

Drug dose adjustment in patients with renal impairment attending a specialized referral hospital, Northwest Ethiopia

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ABSTRACT

Background: Numerous drugs and their metabolites are removed from the body through the kidney. Improper use of drugs in renal impaired patients may therefore, be harmful and have deleterious effects. Thus, this study was aimed at investigating drug dose adjustment in renal impaired patients attending a specialized hospital.

Methods: A prospective cross-sectional study was performed at the medical ward in University of Gondar comprehensive specialized hospital from March to May 2018. During the study period, a total of 2100 patients were admitted to the general medical wards. We located and assessed 210 patient files, of which 189 patient files had complete notes. Based on our inclusion criteria, 105 patients had CrCl of ≥ 59 ml per min per 1.73 m². Therefore, 84 patients fulfilled our inclusion criteria and were included in the final analysis. The collected data were entered into Epi Info version 7 and exported to the statistical package for the social sciences (SPSS) version 20 for statistical analysis. A chi-square test was applied to test the relationship between renal status and dosage adjustment. P-value ≤ 0.05 was considered as statistical significance. Since the number of co-morbidities and number of drugs prescribed was non-normally distributed using the Shapiro-Wilk test ($P < 0.001$), the spearman correlation test was used ($r = 0.228$, $p = 0.037$).

Results: The mean age of study participants was 57 years with 57.1% male and 42.9% female. The highest number of renal impaired patients was in stage three 56(66.7%). The mean creatinine clearance (CrCl) was 41.8 ml/min (IQR 24.8–60.9), and the mean serum creatinine (Scr) value of 2.63 mg/dl (IQR 1.3–3.1). More than two third (76.2%) of the study participants had comorbidities. Eighty-four patients with 257 prescription entries were included in the study. Of which 75 prescription entries need a drug dose adjustment. The overall rate of inappropriate dose adjustment was 42.6% (32/75). Inappropriate dose adjustment was more common with vancomycin (14.3%) and ciprofloxacin (6%). Inappropriate drug dose adjustments were associated with patients having intermediate renal insufficiency ($P < 0.002$) and co-morbid conditions ($P < 0.02$).

Conclusion: The present study demonstrated that inappropriate dose adjustment was common at University of Gondar comprehensive specialized hospital that needs great attention. Vancomycin and ciprofloxacin were the most frequently identified drugs that were inappropriately adjusted. Intermediate renal insufficiency and co-morbidities were statically significant with inappropriate dose adjustment.

1. Background

Kidney disease is increasingly becoming a significant health issue in the world. The incidence and prevalence of kidney failure are rising. For example, according to the world health organization report, the global burden of disease 2015 study estimated that 1.2 million disability-adjusted life –years and 18 million years of life lost from

cardiovascular diseases were directly attributable to patients with renal impairment [1]. Due to the number of elderly people is become increasing in developing countries like China and India, the number of renal impairment cases will also increase disproportionately [2]. The renal impairment case also increases in African countries like Tanzania 15.2% [3] and (9%) in Ethiopia [4].

Many drugs and their metabolites are removed from the body

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through the kidney. Improper use of drugs in renal impaired patients may, therefore, be harmful and have deleterious effects [5]. In addition to this, inappropriate dosing of such drugs can cause adverse drug events (ADEs) ranging from minor discomfort to serious injuries. For example, Imipenem and Cilastatin may extremely accumulate in renal impaired patients that lead to seizures if doses are not reduced based on the patient renal function status [6].

