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Original Research

Discordance in renal function estimates between different equations: impact on treatment and safety in critically ill patients – A retrospective study

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Abstract

Background: Optimizing antibiotic dosages in critically ill patients is challenging. There are several equations to estimate the estimating renal clearance. The combined creatinine and cystatin C equation revealed significant discordance in dosing when compared with creatinine-based equations. Currently, there are no published studies on the impact of discordant antibiotic dosing rates on clinical outcomes in critically ill patients. **Objective:** This study evaluated the treatment and safety outcomes between groups with discordance and concordance regarding overall antibiotic dosing adjustments based on the Cockcroft-Gault (CG) and the CKD-EPI eGFRcr-cys 2021 in critically ill patients. We also compared adverse drug events (ADEs) between the discordance and concordance groups for each antibiotic agent. **Methods:** A retrospective observational study was conducted on adult patients in medical intensive care units who were administered antibiotics as part of the antimicrobial stewardship program. Cystatin C and creatinine levels were measured on the same day. Differences in treatment outcomes and ADEs between the concordance and discordance groups were assessed using Pearson's chi-squared and Mann–Whitney U tests. **Results:** A total of 171 patients with serum cystatin C were included. The mean ± standard deviation (SD) age and BMI were 67.23 ± 17.45 years and 22.71 ± 4.58 kg/m^2. Meropenem was the most frequent antibiotic agent use (75.44%). Thirty-five patients (20.47%) were categorized into the concordance group, while one hundred and thirty-six patients (79.53%) were placed in the discordance group. There were no statistically significant differences between the concordance group and discordance group for treatment outcomes. In the discordance group, there was a significantly higher incidence of acute kidney injury (AKI) compared to the concordance group, with rates of 56.76% versus 22.22% (p = 0.009). Additionally, the discordance group also experienced a significantly higher rate of AKI with colistin, at 77.78% compared to 41.67% in the concordance group (p = 0.012). The highest discordance drug was piperacillin/tazobactam (55.26%), followed by aminoglycosides (50.00%) and vancomycin (49.02%). **Conclusions:** Our study showed that using a cystatin C-based equation may help prevent AKI without negatively impacting clinical outcomes. Future clinical research is required with large populations.

Keywords: Adverse drug events; Antibiotic; Critically ill; Creatinine; Cystatin C

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INTRODUCTION

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[1]. Conversely, the 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 is unreliable[2]. Cystatin C may play a role in accurately predicting renal function, especially in estimating the glomerular filtration rate from the combined creatinine and cystatin C-based equation[3-5]. However, systematic differences in the eGFR equation affect biomarkers in predicting renal function, such as in the elderly, muscle wasting, comorbidity, inflammation conditions, etc[6-8]. Optimization of antibiotic dosing was a challenge in critically ill patients.

Critically ill patients have various factors that affect serum creatinine levels, resulting in overestimating or underestimating the prediction of renal function[9,10]. Improper dosing of medication can lead to treatment failure and may cause drug toxicity. Previous study showed that the cystatin C-base equation had the highest accuracy and least bias compared to other equations for assessing glomerular filtration in critically

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ill patients[8]. Only one study has shown a significant discordance rate in drug dosing for these populations when comparing the CKD-EPI eGFRcr-cys 2021 to the CG equation[11]. Additionally, there are no published studies examining how the discordance in antibiotic dosing impacts clinical outcomes in critically ill patients.

The Antimicrobial Stewardship Program (ASP) was introduced in 2020 at King Chulalongkorn Memorial Hospital (KCMH) for patients in medical intensive care units (MICUs). Pharmacists play a crucial role in dose optimization and therapeutic drug monitoring, thereby improving appropriate antibiotic dosing[12]. Despite guideline recommendations, the creatinine-based equation, especially the CG is still widely used in practice for antibiotic dosing[2,13]. Different equations for estimating renal clearance can result in varying antibiotic dosing. However, the real-world impact of dosing discordance on patients' clinical outcomes and safety, particularly in critically ill patients, remains unclear. Cystatin C is an alternative endogenous biomarker for predicting renal function that is increasingly used in our setting and may influence antibiotic dosing[1,4]. Although cystatin C-based estimated glomerular filtration rate was more predictive of drug levels and clearance than creatinine-based eGFR, there was limited data in critically ill patients[14]. The aim of this study is to evaluate the treatment and safety outcomes between groups with discordance and concordance regarding overall antibiotic dosing adjustments based on the CG and the CKD-EPI eGFRcr-cys 2021 in critically ill patients. Additionally, we also compared adverse drug events (ADEs) between the discordance and concordance groups for each antibiotic agent.

