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(RESEARCH ARTICLE)

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Analysis of prescription pattern and evaluation of possible drug related problems in acute kidney injury patients

Sreelakshmi Mohan *, Josmi Jose, Shibendra Mandal and Neharika Lamsal

Department of Pharmacy Practice, Bapuji Pharmacy College, Rajiv Gandhi University of Health Sciences,Davangere, Karnataka, India.

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Abstract

Introduction: Drug-induced acute kidney injury (AKI) is a significant cause of morbidity and mortality, accounting for 8% to 60% of in-hospital AKI cases. Impaired renal function leads to the accumulation of drugs and their metabolites in the body, increasing the nephrotoxic burden and the risk of AKI.

Objective: The study aims to assess the necessity of appropriate dosage adjustment in patients with acute kidney injury (AKI) and the utilization of previously nephrotoxic drugs.

Method: A prospective observational study was conducted among Acute Kidney Injury patients for a period of about 6 months. The collected data were analyzed using SPSS v.20. Pearson's chi-square tests, correlation, and linear regression analysis were employed to examine the collected data.

Results: A study of 207 patients revealed that 97% were prescribed antibiotics, with penicillin being the most common (46.9%). Cephalosporin and piperacillin/tazobactam were prescribed to 38.80% and 37.81% of patients, respectively. Concerningly, only 24% of prescriptions for acute kidney injury (AKI) patients were appropriate, while 86.9% and 58.4% exhibited overdosing and contraindications. More than half of the AKI patients (114 out of the total) had previously used nephrotoxic medications, potentially contributing to their kidney injury. Improved dosage adjustment practices in AKI treatment and monitoring of nephrotoxic drug use are crucial to prevent renal complications.

Conclusion: The study's findings emphasize AKI development, drug patterns, antibiotics and nephrotoxic drugs highlighting the importance of awareness and effective management of AKI.

Keywords: Drug-induced acute kidney injury; NSAIDS; Contraindication; Nephrotoxic burden; Antibiotics; Nephrotoxicity; Medication dosing errors; Dosage adjustment.

1. Introduction

Drug induced acute kidney injury (AKI) has been involved in 8 % to 60% of all In-hospital AKI episodes, making it a widely acknowledged cause of significant morbidity and mortality [1]. Impaired renal function leads to the progressive accumulation of parent drugs and their metabolites in the body [2]. Increasing nephrotoxic burden is an independent but modifiable risk factor of AKI and one can easily speculate a negative link between them [3]. Potential nephrotoxic drugs widely used in the current scenario are ACE inhibitors, ARBs, NSAIDs, Iodinated contrast media, Cisplatin, Methotrexate, Ciclosporin, Tacrolimus, Vancomycin, Amikacin, Gentamycin, Rifampicin, Sulfadiazine, Cotrimoxazole, Acyclovir, Adefovir, Amphotericin, Voriconazole etc. [4]

* Corresponding author: Sreelakshmi Mohan

Antibiotics are one of the most extensively used drugs, and approximately half of hospitalized patients receive antibiotic therapy [1]. The incidence of antibiotics elicited nephrotoxicity alone could be as high as 36%. In the light of the recent studies, the antibiotics commonly inflicting AKI in monotherapy aswell as combination therapy are Ceftriaxone, Cefazolin, Gentamicin, Vancomycin, Amikacin Cloxacillin, Imipenem, Ceftazidime, Amphotericin-B [1]. Piperacillin Tazobactam has been independently associated with increased risk of AKI with an overall incidence of 8.6% in adults and 18.4% in elderly population [5].

NSAIDS exert their nephrotoxic action through hemodynamically mediated dose dependent mechanism. Advancing age, comorbidities, concomitant usage of multiple drugs, long term use areprecipitating factors of NSAIDS induced AKI.[4].