Adverse drug reactions due to renal impairment are responsible for hospital admissions. For example, Hellden A, found that about 4.62% of hospital admissions were related to impaired renal function [7]. Failure to adjust the dosing of renal excreted drugs may result in adverse effects, which include nephrotoxicity. The incidence of acute kidney injury-induced drug nephrotoxicity in a hospital setting is estimated that 19% [8]. Drug-induced nephrotoxicity and adverse effects of the drug can be decreased by adjusting the dosing of renally excreted drugs according to the patient's creatinine clearance (CrCl), but this is less emphasis is given and ignored by prescribers. For example, previous studies had found that 29–74% of drug prescriptions were inappropriately adjusted or adjustments were not made [9–13]. To minimize morbidity and mortality caused by excessive dosing, to save the cost, and to prevent drug-related toxicity, dose adjustment to renal impaired patients is very vital, and epidemiological studies that investigate drug dose adjustment in renal impaired patients may contribute to identifying the gap.

We found only one single study which evaluates drug dosage adjustment in hospitalized patients with renal impairment in Ethiopia. This is probably an underestimation of dose adjustment in clinical settings.

To the best of our knowledge drug dose adjustment associated with renal impaired patients has not been well studied in Ethiopia. Similarly, due to a lack of local study, the extent of inappropriate drug dose adjustments has not yet been identified in this hospital. Therefore, we conducted this study to determine what proportion of drugs prescribed to patients with renal impairment required dose adjustment; to identify the type of drugs that mostly require a dose adjustment, and to determine whether drug doses were appropriately adjusted in these patients.

2. Methods

2.1. Study setting

The study was conducted at University of Gondar comprehensive specialized hospital, which is found in Gondar town, Amhara region, Ethiopia. UOG is one of the oldest teaching hospitals in the country and it serves around five million surrounding people. University of Gondar comprehensive specialized hospital is a 400 bed and there are 783 health care workers within it. The hospital has different departments and clinics in it: internal medicine, pediatrics, gynecology/obstetrics, surgery, dentistry clinic, psychiatry clinic, HIV clinic, and dermatology.

2.2. Study design and period

This was a prospective cross-sectional study and it was performed at the medical ward in University of Gondar comprehensive specialized hospital on adult patients who were admitted to the hospital from March to May 2018.

2.3. Inclusion and exclusion criteria

All patients, whose ages were above 18 years old, were diagnosed with renal impairment within the study period, and patients had been prescribed at least one medication indicated for his/her diagnosis. Patients with renal impairment, defined as a CrCl < 59 ml per minute per 1.73 m² were included in the study. Whereas, patients whose charts and notes for which background information was incomplete and patients whose charts has no drug orders, pregnant women, and patients with a

CrCl ≥ 59 ml per minute per 1.73 m² were excluded from the study.

2.4. Data collection procedure

Data was taken from patient medical charts and medical records. A standard data recording format was used, it was prepared by reviewing different literature for important variables to drug dose adjustment in renal impaired patients and it was tested in the same setting prior to the main data collection and the necessary adjustment was done. The following data were recorded for each Patient: sex, age, weight of the patient, principal diagnosis, SCr level and concomitant disease states. For each medication chart, the data collected included generic and/or trade names of medications, the number of drugs prescribed for each patient, dosage regimen including (dose, dosing frequency, and duration of therapy), and start date and stop date of the medications. Data of the SCr was extracted from the patient's laboratory record data. Based on this, for patients who had more than three Scr values, we used as a reference for the estimation of renal status was the one closest in time before starting the renally eliminated drug(s).

The K/DOQI clinical practice guideline advocates using the traditional Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) study equation for routine estimation of GFR [14]. Therefore, we used the Cockcroft–Gault equation to calculate CrCl and glomerular filtration from the patient's SCr [15]. As a result, male and female study participants had their CrCl based on the following equation.

$$\text{Male: CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{weight(Kg)}}{\text{Scr} \left(\frac{\text{mg}}{\text{dl}}\right) \times 72}$$

$$\text{Female: CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{weight(Kg)} \times 0.85}{\text{Scr} \left(\frac{\text{mg}}{\text{dl}}\right) \times 72}$$

