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Adjustment of drug dosage according to glomerular filtration rate in elderly people admitted to intensive care units

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Abstract

Objective: This study aimed to evaluate dose adjustment based on glomerular filtration rate in elderly patients admitted to Intensive Care Units. **Methods:** This is a retrospective cross-sectional study conducted with patients aged ≥ 60 years admitted to Intensive Care Units of a public hospital. To evaluate medications requiring dose adjustment according to glomerular filtration rate (GFR), the first prescription after 48 hours of ICU admission was considered. All medications requiring dose adjustment based on GFR were evaluated throughout the patient's hospitalization period in the ICU, as well as creatinine tests for calculating GFR on the day of medication use, to assess the need for dose adjustment individually for each medication. **Results:** Among the 189 patients analyzed, 757 medications requiring dose adjustment based on GFR were identified, distributed among 38 different drugs. Of these, 55.4% actually required adjustment during hospitalization, but only 16.7% received dose adjustment. Of the prescribed medications that require dose adjustment based on glomerular filtration rate and did not receive this adjustment: 68.9% were for patients with nephropathy, 84.4% for patients with altered creatinine who died, 73.3% for patients who underwent hemodialysis, 86.8% for patients who were evaluated by a pharmacist, and 74.7% for patients who were evaluated by a nephrologist. **Conclusion:** This study identified that dose adjustment based on glomerular filtration rate in elderly patients admitted to the ICU was mostly performed for antibiotics, leaving other medications that act on the cardiovascular, digestive, and metabolic systems without dose adjustment.

Keywords: Intensive Care Units; Aged; Drug Dosage Calculations.

Ajuste de dose dos medicamentos de acordo com a taxa de filtração glomerular em idosos internados em unidade de terapia intensiva

Resumo

Objetivo: Este estudo teve como objetivo avaliar o ajuste de dose de acordo com a taxa de filtração glomerular em idosos internados em Unidades de Terapia Intensiva. **Métodos:** Trata-se de um estudo de corte transversal retrospectivo, realizado com pacientes com idade ≥ 60 anos admitidos em Unidades de Terapia Intensiva de um hospital público. Para avaliação dos medicamentos que necessitavam de ajuste de dose conforme a taxa de filtração glomerular (TFG) foi considerada a primeira prescrição após 48 horas de admissão na UTI. Foram avaliados todos os medicamentos que necessitam de ajuste de dose de acordo com a TFG, durante todo o período de hospitalização do paciente na UTI, assim como os exames de creatinina para cálculo da TFG no dia do uso do medicamento para então avaliar a necessidade de realização de ajuste de dose individualmente para cada medicamento. **Resultados:** Entre os 189 pacientes analisados, foram identificados 757 medicamentos que exigiam ajuste de dose com base na TFG, distribuídos entre 38 fármacos diferentes. Destes, 55,4% realmente necessitavam de ajuste durante a hospitalização, mas apenas 16,7% receberam a adequação da dose. Dos medicamentos prescritos, que necessitam de ajuste de dose baseados na taxa de filtração glomerular, que não receberam esse ajuste: 68,9% foram para pacientes com nefropatia, 84,4% para pacientes que apresentaram creatinina alterada e que foram a óbito, 73,3% para pacientes que fizeram hemodiálise, 86,8% para pacientes que foram avaliados pelo farmacêutico e 74,7% para pacientes que foram avaliados pelo nefrologista. **Conclusão:** Este estudo identificou que o ajuste de dose de acordo com a taxa de filtração glomerular dos idosos internados em UTI, foi realizado na sua grande maioria para antibióticos, deixando, porém, os outros medicamentos que agem no aparelho cardiovascular, digestivo e metabólico sem ajuste de dose.

Palavras-chave: Unidade De Terapia Intensiva; Idoso; Cálculos da Dosagem de Medicamento.

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Introduction

The physiological changes associated with aging are characterized by psychological, social, genetic, and biological modifications[1]. Among these, the impairment of renal filtration function stands out due to structural and functional alterations, such as reduced kidney size, decreased number of glomeruli, and vascular changes[2]. These factors can lead to reduced renal blood flow and a decline in the Glomerular Filtration Rate (GFR)[3].

Elderly patients account for 52% of admissions to Intensive Care Units (ICUs) in Brazil, with a mortality rate of approximately 62%[4]. Among them, about 20 to 40% of hospitalized elderly ICU patients develop acute kidney injury (AKI)[5,6,7].