Medication dosing errors are foremost critical drug related issues in patients with renal impairment begetting toxicity and ineffective therapy. Since Drug elimination by kidneys corresponds with the glomerular filtration rate (eGFR) it is subsequently sensible to utilize eGFR or Creatinine clearance for dosage adjustment [2]. In order to avoid overdosing, iatrogenic risk of renal impairment and its exacerbation,dosage adjustment in accordance with renal function is indicated.[6]

2. Material and methods

A prospective observational study was conducted at SSIMS&RC, a tertiary care teaching hospital in Davangere, from March 2022 to August 2022. The study enrolled a total of 207 participants from the ICU, Emergency, and General ward over a six-month period. The study included individuals aged 18 years or older who underwent serum creatinine testing while hospitalized for a duration exceeding 24 hours.

Patients who were under 18 years of age, had a history of chronic kidney disease (CKD), were receiving renal replacement therapy, were pregnant, or had genetic kidney disease were excluded from the study. Informed consent was obtained from all eligible participants using a predesigned consent form.

The collected data were analyzed using appropriate statistical methods. Continuous data were assessed for normality, and if normally distributed, they were presented as Mean ± Standard deviation. Categorical variables were analyzed using the Pearson Chi-square test to determine correlations with patients' past medical and medication history, current therapy, and other relevant risk factors. The statistical significance level was set at $p < 0.05$ in this study.

Linear regression analysis was employed to determine the predictability of various factors. The statistical package for social sciences (SPSS) software version 2.0 was utilized to pool and evaluate all the extracted data.

The observed findings were compiled and presented in either graphical or tabular form, depending on the nature of the data. The study aimed to provide valuable insights into the relationship between serum creatinine levels and the factors under investigation, contributing to a better understanding of kidney function and associated risk factors.

3. Results

The study was designed and conducted to evaluate the need of appropriate dosage adjustment in AKI patients. The study was conducted for a period of six months. A total of 207 AKI patients from emergency, ICU, General ward were included as study participants.

Table 1: Distribution of Drugs Prescribed in AKI Patients

Drugs	Frequency	Percentage
Antibiotics	201	97.1%
Anti-Hypertensive	136	65.7%
Anti-diabetics	106	51.2%
Anti-lipidemic	16	7.7%
Anti-fungal	42	20.3%
Bronchodilator	19	9.2%

Anti-pyretic	136	65.7%
Anti-inflammatory	59	28.5%
Anti-diarrheal	4	1.9%
Anti-emetics	78	37.7%
Laxative	14	6.8%
Proton pump inhibitors	192	92.8%
H2 receptor agonist	16	7.7%
Anti- platelet drugs	38	18.4%
Anti-anxiety	42	20.3%
Diuretics	66	31.9%
Anti-convulsant	35	16.9%

