Assessment of medication Dosage Adjustment in Hospitalized Patients with Chronic Kidney Disease

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ABSTRACT

**Background:** In patients with renal impairment, inappropriate medication dosing can develop adverse drug reactions (ADRs) or ineffective therapy due to declined renal function. This necessitates proper renal dosing adjustment. Using a retrospective analysis of medical records, this study was proposed to evaluate medication dosage adjustment in hospitalized chronic kidney disease (CKD) patients. **Methods:** This retrospective review of medical records was conducted at the Institute of Kidney Disease (IKD), Peshawar. It included all CKD patients hospitalized between June 01, 2019 and May 31, 2020 and receiving at least one medication that needed adjustment. Glomerular filtration rate was calculated using Renal Disease Diet Modification (RDDM) equation, and dose suitability was established by evaluating practice with relevant guidelines. **Results:** Of the total 1537 CKD patients, 231 (15.03%) had evidence of dosing error, which were considered for final analysis. Overall, 1549 drugs were prescribed, 480 (30.99%) drugs required dose adjustment of which 196 (40.42%) were adjusted properly and the remaining 286 (59.58%) were unadjusted. The most common unadjusted drugs were meropenem, cefepime, ciprofloxacin and rosuvastatin, whereas captopril, aspirin, bisoprolol, pregabalin and levofloxacin had the highest percentage of adjusted drugs. On multivariate logistic regression, the number of drugs requiring dosing adjustments and obstructive nephropathy were found to be statistically significant factors that increased the likelihood of the medication dosing errors: A unit increase in the number of drugs requiring dose adjustment increases 5.241 times the likelihood of dosing error. Similarly the presence of obstructive nephropathy (Odds ratio (OR) 0.383, 95% confidence interval (CI) [0.153-0.960] P= 0.041) was found to be significantly associated with dosing error after adjustment for potential confounding factors. **Conclusion:** The dosing of more than half of the prescribed drugs that required adjustment in CKD were not adjusted which showed that medication dosing errors were high. This highlights the importance of medication prescription according to guidelines in CKD patients to improve the outcomes of pharmacotherapy and patients’ quality of life.

**Keywords:** Chronic kidney disease, renal impairment, Medication errors, Dose adjustment
INTRODUCTION

Chronic kidney disease (CKD) is defined as a decrease in glomerular filtration rate (GFR) <60mL/minute /1.73m² for ≥3 months, regardless of the cause and is classified into five stages based on GFR. CKD affects 8%–16% of the people globally, and is one of the major public health challenge [1, 2]. An estimated 5–10 million deaths are attributed to kidney disease every year [3]. The prevalence of CKD in Pakistan is high, affects 12.5% (11.4%–13.8%) of the population [4].

Kidneys are key structures responsible for regulating homeostasis, acid-base equilibrium, as well as electrolytes [5]. Most drug's metabolism and removal depend upon normal kidney function [6]. Maintaining healthy kidney function is indeed necessary for several drugs and potential active metabolites to be metabolized and eliminated. Whereas in patients with healthy kidney function, the recommended dose of medications in patients with renal impairment can cause adverse drug reactions owing to impaired kidney function of patients[5-8] Furthermore, to minimize adverse drug reactions, dosage modifications according to renal function in patients with renal failure need to be individualized.

Patients with CKD take multiple medications not only for preventing the progression of the disease process, but also for CKD-related comorbidities, and other chronic disease conditions. With the decrease in renal function state, the pharmacokinetics of several drugs are so ominously changed that the normal doses transform either to augmented or diminished. [9-11]. In admitted patients, lethal or ineffective doses may increase the hospital stay, treatment cost, and accordingly, adding extra burden on both the patient and the healthcare systems.
In CKD patients, the kidney’s ability to eliminate a drug is impaired leading to the accumulation of drugs in the body, increasing the adverse effects and possibly leading to toxicities/ adverse drug events (ADEs) [7]. Renal injury is a known risk factor for ADEs, but remains ignored very often by Healthcare professionals [12, 13]. A study by Hug BL et al, revealed that 10% of patients with renal impairment experienced an ADE, out of these, 91% were considered preventable and 51% were serious [14]. The most common error from a medical point of view that takes place in the hospitals is medication errors especially in CKD patients. Published articles described considerable dose adjustment related difficulties and medication errors in CKD patients [14-16]. Poor understanding of the importance and need to adjust a medication’s dosage is often a cause of prescribing errors in patients with compromised renal function [15,17].