METHODS

This retrospective observational study was conducted at KCMH 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 as part of the ASP (meropenem, imipenem/cilastatin, ertapenem, piperacillin/tazobactam, cefoperazone/sulbactam, ampicillin/sulbactam, sulbactam, colistin, fosfomycin, amikacin, gentamicin, and vancomycin) during the cystatin C order at MICU; and (iii) Patients who had both serum cystatin C and creatinine tests ordered at least once on the same day during their admission to the MICU. Exclusion criteria consisted of patients undergoing extracorporeal circuit treatments (such as Extracorporeal Membrane Oxygenation or renal replacement therapy), patients who died within 24 hours of being admitted to the MICU, pregnant patients, and those with incomplete medical records. 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.

Data were collected from the e-PHIS-CUH program and medical charts to compile demographic information. We evaluated actual body weight (ABW), serum albumin levels, APACHE II scores, and the presence of septic shock within 24 hours of ordering cystatin C. Additionally, we documented corticosteroid exposure for the 14 days preceding the ordering of cystatin C. Baseline kidney function was assessed following the acquisition of cystatin C and creatinine results. Acute kidney injury (AKI) was evaluated using the KDIGO criteria based on serum creatinine levels[15]. The eGFR equations included CG and CKD-EPI eGFRcr-cys 2021 (Table 1). All patients who met inclusion criteria were included to evaluate the association of discordance with treatment and safety outcomes.

Definition

Concordance group is defined as patients who had all antibiotic agents using the same dose when using the CKD-EPI eGFRcr-cys 2021 equation compared to the CG equation. Discordance group was defined as patients who had the discrepancy in drug dosing for at least one antibiotic agent for using the CKD-EPI eGFRcr-cys 2021 equation compared to the CG equation. Positive discordance indicated a higher dose of antibiotic agents by the CKD-EPI eGFRcr-cys 2021, and a negative discordance indicated a lower dose of antibiotic agents by the CKD-EPI eGFRcr-cys 2021, compared to the CG. The dosing stage was recommended according to the Uptodate and Lexi-drug application or simulation studies used in our setting[16-22]. We utilized the results of renal clearance from the CG equation and CKD-EPI eGFRcr-cys 2021 to guide the dosing stage. Cystatin C and creatinine sampling points were collected from cystatin C orders during MICU admission at the same time.

Treatment failure, evaluated on day 3 after serum cystatin C ordered, was defined as death before the assessment day or meeting at least three of the following criteria: (i) body temperature < 36°C or > 38°C; (ii) systolic blood pressure < 100 mmHg or use of inotropes/vasopressor agents; (iii) respiratory rate > 20 breaths per minute or use of invasive mechanical ventilation; and (iv) white blood cell count < 4,000 or > 12,000 cells/µl. ICU-free days were counted as the days a patient received care outside the ICU within 30 days.

Safety outcomes were assessed to identify ADEs commonly associated with antibiotics. AKI was monitored in patients who received colistin, vancomycin, and aminoglycosides, with AKI defined according to KDIGO by creatinine criteria[15]. or patients with pre-existing AKI, we assessed serum creatinine elevation by at least 50% following the initiation of antibiotic therapy for a minimum duration of 48 hours[23]. Seizures were recorded in patients diagnosed by a physician or indicated by abnormal electroencephalography, receiving beta-lactams antibiotic after at least 24 h. Hypernatremia and hypokalemia were observed in patients who received fosfomycin. Hypokalemia was defined as a serum potassium level below 3.5 mEq/l after at least 24 h of antibiotic treatment, while hypernatremia was defined as a serum sodium level exceeding 145 mEq/l after at least 24 h of antibiotic treatment. International normalized ratio (INR) prolongation, characterized by INR values exceeding three or increasing by at least 25% after at least 24 h of antibiotic treatment, was observed in patients who received cefoperazone/sulbactam.