By using the definition of the national kidney foundation, study participants were divided into five groups according to their renal impairment. stage 1 (normal kidney function, GFR ≥ 90 ml/min/1.73 m²; stage 2 (mild reduction of GFR, 60–89 ml/min/1.73 m²); stage 3 (moderate reduction of GFR, 30–59 ml/min/1.73 m²); stage 4 (severe reduction of GFR, 15–29 ml/min/1.73 m²); stage 5 (kidney failure, GFR, ≤ 15 ml/min/1.73 m²). Stage 1 and stage 2 patients were assumed to have adequate kidney function in relation to drug therapy. Therefore, stage 1 and 2 did not include in the study. However, patients with stage 3, stage 4, and stage 5 had impaired renal function that needs special care with regard to drug therapy and were included in the study [14].

In order to determine whether drug doses were appropriately adjusted or not, we compared the collected data with the guideline “Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children” [16].

To assure the quality of data, the data abstraction format was pre-tested prior to the main data collection on a sample equivalent to 5(5%) of the total sample size in randomly selected patient medical charts, which were not included in the study and appropriate adjustment was done on the data abstraction format. In addition to this, the principal investigator supervised the data collectors during data collection. The collected data were checked for completeness and consistency on daily basis.

2.5. Data analysis and interpretation

The collected data were entered into Epi Info version 7 and exported to the statistical package for the social sciences (SPSS) version 20 for statistical analysis. In order to summarize the result, descriptive statistics including frequency, mean and standard deviation were used. The prevalence of patients with renal impairment was calculated by dividing the number of patients with renal impairment by the total number of medical admissions in the ward. While the prevalence of inappropriate

drug dose adjustment was calculated by dividing the total number of inappropriate prescription entries by the total number of prescriptions that needs dose adjustment. A Chi-square test was applied to test the relationship between renal status and dosage adjustment. P-value ≤ 0.05 was considered as statistical significance. Since number of co morbidities and number of drugs prescribed were non-normally distributed using the Shapiro-Wilk test ($P < 0.001$), spearman correlation test was used ($r = 0.228$, $p = 0.037$).

2.6. Ethical clearance

Letter of ethical clearance was obtained from the ethical review committee of the school of pharmacy, University of Gondar. Privacy and confidentiality were ensured during the review of patients' charts by data collectors. Thus, the name and addresses of patients were not recorded in the data abstraction format.

2.7. Operational definitions

Renal impairment: It is defined as a CrCl of <59 ml per minute per 1.73 m²

Appropriate drug dose adjustment: when the prescribed drug dose is in line with the patient's CrCl as recommended by the guideline "Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children" [16].

Inappropriate drug dose adjustment: when the prescribed drug dose has deviated from the patient's CrCl as recommended by the guideline "Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children" [16].

3. Results

During the study period, a total of 2100 patients were admitted to the general medical wards. We located and assessed 210 patient files, of which 189 patient files had complete notes. Based on our inclusion criteria, 105 patients had CrCl of ≥ 59 ml per min per 1.73 m². Therefore, 84 patients fulfilled our inclusion criteria and were included in the final analysis. The total prevalence of patients with renal impairment was 4% (84/2100). The mean age of study participants was 57 years with 57.1% male and 42.9% female. The highest number of renal impaired patients was in stage three 56(66.7%). The mean CrCl was 41.8 ml/min (IQR 24.8–60.9), with a mean Scr value of 2.63 mg/dl (IQR 1.3–3.1). More than two third (76.2%) of the study participants had comorbidity during their hospital visit. It is difficult to differentiate both whether the patient is admitted due to renal or non-renal related and the distinction between CKD and AKI. Regarding dialysis, no one patient has received dialysis during their hospitalization. A total of 257 prescription entries for the 84 patients with renal impairment. Details of socio-demographic and clinical data of the study participants are described in Table 1.

3.1. Socio-demographic and clinical data of patients

3.2. The most frequently prescribed drugs

The average number of drugs prescribed per patient was 3.3 (minimum of 1 and maximum of 7) and the median value is 3. About 39.3% ($n = 33$), are prescribed 4 or more drugs. There were 14 drug types prescribed to CKD patients. The most prescribed drug was Enalapril (36, %) followed by Amlodipine ($n = 32$, %) Table 2.