The most common error while managing CKD patients is antibiotic dose adjustment, requiring close monitoring and adjustment in these patients based on eGFR [18]. Studies from China, showed antibiotics related dosage error in CKD patients were 38.85%–60.3% [19, 20].

Literature support, that medications that required dose adjustment in CKD patients are not adjusted accurately in admitted patients, and the practice is common in both developed and developing countries; during hospitalization, about 25%- 77% drugs are adjusted inappropriately. [13, 21]. In a developed country like Netherlands a study reveals that the risk of unadjusted dose prescription was on a higher side in CKD patients with a stage III and IV [22].

Similarly, a study in Australia too, a higher level of inappropriate prescription of medicine is reported in elderly CKD patients with diabetes, with a higher number of
prescribed medicines [23]. To address such an important problem, multiple research studies have been published globally to assess the medication dosing errors pattern; although little attention is paid to assessing the predictors of medication dosing errors in CKD patients, particularly in the developing countries.

A literature search showed very limited published material on this subject [estimation of medication dosing in patients with renal impairment] showing high medication dosing error. No published studies were, to our knowledge, carried out in this part of the country (Peshawar) as yet. Considering this, the study was proposed to evaluate medication dosage adjustment in hospitalized chronic kidney disease (CKD) patients in Institute of kidney disease, Peshawar Pakistan.

METHODS
Study Setting

This retrospective study was conducted from June 01, 2019, and May 31, 2020 at the Department of Nephrology, Institute of Kidney Disease (IKD), Hayatabad Medical Complex Peshawar, Pakistan. The Institute is a major public health facility in Peshawar, the capital of Khyber Pakhtunkhwa.

Study Design and Sampling Procedure

Data was extracted from medical record/patients files of CKD patients admitted to nephrology ward on structure format. All diagnosed cases of CKD receiving at least one drug requiring adjustment with length of hospital stay greater than 24 hours were included, The GFR was measured by using the formula Modification of Diet in Renal Disease (MDRD)[24] as in the majority of medical charts GFR was not documented. Cockcroft-Gault formula[25] was not applied to calculate GFR due to missing of patients’ body weight. The associated GFR category was determined for each patient
depending on his current state agreeing to "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease".[26] Patients identified in the analysis belonged to the GFR categories G3a (45-59 ml/min), G3b (30-44 ml/min), G4 (15-29 ml/min), and G5 (<15 ml/min).

**Dosing Guidelines and the Assessment of Medication Dosing Errors**

Unfortunately, due to unavailability of any single national formulary of drug and drug dosing guideline for CKD patient in Pakistan, we had to rely on some of the reputed references and dose adjustment guidelines for the individual drugs doses assessment for appropriateness by comparing practices.

Dosage appropriateness was determined by comparing practice with the established recommendation: “Drug Dosing Adjustments in Patients with Chronic Kidney Disease” published by the American Academy of Family Physicians, and “Drug Information Handbook, 25th edition” published by Lexicomp®[27]. The guidelines were selected in consultation with consultant Nephrologist.

The evaluation of dose appropriateness was performed by a physician and hospital pharmacist. For each drug order, the dose prescribed for the patient concordant with the dose recommended in the guideline, was recorded as adjusted. Nonetheless, inappropriately dosed or doses recommended for patients with normal renal function matched with doses given, neither of the two doses we recorded nor adjusted. Each prescribed order, was, thus, categorized as one of two practice categories: properly adjusted, or not adjusted.
Data Analysis

Statistical Package for social sciences (SPSS, V. 20) was used for data analysis. Simple descriptive statistics were used to present the results such as frequency and percentage for categorical data while mean and standard deviation or Median (IQR) where appropriate for numerical data. Logistic regression models were used to calculate the associated factors “taking all medications per patient” were not adjusted [(Yes/No)] as the main outcome measure that describes the medication error. Results were described as Odd ratios (OR) along with 95%CI. Variables with a p-value <0.2 in the univariate analysis were included in the multivariate analysis. A p-value < 0.05 was measured statistically significant.

Ethical Considerations

The study protocol was approved by the ethical review committee of Hayatabad Medical Complex-Peshawar, Pakistan (Ref number: 1510-2019).