Table 1. Estimated glomerular filtration rate equations[5]

Equation	Gender	Creatinine (mg/dL)	CystatinC (mg/L)	Estimated glomerular filtration rate
Cockcroft-Gault (ml/min)	Female or Male	-	-	((140-Age) x BW)/(72 x Scr)) [× 0.85 if female]
CKD-EPI eGFRcr-cys 2021 (ml/min/1.73m^2)	Female	≤0.7	≤0.8	$130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times 0.9961^{Age}$
			>0.8	$130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times 0.9961^{Age}$
		>0.7	≤0.8	$130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times 0.9961^{Age}$
			>0.8	$130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times 0.9961^{Age}$
	Male	≤0.9	≤0.8	$135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times 0.9961^{Age}$
			>0.8	$135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times 0.9961^{Age}$
		>0.9	≤0.8	$135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times 0.9961^{Age}$
			>0.8	$135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times 0.9961^{Age}$

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated glomerular filtration rate, Scr: Serum creatinine, Scys: Serum cystatin C, BW: body weight.

Statistical analysis

Differences in demographic data between groups were assessed using the student's t-test for normality continuous data, while non-normality data used the Mann–Whitney U test. Pearson's chi-squared and Fisher's exact test assessed categorical data. The concordance and discordance rate between the CG and the CKD-EPI eGFRcr-cys 2021 were analyzed using descriptive statistics. Differences in treatment outcomes and ADEs between the concordance and discordance groups were assessed using Pearson's chi-squared and Mann–Whitney U tests. Adverse drug events of each antibiotic agent were analyzed using Pearson's chi-squared and Mann–Whitney U tests, with statistical significance set at $p < 0.05$. All analyses were conducted using STATA (Version 18.0).

RESULTS

During the study period, serum cystatin C and creatinine levels were measured in 218 patients. We excluded 47 patients for the following reasons: 5 patients did not receive antibiotic agents, 1 patient was younger than 18 years, 20 patients were on extracorporeal circuit devices, 4 patients were incomplete data, 2 patients had died within 24 hours of MICU admission, 1 patient was pregnancy and 14 patients did not receive care in the MICU. Ultimately, 171 patients met the inclusion criteria.

Of these, 35 patients (20.47%) were categorized into the concordance group, while 136 patients (79.53%) were placed in the discordance group. The mean age ± standard deviation (SD) was 67.23 ± 17.45 years. The mean ± SD of body mass index (BMI) and body surface area (BSA) were 22.71 ± 4.58 kg/m² and 1.60 ± 0.21 m², respectively. The most common underlying disease was cardiovascular disease (56.73%), followed by endocrinologic disease (33.33%). The most frequently prescribed antibiotic was meropenem, used by 75.44% of the patients, followed by colistin (31.58%) and vancomycin (29.82%). The baseline characteristics between the two groups showed no significant differences, except for age, sarcopenia index score, serum cystatin C, and CKD-EPI eGFRcr-cys 2021. The median (IQR) estimates of renal function from the CG and CKD-EPI eGFRcr-cys 2021 were 50.82 (61.38) mL/min and 35.42 (34.95) mL/min/1.73 m², respectively. The baseline characteristics are presented in Table 2.

There were no statistically significant differences between the concordance group and discordance group for 28-days ICU mortality, treatment failure, ICU-free days, ICU length of stay, or the duration of ICU inotrope/vasopressor agents and mechanical ventilator use. However, the discordance group experienced significantly higher AKI than the concordance group (56.76% vs. 22.22%, *p* 0.009) Table 3.

Discordance rate for the stage of dosing each antibiotic agent between the CG and CKD-EPI eGFRcr-cys 2021 found negative discordance up to 50.00%. The highest discordance drug was piperacillin/tazobactam (55.26%), followed by aminoglycosides (50.00%) and vancomycin (49.02%). ADEs were commonly in colistin (77.78%), followed by vancomycin (52.00%) and fosfomycin (22.22%) in the discordance group. The discordance group experienced significantly higher ADE of colistin than the concordance group (77.78% vs 41.67%, *p* 0.012) (Table 4).

