Research Article

Pharmaceutical Care Needs and Its Potential Impact on Patients with Renal Impairment: A Retrospective Evaluation

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ABSTRACT

Background: How frequently accurate drug selection and dosage modification occur in actual practice is currently unknown.
Purpose: The purpose of this study was to assess the extent of potential Drug Therapy Problems and its possible impacts on patients with renal impairment in tertiary care hospitals.
Methods: The study was carried out at three tertiary hospitals in Nigeria using a retrospective longitudinal design. A three-year (2018-2020) review of all 12,884 patients' records was done. The 688 eligible (renally impaired patients) folders generated 1,810 prescriptions which were audited and evaluated for potential dosage adjustments (DA), contraindications (CIs) and drug-drug interactions (DDIs). Descriptive statistics, Pearson correlation and linear regression were used, as appropriate, to analyse the data. For all inferential statistics, $p < 0.05$ was considered to be statistically significant.
Results: The overall mean eGFR results (mL/min/1.73m^2) of the patients from the baseline (28.7 ± 18.8) through first (33 ± 27.9), second (28.9 ± 21.5) and third reviews (25.9 ± 24.5) were respectively observed. Findings from the prescription auditing revealed potential DA 281 (15.1%), CIs 95 (5.2%) and DDIs 1,815, (98.0%) with 8.8% potential drug cost savings per encounter. These were translated into 2,185 potential recommendations. The eGFR was associated with number of potential DA (r = -0.195, $p < 0.001$), number of potential CIs (r = -0.187, $p < 0.001$), and potential number of DDIs (r = 0.079, $p = 0.041$). Predictors of number of potential recommendations were; number of potential DDIs ($\beta = 0.217$; 95% CI = 0.209, 0.225; $p < 0.001$), and number of potential DA ($\beta = 0.280$; 95% CI = 0.239, 0.320; $p < 0.001$).
Conclusion: The results showed that prescribers do not adequately consider drug selection and dosage adjustment in patients with renal impairment.

Keywords: Renal impairment, prescribing, dosage adjustment, contraindication, drug-drug interaction.

INTRODUCTION

A vital component of homeostasis, the kidney is both physically and functionally complex. As a result, there are numerous potential causes of renal dysfunction that can result in variety of clinical disorders. Symptoms of renal impairment include fluid, electrolyte, and pH imbalances, hemodynamic imbalance, the build-up of toxins, medicines, and metabolic waste products, the loss of vital metabolites, and endocrine abnormalities such as anaemia and bone diseases[1,2].

Due to comorbidities and polypharmacy, renal failure has become a global public health issue with rising incidence, prevalence, poor outcomes, and high treatment costs. Normal renal function is necessary for the metabolism, excretion, and elimination of numerous medications and their pharmacologically active byproducts [3]. Whereas in patients with kidney insufficiency, the renal excretion of parent drug and its metabolites are usually significantly impaired, thus reduced or absence of excretion by kidneys in this condition causes alteration in the pharmacokinetics of drug and thus leading to its accumulation and resulting in toxicity [4].

Renal insufficiency is a prevalent condition among hospitalized patients and is linked to an increase morbidity and death from hospitalization. Acute and chronic renal disease patients, as well as those with additional comorbidities, are being admitted to hospitals in greater numbers. The complicated interactions between illnesses of other organ systems and renal insufficiency pose constant challenges for medical professionals caring for these individuals. Studies evaluating drug prescription in renal impairment have demonstrated that drug doses modifications are infrequently made, yet, prescribers do not always take into account the implications or possible repercussions of this medicines misuse [5,6].

Currently, there are no studies in Nigeria describing how frequently accurate drug selection and dosage modification occur in actual practice in hospitalised patients. The purpose of this study was to assess the extent of potential Drug Therapy Problems (DTPs) and its possible impacts on patients with renal impairment in tertiary care hospitals.

MATERIALS AND METHODS

Ethical considerations

Ethical approvals were duly sought and granted for this study through the respective Health Research and Ethics Committees of Ahmadu Bello University Teaching Hospital Zaria (ABUTH) (ABUTHZ/HREC/H25/2121), Usman Danfodiyo University Teaching Hospital (UDUTH)

(UDUTH/HREC/2021/1016/V2) and Specialist Hospital Sokoto (SHS) (SHS/SUB/133/VOL1).

Design and Eligibility Requirements

A 3-year (2018 to 2020) retrospective review of the records of all patients with renal insufficiencies who were admitted (for more than 24-hours) into the medical wards of the three tertiary hospitals (conveniently selected); Ahmadu Bello University Teaching Hospital Zaria (ABUTH), Usman Danfodiyo University Teaching Hospital (UDUTH) and Specialist Hospital Sokoto (SHS) was undertaken. Patients' records were selected based on Serum Electrolytes Urea and Creatinine (SrEUCr) investigations. Only folders with complete records and that were for patients 18 years above with derange creatinine clearance were considered eligible for the study.