Results

During the study period from January to December 2017 a total of 1537 CKD patients’ medical record/charts were reviewed. However, a total of 231 patients were considered for final analysis based on the inclusion criteria (15.03% of screened patients). The demographics and clinical characteristics of the patients are listed in table 01. Of the total, 184(79.7%) were males and 47(20.34%) were females. The mean (SD) age of the patients was 46.14±15.90 years (Range: 13-85 years). The mean (SD) length of the hospital stay was 3.97±1.96 days (Range: 02-16 days). Majority of the patients 209 (90.5%) were in G5 stage of CKD, followed by 14(6.1%) in G4. The mean (SD) of the drugs prescribed were 6.7±1.33. About 85.3% patients were prescribed >5 drugs. Similarly majority of the patients 220(95.23%) medications list were comprised of
antibiotics. Comorbidities were present in most of the patients 180(77.92%). Among the comorbid conditions hypertension 148(64%), diabetes mellitus 57(24.67%) and obstructive nephropathy 36(15.58%) were on the top of the list.

A total of 1549 numbers of drugs were prescribed to the study patients. Of the total prescribed drugs 480 (30.99%) required dosage adjustment. Among them, 286 (59.58%) were unadjusted, and the remaining 194(40.42%) were properly adjusted as depicted in table 02.

The descriptive statistics as depicted in table 3 showed that the most common unadjusted drugs were Meropenem (100%), Cefepime (100%), Ciprofloxacin (100%), Rosuvastatin (100%), Cefoperazone/sulbactam (91.33%), Ranitidine (65.71%) and Piperacillin/Tazobactam (85.71%), while in contrast the most accurate properly adjusted drugs were captopril (100%), aspirin (100%), bisoprolol (100%), Pregabalin (100%), levofloxacin (100%), vancomycin (87.5%), domperidone (80.7%), Cefotaxime (78.12%), furosemide (69%), sodium bicarbonate (53.65%) and spironolactone (50%).

Regression analysis was run to determine the factors associated with medication/drug dosing error in CKD patient. Of the total variables, GFR category (odds ratio OR 0.340, 95%CI [0.121-0.955] P= 0.041), total number of drug prescribed (OR 1.826, 95%CI [1.444-2.310] P≤0.01) and drug requiring dose adjustment (OR 4.818, 95%CI [3.054-7.600] P<0.001) were found to be significantly associated with medication error on univariate analysis. Multivariate logistic regression was conducted for the variables that were found to be significant on univariate analysis (P≤0.2). A unit increase in number of drugs requiring dose adjustment increases 5.241 times the
likelihood of medication dosing error. Similarly the presence of obstructive nephropathy
(OR 0.383, 95%CI [0.153-0.960] P= 0.041) was found to be significantly associated with
medication error after adjustment for potential confounding factors.

DISCUSSION

Patients with renal impairment are the high-risk population for medication errors,
and among the drug related problems medication dosing errors are the most prevalent
in these patients[7, 28, 29]. A large number of published studies[7, 15, 19, 22, 28-34]
have focused on the assessment of medication dosing error in CKD patients, but
unfortunately, few to none published studies were, to our knowledge, conducted in this
part of the country.

The economic burden of CKD and its associated complications is incurring the
overall health care expenditures. Moreover, the early presentation of this chronic
condition extends the burden to an even young population and in effect leading to
further financial burdens [3]. The Pakistani health care system is under resourced and
overburdened ,this along with organizational mismanagement [including lack of
pharmacist in the multidisciplinary team and direct patient care ] making it more worst.
Keeping in view the existing health care system, there is likely the possibility of dosing
error in these patients. The present study was proposed to assess medication dosing
error in renal impaired hospitalized patients.

This study revealed that a total of 1549 drugs were prescribed to the patients
with a mean [SD] 6.7±1.33.Of the total, 480(30.99%) medication orders (drugs
prescribed) to the CKD patients needed dose adjustment. Whereof, about 40.42%
prescribed drugs were adjusted and the remaining 59.58% were unadjusted almost
similar to the finding of a study conducted in Bahawalpur, Pakistan by Ahsan Saleem and Imran Masood in CKD patients [29]. Our findings are slightly higher to those obtained by Saad et al who reported that 37% of the prescription entries were adjusted adequately at two university hospitals in, Lebanon[28].