Currently, AKI is diagnosed based on the rise in serum biomarkers or a decrease in urinary output[8,9]. Its incidence is higher in the elderly population than in younger individuals, and age is a significant predictive factor of mortality in these patients[10]. In addition to age-related renal changes, multiple chronic comorbidities, complications related to disease severity, polypharmacy, exposure to nephrotoxic drugs (defined as those capable of causing injury or damage to renal cells), oxidative stress, hypovolemia, and surgery may also increase the risk of AKI in elderly ICU patients[11,12].

In China, the incidence of AKI was 15.4% in patients aged 65 to 80 years and 22.22% in patients over 80 years old, with elderly patients being more likely to be exposed to nephrotoxic medications[13]. In 38.6% of cases in the 65 to 80 age group and 51.4% in those over 80, AKI was possibly drug-induced. A study conducted at a tertiary hospital in São Paulo analyzed 130 patients over the age of 70 diagnosed with AKI. Nephrotoxic causes were found in 35% of this population. Mortality among elderly patients with AKI was approximately 53%, especially high in cases of oliguria, need for dialysis, ICU admission, and postoperative conditions[14].

The aforementioned physiological changes can also alter the pharmacokinetics of medications, potentially reducing or increasing the effective dose, frequency of administration, duration of treatment, and/or drug selection[15]. From this perspective, some medications require dose adjustment in elderly patients, with dosage modifications based on the patient's glomerular filtration rate to prevent adverse drug reactions and/or worsening of renal injury[16].

Thus, recognizing the risk of early decline in renal filtration function becomes crucial, as it enables interventions for the prevention and treatment of adverse outcomes. In light of the above, this study aimed to assess dose adjustment according to the glomerular filtration rate in elderly patients admitted to Intensive Care Units.

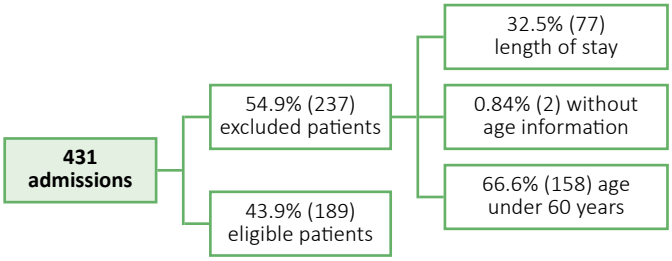
Methods

This is an observational and exploratory study with a retrospective cross-sectional design. The data used in this study were extracted from the database of the research project titled *"Pharmaceutical Care: evaluation of medication use in a regional hospital."*

The study was conducted in a public hospital located in the Médio Rio de Contas region. It is an open-door facility offering medium- and high-complexity care, with a focus on trauma and orthopedics, and primarily serves Urgent and Emergency cases. At the time of the study, the hospital had 275 beds, 29 of which were ICU beds. This hospital serves the population of 27 municipalities and is a regional reference center.[17]

The study population consisted of elderly patients admitted to the ICU. Inclusion criteria were all patients aged ≥60 years, of both sexes, who were admitted to the ICU. Patients who remained in the ICU for less than 24 hours were excluded, as shown in Figure 1.

Figure 1. Flowchart of the patient inclusion process in the study. Bahia, Brazil, 2019.



Source: Prepared by the authors.

Data were collected using a structured form specifically developed for this study, with the patient's medical records as the data source. A pilot test of the data collection instrument was conducted using medical records of ten patients who were not included in the final sample. The study considered patients admitted to the ICU between July and December 2019, and data collection took place from August 2020 to April 2021 by a previously trained team.

The dependent variable was dose adjustment, categorized as "yes" or "no." Dose adjustment categorization was based on GFR, which was classified as either altered or not altered, considering the need for individual dose adjustment for each medication according to the GFR (creatinine clearance) and based on GFR ranges as indicated in medical databases.[17] In cases of discrepancy, dose adjustments recommended by *UpToDate®* were considered, as it is an online and frequently updated resource.

GFR was calculated using the Cockcroft-Gault (CG) equation [CG: (140 - age) × weight / (72 × creatinine) × 0.85 (if female)][18] when patient weight was available, and/or using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[19] when race was documented. Both equations are available on the Brazilian Society of Nephrology (SBN) website. The weight used in the CG equation was the estimated weight, recorded in the nutritional assessment section of the patient's chart, and calculated according to the patient's sex.[20]

The CG equation was chosen due to its national and international acceptance in studies involving elderly populations for the evaluation of renal filtration function,[21,22] and in clinical practice, the KDIGO guidelines recommend the CKD-EPI formula for estimating GFR.[23]

To assess the medications requiring dose adjustment according to GFR, the first prescription issued after 48 hours of ICU admission was considered. This prescription included all medications prescribed, including those classified as "as needed" and "at physician's discretion," while excluding large-volume parenteral solutions, nebulization solutions, and sliding-scale insulin.