DISCUSSION

This retrospective observational study gathered data on cystatin C over a three-year period. It is not surprising that cystatin C measurements are less common in our setting, as serum cystatin C is a relatively new biomarker in Thailand. Additionally, it is more expensive than serum creatinine, and there is limited data available to support its use for antibiotic dose adjustments, particularly in critically ill patients. This reason led to the CG equation being widely used to adjust the dose of antibiotic agents in clinical practice. Our results showed that cystatin C was commonly used in critically ill patients who had elderly patients with low sarcopenia index (<0.8) and hypoalbuminemia. In the discordance group, serum cystatin C showed significantly higher than in the concordance group, while serum creatinine was not different between groups. Patients in the discordance group also had lower Sarcopenia index. These results led to a higher median

Table 2. Baseline characteristics (N = 171).

Baseline characteristics	Overall (n = 171)	Concordance group (n=35)	Discordance group (n=136)	*P-value*
Age (year), mean (SD)	67.23 (17.45)	72.54 (17.25)	65.86 (17.29)	0.043
Female, n (%)	86 (50.29)	16 (45.71)	70 (51.47)	0.544
Weight (kg), mean (SD)	58.15 (13.28)	56.42 (14.02)	58.59 (13.09)	0.391
Body mass index (kg/m^2), mean (SD)	22.71 (4.58)	21.71 (4.49)	22.97 (4.59)	0.149
Body surface area (m^2), mean (SD)	1.60 (0.21)	1.58 (0.22)	1.60 (0.20)	0.504
Sarcopenia index (SI), median (IQR)	0.45 (0.26)	0.57 (0.24)	0.42 (0.23)	0.002
Underlying disease, n (%)	150 (87.72)	34 (97.14)	116 (85.29)	0.080
Cardiovascular disease	97 (56.73)	22 (62.86)	75 (55.15)	0.412
Endocrinologic disease	57 (33.33)	15 (42.86)	42 (30.88)	0.180
Thyroid dysfunction	10 (5.85)	3 (8.57)	7 (5.15)	0.429
Oncologic disease	48 (28.07)	10 (28.57)	38 (27.94)	1.000
Solid tumors	35 (20.47)	9 (25.71)	26 (19.12)	0.388
Hematologic malignancies	13 (7.60)	1 (2.86)	12 (8.82)	0.472
Neurological disease	33 (19.30)	9 (25.71)	24 (17.65)	0.281
Pulmonary disease	29 (16.96)	9 (25.71)	20 (14.71)	0.122
Gastrointestinal disease	26 (15.20)	5 (14.29)	21 (15.44)	0.865
Renal disease	16 (9.36)	4 (11.43)	12 (8.82)	0.744
Transplantation	5 (2.92)	0	5 (3.68)	0.585
Current smoker, n (%)	15 (8.77)	1 (2.86)	14 (10.29)	0.311
Past corticosteroid use within 14 days[c], n (%)	121 (70.76)	22 (62.86)	99 (72.79)	0.249
Immunocompromised[a], n (%)	47 (27.49)	10 (28.57)	37 (27.21)	0.872
Immunosuppressive agents use[b], n (%)	13 (7.60)	2 (5.71)	11 (8.09)	1.000
Serum albumin[c] (gm/dl), mean (SD)	2.90 (0.54)	2.84 (0.63)	2.91 (0.51)	0.511
Septic shock[c], n (%)	57 (33.33)	12 (34.29)	45 (33.09)	0.893
APACHE II Score[c], mean (SD)	20.85 (5.26)	22.34 (5.68)	20.47 (5.10)	0.060
Charlson comorbidity index, mean (SD)	3.19 (2.86)	3.80 (2.65)	3.04 (2.90)	0.160
AKI at baseline, n (%)	67 (39.18)	10 (28.57)	57 (41.91)	0.149
Site of infection, n (%)				
Respiratory tract	104 (60.82)	25 (71.43)	79 (58.09)	0.149
Unknown sources	28 (16.37)	2 (5.71)	26 (19.12)	0.056
Bloodstream	24 (14.04)	4 (11.43)	20 (14.71)	0.788
Intra-abdominal	12 (7.02)	1 (2.86)	11 (8.09)	0.463
Urinary tract	5 (2.92)	1 (2.86)	4 (2.94)	1.000
Skin and soft tissue	3 (1.75)	1 (2.86)	2 (1.47)	0.499
Bone and joint	3 (1.75)	0	3 (2.21)	1.000
Antibiotic use, n (%)				
Meropenem	129 (75.44)	28 (80.00)	101 (74.26)	0.482
Colistin	54 (31.58)	13 (37.14)	41 (30.15)	0.427
Vancomycin	51 (29.82)	6 (17.14)	45 (33.09)	0.066
Piperacillin/tazobactam	38 (22.22)	10 (28.57)	28 (20.59)	0.311
Sulbactam(including ampicillin/sulbactam cefoperazone/ sulbactam[d], and sulbactam)	30 (17.54)	7 (20.00)	23 (16.91)	0.668
Fosfomycin	19 (11.11)	3 (8.57)	16 (11.76)	0.767

