Progress in Microbes and Molecular Biology

HH PUBLISHER

Original Research Article

Assessment of Inappropriate Dose Adjustment of Antimicrobials and Other Medicines Among Chronic Kidney Disease Patients: A Multicenter Observational Study

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Article History

Received: 28 July 2023;

Received in Revised Form: 12 September 2023;

Accepted: 27 September 2023;

Available Online: 31 October 2023

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Abstract: Most drugs undergo metabolism and elimination primarily by the kidneys. Consequently, drug dosages are largely contingent upon kidney function and require careful adjustment in patients with compromised renal function. Inaccurate dosage adjustments can lead to toxicities, therapeutic failures, and adverse drug reactions. This study sought to assess the appropriateness of dose adjustments for antimicrobials and other medicines among patients with Chronic Kidney Disease (CKD) attending both a public and a private hospital. A multicenter, retrospective observational study was carried out from January 1st to February 28th, 2023, among hospitalized CKD patients in two distinct facilities: Northwest General Hospital & Research Centre (a private institution) and the Institute of Kidney Diseases, Peshawar, Pakistan (a public institution). The goal was to compare adherence to dosing guidelines and to identify factors contributing to incorrect renal dose adjustments for antimicrobials and other medications. The study incorporated 358 CKD patients, with 179 patients from each hospital. Medications necessitating dosage adjustments were more frequently prescribed in the private hospital (n=515) compared to the public one (n=368). Nonetheless, dosages were more accurately adjusted in the private hospital (52.6%) than in the public hospital (40.5%). Of all the prescribed medications, 71.1% of antimicrobials in both hospitals were inaccurately adjusted. Multivariate logistic regression analysis showed

that the number of drugs requiring adjustment (AOR=0.6; p=0.001) was independently correlated with inappropriate drug adjustments in the private hospital. Conversely, in the public hospital, both the number of drugs requiring adjustment (AOR=0.6; p=0.019) and the length of hospital stay (AOR=0.8; p=0.048) were independently linked with inappropriate drug adjustments. The research revealed that a significant number of hospitalized CKD patients receive inappropriate drug dosages, especially in public hospitals. This predisposes these patients to heightened risks, including therapeutic failure.

Keywords: Chronic kidney diseases; Comparison; Dose-adjustment; Pakistan

1. Introduction

Chronic Kidney Disease (CKD) is a significant global health challenge, affecting 10-15% of the worldwide population [1, 2]. In Asia, the prevalence stands at 10-18%, even though many Asian countries have limited data [3, 4]. Despite proactive referrals and comprehensive care, the incidence of CKD is rising at a worrying pace [5]. Since 1990, CKD prevalence has surged by 29.3%, with a 43.5% rise in global mortality attributed to CKD as of 2017 [6]. Current estimates suggest approximately 700 million people suffer from CKD globally [6] with 387.5 million residing in developing nations [7]. Intriguingly, the incidence of CKD in these countries is quadruple that of their developed counterparts [2]. Hypertension and diabetes remain the predominant CKD causes globally [8, 9]. Of note, recent studies highlighted various aspects of antihypertensive medication prescribing patterns and costs. These factors can significantly affect CKD patients who may already be facing economic constraints. The choice of medications, the use of non-fixed dose combinations, deviations from recommended doses, and adherence to guidelines can all contribute to increased prescription costs, potentially complicating the management of CKD and hypertension in affected individuals [10, 11].

The global COVID-19 pandemic that emerged in 2019 and persisted in the following years [12-14] has inadvertently heightened the complexity of addressing and treating chronic diseases, such as antibiotic resistance [15-19], stroke [20] as well as CKD [21]. Most countries have to shift healthcare human resources as well as budget for non-communicable diseases to COVID-19 treatment and vaccination [22-26]. Global healthcare systems experienced substantial strain, prompting a reorientation of priorities toward the containment and management of the virus, notably in response to the emergence of worrisome variants like Delta and Omicron [27-30]. Consequently, countries, regardless of their development status, faced disruptions in their routine CKD care protocols. For instance, patients in many Asian countries, where CKD prevalence is notably high, faced interrupted treatment regimens due

to lockdowns, reduced clinical visits, and reallocation of medical resources to the pandemic [13, 31-34]. Furthermore, those residing in developing nations were disproportionately affected. The inadequate healthcare infrastructures in these regions struggled to balance the demands of a novel virus while addressing a burgeoning CKD population, which was already quadruple that of developed countries [31, 35, 36]. Moreover, since hypertension and diabetes - both significant risk factors for severe COVID-19 outcomes - are predominant causes of CKD, individuals with these coexisting conditions face dual jeopardy. The pandemic, therefore, not only highlighted the existing disparities in CKD care across nations but also underscored the urgent need for resilient and adaptive healthcare systems capable of addressing multifaceted global health challenges.