Medications were classified according to the first, fourth, and fifth levels of the Anatomical Therapeutic Chemical (ATC) classification system, developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology.[28]

The need for dose adjustment and the recommended adjusted dose for each medication were assessed individually and classified as either appropriate or inappropriate.

All medications requiring dose adjustment based on GFR were evaluated throughout the patient's ICU stay, as well as the corresponding creatinine test results from the day the medication was administered, in order to determine whether an individual dose adjustment was necessary for each drug.

Serum creatinine levels were categorized as follows: elevated creatinine, defined as an increase of ≥0.3 mg/dL within 48 hours or a 1.5-fold increase compared to the presumed baseline creatinine within the last seven days; and normal creatinine, defined as serum creatinine levels ranging from 0.5 to 1.5 mg/dL, based on the reference values established by the hospital laboratory.[25]

Age was categorized into three groups: 60–69 years, 70–79 years, and ≥80 years. Sex was categorized as female or male.

Health conditions were collected from medical records and assessed based on the following information: smoking status (yes, no, or no information), alcohol use (yes, no, or no information), diabetes mellitus (yes, no, or no information), systemic arterial hypertension (yes, no, or no information), heart disease (yes, no, or no information), kidney disease (yes, no, or no information), and allergies (yes, no, or no information).

Diagnostic hypotheses were collected from the medical record on the day of ICU admission and were assessed according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Excessive polypharmacy was categorized as either no or yes, defined respectively as the use of fewer than 10 medications or the use of 10 or more medications.[26] The use of potentially inappropriate medications for older adults (PIMs) was identified in prescriptions based on the 2019 update of the Beers Criteria.[27] PIM use was categorized as yes or no, considering medications listed in the following categories:

(A) Medications that are potentially inappropriate for most older adults — the presence of any medication from this list in the prescription was considered PIM use;

(B) Medications that should be used with caution — the prescription of any medication from this list was considered as presence of PIM;

(C) Medications that should be avoided or have their dosage adjusted based on renal function — the use of at least one medication from this list, when prescribed to a patient with creatinine clearance below the recommended threshold, was considered PIM use.

Pharmaceutical evaluation was categorized as yes or no. This information was collected from the progress notes section, where a search for "pharmaceutical evaluation" was conducted. Referral to a nephrologist was also categorized as yes or no, with the information gathered from the interconsultation records.

For descriptive data analysis, absolute and relative frequencies, means, and standard deviations were calculated. Associations between medication dose adjustment and sociodemographic variables, clinical profile, and ICD-10 classification were tested using Pearson's Chi-square test or Fisher's Exact test. For variables with statistically significant results in the Chi-square test, crude analysis was also performed using bivariate logistic regression (OR) and respective 95% confidence intervals (95% CI). For all analyses, the significance level was set at 5% ($p < 0.05$). Data were tabulated and analyzed using SPSS software, version 21.0.

This study adhered to all ethical standards in accordance with the Brazilian National Health Council Resolution CNS 466/12. The project *"Pharmaceutical Care: evaluation of medication use in a regional hospital"* was approved by the Research Ethics Committee (CEP) of UESB, under protocol no. 4.229.023, CAAE 34826020.1.0000.0055.

Results

A total of 189 patients were included in the study, for whom 2,779 medications were identified. Of these, 757 were classified as requiring dose adjustment based on glomerular filtration rate (GFR), corresponding to 38 different drugs. Among the medications requiring dose adjustment according to GFR, 55.4% (419) actually required adjustment based on patients' creatinine clearance during hospitalization; however, only 16.7% (70) of them received the appropriate dose adjustment.

The patients had a mean age of 74.63 ± 9.6 years. It was also observed that 89.9% of the patients were on excessive polypharmacy, with a mean of 16.1 ± 5 medications per patient.

Table 1 presents the sociodemographic characteristics of the patients. It was observed that 53.0% of the medications were prescribed to female patients, 33.9% to elderly individuals aged ≥ 80 years, 96.6% to patients who self-identified as mixed race ("pardo"), and 67.0% to those without a partner. No statistically significant association was found between sociodemographic variables and dose adjustment ($p > 0.05$).

Table 1. Sociodemographic profile of patients using medications requiring dose adjustment (N: 757). Bahia, Brazil, July to December 2019.