3.3. Appropriateness of dosing of the medications

In total, 35 different drugs were prescribed, and some were

Table 1

Demographic and clinical data of patients with renal impairment at University of Gondar comprehensive specialized hospital Ethiopia, April 2018.

Demographic and clinical data	Number (%)
Total Number of patients	2100(4%)
Number of Patients with renal impairment	84
Male	48(57.1%)
Female	36(42.9%)
Age (Median)	57 range(18–70)
18–29	11 (13.1%)
30–39	13 (15.5%)
40–49	9(10.7%)
50–59	11(13.1%)
≥ 60	40(40.7%)
Serum creatine ($\frac{mg}{dl}$)	
1.2–2	43(51.2%)
2.1–3	18(21.4%)
≥ 3	22(26.2%)
Estimated GFR (ml/min/1.73m²) (Mean) \pm SD	41.8
Drugs per patient (Mean) \pm SD	3.04
Drugs required dose adjustment per patient (Mean) \pm SD	0.4
Stages of renal impaired patients	
Stage 3	56(66.7%)
Stage 4	19(22.6%)
Stage 5	9 (10.7%)
Presence and Absence of co-morbidities	
Present	64(76.2%)
Absent	20(23.8%)

Table 2

Most frequently prescribed Drugs in renal impairment patients at University of Gondar comprehensive specialized hospital, Ethiopia.

Drug names	Frequency	Percentage
Enalapril	36	14%
Amlodipin	32	12.5%
Lasix	28	11%
Hydrochlorothiazide	18	7%
Acetylsalicylic acid	17	6%
Atrovastatin	14	5%
spiroactone	10	4%
Ciprofloxacin	8	3%

prescribed on multiple occasions. A total of 75/257 (29.1%) prescription entries required dose adjustment. From the total required dose adjustment 32/75(42.6%) prescription entries were found to be inappropriately adjusted Fig. 1.

3.4. Inappropriate drug dose adjustment and stages of renal impairment

The present study data showed that a total of 19/75 (25.3%) prescription entries were inappropriately dose adjusted in patients with stage 3. Of the 19 prescription entries, 8 (11%) were inappropriately adjusted for patients with stage 4. Patients in stage 5 had a total of 9 prescription entries of which 5 (7%) were inappropriately adjusted the details are presented in Fig. 2.

3.5. Inappropriate drug dose adjustment and drugs

Vancomycin was the most frequently prescribed drug that required dose adjustment, which was done inappropriately in 14.3% (12/48) of cases; followed by Ciprofloxacin and Others, both were inappropriately adjusted in 6% (5/13) and 4.8% (4/46) of cases respectively. Metformin also required dose adjustment in 3.6% (3/7) of cases and remained unadjusted in all cases. However, of the most frequently prescribed drugs, Cotrimoxazole, Atrovastatin, glibenclamide, Lasix, Amlodipine, and Aspirin were the only drugs that were correctly dose adjusted in all cases. The details are presented in Table 3.