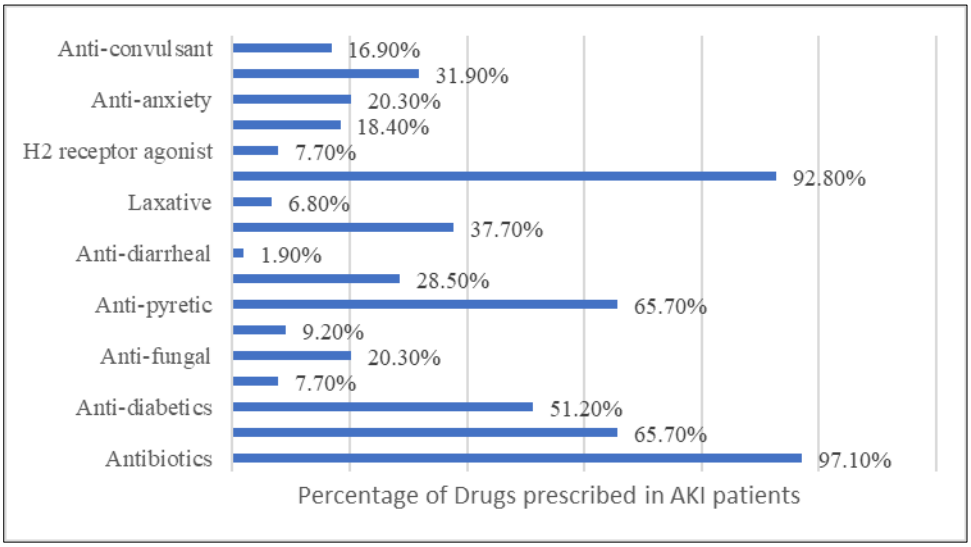

Figure 1 Distribution of Drugs Prescribed in AKI Patients

In the study, the most commonly prescribed drug was antibiotics, which were prescribed to 97.1% of the patients. Proton pump inhibitors followed closely at 92.8%. Anti-hypertensive and anti-pyretic medications were prescribed to 65.7% of AKI patients. Approximately 51.2% of the patients were on anti-diabetic medications. Anti-emetics were administered to 37.7% of the patients, while 31.9% received diuretics. Anti-inflammatory drugs were prescribed to 28.5% of the patients, followed by anti-anxiety drugs at 20.3% and anti-platelet drugs at 18.4%. Anti-fungal medications were given to 20.3% of the patients, and anti-convulsants to 16.9%. The least prescribed medications were bronchodilators at 9.2%, H2RB at 7.7%, anti-lipidemic agents at 7.7%, laxatives at 6.8%, and anti-diarrheal medications at 1.9%.

The study revealed a high prevalence of antibiotic and proton pump inhibitor prescriptions, indicating the significant usage of these medications in the study population. Additionally, a variety of other drug classes, such as anti-hypertensives, anti-diabetics, and anti-inflammatory drugs, were commonly prescribed, highlighting the complex medication profiles of the patients.

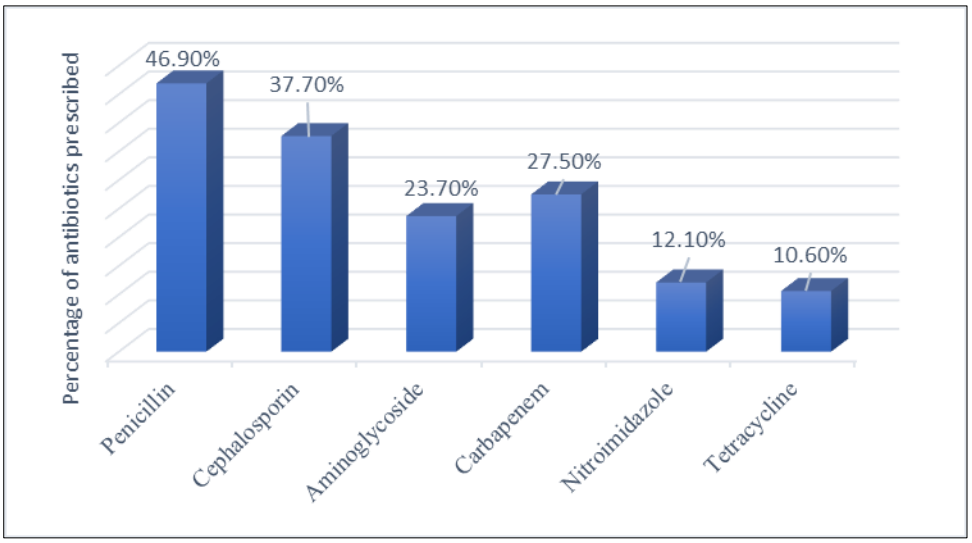

Figure 2 Distribution of Antibiotics use in AKI patients

In the study, penicillin was prescribed to 46.9% of the patients, followed by cephalosporin at 37.7%, carbapenem at 27.5%, and aminoglycoside at 23.7%. Nitroimidazole and tetracycline were prescribed to 12.1% and 10.6% of the patients, respectively, reflecting the diverse range of antibiotic prescriptions in the study population.