In the present study, the prevalence of medication dosing error was considerably lower as compared with previous reports from India (81%), Palestine (73.6%), South Africa (68%) and Lebanon (63%).[29, 34, 35]. The low percentage of medication error in these CKD patients might be due to the reason that they received treatment from trained nephrologist. In contrast to our study the result of medication dosing error was higher than even less developed countries such as Indonesia and Nepal where the percentage of unadjusted drugs were 20.0% and 13.5% respectively [30, 33]. The percentage of dosing error in our study was also higher than the studies conducted in Saudi Arabia, Australia and France which is 53.1%, 44.8% and 34.0%, respectively[17, 31, 32]. This suggests that either the physician’s knowledge is inadequate or the clinical pharmacy services in our setting are lacking, compared to developed states. In the less developed nations such as Indonesia and Nepal, the lower prevalence of medication dosing errors could be attributed to active involvement of clinical pharmacist in direct patient care. Whereas, Altunbas et al. reported considerably lower prevalence of medication dosing errors (12.6%), however the authors explained that majority of the study participants had renal impairment thereby necessitating nephrology consultation and optimized drug regimen, which could limit the generalizability of study findings[36].

In developed nations, the active involvements of clinical pharmacists coupled with computerized dosage optimization systems are primarily responsible for the
appropriate medication therapy. Most automated dosage adjustment systems automatically alert the healthcare professionals including physicians and clinical pharmacist regarding renal function status and the need for dose optimization [17, 34]. Therefore, lack of pharmacist in clinical setting, lack of national dosing formulary and computerized dose adjustment programs in Pakistan lead to higher medication dosing error.

The unadjusted drug proportion was higher in patients with G5, where 97/209 drug entries were unadjusted despite the fact that G5 is more advanced disease stage. A study conducted in Ethiopia reported that patients in stage 5 had a total of 10 prescription entries of which 8 (80 %) were inappropriately adjusted [37]. A study results by Saad et al described that 36.8% drug orders that required dose adjustment were prescribed to patients with stage 5 [28].

Another important aspect in this study is the unusual age distribution where the patient mean age is 46.14±15.90 years which is much different from those in the developed and even under developing countries [17, 30, 31]. This difference might be due to low expectancy of life in a normal healthy Pakistani which is almost 65 years, dying at an early age, before reaching the average life expectancy. The high prevalence of CKD in young adult in Pakistan is due to high prevalence of hypertension, diabetes mellitus and renal stone, evident in our study result as well [38, 39].

While assessing the pattern of medication dosing error, the majority of drugs were prescribed without consulting any dose adjustment guideline. These include cephalosporin antibiotics (Cefoperazone/sulbactam, Cefotaxime, and Cefepime), Meropenem, Sodium bicarbonate, Ranitidine, Metoclopramide, Furosemide,
Spironolactone, and Rosuvastatin. These findings are in line with previous studies with the exception of Vancomycin and the cardiovascular medicines that were prescribed more appropriately in our study setting [34, 37]. These findings show that Pakistani Physicians working in public sector hospitals are underestimating the adverse outcomes associated with several important medicines. For instance, the medicines like Amikacin, Vancomycin and cephalosporin antibiotics are well reported to induce nephrotoxicity[37].

Considering, “unadjusted of all medication per patient” [yes or No] as dependent variable the results of logistic regression revealed that age, sex, length of hospital stay, antibiotics prescribed, Serum Creatinine, blood urea nitrogen, Potassium, diabetes mellitus, Hypertension, Ischemic heart disease, Urinary tract infection, Hepatitis B and C and obstructive nephropathy etc. did not show statistical significance. Similar findings have been reported by previous studies [28, 29, 37]. However, GFR categories G5(cOR=0.340) had more unadjusted drugs compared to G3b and G4, whereas a unit increase in drug in prescription was associated to an increase in the likelihood of unadjusting dose of medications by a factor of 1.826. Similarly number of medications that required dose adjustment per patient were found to be significantly associated with medication error on univariate analysis. The findings of the present study are consistent with previous report by Ahsan Saleem and Imran[29] ), in which, severe and/or end stage chronic renal impairment, and the number of prescribed medications were significant predictors of medication dosing errors. In contrast, Getachew H et al. reported that severity of renal impairment, prescribed medications requiring dose
optimization, and number of prescribed medications per patient differs with the percentage of properly adjusted drugs per patient[37].