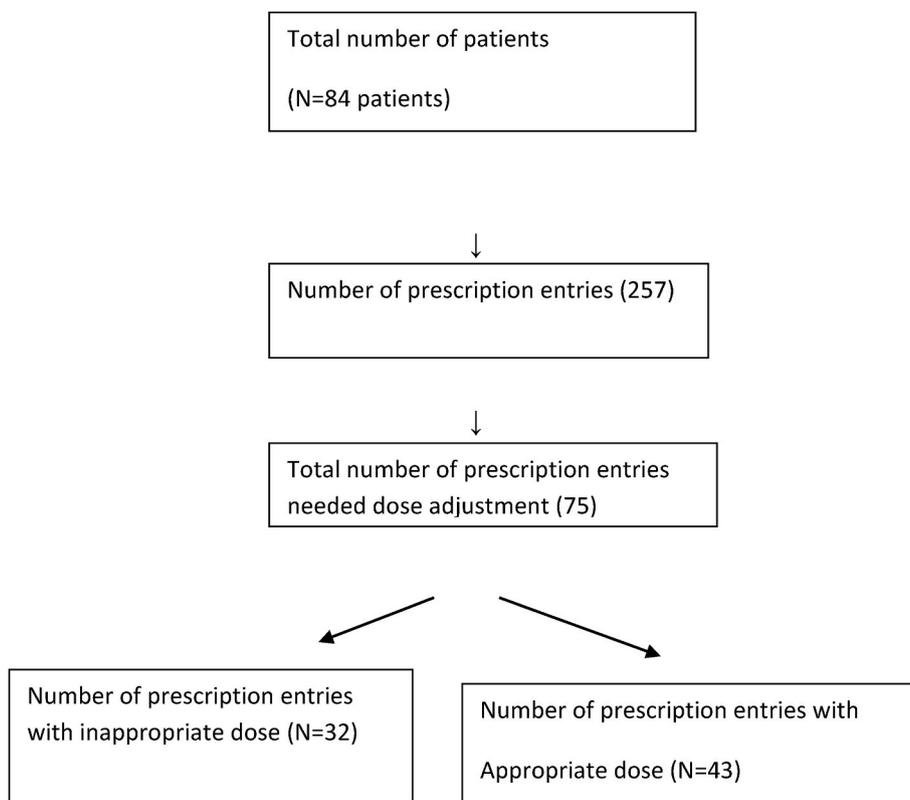


Fig. 1. Appropriateness of dosing of the medications in the study at University of Gondar comprehensive specialized hospital.

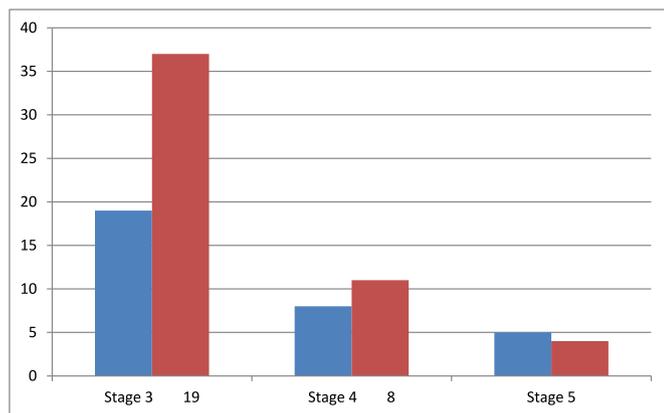


Fig. 2. Inappropriate dose adjustment and stages of renal impairment at University of Gondar comprehensive specialized hospital.

Table 3

Top 10 drugs that are inappropriately dose adjusted at University of Gondar comprehensive specialized hospital.

Drug Name	Frequency with Percentage (%)
Amoxicillin	2 (2.4%)
Ciprofloxacin	5 (6%)
Cotrimoxazole	2 (2.4%)
Vancomycin	12 (14.3%)
Hydrochlorothiazide	3 (3.6%)
Metformin	3 (3.6%)
Norfloroxacin	2 (2.4%)
Others	4 (4.8%)
Spirolactone	1 (1.2%)

4. Inappropriate drug dose adjustment and stages of renal impairment

The average number of drugs prescribed per patient was 3.3 (minimum of 1 and maximum of 7) about 39.3% (n = 33), were prescribed with 4 or more drugs. The overall rate of inappropriate dose adjustment was 42.6% (32/75). Vancomycin was the most frequently prescribed drug that required dose adjustment, which was done inappropriately in 14.3% (12/48) of cases; followed by ciprofloxacin and others. A total of 19/75 (25.3%) prescription entries were inappropriately dose adjusted in patients with stage 3. Of the 19 prescription entries, 8 (11%) were inappropriately adjusted for patients with stage 4. Patients in stage 5 had a total of 9 prescription entries of which 5 (7%) were inappropriately adjusted (Table 4).