Amikacin	10 (5.85)	1 (2.86)	9 (6.62)	0.689
Imipenem/cilastatin	3 (1.75)	1 (2.86)	2 (1.47)	0.499
Serum creatinine (mg/dl), median (IQR)	0.97 (0.63)	0.64 (1.39)	0.99 (0.86)	0.189
Serum cystatin C (mg/l), mean (SD)	2.46 (1.22)	1.84 (1.07)	2.61 (1.21)	<0.001
Cockcroft–Gault, CrCl (ml/min), median (IQR)	50.82 (61.38)	57.16 (138.37)	50.69 (54.51)	0.881
CKD-EPI eGFRcr-cys 2021 (ml/min/1.73m^2), median (IQR)	35.42 (34.95)	51.81 (81.56)	35.04 (29.85)	0.026

[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], tumor necrosis factor-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%). CKD-EPI eGFR, chronic kidney disease-epidemiology collaborative estimated glomerular filtration rate calculated using serum creatinine concentration, serum cystatin C concentration, or both; MDRD, modification of diet in renal disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; Scys, serum cystatin C; kg, kilogram; IQR, interquartile range; mg/dl, milligram per deciliter; SD, standard deviation; ml/min/1.73m^2, milliliters per minute per 1.73 square meters of body surface area.

Table 3. Comparison of treatment and safety outcomes between the concordance and discordance groups.

Patients' outcomes	**Concordance (n = 35)**	**Discordance (n = 136)**	***p*-value**
Treatment outcomes			
28 days ICU mortality, n (%)	16 (45.71)	49 (36.03)	0.292
Treatment failure, n (%)	13 (37.14)	35 (25.74)	0.180
ICU-free days, median (IQR)	19 (10-24)	15 (3-22)	0.076
ICU length of stay, median (IQR)	11 (6-20)	15 (8-27)	0.074
Duration of inotrope and vasopressor agents, median (IQR)	4 (2-10)	6 (3-10)	0.294
Duration of mechanical ventilator, median (IQR)	10 (5-19)	13 (7-25)	0.116
Safety outcomes			
Overall adverse drug events, n (%)	6 (17.14)	46 (33.82)	0.056
Acute kidney injury (AKI), n/total (%)	4/18 (22.22)	42/74 (56.76)	0.009
Seizure, n/total (%)	0	0	-
Hypernatremia, n/total (%)	0/3	4/16 (25.00)	1.000
Hypokalemia, n/total (%)	1/3 (33.33)	4/16 (25.00)	1.000
INR prolongation, n/total (%)	1/4 (25.00)	1/10 (10.00)	0.469

INR, international normalized ratio; ICU, intensive Care Unit; IQR, interquartile range.

Table 4. The discordance of each antibiotic agents and adverse drug events.