CKD patients are particularly vulnerable to the substantial accumulation of drugs that are excreted through the renal route [37, 38], which is especially pertinent among older people [39]. Incorrect medication dosages can lead to severe complications for CKD patients, encompassing morbidity, extended hospital stays, and even mortality [37, 40]. This inadvertently can contribute to excessive spending on medications that leads to the potential cost burden and unnecessary medication wastages, as demonstrated in a recent study conducted using observational study design in a public hospital [41]. The confluence of multiple comorbidities exposes CKD patients to polypharmacy, escalating the potential for drug-related issues [42]. This can amplify the risk of significant, sometimes irreversible, toxicity. To mitigate drug-related adverse reactions, therapeutic failures, and toxicity, a tailored dosage adjustment, informed by renal function, is paramount [43, 44]. Notably, failures in dosage adjustments compound treatment costs and lengthen hospital stays, placing further strain on both patients and healthcare infrastructures [43]. Past research has indicated that between 25-77% of drugs, which required dosage modifications, were adjusted improperly [45, 46]. Many such drugs, crucial for CKD patients, are routinely disregarded, inviting health complications [44]. Research from China has brought attention to antibiotic dosing inaccuracies, with reported error rates ranging from 38-63% in the context of CKD patients [43]. Moreover, a Lebanese study reported that 51.6% of CKD patients received antibiotic prescriptions without the essential renal dose adjustments, with the most frequent inaccuracies observed in the dosing of penicillin [47]. It is noteworthy that irrational utilization of antimicrobials can also lead to the emergence of antimicrobial resistance, particularly in the case of pathogens such as Methicillin-resistant Staphylococcus aureus (MRSA) which is widespread in Asia [48, 49]. The approach to rationalizing the use of medicines should address all the factors that contribute to the irrational use of medicines, including patient-centered factors, prescriber-related factors, social and economic factors, healthcare system factors, and disease factors [50].

Despite the criticality of the situation, there is a pronounced data gap concerning drug dosing adjustments in Low- and Middle-Income Countries (LMICs). In nations like Pakistan, direct comparisons between private and public hospitals' drug adjustment practices remain absent. As a result, this study aims to evaluate the appropriateness of antimicrobial and other medication dose adjustments in CKD patients across a public and a private hospital.

2. Materials and Methods

2.1. Study Design

The study was conducted at the nephrology units of two hospitals: Institute of Kidney Diseases, Peshawar Pakistan (a public sector hospital), and Northwest General Hospital & Research Centre, Peshawar Pakistan (a private sector hospital), using a retrospective cross-sectional study design to compare the dosage adjustment of drugs and the factors associated with inappropriate renal dose adjustments in hospitalized CKD patients in these two hospitals. For research purposes, data were accessed for the full year starting from January 1st 2022 to December 30th 2022, from hospital systems/profiles. The eligible patients' profiles were collected within two months i.e., January, 1st 2023 to February, 28th 2023, based on the inclusion/exclusion criteria.

2.2. Study procedure and inclusion and exclusion criteria

Data were sourced from the medical records of CKD patients admitted to the nephrology units of both hospitals. Each patient was assigned a unique ID. Characteristics recorded from their profiles included age, gender, length of hospital stay, CKD stage, serum creatinine, blood urea nitrogen, potassium level, total number of prescribed drugs, number of antibiotics prescribed, and the presence of other comorbidities, such as diabetes, hypertension, cardiovascular disease, and hepatitis B or C.

2.3. Inclusion and exclusion criteria

The study included adult patients aged 18 and above, of both genders, who were diagnosed with a CKD-related issue and/or were undergoing dialysis. Additionally, they had to be receiving at least one drug that necessitated renal dose adjustment. Exclusion criteria encompassed those with an eGFR greater than 90 ml/min/1.73 m^2 and pregnant individuals.

2.4. Outcome assessment

In our study, to evaluate dose appropriateness, we referred to two primary sources:

the "Drug Information Handbook, 25th edition" published by Lexicomp® [51], and "Drug Dosing Adjustments in Patients with Chronic Kidney Disease" issued by the American Academy of Family Physicians [52]. These were consulted in collaboration with a practicing nephrologist. Pharmacological agents were categorized based on their prescribed doses in relation to the recommended guidelines. Agents dosed according to these guidelines were labeled as "adjusted," while those prescribed at doses deviating from the guidelines were categorized as "unadjusted."

2.5. Sample size

Data were collected from a total of n=358, with 179 patients from each hospital based on the anticipated prevalence of CKD (12.5%) [53] using a recommended formula [54] with a confidence interval of 95%, and 5% precision.

2.6. Ethics approval and statistical analysis

The study received approval from the ethics committee of Abdul Wali Khan University Mardan (Approval no: EC/AWKUM/2021/27) and the Institutional Review Boards (IRB) of both the Northwest General Hospital & Research Centre (Approval no: NWGH/DMER/EC/1726) and the Institute of Kidney Diseases in Peshawar, Pakistan (Approval no: 454). Given the retrospective nature of the study, all data were fully anonymized prior to our access. The IRB of Northwest General Hospital & Research Centre and the ethics committee of the Institute of Kidney Diseases both waived the requirement for informed consent.

Data analysis was performed using SPSS version 22.0®. Descriptive statistics provided insights into demographic characteristics, frequency of prescribed antibiotics, and whether drugs were adjusted/unadjusted according to recommended guidelines. Since the data were not normally distributed, the median and interquartile range (IQR) were presented. Univariate logistic regression was initially carried out, and factors with a p-value <0.25 progressed to multivariate binary logistic regression. This regression aimed to discern associations between various predictors and risk factors with drug adjustments (either appropriate or inappropriate). Results from the regression were communicated as odds ratios (OR) with 95% confidence intervals. A p-value <0.05 was deemed statistically significant.