Variables	Response rate (%)	Total (757)
Sex	**100**	
Female		401(53.0%)
Male		356 (47.0%)
Age	**100**	
60–69		284 (37.5%)
70–79		216 (28.5%)
≥ 80		257 (33.9%)
Race	**82.5**	
White		1 (0.5%)
Non-White		155 (82.0%)
Marital Status	**85.5**	
Without partner		439 (67.9%)
With partner		208 (32.1%)

Source: Prepared by the authors. Pearson's Chi-square or Fisher's Exact Test, significance level < 0.05.

Table 2. International Classification of Diseases and Related Health Problems according to dose adjustment for medications. Bahia, Brazil, July to December 2019.

Variables	Response rate	Total (757) n (%)	Medications without dose adjustment n (%)	Medications with dose adjustment n (%)	*p-value	OR (95% CI)
Infectious/parasitic diseases	63.9				0.678	
Yes		16 (3.3)	14 (87.5)	2 (12.5)		
No		468 (96.7)	424 (90.6.0)	44 (9.4)		
Neoplasms	63.4				0.719	
Yes		27 (5.6)	24 (88.9)	3 (11.1)		
No		453 (94.4)	412 (90.9)	41 (9.1)		
Diseases of the blood	63.4					
Yes		7 (1.5)	6 (85.7)	1 (14.3)	0.636	
No		473 (98.5)	430 (90.9)	43 (9.1)		
Endocrine diseases	63.4					
Yes		36 (7.5)	29 (80.6)	7 (19.4)	0.026	2.66 (1.09 – 6.47)
No		444 (92.5)	407 (91.7)	37 (8.3)		1
Mental and behavioral disorders	63.4					
Yes		9 (1.9)	9 (100.0)	0 (0.0)		-
No		471 (98.1)	427 (90.7)	44 (9.3)	0.336	
Diseases of the nervous system	63.4					
Yes		8 (1.7)	8 (100.0)	0 (0.0)		-
No		472 (98.3)	428 (90.7)	44 (9.3)	0.365	
Eye diseases	63.4					
Yes		05 (1.0)	5 (100.0)	0 (0.0)		-
					0.475	
No		475 (99.0)	431 (90.7)	44 (9.3)		
Injuries and poisonings	63.4					
Yes		85 (17.7)	79 (92.9)	6 (7.1)		
No		395 (82.3)	64 (73.6)	23 (26.4)	0.458	
Diseases of the circulatory system	63.4					
Yes		232 (48.3)	217 (93.5)	15 (6.5)		0.52 (0.27 – 1.00)
No		248 (51.7)	219 (88.3)	29 (11.7)	0.047	1
Diseases of the respiratory system	63.4					
Yes		148 (30.8)	140 (94.6)	8 (5.4)		
No		332 (69.2)	296 (89.2)	36 (10.8)	0.057	
Diseases of the digestive system	63.4					
Yes		24 (5.0)	12 (50.0)	12 (50.0)		13.25 (5.51 – 31.85)
No		456 (95.0)	424 (93.0)	32 (7.0)	0.000	1
Symptoms, signs, and abnormal findings	63.4					
Yes		55 (11.5)	42 (76.4)	13 (23.6)		3.93 (1.91 – 8.10)
No		425 (88.5)	394 (92.7)	31 (7.3)	0.000	1
Musculoskeletal diseases	63.4					
Yes		05 (1.0)	5 (100.0)	0 (0.0)		-
No		475 (99.0)	431 (90.7)	44 (9.3)	0.475	
Diseases of the genitourinary system	63.4				0.052	
Yes		32 (6.7)	26 (81.3)	6 (18.8)		2.49 (0.97 – 6.42)
No		448 (93.3)	410 (91.5)	38 (8.5)		
Factors influencing health status	63.4				0.523	
Yes		4 (0.8)	4 (100.0)	0 (0.0)		-
No		476 (99.2)	432 (90.8)	44 (9.2)		

Source: Prepared by the authors. Pearson's Chi-square and Fisher's Exact Test, significance level < 0.05. Bivariate logistic regression, p < 0.05 considered significant. OR: odds ratio. CI: 95% confidence interval.

Table 3. ATC Classification of Medications Requiring Dose Adjustment According to Renal Function in Elderly Patients Admitted to Intensive Care Units. Bahia, Brazil, 2019 (N = 757).