Antibiotic agents	**Breakpoint (ml/min)**	**No. Stage of dosing**	**Discordance rate by drug n/total (%)**		**Adverse drug event n/total (%)**		***p-value***
			Negative	**Positive**	**Concord[a]**	**Discord[b]**	
Meropenem	50	4	48/129 (37.21)	2/129 (1.55)	0/79	0/50	-
Imipenem/cilastatin	60	4	0/3	0/3	0/3	0	-
Ertapenem	30	2	0	0	0	0	-
Piperacillin/tazobactam	100	4	19/38 (50.00)	2/38 (5.26)	0/19	0/21	-
Sulbactam (including ampicillin/ sulbactam cefoperazone/sulbactam, and sulbactam)	30-90 (depend on albumin)	2-4 (depend on albumin)	10/30 (33.33)	0/30	2/20 (10.00)	0/10	0.540
Colistin	80	4	18/54 (33.33)	0/54	15/36 (41.67)	14/18 (77.78)	0.012

Aminoglycosides (including amikacin and gentamicin)	60	4	4/10 (40.00)	1/10 (10.00)	2/5 (40.00)	1/5 (20.00)	1.000
Fosfomycin	90	4	8/19 (42.11)	1/19 (5.26)	6/10 (60.00)	2/9 (22.22)	0.170
Vancomycin	40	4	24/51 (47.06)	1/51 (1.96)	10/26 (38.46)	13/25 (52.00)	0.331

[a]concord, concordance of drug dosing for each antibiotic agent between the CG equation and CKD-EPI eGFRcr-cys 2021; [b]discord, discordance of drug dosing for each antibiotic agent between the CG equation and CKD-EPI eGFRcr-cys 2021.

difference in estimates of renal function between the CG and CKD-EPI eGFRcr-cys 2021 in discordance group. Previous studies comparing the different equations to assess GFR with standard reference in critically ill patients showed cystatin C-based equations, especially CKD-EPI eGFRcr-cys, the highest accuracy, least bias, and more precision (R = 0.805) compared to other methods[8]. In contrast, the CG equation showed a lower correlation with inulin clearance (R=0.680)[8]. Our study lacked measured GFR (mGFR) to assess the accuracy and precision of creatinine-based and cystatin C-based equations. However, mGFR was mainly used for research more than applied to clinical practice for drug dosing[8,24]. This study aims to demonstrate the differences in antibiotic dosing and the impact on clinical outcomes between the CG and CKD-EPI eGFRcr-cys 2021 in real-life practice. The overall discordance rate by drug dosing from a recent study showed 32.3%, while our result showed 79.53%[11]. Critically ill patients had various non-GFR determinant effects on biomarkers that led to underestimating or overestimating renal function[8,25]. Additionally, Biomarkers may fluctuate depending on time and clinical condition of patients. This reason may lead to more discordance of drug dosing between equations in critically ill patients.

Our study showed no difference in most treatment outcomes between the concordance and discordance groups. However, safety outcomes revealed a statistically significant difference in AKI between the two groups. In particular, the concordance group had a lower prevalence of AKI compared to the discordance group. Similarly, a previous study when comparing CKD-EPI eGFRcr 2021 with CKD-EPI eGFRcys 2012, most ADEs occurred in cancer patients whose eGFRcys were >30% lower than their eGFRcr[26]. Furthermore, previous study in patients who received cefepime showed no significant difference in mortality between CKD-EPI eGFRcr 2012 and CKD-EPI eGFRcys 2012-based dosing. Notably, cystatin C-based dosing results in a reduced risk of morbidities, including AKI and encephalopathy[27]. In another study on vancomycin-based dosing, CKD-EPI eGFRcr-cys-based dosing enhanced the target trough concentration level compared to CG-based dosing, without resulting in treatment failure or toxicity[28,29].