Diabetes was not associated with medication dosing errors in this study, which is in contrast to an Australian study [23] Moreover, the presence of antibiotic in patient prescription was also not associated with medication dosing errors similarly reported by Ahsan Saleem[29].

Multivariate analysis showed that a unit increase in number of drugs requiring dose adjustment increases 5.241 times the medication error. Similarly the presence of obstructive nephropathy aOR 0.383 was found to be significantly associated with medication error after adjustment for potential confounding factors. Similar results have been described by a local study[29] where the numbers of prescribed medicines and comorbidities presence were significantly associated with the medication dosing errors.

In CKD patients the medications should be selected and prescribed with extreme precaution and appropriateness to avoid the possible drug related problems and adverse outcomes. The predictors identified should be paid attention to.

**Strength and Limitations**

This study envisages several strengths. The first strength among them is that this is the first study performed in tertiary care hospital of Peshawar Khyber Pakhtunkhwa and second in Pakistan. Secondly, in comparison to the previous study it is more detailed and to look into pattern and determinants of medication dosing errors identified in hospitalized CKD patients. Despite the strength the present study has several limitations. Firstly, the sample size may be considered small as compared to the whole CKD population patients. Secondly, being a retrospective study we could not
intervene which restricted us from possibly suggesting intervention and observing actual drug reaction. Thirdly, the MDRD equation was used due to lack of data on patient medical charts such as weight which is unsuitable for higher muscle mass patients and those with malignant condition such as cancer. Fourthly, the nephrologist may have used dose adjustment guidelines other than the one we used in the present study to make dose adjustments. It is plausible to conclude that apart from renal function status, physicians may have based dosage optimization on blood pressure, serum electrolytes and heart rate. Finally, due to the lack of resources the present study was conducted on a tertiary care kidney center data and their finding cannot be generalized across Pakistan.

**Clinical Implications and Future Recommendations**

An appraisal of the literature in correlation with the findings of the present study revealed that errors in medication dosing are a common clinical issue, particularly in patients with chronic renal impairment. Dosing errors necessitate adequate attention by healthcare professionals and patients with renal impairment need to be specifically evaluated for dosage optimization before prescribing medication therapy. Moreover, there exists considerable confusion regarding the need and extent of dosage adjustment in patients with varying degree of renal impairment, hence harmonized and universally acceptable guidelines should be formulated and adopted regarding the dosage optimization of renally excreted drugs so as to safeguard the patient’s health. In developing countries including Pakistan, the active involvement of trained clinical pharmacists in direct patient care should be ensured in order to promote appropriate and optimized medication therapy. Furthermore, continuous medical educational
programs, seminars, and workshops need to be organized on a regular basis regarding the optimization of medication therapy, particularly in patients with renal impairment.

CONCLUSION

More than half of the drugs ordered to CKD patients needing dose adjustment, were unadjusted which indicated that medication dosing errors were high in this study. The result also showed that appropriate dose adjustment for impaired kidney function was not accomplished in a large number of patients in the province's largest teaching hospital with specialist nephrologists and qualified residents who are expected to have a greater knowledge of dose adjustment in patients with renal insufficiency compared to doctors in general hospitals. This result suggests the need to provide physicians with dose adjustment information and recommendations in patients with renal impairment in order to avoid dosing errors in such patients. Therefore, intensified collaboration between healthcare workers (such as general practitioners (GPs), clinical pharmacists and nephrologists) is recommended with the exchange of relevant patient information (medical history and comorbidities) in a bid to reducing the rate of inappropriate prescription and medication dosing errors.

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AUTHOR CONTRIBUTIONS

Conception and design: ZH, IA and AR, U. Data collection: ZH, RA. Data analysis and interpretation, Results: IA, ZH. Manuscript drafting and writing: IA, ZH, SR.
Language editing, appropriateness, critical revision: AR U, AZ, And IA. All authors read and approved the final version of the paper.