5. Discussion

This study aimed at investigating drug dose adjustment in renal impairment patients attending a specialized hospital. The prevalence of inappropriate dose adjustment in this study was 42.6%. The most frequently inappropriate dose adjustment was done on vancomycin and ciprofloxacin. Patients having intermediate renal insufficiency and comorbidity conditions were statically significant with inappropriate dose adjustments.

The study has shown that 32/75 (42.6%) of the drug orders had some kind of inappropriate dose adjustment. Of the total prevalence of inappropriate dose adjustment, as shown in Table 2 more than half occurred in elderly patients. This is because many elderly patients have a degree of renal impairment, which is due to reduced muscle mass. It is therefore important to calculate the CrCl for this patient group for the purpose of dose adjustment. When comparing this prevalence in other studies, a higher proportion of inappropriate dose adjustment was reported by an earlier study from South Africa (59%) [17]. However, a much lower prevalence (20%) was reported in Thailand [18]. This reflects that renal

Table 4
Inappropriate drug dose adjustment of prescription entries at University of Gondar comprehensive specialized hospital Ethiopia.

Variables	Inappropriately dose adjusted medications		P(X ²)
	Yes	No	
Sex			
Male	15(46.9%)	33(63.5%)	0.13
Female	17(53.1%)	19(36.5%)	1.00
Age (years)			
18–29	3(9.4%)	8(15.4%)	1.00
30–39	5(15.6%)	8(15.4%)	
40–49	2(6.2%)	7(13.5%)	0.2
50–59	3(9.4%)	8(15.4%)	0.5
≥60	19(59.4)	21(40.4%)	0.1
			0.2
Stage			
Stage 3	19(59.4%)	37(71.2%)	0.002*
Stage 4	8(25.0%)	11(21.2%)	0.1
Stage 5	5(15.6%)	4(7.7%)	0.1
Scr ($\frac{mg}{dl}$)			
1.2–2	12(38.7%)	31(59.6%)	1.00
2.1–3	10(32.3%)	8(15.4%)	0.02*
≥3	9(29.0%)	13(25.0%)	0.82
Co morbidities			
Present	31(96.9%)	33(63.5%)	0.02*
Absent	1(3.1%)	19(36.5%)	1.00
Prescribed medications			
Ciprofloxacin	5(15.6%)	3(5.8%)	0.15
Cotrimoxazole	2(6.2%)	0	0.9
Vancomycin	18(56.2%)	18(34.6%)	0.05*
Hydrochlorothiazide	3(3.6%)	15(55.6%)	0.5
Metformin	3(9.4%)	1(1.9%)	0.15
Norfloxacin	2(6.2%)	0	0.9
Spirolactone	2(6.2%)	8(15.4%)	0.2
Others	4(12.5%)	0	0.9

*: statistically significant at P < 0.05.

function was not a primary consideration on many occasions by the prescribers in the University of Gondar comprehensive specialized hospital. There are many explanations for this finding. Primarily, Physicians may not review the result of the renal function test because of the overwhelming other clinical information. Secondly, it is obvious that CrCl should be calculated and documented for all patients with impaired renal function for the benefit of dosage adjustment. However, University of Gondar comprehensive specialized hospital as well as other private laboratories found in Gondar town does not routinely calculate CrCl when a creatinine test is requested. Accordingly, physicians would therefore, have to calculate CrCl by themselves before prescribing. However, this may lead to some mathematical calculation errors or sometimes may not be done in our hospitals. In addition; there is a lack of nephrologist physicians on in this hospital. So patients are treated by residents who were taking specialty training in internal medicine. As a result of these, physicians may not do drug dose adjustments due to underestimation of the consequences of mild renal impairment in terms of subsequent iatrogenic risks or their poor knowledge of the medications requiring an adjustment in renal impairment [19].