3. Results

3.1. Patients' Socio-demographic Characteristics

A total of n=358 patients were selected, evenly distributed between a private hospital and a public hospital, with n=179 patients from each. In both institutions, males were the majority: 59.8% in the private hospital and 77.7% in the public one. The median age differed between the two, with the private hospital's patients being older at a median age of 62.00 years (IQR: 15.00) compared to the public hospital's median age of 50.00 years (IQR: 22.00). The public hospital had a longer median duration of patient stay. Most patients were diagnosed with CKD stage 5: 62.6% in the private hospital and 88.3% in the public one, as detailed in Table 1. In terms of medication, the vast majority (97.2%) in the private hospital and 82.1% in the public hospital were prescribed more than five drugs. The frequency of drugs not adjusted for dosage was notably higher in the public hospital (87.2%) compared to the private one (41.3%), as also indicated in Table 1.

Table 1. Demographic and clinical characteristics of the patients (n=179 each).

Variables	**Private**		**Public**	
	N	**%**	**N**	**%**
Age in years Median [IQR]	62.00 [15.00]		50.00 [22.00]	
Gender				
Male	107	59.8	139	77.7
Female	72	40.2	40	22.3
Length of hospital stay in days Median [IQR]	3.00 [3.00]		4.00 [2.00]	
Stages of CKD				
Stage 2	4	2.2	5	2.8
Stage 3	25	14	4	2.2
Stage 4	38	21.2	12	6.7
Stage 5	112	62.6	158	88.3
Serum creatinine (mg/dL) Median [IQR]	5.81 [5.33]		9.40 [7.20]	
eGFR (mL/min/1.73 m^2) Median [IQR]	11.20 [16.90]		6.00 [5.00]	
BUN (mg/dL) Median [IQR]	143.00 [109.00]		184.00[87.00]	

Potassium (mmol/L) Median [IQR]	4.68 [1.22]		4.90 [1.02]	
Number of drugs prescribed				
Less than 5	5	2.8	32	17.9
More than 5	174	97.2	147	82.1
Antibiotics prescribed				
Yes	165	92.2	175	97.8
No	14	7.8	4	2.2
Patients with unadjusted drugs				
Yes	74	41.3	156	87.2
No	105	58.7	23	12.8
Comorbidities present				
Yes	176	98.3	177	98.9
No	3	1.7	2	1.1
Diabetes Mellitus				
Yes	104	58.1	60	33.5
No	75	41.9	119	66.5
Hypertension				
Yes	145	81	146	81.6
No	34	19	33	18.4
Cardiovascular Diseases				
Yes	67	37.4	22	12.3
No	112	62.6	157	87.7
Urinary tract infection				
Yes	37	20.7	18	10.1
No	142	79.3	161	89.9
Hepatitis B				
Yes	2	1.1	9	5
No	177	98.9	170	95
Hepatitis C				
Yes	12	6.7	21	11.7
No	167	93.3	158	88.3

Abbreviations: eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; IQR: interquartile range.

3.2. Drugs adjusted / unadjusted

A total of n=331 antibiotics were prescribed to patients hospitalized in a private hospital and n=175 antibiotics were prescribed to the patients in a public hospital (as shown in Table 2). The number of drugs properly adjusted in a private hospital were higher as compared to a public hospital 52.62% and 40.49% respectively.

Table 2. Number of properly adjusted and unadjusted drugs prescribed.

	Private	**Public**
	N (%)	**N (%)**
Total number of antibiotics prescribed	331*	175*
Total number of drugs prescribed requiring adjustment	515	368
Total number of drugs properly adjusted	271/515 (52.62)	149/369 (40.49)
Number of drugs unadjusted	244/515 (47.38)	219/369 (59.51)

*Multiple antibiotics and medicines were prescribed to patients, so the sum cannot be 100%.

The results revealed that, in the category of antibiotics/antimicrobials, Meropenam was the most frequently prescribed and consistently unadjusted drug in both hospitals. This was closely followed by piperacillin-tazobactam and vancomycin, as detailed in Table 3. Among diuretics, spironolactone prescriptions were predominantly unadjusted in both institutions. In the realm of antihypertensive medications, Ramipril and Bisoprolol emerged as the most commonly unadjusted drugs, as also indicated in Table 3.

Table 3. List of drugs needing adjustment, properly adjusted, or unadjusted.

	Private			**Public**		
Drug name	**n**	**Adjusted**	**Unadjusted**	**n**	**Adjusted**	**Unadjusted**
		n (%)	**n (%)**		**n (%)**	**n (%)**
Antibiotics/antimicrobials						
Meropenam	81	1 (1.2)	80 (98.8)	12	0 (0)	12 (100)
Cefoperazone - Sulbactam	12	0 (0)	12 (100)	97	8 (8.2)	89 (91.8)
Cefotaxime	24	22 (91.67)	2 (8.3)	25	21 (84.0)	4 (16.0)
Piperacillin-tazobactam	18	1 (5.56)	17 (94.4)	5	1 (25.0)	4 (80.0)
Vancomycin	22	1 (4.5)	21 (95.5)	4	3 (75.0)	1 (25.0)
Ciprofloxacin	18	18 (100)	0 (0)	2	0 (0)	2 (100)