Declaration of Conflicting of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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| Variable                        | N (%)        |
|--------------------------------|--------------|
| **Age (years)** [mean (SD)]    | 46.14±15.90  |
| **Gender**                     |              |
| Male                           | 184(79.65)   |
| Female                         | 47(20.35)    |
| **Length of hospital stay (days)** [mean (SD)] | 3.97±1.96 |
| **GFR category**               |              |
| G3b                            | 08(3.46)     |
| G4                             | 14(6.06)     |
| G5                             | 209(90.48)   |
| **eGFR ml/min./1.73m²** [mean (SD)] | 8.07±7.8 |
| **BUN mg/dl** [mean ±SD]       | 205.29±93.02 |
| **Serum Creatinine mg/dl** [mean ±SD] | 10.33±5.43 |
| **K mmol/l** [mean ±SD]        | 4.89±1.01    |
| **Number of drug prescribed** [mean ±SD] | 6.7±1.33 |
| ≤5                             | 34(14.72)    |
| >5                             | 197(85.28)   |
| **Antibiotics prescribed**     |              |
| Yes                            | 220(95.24)   |
| No                             | 11(4.76)     |
| **Comorbidities present**      |              |
| Yes                            | 180(77.92)   |
| No                             | 51(22.07)    |
| **Diabetes Mellitus**          |              |
| Yes                            | 57(24.68)    |
| No                             | 174(75.32)   |
| **Hypertension**               |              |
| Yes                            | 148(64.07)   |
| No                             | 43(18.61)    |
| **Ischemic Heart Disease**     |              |
| Yes                            | 21(9.09)     |
| No                             | 210(90.91)   |
| **Urinary Tract infection**    |              |
| Yes                            | 19(8.23)     |
| No                             | 212(91.77)   |
| **Hepatitis B**                |              |
| Yes                            | 09(3.90)     |
| No                             | 222(96.10)   |
| **Hepatitis C**                |              |
| Yes                            | 21(9.09)     |
| No                             | 210(90.91)   |
| **Obstructive Nephropathy**    |              |
| Yes                            | 36(15.58)    |
| No                             | 195(84.42)   |
Table 2 Number and mean or median of properly adjusted and unadjusted drugs prescribed