As a result of this inappropriate dosing in patients with renal impaired patients can cause toxicity or ineffective therapy. This is particularly magnified in older patients due to they are at a higher risk of developing advanced disease and related adverse drug events. This is caused by an age-related decline in renal function and the use of complex medications to treat their co-morbid conditions. As inappropriate dosing in patients with renal impaired patients can affect patient's clinical outcome, quality of life, as well as contribute to unnecessary health care costs. Therefore, correctly adjusting the drug dosage in renal dysfunction, contributes to fewer adverse drug effects, decreases the therapeutic costs [20], decreases, the duration of hospital stay and mortality as well as maintains therapeutic effectiveness [21]. As a result of this study, a greater focus on improvement of the safety of drugs used

in the renal impaired patient is necessary. Therefore, clinicians in University of Gondar comprehensive specialized hospital often need to proactively design individualized therapeutic regimens to optimize the achievement of the desired outcomes while minimizing adverse events.

The drug that most frequently inappropriate dose adjustment done in this study is antibiotics specifically vancomycin. This finding is in agreement with that found in Saudi Arabia, with antibiotics as the most ranked inappropriate dose adjustment [22].

It is very vital to realize that the required dose adjustment could be calculated proportionally to the changed elimination rate (I.e, in reverse proportional to the half-life). Either the dose of a drug must be reduced in inverse proportion to the half-life or else the interval between doses must be prolonged proportionally to the half-life. If for example, the half-life of a drug is five times longer because of renal insufficiency, its dose should be reduced to 20% of the normal dose ($1/5 = 0.20$). If the dose is thus reciprocally lowered and the interval between doses is unchanged, then the area under the curve will be the same as in the normal case but with higher trough values which are what is customarily measured in drug monitoring [16]. Therefore, in order to achieve effective levels in patients with renal failure, the trough values of vancomycin should lie between 10 and 15 mg/L [23].

The different variables that predict inappropriate dose adjustment is that patients with their SCr values increase from the normal values, the presence of co-morbidities, and patients with stage 3 renal impairment were significantly associated with inappropriate dose adjustment. While, age, sex, and type of drugs used were not significantly associated with inappropriate dose adjustment. This is obvious that as the co-morbidities increase the number of drugs taken by patients will increase, thus the probabilities of drugs inappropriately dose adjustment will also increase. The high prevalence of inappropriate dosage adjustments in this study would make this an important area requiring further investigation. In addition, the hospital should implement a strategy towards the creation of awareness and education regarding drug dosage adjustment in renal impaired patients for the health care team could be helpful to reduce the problems. Furthermore, implementing the computing system would be the best strategy for providing the lab data in a form that is convenient to be used by prescribers (for example, calculated CrCl, calculated GFR) to assess and monitor the renal function of the patients, thereby, reducing the inappropriate dosing [24,25].

This study has some limitations; some important data were missed and incomplete in the patient's files. For example, a total of 30% of patient files were excluded in the current study due to missing and incomplete data, which decreased our sample size. This directly affects the generalizability of the study.

6. Conclusion

According to the present study, 42.6% of orders written for patients were inappropriately dose adjusted for renal impaired patients. In order to reduce the occurrence of inappropriate drug dose adjustments, the hospital should have a continuous training program for the physicians. Furthermore, the hospital should implement a computerized system.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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CRedit authorship contribution statement

Mequqent Kassa Birarra: Data curation, Formal analysis, Supervision. **Gashaw Binega Mekonnen:** Data curation, Formal analysis,

Supervision. **Dessaegn Asmelashe Gelayee:** Data curation, Formal analysis, Supervision. **Nega Tezera Assimamaw:** Data curation, Formal analysis, Supervision. **Zemene Demelash Kifle:** Data curation, Formal analysis, Supervision.

Declaration of competing interest

The authors' declare that they have no conflict of interest.

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