Cefepime	1	0 (0)	1 (100)	26	0 (0)	26 (100)
Levofloxacin	4	3 (75.0)	1 (25.0)	1	0 (0)	1 (100)
Linezolid	17	17 (100)	0 (0)	1	1 (100)	0 (0)
Amoxicillin-Clavulanic Acid	11	0 (0)	11 (100)	0	0 (0)	0 (0)
Nitrofurantoin	4	0 (0)	4 (100)	0	0 (0)	0 (0)
Clarithromycin	4	4 (100)	0 (0)	0	0 (0)	0 (0)
Co-trimoxazole	3	0 (0)	3 (100)	0	0 (0)	0 (0)
Fluconazole	0	0	0	4	1 (25.0)	3 (75.0)
Diuretics						
Spironolactone	32	11 (34.4)	21 (65.6)	3	1 (33.3)	2 (66.7)
Furosemide	0	0	0	50	35 (70.0)	15 (30.0)
Antihypertensive						
Ramipril	10	3 (30.0)	7 (70.0)	2	1 (50.0)	1 (50.0)
Atenolol	3	0 (0)	3 (100)	0	0 (0)	0 (0)
Bisoprolol	32	26 (81.3)	6 (18.7)	2	2 (100)	0 (0)
Captopril	0	0	0	3	3 (100)	0 (0)
Statins						
Rosuvastatin	54	43 (79.6)	11 (20.4)	4	0 (0)	4 (100)
Miscellaneous agents						
Soda bicarbonate	25	25 (100)	0 (0)	30	19 (63.3)	11 (36.7)
Domperidone	33	33 (100)	0 (0)	33	28 (84.8)	5 (15.2)
Ranitidine	16	4 (25.0)	12 (75.0)	51	16 (31.4)	35 (68.6)
Metoclopramide	12	12 (100)	0 (0)	4	1 (25..0)	3 (75.0)
Aspirin	53	35 (66.0)	18 (34.0)	5	5 (100)	0 (0)
Pregabilin	12	5 (41.7)	7 (58.3)	2	2 (100)	0 (0)
Acyclovir	2	0 (0)	2 (100)	0	0 (0)	0 (0)
Allopurinol	1	0 (0)	1 (100)	0	0 (0)	0 (0)
Rivaroxaban	2	2 (100)	0	0	0 (0)	0 (0)
Fexofenadine	6	3 (50.0)	3 (50.0)	0	0 (0)	0 (0)
Morphine	3	2 (66.7)	1 (33.3)	0	0 (0)	0 (0)
Tranexamic acid	0	0	0	2	1 (50.0)	1 (50.0)

n=frequency

A univariate binary logistic regression was conducted, with the categorization of dose (either inappropriately adjusted or properly adjusted) as the dependent variable, and other parameters as independent variables. Only those variables with a p-value less than 0.25 were then subjected to a multivariate logistic regression. This multivariate analysis revealed that in the private hospital, the number of drugs needing adjustment (AOR=0.6; p=0.001) was independently linked to inappropriate drug adjustment. In contrast, in the public hospital, both the number of drugs requiring adjustment (AOR=0.6; p=0.019) and the duration of hospital stay (AOR=0.8; p-value=0.048) were independently associated with inappropriate drug adjustment, as detailed in Table 4.

Table 4. Regression analysis of demographic and clinical variables with medication doses adjusted and unadjusted.

Variable	**Private**						**Public**					
	Univariate			**Multivariate**			**Univariate**			**Multivariate**		
	OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
Age in years	10	0.966; 1.006	0.170	1.0	0.960; 1.004	0.115	1.0	0.988; 1.027	0.467			
Gender	0.8	0.438; 1.632	0.616				1.8	0.882; 3.798	0.104	2.1	1.000; 4.751	0.05
Hospital stay in days	1.0	0.889; 1.060	0.510				0.8	0.687; 0.982	0.031*	0.8	0.679; 0.998	0.048 *
Creatinine	1.0	0.971; 1.118	0.258				1.0	0.974; 1.086	0.31			
BUN	1.0	0.996; 1.004	0.894				1.0	0.999; 1.006	0.144	1	0.999; 1.006	0.201
Potassium	1.0	0.715, 1.521	0.827				1.0	0.780; 1.364	0.829			
GFR	1.0	0.976; 1.015	0.628				1.0	0.955; 1.037	0.806			
Number of drugs requiring adjustment	0.6	0.442; 0.735	<0.001 *	0.6	0.437; 0.731	<0.001*	0.6	0.400; 0.847	0.004*	0.6	0.415; 0.923	0.019 *
Comorbidities	1.3	0.112; 14.208	0.852				-	-	-			

Binary Logistic regression was used, Ref: Gender: Female; Number of drugs prescribed: Less than 5 drugs; Comorbidities: Yes, * p-value <0.05 statistically significant.

4. Discussion

CKD patients, due to compromised renal function, tend to be at a higher risk for drug-related problems, of which medication dosing errors are on top [55, 56]. It is evident from the existing literature [43, 55-57] that dose adjustment and medication dosing error among CKD patients are more prevalent, but to our knowledge, no comparison has been done yet in this region between a public and a private hospital. To evaluate adherence to the recommended dosing guidelines for CKD patients, this study aimed to compare the medication dosage adjustment and the factors associated with inappropriate renal dose adjustments in hospitalized CKD patients in a private and a public hospital.

The results of our study revealed that in a private hospital 52.62% and in a public hospital 40.49% of the drugs were properly adjusted. The findings are aligned with other studies in which 40.42% [43] and 37% [55] were adjusted among CKD patients, respectively. Another study in Ethiopia also reported that 49% of the drugs were adequately adjusted for dosing in CKD patients which is also in line with our study findings [58]. However, almost half of the patient's doses were not properly adjusted is alarming, particularly in CKD patients, which may be attributed to the overburdened and lower number of nephrologists in Pakistan [59]. Secondly, it may be due to low referral to a nephrologist as the majority of patients with compromised renal functions are managed by general physicians [60, 61]. If this issue is not properly addressed, it will lead to longer hospitalization, thus exhibiting additional economic burden on both patients and the already overburdened healthcare system of the country [41, 50].