ATC Level 1	ATC Level 4	Medications	Dose Adjustment Perform	
			Yes	No
Alimentary tract and metabolism (A)	A02BA	Ranitidine	4	123
	A03FA	Metoclopramide	0	136
		Domperidone		
Blood and blood-forming organs (B)	B01AB	Enoxaparin	1	75
	B01AC	Aspirin (ASA)	0	32
	B01AF	Rivaroxaban	0	1
	B02AA	Tranexamic Acid	0	1
	B05BC	Mannitol Solution	0	4
	B05CB	Sodium Bicarbonate	0	5
Cardiovascular system (C)	C01AA	Deslanoside	0	4
	C01BD	Amiodarone	0	8
	C03AA	Hydrochlorothiazide	0	10
	C03DA	Spironolactone	0	12
	C07AB	Metoprolol	0	9
	C09AA	Enalapril	0	24
		Captoril		
	C10AA	Simvastatin	0	40
ATC Level 1	ATC Level 4	Medications	Adjustment Perform	
			Yes	No
Systemic hormonal preparations (H)	H03AA	Levothyroxine	0	1
Antiinfectives for systemic use (J)	J01CF	Oxacillin	0	2
	J01CR	Piperacillin + Tazobactam	26	72
		Ampicillin + Sulbactam		
Antiinfectives for systemic use (J)	J01DB	Cefazolin	0	18
		Cefalotin		
	J01DE	Cefepime	0	1
	J01DH	Meropenem	18	29
	J01FA	Azithromycin	0	4
	J01GB	Gentamicin	1	13
		Amikacin		
	J01MA	Ciprofloxacin	1	9
		Levofloxacin		
	J01XA	Teicoplanin	16	36
		Vancomycin		
	J01XD	Metronidazole	0	6
	J01XX	Linezolid	0	1
	J02AA	Amphotericin B	0	1
	J02AC	Fluconazole	4	5
	J05AB	Acyclovir	0	3
Nervous system (N)	N02AA	Morphine	0	1

Source: Prepared by the authors.

Table 4. Clinical profile of elderly patients admitted to Intensive Care Units according to medication dose adjustment based on renal function. Bahia, Brazil, July to December 2019.

Variables	Response rate	Total (757) n (%)	Medications without dose adjustment n (%)	Medications with dose adjustment n (%)	*p-value	OR (95% CI)
Alcohol user	34.3				0.210	
No		219 (84.2%)	205 (93.6%)	14 (6.4%)		
Yes		41 (15.8%)	34 (82.9%)	7 (17.1%)		
Smoker	36.9				0.889	
No		229 (82.1%)	212 (92.6%)	17 (7.4%)		
Yes		50 (17.9%)	46 (92.0%)	4 (8.0%)		
SAH	91.3				0.516	
No		166 (24.0%)	148 (89.42%)	18 (10.8%)		
Yes		525 (76.0%)	477 (90.9%)	48 (9.1%)		
DM	86.5				0.876	
No		383 (58.5%)	345 (90.1%)	38 (9.9%)		
Yes		272 (41.5%)	244 (89.7%)	28 (10.3%)		
Heart disease	60.0				0.798	
No		297 (65.4%)	269 (90.6%)	28 (9.4%)		
Yes		157 (34.6%)	144 (91.7%)	13 (8.3%)		
Nephropathy	53.1				0.000	
No		341 (84.8%)	319 (93.5%)	22 (6.5%)		1
Yes		61 (15.2%)	42 (68.9%)	19 (31.1%)		6.56 (3.28 – 13.12)
Allergy	83.4				1.000	
No		573 (90.8%)	522 (91.1%)	51 (8.9%)		
Yes		58 (9.2%)	54 (93.1%)	4 (6.9%)		
Outcome	100				0.000	
Discharge		436 (57.6%)	415 (95.2%)	21 (4.8%)		1
Death		321 (42.4%)	271 (84.4%)	50 (15.6%)		3.65 (2.14 – 6.21)
Altered creatinine	100				0.000	
No		347 (45.8%)	340 (98.0%)	7 (2.0%)		1
Yes		410 (54.2%)	346 (84.4%)	64 (15.6%)		8.98 (4.06 – 19.89)
HD	100				0.000	
No		620 (81.9%)	586 (94.5%)	34 (5.5%)		1
Yes		137 (18.1%)	100 (73.0%)	37 (27.0%)		6.38 (3.82 – 10.64)
Polypharmacy	100				0.102	
5–10 medications		43 (5.7%)	42 (97.7%)	1 (2.3%)		
>10 medications		714 (94.3%)	644 (90.2%)	70 (9.8%)		
Use of PIM	100				0.013	
No		83 (11.0%)	69 (83.1%)	14 (16.9%)		1
Yes		674 (89.0%)	617 (91.5%)	57(8.5%)		0.46 (0.24 – 0.86)
Required dose adjustment	99.6				0.000	
No		338 (44.6%)	337 (99.7%)	1 (0.3%)		1
Yes		419 (55.4%)	349 (83.3%)	70 (16.7%)		67.59 (9.34 – 489.35)
Pharmacist evaluation	100				0.006	
No		485 (64.1%)	450 (92.8%)	35 (7.2%)		1
Yes		272 (35.9%)	236 (86.8%)	36 (13.2%)		1.96 (1.20 – 3.21)
Nephrology consultation	79.4				0.000	
No		455 (75.7%)	428 (94.1%)	27 (5.9%)		1
Yes		146 (24.3%)	109 (74.7%)	37 (25.3%)		5.38 (3.14 – 9.22)