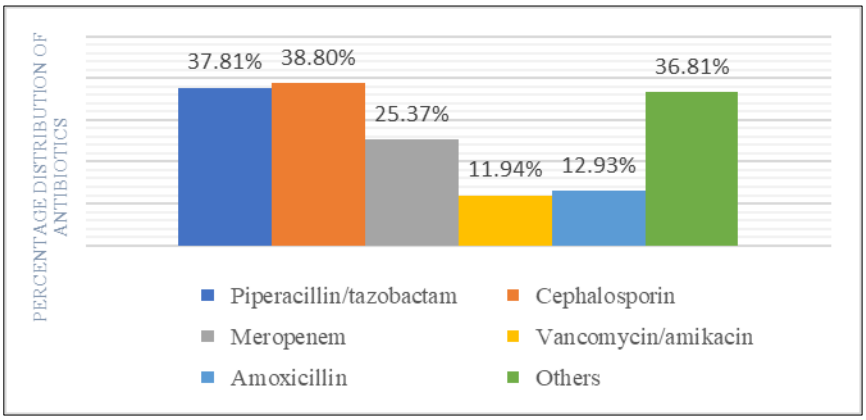

Figure 3 Distribution of drug-specific antibiotics used in AKI patients

Among the 207 participants, 38.80% of patients were prescribed cephalosporin, followed by 37.81% who received piperacillin/tazobactam. Additionally, 36.81% of patients were prescribed other drugs such as azithromycin, doxycycline, clindamycin, metronidazole, antivirals, and sulfadiones. The least prescribed antibiotics, vancomycin or amikacin, were given to 11.94% of the patients.

3.1. Dosage adjustment in AKI patients

Table 2 Distribution of Dosage adjustment in AKI patients

Parameter		Frequency	Percentage
Appropriateness		50	24.1%
Inappropriateness	Underdose	12	5.7%
	Overdose	180	86.9%
	Contraindicated	121	58.4%

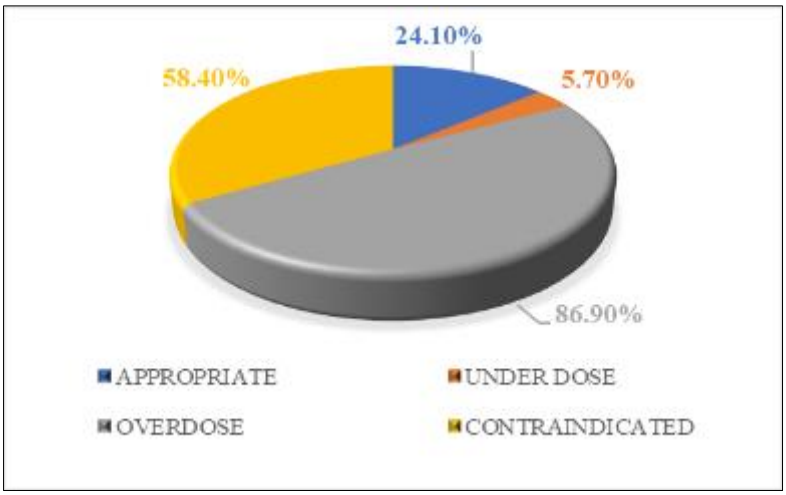

Figure 4 Distribution of Dosage adjustment in AKI patients

The study revealed that 24.1% of prescriptions were deemed appropriate, while 86.9% and 58.4% of prescriptions exhibited overdosing and contraindications, respectively. Additionally, 5.7% of the prescriptions were found to be underdosed, highlighting the need for improved adherence to proper dosage guidelines and contraindication considerations.

Table 3 Distribution of number of Drugs requiring dosage adjustments

No: of drugs requiring dosage Adjustment in AKI	frequency	percentage
1-2	60	29 %
3-4	127	61.4%
5-6	20	9.7%