Antimicrobials have been used for generations as prophylaxis to prevent initial or recurrence of infection [62-64]. Antimicrobials are a class of drugs that are frequently dosed inappropriately while managing CKD patients [43, 65, 66] which is evident from our study reporting that 71.1% of prescribed antimicrobials requiring dose adjustment were inappropriately adjusted. Of the total unadjusted antimicrobials (71.1%), 80.2% were unadjusted in a public hospital and 45.9% in a private hospital, respectively, signifying an alarming situation in a public hospital which is a designated hospital for managing patients with compromised renal function. A study from China reported inappropriate doses of antibiotics in 51.6% of CKD patients [47]. Furthermore, other studies reported that 36.25% [67] and 38.4% [68] of the antibiotics were inappropriately adjusted for doses. As the mode of excretion for antibiotics is renal; therefore, the dose adjustments of antibiotics are very crucial according to renal function to avoid unexpected adverse effects [67]. In our study the most common antibiotics prescribed with inappropriate dose adjusted were Meropenam,

Cefoperazon-sulbactam, and Piperacillin-tazobactam, our study findings are aligned with findings of other studies in which piperacillin-tazobactam were on top with inappropriately adjusted [69, 70]. The inappropriate dose adjustment of the antibiotics may lead to the worsening and progression of CKD [71]. In order to minimize the adverse drug reactions, toxicities, and therapeutic failure in CKD patients, the dosage modifications according to renal function in patients need to be individualized [43, 72].

Proper dose adjustments in renal-compromised patients are vital. Inappropriate dosing can lead to extended hospital stays, a conclusion our study also drew upon. Notably, we found that patients with prolonged hospital stays were more likely to have drugs inaccurately adjusted. By adhering to correct dosing protocols, hospital stays could be reduced, alleviating economic burdens, a sentiment supported by prior literature [73, 74].

Previous studies have also identified that each additional drug requiring dose adjustment raises the risk of medication errors [43, 56, 75]. Our findings align with this, showing that as the number of drugs needing adjustments rises, the chances of dosing errors also increase in both public and private hospitals. The sheer number of medications prescribed to CKD patients significantly increases the likelihood of dosing mishaps. Potential reasons include the challenges posed by polypharmacy and the associated workload, further compounded by co-existing medical conditions. It's particularly concerning that CKD patients with other health issues tend to have higher chances of inappropriate dosing [76-78].

Moreover, our study illuminated a clear difference between public and private hospitals regarding drug adjustments. Regrettably, in the public hospital setting, drugs were often inadequately dosed compared to their private counterparts. This disparity might arise from the public sector's potential deviation from dosing guidelines.

In light of these findings, clinicians should lean towards drugs that don't need dosage adjustments. When this isn't feasible, and they must prescribe drugs that require adjustments, they must adhere to updated dosing guidelines and make adjustments proportionate to altered elimination rates. Ensuring correct dosing not only endorses the judicious use of medications, enhancing patient outcomes, but also translates to economic savings [79-81].

Based on our study's results, there is a concerning trend of overlooked dosage adjustments among CKD patients in both private and public hospitals as seen in other part of the world too [82-84]. Many CKD patients are at an elevated risk of adverse outcomes due to inappropriate renal dosing. This may stem from clinicians' inattentiveness, lack of available dosing guidelines, or permissive prescribing standards. Thus, we strongly advocate for

continuous medical education for clinicians, complemented by collaboration with pharmacists, to promote the rational prescription of drugs for renal-impaired patients.

5. Conclusions

Our study reveals a substantial proportion of CKD patients in both private and public hospitals receiving incorrect drug doses. Such oversights can lead to adverse effects, heightened drug toxicities, and therapeutic failures. Physicians must prioritize precision when prescribing to this vulnerable group, ensuring strict adherence to dosing guidelines. Neglecting this critical aspect risks exacerbating patient distress and places additional economic strains on the healthcare system.

Author Contributions: RZ, YS, and IUR was responsible for the conceptualization of research idea and design, obtaining ethical permission and methodology; supervised data collection, management and data analysis, and interpretation; wrote the original manuscript; RZ, LCM, KWG, IUR reviewed and edited drafts. RZ and IUR ran the analysis, contributed to data interpretation and commented on the manuscript. All authors approved the final version of this manuscript.

Funding: No external funding was provided for this research.

Acknowledgments: None

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rehman IU, Khan TM. Effect of chronic kidney diseases-associated pruritus on patients' sleep quality, well-being and its management. Prog Microbes Mol Biol 2020; 3(1).

2. Alemu H, Hailu W, Adane A, et al. Prevalence of chronic kidney disease and associated factors among patients with diabetes in northwest Ethiopia: a hospital-based cross-sectional study. Curr Ther Res 2020; 92: 100578.

3. Khan YH, Mallhi TH, Sarriff A, et al. Prevalence of chronic kidney disease in Asia: A systematic review of population-based studies. J Coll Physicians Surg Pak 2018; 28(12): 960-6.

4. Begum R, Khan TM, Ming LC. Burden of chronic kidney disease and its risk factors in Malaysia. J Epidemiol Glob Health 2016; 6(4): 325-326.