Data Collection

All the 688 folders of the patients that met the eligibility criteria from the three hospitals were consecutively reviewed. For each patients' folder, information on sociodemographic data and clinical characteristics were extracted using a structured data collection form. The records of SrEUCr and all prescriptions from the date of admission to the date of discharge were extracted and documented.

Prescription Auditing

With the recorded age, gender, race and serum creatinine (SrCr), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) software (from an online eGFR calculator by American Society of Nephrology and National Kidney Foundation (NKF) 2021) was used to get estimated glomerular filtration rate (eGFR) for each patient [7].

Using the eGFR values, each prescription was then subjected to individual auditing using British National Formulary (BNF 2021) to determine potential dosage adjustments and contraindications. Medscape and Epocrate online softwares were also used to determine potential drug-drug interactions (DDIs).

Data Analysis

The data were analysed using the Microsoft excel and SPSS version 25. The trends in the percentage of patients on different clinical stages (I to V) from different health facilities were presented using line graph. Descriptive analyses were used to analyse the patients' dosage adjustment need, contraindications, drug-drug interactions, possible recommendations and potential cost savings. Correlation and linear regression analyses were used to identify association and predictors of possible treatment outcomes. The natural logarithm (LN) of all the dependent variables that were not normally distributed was used for the regression analysis. The level of statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Sociodemographic and clinical characteristics of the patients

There is a significant rise in the cases of renal impairments globally due to increasing incidences of diabetes and cardiovascular diseases. Inappropriately prescribed medications, multi-drug prescriptions, improper use of over the counter (OTC) as well as herbal drugs have contributed immensely to the vulnerability of population to kidney diseases [8]**.** According to Table 1 which described the sociodemographic characteristics of the patients, the mean age of the patients in this study was found to be 52.8±17.5 years. This is in line with a longitudinal study that reported declining kidney function with increasing age[9]. The patients who were mostly female (64%) had predominantly informal and basic education, were mostly married and self-employed. This is consistent with an earlier study done in Eastern Nigeria [10] but in contrast to a number of studies done outside Nigeria that indicated higher prevalence of renal impairments in male patients[11,12]. There are also significant differences among the individual groups ($p<0.001$).

Most of the patients were managed for stage III CKD (34.6) and AKI (26.7) as shown in Table 2. Diabetes and cardiovascular (Hypertension, CHD, HF) diseases were the major comorbidities observed. These findings agree with a number of studies both in Nigeria and elsewhere [10,13,14] These conditions require that the therapeutic management of the patients be done with extra vigilance to prevent further injury to the ailing kidneys. This study is in agreement with a study in Nigeria that described the pattern of morbidity and clinical characteristics of patients with renal insufficiencies.[10]

Mean laboratory Values of the Patients at baseline and after clinical reviews

Table 3 presents mean laboratory values of the patients at baseline and after clinical reviews.

Several drugs are mainly excreted by the kidneys and are therefore likely to accumulate in patients with kidney impairments if not properly administered. This could precipitate other abnormal conditions such as malnutrition, nerve damage and potentially deteriorate kidney functions [15,16]

The results of eGFR analysis of our patients had shown consistent fluctuation in renal function. While many literatures have provided evidence for declining kidney function with aging process, the condition tends to worsen with certain chronic diseases and/ or the use of drugs for the management of comorbid conditions [9].

Table 1: Sociodemographic characteristics of the patients, N = 688

VARIABLES	ABUTH n(%)	UDUTH n(%)	SHS n(%)	OVERALL n(%)	$\chi^{2(df)}$	*p* – value
Gender						
Male	93 (57.8)	192 (64.0)	152 (69.4)	245 (35.8)	412.6 (2)	<0.001
Female	68 (42.2)	108 (36.0)	67 (30.6)	439 (64.2)		
Total	161(100.0)	300(100.0)	219(100.0)	684 (100.0) *		
Level of Education						
Primary Education		4(3.8)	38 (17.4)	42(12.4)	66.9 (3)	<0.001
Secondary Education	5(38.5)	33(31.1)	66 (30.1)	104(30.8)		
Post-secondary Education	5(38.5)	36(34.0)	15 (6.8)	56(16.6)		
Informal Education	3(23.0)	33(31.1)	100(45.7)	136(40.2)		
Total	13(100.0)	106(100.0)	219(100.0)	338(100.0) *		
Marital Status						
Married	99(79.8)	219(87.3)	187(85.4)	505(85.0)	714.2 (2)	<0.001
Single	10(8.1)	12(4.8)	18(8.2)	40(6.7)		
Divorced/Widowed	15(12.1)	20(7.9)	14(6.4)	49(8.3)		
Total	124(100.0)	251(100.0)	219(100.0)	594(100.0) *		
Employment Status						
Employed	13(12.0)	33(14.2)	4(1.8)	50(9.0)	511.3 (4)	<0.001
Unemployed	19(17.6)	23(9.9)	1(0.5)	43(7.7)		
Self-employed	45(41.7)	114(49.1)	143(65.3)	302(54.0)		
Dependant	30(27.8)	54(23.3)	71(32.4)	155(27.7)		
Retired	1(0.9)	8(3.5)	-	9(1.6)		
Total	108(100.0)	232(100.0)	219(100.0)	559(100.0) *		
Ethnicity						
Hausa	139(92.7)	264(94.3)	219(100)	622(95.8)	1737.6 (3)	<0.001
Yoruba	1(0.7)	4(1.4)	-	5(0.8)		
Igbo	2(1.3)	3(1.1)	-	5(0.8)		
Others	8(5.3)	9(3.2)	-	17(2.6)		
Total	150(100.0)	280(100.0)	219(100.0)	649(100.0) *		