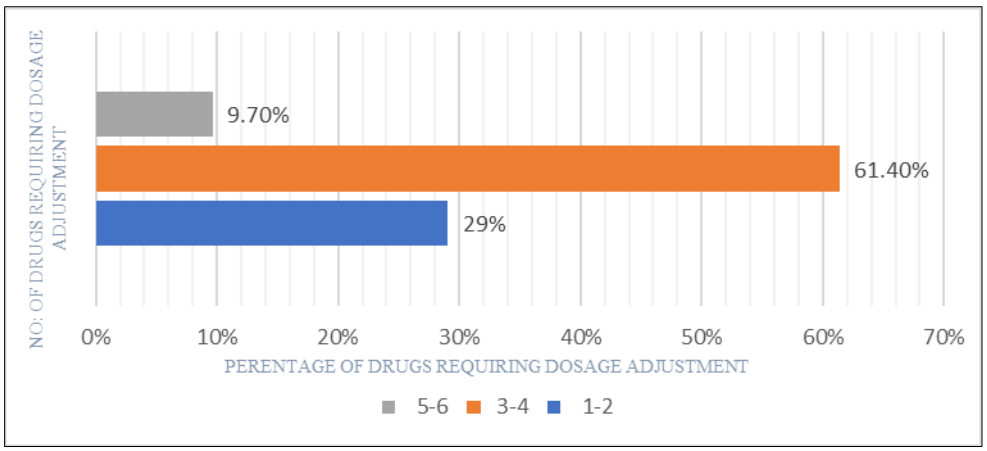

Figure 5 Distribution of number of Drugs requiring dosage adjustments

Among the 207 patients included in the study, a substantial majority of 127 individuals (61.4%) were prescribed at least 3-4 drugs that warranted dosage adjustment. Additionally, 60 patients (29%) necessitated dosage adjustment for 1-2 drugs. It was observed that a smaller subset of 20 patients (9.7%) required dosage adjustment for 5-6 drugs, indicating a distinct subgroup with a higher number of medications requiring modifications.

Table 4 Distribution of drug-related parameters affecting different stages of AKI

Parameter		Stages of AKI					Total	p- value
		RISK	INJURY	FAILURE	LOSS	ESRD		
		frequency						
No: of drugs requiring dosage adjustment	1 drug	4	13	18	0	0	35	0.001*
	2 drugs	6	6	8	5	0	25	
	3 Drugs	5	17	30	26	1	79	
	4 drugs	6	15	19	7	1	48	
	5 drugs	4	4	4	3	2	17	
	6 drugs	0	0	0	3	0	3	
Underdose		4	1	5	0	1	11	0.026*
Overdose		21	43	60	43	4	171	0.027*
Contra-indicated		11	31	42	33	4	121	0.00**

*statistically significant (p-value ≤0.05); ** statistically very significant (p-value ≤0.01)

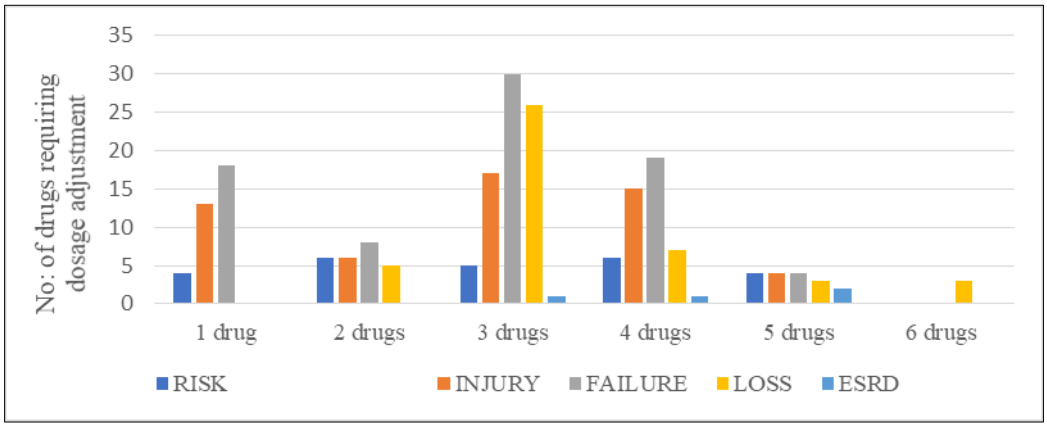

Figure 6 No: of drugs requiring dosage adjustment in different stages of AKI

Among the patients, 21% in the INJURY stage, 38% in the FAILURE stage, and 33% in the LOSS stage required dosage modification. Inappropriately dosed at least 2-3 medicines were commonly observed across patients. In the FAILURE stage, 51% of patients had at least 1 drug requiring dosage adjustment. For patients in the RISK stage, 24% required adjustment for a minimum of 2 drugs, while 20% of patients in the LOSS stage needed dosage adjustment. The number of medications requiring dosage adjustments significantly influenced AKI progression, as evidenced by a p-value of 0.001**.**

The predominant drug-related concern among AKI patients was the use of contraindicated medications, which was followed by instances of overdosing and underdosing, particularly prominent in the INJURY, FAILURE, and LOSS stages. In the FAILURE stage, 35% of patients experienced drug overdosing, while 35% were prescribed contraindicated medications. Overdosing was reported in 25% of patients in the LOSS stage, closely followed by 25% in the INJURY stage. Contraindication was observed in 27% of patients in the LOSS stage and 26% in the INJURY stage. Overdosing, contraindicated medications, and underdosing played a significant role in influencing renal function in AKI patients, as indicated by respective p-values of 0.027, 0.00, and 0.026.