Piperacillin/tazobactam had the highest discordance rate in the dosing stage among the equations from this study. Conversely, a recent study showed a discordance rate of 11.6% for piperacillin/tazobactam, 45.00% for meropenem, and 38.3% for vancomycin[11]. This study had a lower discordance rate than our result. The differences in discordance rates among studies can be explained by population characteristics such as age, body weight, and sarcopenia index, as well as variations in dosing breakpoints and the number of dosing stages. Patients in our study were older and had lower weights and body mass index (BMIs) than those in the previous study[11]. These differences might explain why our study had more discordance. Additionally, antibiotics with low breakpoints and few dosing adjustments, such as ertapenem, showed no discordance when using either CG or CKD-EPI eGFRcr-cys 2021 to suggest the antibiotic dose. Health care professionals should be cautious when using equations to predict patients' renal function. Different equations may lead to varying antibiotic doses, especially for antibiotics with high breakpoints and multiple dosing stages. Previous study showed that pharmacist-led education and prospective audit and feedback on antibiotic dose optimization within MICU can decrease the ICU mortality and length of ICU stay[12]. Given the high rates of discordance observed and the significantly higher incidence of AKI in the discordance group, pharmacists play a crucial role in evaluating renal function and optimizing drug dosing. They are essential in applying research results to effective real-world practice, thereby collaborating with other healthcare professionals to develop protocols for using cystatin C in clinical settings.

The statistically significant differences in AKI and colistin-related ADEs observed in our study suggest that relying solely on creatinine-based equations may lead to ADEs. These findings carry profound implications for pharmacy practice. Cystatin C-based equations tends to decrease ADEs, particularly with nephrotoxic agents, without worsening treatment outcomes[26,27,29]. Prior research has discussed drug-specific models for eGFR assessment and individualized dosing[6], supported by studies showing varied correlations between eGFR and drug clearance[14]. Urinary creatinine clearance (CrCl) provided the best model fit for clearance in critically ill patients receiving meropenem, followed by Hoek's formula and then the CG equation[30]. Similar results were observed in vancomycin studies, where vancomycin trough levels correlated better with eGFRcys or eGFRcr-cys, followed by eGFRcr[28,29,31]. Pharmacists, as key members of the healthcare team, should be enabled to more effectively utilize cystatin C-based equations in clinical decision-making, particularly for high-risk patients. Moreover, pharmacist-led protocol could be developed to guide the appropriate use of cystatin C for antibiotic dosing, especially for drugs with narrow therapeutic index or high nephrotoxic potential. Such initiatives would enable pharmacists to play an even more proactive role in preventing adverse outcomes related to inappropriate antibiotic dosing in critically ill patients. Further studies with larger populations, are necessary to potentially influence clinical practice for optimizing drug

dosing.

Our study had some strengths and limitations. This study was the first to compare the discordance of antibiotic dosing across eGFR equations and assess the impact on clinical outcomes in critically ill patients with infections. Although the CG equation is not considered a good standard compared to the eGFR equation for predicting renal function, it is still used in manufacturing for the pharmacokinetic assessments of antibiotics. Our study had several limitations. First, we assessed serum cystatin C and creatinine at a single time point during ICU admission, which may not capture fluctuations in biomarker levels over time. Second, therapeutic drug monitoring, particularly for colistin and beta-lactams, was limited in our setting, which could have helped confirm drug-specific models and optimize dosing. Third, the small sample size of our study may have impacted the evaluation of treatment and safety outcomes. Last, the estimates of the GFR equations were not adjusted for body surface area (BSA) because most patients had an average weight. Since their BSA was below 1.73 m^2, this likely had a minimal effect on the dosing stage for our patients.

CONCLUSIONS

The potential impact of our finding on critically ill patient care is significant: discordance in dosing stage of antibiotic agents between equations, especially cystatin C based equations can lead to decreasing the risk of drug toxicity. Cystatin C may help to prevent risk of AKI for antibiotic agents that have nephrotoxic effects. Collaboration among pharmacists and healthcare professionals is crucial for creating protocol on using the combined creatinine and cystatin C equation to adjust antibiotic doses in critically ill patients with renal impairment, ultimately improving clinical outcomes. Future clinical research should evaluate the pharmacokinetic and clinical outcomes in large populations to optimize drug dosing in critically ill patients.

AUTHOR CONTRIBUTIONS

W.S.: conceptualization, data curation, formal analysis and writing- original draft, and final approval of the version to be published. C.N.: conceptualization, writing- reviewing and editing, methodology, supervision, and final approval of the version to be published. W.C. and N.S.: conceptualization, writing-review and editing, and final approval of the version to be published.

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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