| Variable                              | N       | %     | Mean(SD)   | Median (IQR) |
|---------------------------------------|---------|-------|------------|--------------|
| Total number of drugs prescribed      | 1549    | 100   | 6.7±1.33   |              |
| Total number of drug prescribed       | 480/1549| 30.99 | 2.08±0.86  |              |
| requiring adjustment                  |         |       |            |              |
| Total number of drugs properly        | 194/480 | 40.42 |           | 1(0-3)       |
| adjusted                              |         |       |            |              |
| Number of drugs unadjusted            | 286/480 | 59.58 |           | 1(0-3)       |
| Drug name                  | Drugs needing adjustment (N) | Drugs adjusted N (%) | Drugs unadjusted N (%) |
|---------------------------|------------------------------|----------------------|------------------------|
| Meropenem                 | 17                           | -                    | 17 (100)               |
| Sodium Bicarbonate        | 41                           | 22 (53.66)           | 19 (46.34)             |
| Domperidone               | 52                           | 42 (80.77)           | 10 (19.23)             |
| Cefoperazone/Sulbactam    | 127                          | 11 (8.66)            | 116 (91.34)            |
| Ranitidine                | 70                           | 24 (34.29)           | 46 (65.71)             |
| Furosemide                | 55                           | 38 (69.09)           | 17 (30.91)             |
| Cefotaxime                | 32                           | 25 (78.12)           | 7 (21.87)              |
| Metoclopramide            | 6                            | 1 (16.66)            | 5 (83.33)              |
| Piperacillin/Tazobactam   | 7                            | 1 (14.28)            | 6 (85.71)              |
| Tranxemic acid            | 3                            | 1 (33.33)            | 2 (66.66)              |
| Vancomycin                | 8                            | 7 (87.5)             | 1 (12.5)               |
| Captopril                 | 3                            | 3 (100)              | -                      |
| Aspirin                   | 6                            | 6 (100)              | -                      |
| Ciprofloxacin             | 3                            | -                    | 3 (100)                |
| Cefepime                  | 27                           | -                    | 27 (100)               |
| Spironolactone            | 6                            | 3 (50)               | 3 (50)                 |
| Rosuvastatin              | 3                            | -                    | 3 (100)                |
| Ramipril                  | 2                            | 1 (50)               | 1 (50)                 |
| Bisoprolol                | 2                            | 2 (100)              | -                      |
| Fluconazole               | 5                            | 2 (40)               | 3 (60)                 |
| Pregabalin                | 2                            | 2 (100)              | -                      |
| Levofloxacin              | 2                            | 2 (100)              | -                      |
| Linezolid                 | 1                            | 1 (100)              | -                      |
|                          | **480**                      | **194 (40.42)**      | **286 (59.58)**        |
| Variable                      | Unadjusted | Odds Ratio (cOR) | 95% CI       | p-value |
|-------------------------------|------------|-----------------|--------------|---------|
|                               | All medication per patient were un adjusted |                               |             |         |
|                               | No         | Yes             | Odds Ratio (cOR) | 95% CI       | p-value |
| Age (years) [mean]            | 46.43      | 45.53           | 1.004        | [0.988-1.021] | 0.601   |
| Gender                        |            |                 |              |           |         |
| Male                          | 100(77.5)  | 84(82.4)        | 0.739        | [0.384-1.424] | 0.366   |
| Female                        | 29(22.5)   | 18(17.6)        | Reference    |           |         |
| Length of Hospital stay (days) [mean] | 3.94       | 3.99            | 0.989        | [0.867-1.128] | 0.865   |
| Serum Creatinine (mg/dl)      | 10.01      | 10.75           | 0.975        | [0.929-1.023] | 0.303   |
| BUN (mg/dl)                   | 204.68     | 206.06          | 1.000        | [0.997-1.003] | 0.911   |
| K+ (mmol/l)                   | 4.91       | 4.87            | 1.038        | [0.802-1.344] | 0.777   |
| GFR category                  |            |                 |              |           |         |
| G3b and G4                    | 17(13.2)   | 5(4.9)          | Reference    |           |         |
| G5                            | 112(86.8)  | 97(95.1)        | 0.340        | [0.121-0.955] | 0.041   |
| Total of drugs prescribed [mean] | 7.12       | 6.18            | 1.826        | [1.444-2.310] | <0.001  |
| Antibiotics Prescribed        |            |                 |              |           |         |
| No                            | 4(3.1)     | 7(6.9)          | Reference    |           | 0.193   |
| Yes                           | 125(96.9)  | 95(93.1)        | 0.434        | [0.124-1.527] |         |
| Drugs requiring dose adjustment [mean] | 2.46       | 1.60            | 4.818        | [3.054-7.600] | <0.001  |
| Comorbidity present           |            |                 |              |           |         |
| Yes                           | 98(74.8)   | 84(82.4)        | Reference    |           |         |
| No                            | 33(25.2)   | 18(17.6)        | 0.623        | [0.327-1.188] | 0.151   |
| Diabetes Mellitus             |            |                 |              |           |         |
| Yes                           | 38(29.5)   | 19(18.6)        | 1.824        | [0.976-3.411] | 0.060   |
| No                            | 91(70.5)   | 83(81.4)        | Reference    |           |         |
| Hypertension                  |            |                 |              |           |         |
| Yes                           | 79(61.2)   | 69(67.6)        | 0.756        | [0.438-1.304] | 0.314   |
| No                            | 50(38.8)   | 33(32.4)        | Reference    |           |         |
| Ischemic heart disease        |            |                 |              |           |         |
| Yes                           | 15(11.6)   | 6(5.9)          | 2.105        | [0.786-5.637] | 0.138   |
| No                            | 114(88.4)  | 96(94.1)        | Reference    |           |         |
| Urinary Tract infection       |            |                 |              |           |         |
| Yes                           | 10(7.8)    | 9(8.8)          | 0.868        | [0.339-2.224] | 0.769   |
| No                            | 119(92.2)  | 93(91.2)        | Reference    |           |         |
| Hepatitis C                   |            |                 |              |           |         |
| Yes                           | 11(8.5)    | 10(9.8)         | 0.858        | [0.349-2.107] | 0.738   |
| No                            | 118(91.5)  | 92(90.2)        | Reference    |           |         |
| Hepatitis B                   |            |                 |              |           |         |
| Yes                           | 4(3.1)     | 5(4.9)          | 0.621        | [0.162-2.374] | 0.486   |
| No                            | 125(96.9)  | 97(95.1)        | Reference    |           |         |
| Obstructive Nephropathy       |            |                 |              |           |         |
| Yes                           | 15(11.6)   | 21(20.6)        | 0.508        | [0.247-1.044] | 0.065   |
| No                            | 114(88.4)  | 81(79.4)        | Reference    |           |         |