5. Hsu H-J, Wu I-W, Hsu K-H, et al. The association between chronic musculoskeletal pain and clinical outcome in chronic kidney disease patients: a prospective cohort study. Ren Fail 2019; 41(1): 257-266.

6. Cockwell P, Fisher LA. The global burden of chronic kidney disease. Lancet 2020; 395(10225): 662-664.

7. Stanifer JW, Muiru A, Jafar TH, et al. Chronic kidney disease in low-and middle-income countries. Nephrol Dial Transplant 2016; 31(6): 868-874.

8. Deng Y, Li N, Wu Y, et al. Global, regional, and national burden of diabetes-related chronic kidney disease from 1990 to 2019. Front Endocrinol 2021; 12: 672350.

9. Weaver VM, Fadrowski JJ, Jaar BG. Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? BMC Nephrol 2015; 16(1): 1-8.

10. Ng JM, Kua KP, Lee SWH. Prescribing patterns of antihypertensive medications and blood pressure control among hypertensive patients in a primary care setting in Malaysia. Prog Drug Discov Biomed Sci 2020; 3(1).

11. Ravinthiran E, Tan CS, Menon S, et al. Utilization review of antihypertensive agents at an outpatient pharmacy setting of a private hospital, Selangor, Malaysia. Prog Drug Discov Biomed Sci 2020; 3(1).

12. Goh HP, Mahari WI, Ahad NI, et al. Risk factors affecting COVID-19 case fatality rate: A quantitative analysis of top 50 affected countries. Prog Microbes Mol Biol 2020; 3(1).

13. Loo KY, Letchumanan V, Tan LTH, Law JWF. Updated COVID-19 Condition in Australia. Prog Microbes Mol Biol 2021; 4(1).

14. Ismail SN, Abdul Halim Zaki I, Noordin ZM, et al. Clinical characteristics and risk factors for mortality in patients with COVID-19: A retrospective nationwide study in Malaysia. Proc Singapore Healthcare 2022; 31: 20101058221085743.

15. Loo KY, Tan LTH, Law JWF, et al. Vibrio parahaemolyticus: Exploring its Incidence in Malaysia and the Potential of Streptomyces sp. as an Anti-Vibrio Agent. Prog Microbes Mol Biol 2023; 6(1).

16. Venggadasamy V, Tan LTH, Law JWF, et al. Incidence, Antibiotic Susceptibility and Characterization of Vibrio parahaemolyticus Isolated from Seafood in Selangor, Malaysia. Prog Microbes Mol Biol 2021; 4(1).

17. Goh JXH, Tan LT, Law JW, et al. Insights into Carbapenem Resistance in Vibrio Species: Current Status and Future Perspectives. Int J Mol Sci 2022; 23(20).

18. Pusparajah P, Letchumanan V, Law JW, et al. Streptomyces sp.-A Treasure Trove of Weapons to Combat Methicillin-Resistant Staphylococcus aureus Biofilm Associated with Biomedical Devices. Int J Mol Sci 2021; 22(17).

19. Low CX, Tan LT, Ab Mutalib NS, et al. Unveiling the Impact of Antibiotics and Alternative Methods for Animal Husbandry: A Review. Antibiotics (Basel) 2021; 10(5).

20. Loh HC, Neoh KK, Tang ASN, et al. Stroke Patients' Characteristics and Clinical Outcomes: A Pre-Post COVID-19 Comparison Study. Medicina 2021; 57(5): 507.

21. Paneerselvam GS, Goh KW, Kassab YW, et al. Health-related quality of life of dialysis patients during early COVID-19 lockdowns: a snapshot from a public hospital in Malaysia. Front Med 2023; 10: 992870.

22. Ang WS, Law JWF, Letchumanan V, et al. COVID-19 Pandemic in Brunei Darussalam. Prog Microbes Mol Biol 2023; 6(1).

23. Johnson D, Ren SEC, Johnson HD, Letchumanan V. COVID-19: Are Malaysians embracing or suffering the new normality? Prog Microbes Mol Biol 2020; 3(1).

24. Kuai YH, Ser HL. COVID-19 Situation in Thailand. Prog Microbes Mol Biol 2021; 4(1).

25. Loo KY, Thye AYK, Law LNS, Law JWF. COVID-19: An Updated Situation from Singapore. Prog Microbes Mol Biol 2021; 4(1).

26. Ser HL, Letchumanan V. PMMB COVID-19 Bulletin: Spain (18th April 2020). Prog Microbes Mol Biol 2020; 3(1).

27. Loo KY, Letchumanan V. COVID-19: Understanding the New Variants of Concern. Prog Microbes Mol Biol 2022; 5(1).

28. Thye AYK, Law JWF. A Variant of Concern (VOC) Omicron: Characteristics, Transmissibility, and Impact on Vaccine Effectiveness. Prog Microbes Mol Biol 2022; 5(1).

29. Thye AYK, Loo KY, Tan KBC, et al. Insights into COVID-19 Delta variant (B.1.617.2). Prog Microbes Mol Biol 2021; 4(1).

30. Law LNS, Loo KY, Goh JXH, Pusparajah P. Omicron: The rising fear for another wave in Malaysia. Prog Microbes Mol Biol 2021; 4(1).

31. Hoo HE, Loh HC, Ch'ng ASH, et al. Positive Impacts of the COVID-19 Pandemic and Public Health Measures on Healthcare. Prog Microbes Mol Biol 2021; 4(1).