χ^2 = Chi Square; df = degree of freedom for chi square test of proportion between variables; * figures did not add up to total because of missing values

Table 2: Clinical characteristics of the patients, N = 688

VARIABLES	ABUTH n(%)	UDUTH n(%)	SHS n(%)	OVERALL n(%)
Diagnosis				
CKD	56(28.4)	103(31.5)	79(54.1)	237(34.6)
AKI	49(24.9)	92(28.1)	46(31.5)	183(26.7)
HTN	49(24.9)	64(19.6)	11(7.5)	133(19.4)
DM	43(21.8)	68(20.8)	10(6.9)	132(19.3)
TOTAL	197 (100.0)	327 (100.0)	146 (100.0)	685(100.0) *
Presenting Complaints				
Difficulty Breathing	59(10.7)	105(22.2)	61(10.4)	225(13.9)
Decrease Urine Output	27(4.9)	64(13.5)	59(10.0)	150(9.3)
Body swelling	65(11.8)	126(26.6)	129(21.9)	320(19.9)
Body weakness	49(8.9)	109(23.0)	130(22.1)	288(17.9)
Others	350(63.6)	69(14.6)	209(35.5)	628(38.9)
Total	550(100.0)	473(100.0)	588(100.0)	1,611(100.0) [a]
Comorbidities				
HTH	106(50.5)	197(49.2)	128(59.3)	431(52.2)
DM	63(30.0)	148(37.0)	45(20.8)	256(30.9)
CHF	29(13.8)	39(9.8)	11(5.1)	79(9.6)
IHD	12(5.7)	16(4.0)	32(14.8)	60(7.3)
TOTAL	210 (100.0)	400 (100.0)	216 (100.0)	826(100.0) *
Clinical Staging (Baseline)				
>=90 (1-Normal)	3(1.9)	4(1.3)	-	7(1.0)
60-89(2-Mild)	8(5.0)	13(4.3)	4(1.8)	25(3.7)
30-59(3-Moderate)	60(37.5)	112(37.2)	92(42.0)	264(38.8)
15-29(4-Severe)	44(27.5)	92(30.6)	84(38.4)	220(32.4)
<15(5-Failure)	45(28.1)	80(26.6)	39(17.8)	164(24.1)
TOTAL	160(100.0)	301(100.0)	219(100.0)	680(100.0) *

* Figures did not add up to total because of missing values; [a] patient can have more than one comorbidity

Table 3: Average laboratory Values of the Patients During Reviews. N = 688

Variables	(Mean ± SD)				
	Reference	Baseline	First Review	Second Review	Third Review
Na	135 – 149 mmol/L				
ABUTH		136.6±11.1	135.4±8.0	135.8±6.6	136.7±8.4
UDUTH		136.2±11.6	135.6±8.9	134.9±6.9	135.8±7.7
SHS		143.2±7.9	142.7±7.7	138.5±24.1	144.7±4.3
Overall		138.6±10.9	137.8±9.0	136.1±13.7	138.1±7.9
K	3.5 – 5.2 mmol/L				
ABUTH		4.8±4.3	4.5±1.2	4.0±1.1	4.1±1.1
UDUTH		4.8±3.9	4.5±1.1	4.5±1.2	4.5±1.1
SHS		4.7±1.3	5.2±4.3	4.7±0.9	4.7±0.7
Overall		4.8±3.4	4.7±2.6	4.4±1.2	4.5±0.9
BUN	8.0 – 20.0 mg/dL				
ABUTH		16.4±10.3	16.1±8.9	13.8±6.1	15.5±6.8
UDUTH		16.9±9.6	17.1±9.2	16.6±8.0	19.2±8.6
SHS		20.0±8.1	19.5±9.9	20.7±7.5	19.4±4.5
Overall		17.8±9.5	17.6±9.4	17.0±7.8	18.4±7.4
SrCr	0.6 – 1.3 mg/dL				
ABUTH		4.3±4.2	4.4±5.2	3.6±2.5	5.0±3.8
UDUTH		4.4±4.3	4.0±4.2	3.8±2.5	5.0±3.2
SHS		3.5±2.4	3.7±3.2	4.6±3.8	3.1±1.5
Overall		4.1±3.8	4.0±4.2	4.0±2.9	4.6±3.1
eGFR	90 – 120 mL/min per 1.73 m^2				
ABUTH		29.5±2.2	33.6±30.1	30.3±21.2	25.8±31.9
UDUTH		28.3±19.9	32.7±27.1	28.1±19.1	23.2±24.1
SHS		28.6±14.2	35.3±27.5	29.2±26.3	32.1±15.9
Overall		28.7±18.8	33.7±27.9	28.9±21.5	25.9±24.5