Source: Prepared by the authors. *Pearson's Chi-square and Fisher's Exact Test, significance level < 0.05. *Bivariate logistic regression, p < 0.05 considered significant. OR: odds ratio. CI: 95% confidence interval.
SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; HD: Hemodialysis; PIM: Potentially Inappropriate Medications for the elderly.

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Regarding the admission diagnoses, the most common were diseases of the circulatory system, respiratory system, and injuries or poisonings, according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Among the medications that were adjusted for dose, 19.4% were prescribed to patients with endocrine diseases (OR = 2.66; 95% CI = 1.09–6.47), 50.0% to those with digestive system diseases (OR = 13.25; 95% CI = 5.51–31.85), and 23.6% to those with signs, symptoms, and abnormal clinical findings (OR = 3.93; 95% CI = 1.91–8.10), as shown in Table 2.

The medications requiring dose adjustment were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The class with the highest proportion of dose adjustments based on patient GFR was class J (anti-infectives for systemic use), while class A (drugs acting on the alimentary tract and metabolism) had the lowest proportion, as shown in Table 3.

Table 4 shows the association between medications requiring dose adjustment based on GFR and whether or not the adjustment was made in ICU patients. It was found that among the prescribed medications requiring dose adjustment that did *not* receive such adjustment: 68.9% were prescribed to patients with nephropathy (OR = 6.56; 95% CI = 3.28–13.12), 84.4% to patients with altered creatinine levels (OR = 8.98; 95% CI = 4.06–19.89), 84.4% to patients who died (OR = 3.65; 95% CI = 2.14–6.21), 73.3% to patients undergoing hemodialysis (OR = 6.38; 95% CI = 3.82–10.64), 91.5% to patients with potentially inappropriate medications (PIMs) in their prescriptions (OR = 0.46; 95% CI = 0.24–0.86), 83.3% to drugs that required dose adjustment (OR = 67.59; 95% CI = 9.34–489.35), 86.8% to patients evaluated by a pharmacist (OR = 1.96; 95% CI = 1.20–3.21), 74.7% to patients evaluated by a nephrologist (OR = 5.38; 95% CI = 3.14–9.22).

Discussion

The main findings of this study revealed a low rate of dose adjustment, despite a high clinical need. More than half of the evaluated medications required dose adjustments based on glomerular filtration rate (GFR), yet fewer than 20% were actually adjusted. Notably, some patients who did not receive appropriate dose adjustments had been evaluated by either a pharmacist or a nephrologist.

Impaired renal filtration function is commonly associated with dosing errors when medications are not adjusted according to GFR or when their use is contraindicated under reduced renal function. Reports of unadjusted or contraindicated doses in hospitalized patients requiring renal adjustment range from 19% to 67%[28,29].

Other studies have found that 34% to 53% of medications requiring adjustment were not appropriately managed, often due to prescribers underestimating the impact of mild to moderate renal impairment or being unaware of which medications require dose adjustments in the context of acute kidney injury (AKI). Although serum creatinine is commonly used to estimate renal function, it may underestimate renal impairment, particularly in older adults[30,31].

According to the literature, patients admitted to intensive care units (ICUs) commonly present with neurological, respiratory, oncological, or cardiovascular conditions[32,33]. This study supports those findings, with circulatory and respiratory diseases being among the most prevalent admission diagnoses. However, ICU patients are at increased risk for complications, often requiring invasive interventions such as mechanical ventilation and vasopressor support. The excessive use of these interventions, particularly nephrotoxic drugs and vasoactive agents (VAAs), can overload the renal system and contribute to AKI development[34].

Among patients who were prescribed medications that required dose adjustments but did not receive them, several factors stood out. These included the presence of nephropathy, elevated creatinine levels, the use of potentially inappropriate medications (PIMs), undergoing hemodialysis, and mortality.