32. Joseph RJ, Ser HL. Stories from the East: COVID-19 Situation in India. Prog Microbes Mol Biol 2021; 4(1).

33. Loo KY, Law JWF, Tan LTH, Letchumanan V. South Africa's Battle Against COVID-19 Pandemic. Prog Microbes Mol Biol 2022; 5(1).

34. Tan LTH, Letchumanan V, Ser HL, et al. PMMB COVID-19 Bulletin: United Kingdom (22nd April 2020). Prog Microbes Mol Biol 2020; 3(1).

35. Lee HT, Loh HC, Ramlee SNL, Looi I. Oral Dietary Supplements Use Among Healthcare Workers During the COVID-19 Pandemic in Malaysia. Prog Microbes Mol Biol 2021; 4(1).

36. Rayanakorn A, Leong SL, Chaiprom P, Lee SWH. Cost-effectiveness of Public Health Strategies on COVID-19 Control: A Systematic Review. Prog Microbes Mol Biol 2022; 5(1).

37. Miners JO, Yang X, Knights KM, Zhang L. The role of the kidney in drug elimination: transport, metabolism, and the impact of kidney disease on drug clearance. Clin Pharmacol Ther 2017; 102(3): 436-449.

38. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. Clin J Am Soc Nephrol 2018; 13(7): 1085.

39. Zailani IS, Moshawih S, Kifli N, et al. Drug/Natural Products-Related problems in Elderly. Prog Drug Discov Biomed Sci 2022; 5(1).

40. Bano T, Haq N, Nasim A, et al. Evaluation of medication errors in patients with kidney diseases in Quetta, Pakistan. PLoS One 2023; 18(8): e0289148.

41. Nasir HHA, Dhaliwal JS, Goh HP, et al. Patient's Own Medication Use During Hospitalization. Prog Microbes Mol Biol 2022; 5(1).

42. Santos-Díaz G, Pérez-Pico AM, Suárez-Santisteban MÁ, et al. Prevalence of Potential Drug–Drug Interaction Risk among Chronic Kidney Disease Patients in a Spanish Hospital. Pharmaceutics 2020; 12(8): 713.

43. Hassan Z, Ali I, Ullah AR, et al. Assessment of Medication Dosage Adjustment in Hospitalized Patients With Chronic Kidney Disease. Cureus 2021; 13(2): e13449.

44. Yang P, Chen N, Wang RR, Li L, Jiang SP. Inappropriateness of medication prescriptions about chronic kidney disease patients without dialysis therapy in a Chinese tertiary teaching hospital. Ther Clin Risk Manag 2016; 12: 1517-1524.

45. Teh XR, Lee SWH. Pharmacists' attitude, self-reported knowledge and practice of dosage adjustment among chronic kidney disease patients in Malaysia. J Pharm Pract Res 2019; 49(2): 179-185.

46. Drenth-van Maanen AC, van Marum RJ, Jansen PAF, Zwart JEF, van Solinge WW, Egberts TCG. Adherence with Dosing Guideline in Patients with Impaired Renal Function at Hospital Discharge. PLOS ONE 2015; 10(6): e0128237.

47. Chahine B. Antibiotic dosing adjustments in hospitalized patients with chronic kidney disease: a retrospective chart review. Int Urol Nephrol 2022; 54(1): 157-163.

48. Chow YL, Tham HW. Methicillin-resistant Staphylococcus aureus (MRSA) on dispensing counters of community pharmacies in Klang Valley. Prog Microbes Mol Biol 2020; 3(1).

49. Ahmed I, Rabbi MB, Sultana S. Antibiotic resistance in Bangladesh: A systematic review. Int J Infect Dis 2019; 80: 54-61.

50. Manan MM, Baharuddin AY, Lean QY, et al. Comparison of the factors that influence the pattern of procurement and usage of antithrombotic drugs. Prog Microbes Mol Biol 2022; 5(1).

51. Drug information handbook: A clinically relevant resource for all healthcare professionals. Lexi Comp 2014.

52. Munar MY, Signh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician 2007; 75(10): 1487-1496.

53. Jessani S, Bux R, Jafar TH. Prevalence, determinants, and management of chronic kidney disease in Karachi, Pakistan-a community based cross-sectional study. BMC Nephrol 2014; 15(1): 1-9.

54. Daniel W. Biostatistics: A Foundation for analysis in the health sciences, 7th ed. Wiley. New York 1999; 141-142.

55. Saad R, Hallit S, Chahine B. Evaluation of renal drug dosing adjustment in chronic kidney disease patients at two university hospitals in Lebanon. Pharmacy practice 2019; 17(1): 1304.

56. Saleem A, Masood I. Pattern and predictors of medication dosing errors in chronic kidney disease patients in Pakistan: a single center retrospective analysis. PLoS One 2016; 11(7): e0158677.

57. Yang P, Chen N, Wang RR, Li L, Jiang SP. Inappropriateness of medication prescriptions in chronic kidney disease patients without dialysis in a Chinese tertiary teaching hospital. Ther Clin Risk Manag 2016; 1517-1524.

58. Getachew H, Tadesse Y, Shibeshi W. Drug dosage adjustment in hospitalized patients with renal impairment at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. BMC Nephrol 2015; 16(1): 1-9.

59. Anees M, Ibrahim M, Nazir M. Comparison of awareness about nephrology and kidney diseases amongst doctors in institutes with and without nephrology departments. Pakistan J Med Sci 2014; 30(4): 891.