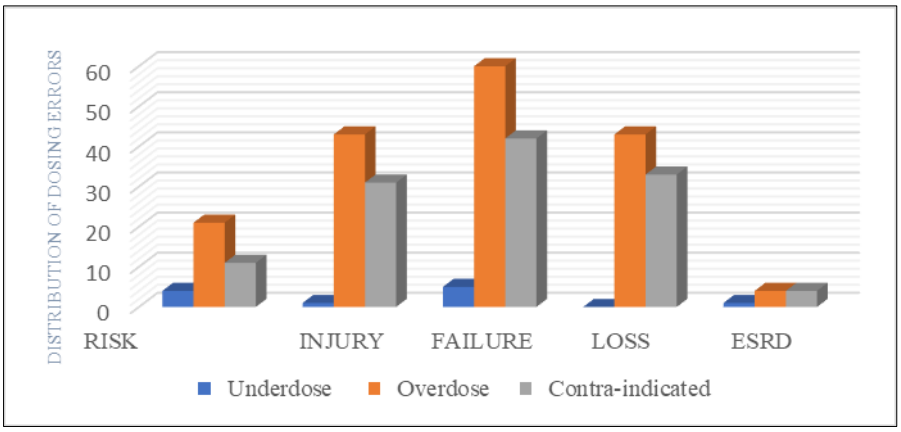

Figure 7 Distribution of under dosing, overdosing and contraindication in studyparticipants as per RIFLE

Table 5 Distribution of Risk factors associated with dosage adjustment

Age	**Dosage adjustment**			**Total**	**P value**
	1-2 Drugs	**3-4 Drugs**	**5-6 Drugs**		
	Frequency				
Age < 50	15	40	0	55	0.012*
50 & above	45	87	20	152	
Total	60	127	20	207	
BMI					
Normal	45	52	9	106	0.00**
Overweight	15	67	11	93	
Obese	0	8	0	8	
Total	60	127	20	207	
DURATION OF HOSPITAL STAY					
1-7	1	3	1	5	0.000**
8-15	51	55	3	109	
>15 day	8	69	16	93	
Total	60	127	20	207	
NUMBER OF CO-MORBIDITIES					
00	9	15	0	24	0.00**
1.00	16	23	0	39	
2.00	25	27	9	61	
3.00	8	45	5	58	
4.00	2	17	4	23	
5.00	0	0	2	2	
Total	60	127	20	207	
WARD					

ICU	4	64	10	78	0.00**
Emergency	33	60	7	100	
General medicine	23	3	3	29	
DAY OF SERUM CREATININE ELEVATION					
1-5 days	44	27	10	81	0.00**
6-10 days	15	79	15	109	
10-15 days	1	21	4	26	
STAGE OF KIDNEY DISEASE					
RISK	10	11	4	25	0.001**
INJURY	16	32	4	52	
FAILURE	26	49	4	79	
LOSS	5	33	6	44	
ESRD	0	2	2	4	

*statistically significant (p-value ≤0.05); ** statistically very significant (p-value ≤0.01)

Multiple parameters indicate the necessity for dosage adjustment in renal impairment patients, including age, BMI, hospital stay duration, co-morbidities, ward, day of serum creatinine rise, and, notably, the stage of kidney disease. Among patients aged 50 and above, 57% required dosage adjustments for 3-4 medicines (p-value 0.012). In patients with normal BMI, 49% required adjustment for 3-4 drugs, while 42% needed 1-2 drugs changed. However, 67 overweight patients needed adjustment for 3-4 drugs (p-value 0.00). Among ICU and emergency patients, 82% and 60% respectively required adjustment for 3-4 drugs (p-value 0.00). Patients with creatinine elevation within 6-10 days needed adjustment for 3-4 drugs (p-value 0.00). Majority of patients requiring changes were in FAILURE stage, followed by INJURY & LOSS. AKI stage had the most significant influence on dosage recommendation (p-value 0.00).