Specifically, patients with nephropathy were 6.56 times more likely not to receive a dose adjustment. Those with altered creatinine had 8.98 times greater odds of receiving no adjustment. Patients who died were 3.65 times more likely to have had unadjusted medications, and those who underwent hemodialysis were 6.38 times more likely to have missed necessary dose adjustments.

The mortality rate related to AKI in Brazil was 12.81% between December 2016 and 2021, highlighting AKI as a global public health issue due to its association with increased morbidity, mortality, and length of hospital stay, especially when compared to individuals without AKI[35,36]. It is also considered one of the most dangerous conditions in the ICU setting[37]. Therefore, timely and effective management of these patients is critical, as AKI is a highly prevalent and serious condition.

Failure to properly adjust the doses of medications according to renal function represents a significant cause of iatrogenesis among elderly ICU patients. AKI remains one of the most serious complications in hospitalized patients, with an incidence that ranges from 20% to 40% in ICUs depending on patient condition[5].

For patients with AKI, the dosage of renally eliminated medications must be adjusted based on the patient's actual GFR. This can be estimated using the Cockcroft-Gault (CG) equation, the Modification of Diet in Renal Disease (MDRD) formula, or the more recent CKD-EPI equation. However, these formulas often produce different GFR values, leading to confusion among prescribers. Currently, no clear consensus exists on which formula provides the most accurate GFR estimates[38].

Patients with acute kidney injury (AKI) commonly face medication dosing issues, as improper doses may lead to either toxicity or therapeutic failure. This situation becomes more critical when doses are not adjusted according to renal function. Appropriate dose adjustments not only help prevent adverse drug events but also contribute to reduced healthcare costs, shorter hospital stays, decreased mortality rates, and sustained therapeutic efficacy[39].

Since the majority of drugs used in clinical practice are eliminated via the kidneys, their efficacy and safety are directly linked to renal function. Many drugs—especially antimicrobials—are known to be highly nephrotoxic and may accumulate in the body if administered at standard doses. In these cases, dose adjustment according to renal function is crucial after the loading dose has been administered[40].

ICU patients often require multiple medications to manage a wide range of clinical conditions. However, while these therapies are essential, they also increase the risk of adverse events such as AKI. The risk is further exacerbated by nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), diuretics, and even proton pump inhibitors (PPIs), especially when used in combination[41,42].

In this study, the ATC class J drugs—systemic anti-infectives—were the most frequently adjusted according to renal function. This finding suggests that prescribers and pharmacists tend to be more vigilant with this drug class, likely due to their well-documented nephrotoxic potential.

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However, dose adjustment alone is not sufficient for achieving optimal outcomes in infection management. A comprehensive understanding of the pharmacokinetics and pharmacodynamics of these agents is essential, especially because some antimicrobials are dialyzable, which may alter the intended dosing regimen and compromise treatment effectiveness[43].

Among the antimicrobials adjusted for renal function, piperacillin + tazobactam and ampicillin + sulbactam were most prominent. These results align with findings by Azevedo[44], who identified beta-lactams as among the most commonly prescribed antimicrobials in medical practice, typically warranting careful attention to dosing due to their potential risks.

Inadequate dose adjustments of beta-lactams can lead to central nervous system (CNS) complications, such as confusion, myoclonus, and seizures. These adverse effects are thought to result from reduced renal clearance leading to elevated CNS concentrations of beta-lactams. Uremic patients are especially vulnerable due to altered drug-protein binding and uremia-induced changes in brain physiology, increasing susceptibility to neurotoxicity[45].

On the other hand, certain drug classes—especially those acting on the cardiovascular system, digestive system, and metabolism—were frequently not adjusted as needed. Of particular concern is metoclopramide, which was never adjusted in any patient, even when renal impairment warranted it. Approved by the U.S. Food and Drug Administration (FDA) for treating nausea, vomiting, and diabetic gastroparesis, metoclopramide is also used prophylactically in chemotherapy and postoperative settings[46].

In patients with renal impairment, maintenance doses of metoclopramide should be reduced to prevent accumulation and associated toxicities[47]. Common signs of overdose include sedation, diarrhea, and extrapyramidal symptoms such as tardive dyskinesia[48]. The lack of dose adjustment for metoclopramide observed in this study may stem from a general lack of awareness about its need for renal dosing adjustments and the serious risks it poses if improperly dosed. This highlights the urgent need for enhanced education and decision support tools for prescribers and pharmacists, particularly regarding medications that are often overlooked for renal adjustment but can lead to significant adverse outcomes when not properly managed.