60. Yaqub S, Kashif W, Raza M, et al. General practitioners' knowledge and approach to chronic kidney disease in Karachi, Pakistan. Indian J Nephrol 2013; 23(3): 184.

61. Tamizuddin S, Ahmed W. Knowledge, attitude and practices regarding chronic kidney disease and estimated GFR in a tertiary care hospital in Pakistan. JPMA 2010; 60(5): 342-346.

62. Ong KS, Letchumanan V, Law JWF, et al. Microbes from Peat Swamp Forest — The Hidden Reservoir for Secondary Metabolites? Prog Microbes Mol Biol 2020; 3(1).

63. Mangzira Kemung H, Tan LTH, Chan KG, et al. Streptomyces sp. strain MUSC 125 from mangrove soil in Malaysia with anti-MRSA, anti-biofilm and antioxidant activities. Molecules 2020; 25(15): 3545.

64. Pusparajah P, Law JWF, Chan KG, et al. Whole-Genome Sequence of Streptomyces pluripotens strain MUM 16J, a Potential Resource for Glycopeptide Antibiotic and Biocontrol Agent against Biofilm-forming Bacteria. Prog Microbes Mol Biol 2023; 6(1).

65. Zhu JX, Nash DM, McArthur E, et al. Nephrology comanagement and the quality of antibiotic prescribing in primary care for patients with chronic kidney disease: a retrospective cross-sectional study. Nephrol Dial Transplant 2019; 34(4): 642-649.

66. Hayat M, Ahmad N, Khan SLA, et al. Pattern, frequency and factors associated with inappropriate high dosing in chronic kidney disease patients at a tertiary care hospital in Pakistan. BMC Nephrol 2023; 24(1): 118.

67. Jarab F, Jarab AS, Mukattash TL, et al. Antibiotic dosing adjustments in patients with declined kidney function at a tertiary hospital in Jordan. Int J Clin Pract 2020; 74(10): e13579.

68. Silva MA, Dias G, Cardoso T. Correlation of estimated creatinine clearance and glomerular filtration rate in very elderly patients and antibiotic prescribing errors: Cohort study. Acta Méd Portuguesa 2021; 34(5): 335-341.

69. Zeenny R, Nasr Z, Adaimy I. Retrospective evaluation of the appropriate use of piperacillin/tazobactam in a tertiary care teaching hospital in Lebanon. Acta Med Mediterranea 2014; 30(3): 655-663.

70. Alsaleh NA, Al-Omar HA, Mayet AY, et al. Evaluating the appropriateness of carbapenem and piperacillin-tazobactam prescribing in a tertiary care hospital in Saudi Arabia. Saudi Pharm J 2020; 28(11): 1492-1498.

71. Arcoraci V, Barbieri MA, Rottura M, et al. Kidney disease management in the hospital setting: a focus on inappropriate drug prescriptions in older patients. Front Pharmacol 2021; 2763.

72. Azhar A, Hussain K, Majid A. Drug management in patients with reduced kidney function. Prescriber 2019; 30(2): 18-22.

73. Jiang SP, Zhu ZY, Ma KF, et al. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. Scand J Infect Dis 2013; 45(12): 891-899.

74. Mechta Nielsen T, Frøjk Juhl M, Feldt-Rasmussen B, Thomsen T. Adherence to medication in patients with chronic kidney disease: a systematic review of qualitative research. Clin Kidney J 2018; 11(4): 513-527.

75. Rasool MF, Rehman AU, Imran I, et al. Risk factors associated with medication errors among patients suffering from chronic disorders. Front Public Health 2020; 8: 531038.

76. Won H-J, Chung G, Lee KJ, et al. Evaluation of medication dosing errors in elderly patients with renal impairment. Int J Clin Pharmacol Ther 2018; 56(8): 358.

77. Sheikh AM, Rwegerera GM, Godman B, Habte D. Adjustments of medication dosages in patients with renal impairment in Botswana; findings and implications to improve patient care. Hospital Practice 2019; 47(5): 231-240.

78. Mnukwa L, Schellack N, Matlala M. Medicine prescribing practices in renally-impaired patients admitted to the internal medicine wards at Dr George Mukhari academic hospital, Ga-Rankuwa, South Africa. Afr J Phys Act Health Sci 2017; 2017(suppl1_1): 54-63.

79. Alahdal AM, Elberry AA. Evaluation of applying drug dose adjustment by physicians in patients with renal impairment. Saudi Pharm J 2012; 20(3): 217-220.

80. Falconnier AD, Haefeli WE, Schoenenberger RA, et al. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. J Gen Intern Med 2001; 16: 369-375.

81. Fahimi F, Emami S, Farokhi FR. The rate of antibiotic dosage adjustment in renal dysfunction. Iranian J Pharm Res 2012; 11(1): 157.

82. Sommer J, Seeling A, Rupprecht H. Adverse drug events in patients with chronic kidney disease associated with multiple drug interactions and polypharmacy. Drugs & Aging 2020; 37: 359-372.

83. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY. Analgesic use and the risk for progression of chronic kidney disease. Pharmacoepidemiology and Drug Safety 2010; 19(7): 745-751.

84. Solak Y, Biyik Z, Gaipov A, Kayrak M, Ciray H, Cizmecioglu A, Tonbul HZ, Turk S. Drug dose adjustment in dialysis patients admitted in clinics other than internal medicine. American Journal of Therapeutics 2016; 23(1): e68-e73.