3.2. Distribution of past nephrotoxic drug use in AKI patients

Table 6 Distribution of past nephrotoxic drug use

Parameter		Frequency	Percentage
NEPHROTOXIC DRUG USE	YES	114 patients	55%
	NO	93 patients	45%

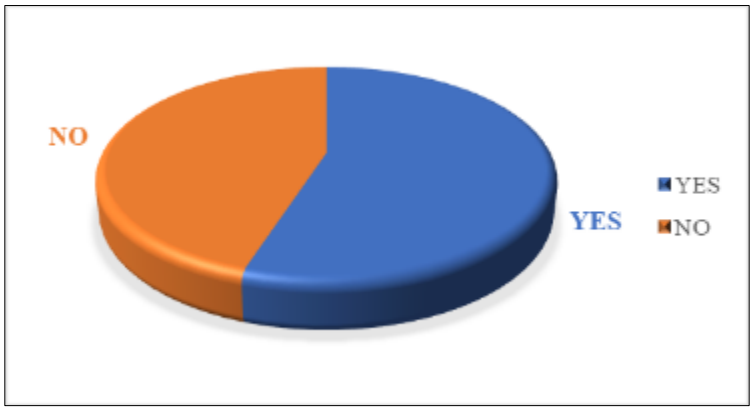

Figure 8 Distribution of past nephrotoxic drug use

Amongst 207 patients with AKI, 114 patients, had formerly used nephrotoxic medications, while 93 patients did not. More than half of the AKI patients in the research had a history of nephrotoxic medication usage.

Table 7 Drug-specific distribution of past nephrotoxic medication

Drugs	Frequency	Percentage
NSAIDS	65	31.4%
Analgesic/Antipyretic	11	5.31%
Antihypertensive	17	8.21%
Hypoglycemic agent	23	11.11%
Neurologic drugs	15	7.2%
Hypolipidemic agents	10	4.83%
Others	3	1.5%

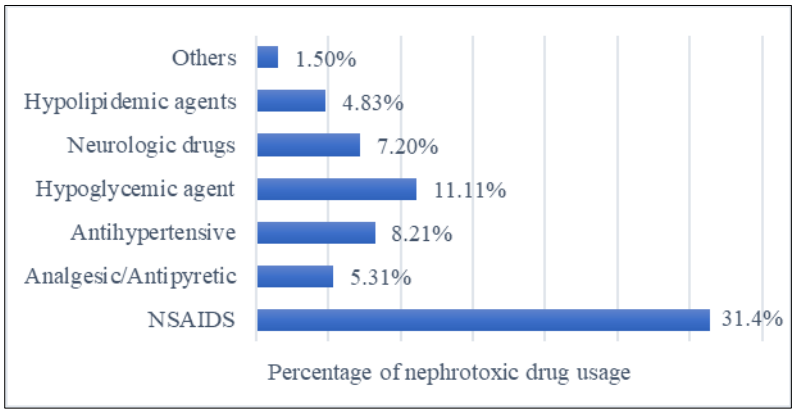

Figure 9 Drug-specific distribution of past nephrotoxic medication

Out of the 144 patients with a prior history of nephrotoxic medication use, the highest proportion of patients (31.45%) had been prescribed NSAIDs, followed by hypoglycemic medicines (11.1%). In comparison, a smaller percentage of patients were taking hypolipidemic medications (4.83%) and other drugs like vancomycin (1.5%).

4. Discussion

Acute kidney injury (AKI) is a prevalent clinical syndrome affecting approximately one-quarter of hospitalized patients worldwide, resulting in substantial healthcare costs. The study was conducted at SSIMS&RC over a 6-month period from January 2022 to June 2022, monitoring 207 AKI patients aged 18 and above across ICU, emergency, and general wards.

