/antibiotics9090615.
28. Tlemsani C, Durand JP, Raynard B, Revel MP, Deluche E, Di Palma M, *et al*. Relationship between the creatinine/cystatin C ratio and muscle mass measured by CT-scan in cancer patients. Clin Nutr ESPEN. 2022;51:412–8. doi: https://doi.org/10.1016/j.clnesp.2022.07.010
29. Sungsana W, Nakaranurack C. The difference of antibiotic dosing based on serum creatinine versus cystatin C in critically ill patients. The 22nd Asian Conference on Clinical Pharmacy; July 13th - 15th, 2023; Haiphong City, Vietnam 2023.
30. Bujang MA, Baharum N. Guidelines of the minimum sample size requirements for Cohen's Kappa. Epidemiol Biostat Public Health. 2017;14:e12267–1. doi: https://doi.org/10.2427/12267
31. Altman DG. Practical statistics for medical research: Chapman and Hall/CRC; 1990.
32. Akoglu H. User's guide to correlation coefficients. Turk J Emerg Med. 2018;18(3):91–3. doi: https://doi.org/10.1016/j.tjem.2018.08.001
33. Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, *et al*. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int. 2004;65(4):1416–21. doi: https://doi.org/10.1111/j.1523-1755.2004.00517.x
34. Teaford HR, Barreto JN, Vollmer KJ, Rule AD, Barreto EF. Cystatin C: a primer for pharmacists. Pharmacy (Basel). 2020;8(1):35. doi: https://doi.org/10.3390/pharmacy8010035.
35. Spencer S, Desborough R, Bhandari S. Should cystatin C eGFR become routine clinical practice? Biomolecules. 2023;13(7):1075. doi: https://doi.org/10.3390/biom13071075.
36. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol. 2020;16(1):51–64. doi: https://doi.org/10.1038/s41581-019-0191-y
37. Dahlén E, Björkhem-Bergman L. Comparison of creatinine and cystatin C to estimate renal function in geriatric and frail patients. Life (Basel). 2022;12(6):846. doi: https://doi.org/10.3390/life12060846.
38. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft-Gault and modification of diet in renal disease. Pharmacotherapy. 2008;28(9):1125–32. doi: https://doi.org/https://doi.org/10.1592/phco.28.9.1125
39. Kim M-C, Kim SO, Kim S-H, Shin J-h, Choi S-H, Chung J-W, *et al*. Efficacy and safety of cystatin C-guided renal dose adjustment of cefepime treatment in hospitalized patients with pneumonia. J Clin Med. 2020;9(9):2803. doi: https://doi.org/10.3390/jcm9092803

40. Frazee E, Rule AD, Lieske JC, Kashani KB, Barreto JN, Virk A, *et al*. Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. Am J Kidney Dis. 2017;69(5):658–66. doi: https://doi.org/10.1053/j.ajkd.2016.11.016
41. Hermsen ED, Maiefski M, Florescu MC, Qiu F, Rupp ME. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy. 2009;29(6):649–55. doi: https://doi.org/10.1592/phco.29.6.649
42. Moranville MP, Jennings HR. Implications of using modification of diet in renal disease versus Cockcroft-Gault equations for renal dosing adjustments. Am J Health Syst Pharm. 2009;66(2):154–61. doi: https://doi.org/10.2146/ajhp0800
43. Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, Rodby R, *et al*. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis. 2009;54(1):33–42. doi: https://doi.org/10.1053/j.ajkd.2009.03.008

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SUPPLEMENTARY MATERIAL

The supplementary material can be accessed at the link here: [https://japsonline.com/admin/php/uploadss/4694_pdf.pdf]