This study also highlights the use of potentially inappropriate medications (PIMs) without proper dose adjustment according to renal function. Some medications may pose more risks than benefits for older adults, and their prescription should therefore be approached with caution. According to the literature, the use of PIMs is associated with the occurrence of several adverse events (falls, fractures, postoperative confusion, gastrointestinal bleeding, constipation, worsening of congestive heart failure, depression, cognitive impairment, and renal dysfunction)[49,50], as well as increased hospitalization and mortality rates among the elderly[51,52].

Another noteworthy finding in this study was the high prevalence of excessive polypharmacy in the majority of prescriptions. This issue has raised concerns in recent decades, as patients subjected to excessive polypharmacy are more vulnerable to inappropriate prescribing, drug interactions, adverse drug reactions, functional decline, prolonged hospitalization, and higher mortality. The incidence of excessive polypharmacy increases with age, with the risks growing proportionally as patients become older[53].

One limitation of this study was the retrospective nature of data collection, which prevented prospective follow-up of the patients. As a result, it was not possible to assess the incidence or severity of potential adverse drug reactions (ADRs) resulting from a lack of dose adjustment. This lack of follow-up limits the ability to establish a direct causal relationship between the absence of dose adjustment and the occurrence of ADRs, as well as to quantify the clinical impact of this practice on the studied population. Future studies with prospective designs are necessary to investigate this relationship and provide more robust evidence regarding the risks associated with inadequate dose adjustment.

From the perspective of pharmacological treatment in patients with acute kidney injury (AKI), it is essential to consider the importance of daily evaluation, including the patient's ongoing volume needs and the risk of fluid overload, as well as the necessity and appropriate dosing of nephrotoxic medications[54].

This study demonstrated that, in clinical practice, prescribers often neglect, and pharmacists frequently fail to intervene regarding the need for dose adjustments for many medications, which may compromise the patient's clinical status. Therefore, the daily follow-up of these patients by the multidisciplinary team should include regular discussions of the patient's prognosis and potential therapeutic approaches. The clinical pharmacist should review all prescribed medications and identify those that require substitution or dose adjustment according to the patient's clinical condition.

It is also worth noting that the clinical intensive care pharmacist plays a critical role in ensuring patient safety, serving as a reference for prescribers and other healthcare professionals, and contributing to cost-effectiveness in hospital settings[55]. However, in this study, the dose adjustment of medications based on renal function appears to have been overlooked by these professionals.

In this regard, the present study suggests implementing health education strategies as a way to empower healthcare professionals regarding the need for dose adjustments, based on the guideline developed in parallel with this study, which may be implemented in the institution.

The implementation of a clinical protocol for dose adjustment in patients with AKI could represent a significant advancement in healthcare practices by providing standardized support to the multidisciplinary team in decision-making. Well-defined protocols promote greater speed and accuracy in interventions, reducing the risk of medication dosing errors and contributing to patient safety. Thus, standardization through specific protocols strengthens the clinical role of the pharmacist and the entire care team, promoting safer and more effective care.

This study addresses a clinically relevant and frequent topic. Its external validity applies to healthcare settings with patients of similar age groups; however, institutional factors, healthcare professionals' practices, and local prescribing behaviors may significantly influence the results. Therefore, this study provides relevant data and may serve as a basis for reflection and the development of improved protocols for dose adjustment based on renal function in hospitalized patients, particularly in institutions with similar care profiles.

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Conclusion

This study identified that dose adjustment based on glomerular filtration rate for elderly patients admitted to the ICU was performed primarily for antimicrobials, leaving other medications—those acting on the cardiovascular, digestive, and metabolic systems—without appropriate dose adjustment. In these cases, both prescribers and pharmacists failed to adjust doses accordingly.

Patients with kidney disease, altered creatinine levels, those who died, and those who underwent hemodialysis were more likely not to receive dose adjustments, particularly for medications outside the antimicrobial class.

Contributors

TDBS: Study conception and design; Data acquisition; Data analysis and interpretation; Statistical analysis; Manuscript drafting; Critical revision of intellectual content. AMSM: Data acquisition; Critical revision of intellectual content. MSS: Data acquisition; Critical revision of intellectual content. BSS: Data acquisition; Data analysis and interpretation. BOS: Data acquisition. DBM: Data acquisition. NJSS: Critical revision of intellectual content. DSL: Critical revision of intellectual content. JAOC: Data analysis and interpretation; Critical revision of intellectual content. TSS: Critical revision of intellectual content. LBL: Study conception and design; Resource provision; Critical revision of intellectual content. GSL: Study conception and design; Data analysis and interpretation; Statistical analysis; Manuscript drafting; Resource provision; Critical revision of intellectual content.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this article.

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