The misuse of NSAIDs was significantly associated with AKI stages of risk, injury, failure, and loss (p-value 0.00). Patients who overuse NSAIDs have a higher likelihood of experiencing AKI at any stage, emphasizing the importance of this risk factor. This finding aligns with the study conducted by Hossein Khalili and Samaneh Bairami [1], where 17% of AKI patients were using NSAIDs (p-value <0.001).

Drug-induced nephrotoxicity is a prevalent problem that can burden patients, leading to various interventions, including hospitalization. Antibiotics were the most commonly prescribed medications, accounting for 97.1%, followed by proton pump inhibitors (92.8%). Over half of the patients were taking anti-diabetic, anti-hypertensive, and antipyretic drugs. The least prescribed medications included H2RB, laxatives, anti-diarrheal drugs, bronchodilators, and anti-lipidemic medications. Regarding the antibiotic class used among AKI patients, penicillin was prescribed for 46.9% of them, followed by cephalosporins. Within the penicillin class, piperacillin-tazobactam was administered to 37.81% of patients. Carbapenem was given to 27.5% of AKI patients, while aminoglycosides were administered to 23.7%. Nitroimidazole and tetracyclines were prescribed to a smaller number of patients. Penicillins, cephalosporins, nitroimidazole, and aminoglycosides were identified as potential risk factors negatively affecting renal function, with statistically significant p-values of 0.001, 0.002, 0.009, and 0.013, respectively. Our findings differ from the study

conducted by Hossein Khalili and Samaneh Bairami[1], where ceftriaxone (43%) was the most widely prescribed and identified nephrotoxic medication, followed by aminoglycosides (40%).

When investigating the participants' medication histories, 55% had a prior history of using nephrotoxic drugs, while 45% had no such record. A significant proportion of them had used NSAIDs. These findings align with the research outcomes reported by Hossein Khalili and Samaneh Bairami[1], where 30% of AKI patients had a history of using other nephrotoxic drugs like NSAIDs, consistent with the data obtained in our study.

According to the analysis of prescriptions, the most commonly reported drug-related problem among patients with renal insufficiency is overdose (86.9%), followed by the use of contraindicated medications (58.4%). The p-values for underdosing, overdosing, and the use of contraindicated medications were reported as 0.013, 0.026, and 0.027, respectively, indicating their significant association with kidney injury.

Among the patients prescribed with overdoses and contraindicated drugs, the majority were in the FAILURE stage, followed by INJURY and LOSS stages. Notably, 61.4% of the analyzed prescriptions required dosage adjustments for at least three or four medications. The number of medications requiring dosage modification was found to be a significant factor contributing to renal damage, with a p-value of 0.001. The study participants had an average of 2.98±1.22 drugs that required dosage adjustment. These findings align with the results obtained in the study conducted by Henok Getachew and Yewondwossen Tadesse[7], which reported 20% of prescriptions with drug overdoses and 14% with contraindicated medications. However, data on the impact of medication errors with specific stages of AKI is limited.

5. Conclusion

AKI, a potentially life-threatening yet often underdiagnosed kidney disease, receives significant focus in the present study, shedding light on its development and providing insights into the prescribing patterns of drugs for hospitalized patients. The study highlights the influence of co-morbid conditions such as cardiovascular disorders, infections, surgery, type 2 diabetes mellitus (T2DM) and its complications, as well as the misuse of NSAIDs on the progression of AKI stages. Antibiotics were found to be the most frequently prescribed medications for AKI patients, closely followed by proton pump inhibitors (PPIs), with piperacillin+tazobactam being the most commonly prescribed antibiotic. Importantly, more than half of the participants had a history of nephrotoxic drug use. The analysis of prescriptions reveals that drug overdose is the primary drug-related concern among patients with renal insufficiency, followed by the utilization of contraindicated medications. It is crucial to enhance awareness about AKI and provide caregivers and patients with the necessary knowledge and tools to identify and manage individuals at risk.

Compliance with ethical standards

Acknowledgment

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was approved by BAPUJI PHARMACY COLLEGE Institutional Ethics Committee on human subjects research Ref no: BPC/IEC/78/2021-22 dated 21/02/2022.Subject Confidentiality was maintained during and after data collection.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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