Na = Sodium; K = Potassium; BUN = Blood Urea Nitrogen; SrCr = Serum Creatinine; eGFR = Estimated Glomerular Filtration Rate.

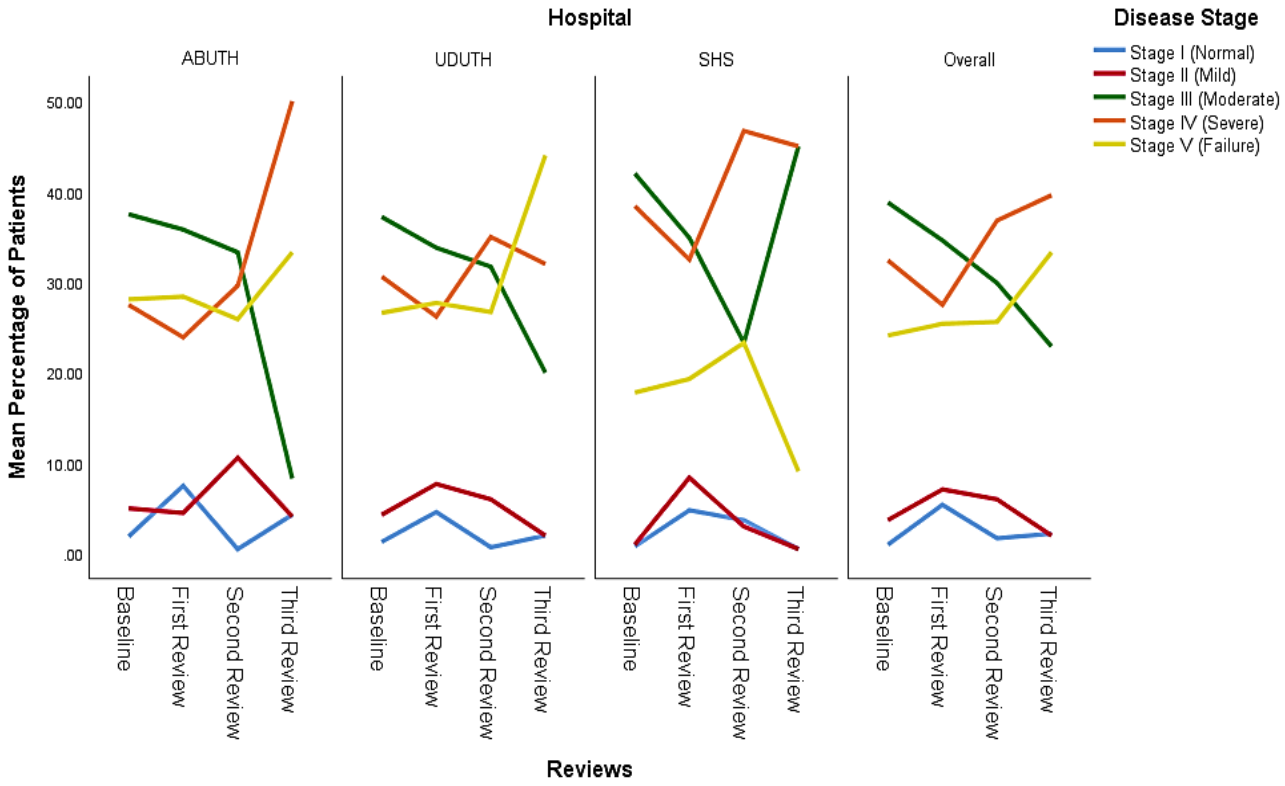

Figure 1: Pattern of the disease progression (eGFR) across the management periods in the three hospitals

Table 4: Pharmaceutical care needs among patients managed with renal insufficiencies in the three hospitals, N = 688

Variables	Proportions – n (%) *			
	ABUTH E = 362	UDUTH E = 740	SHS E = 708	Overall E = 1,810
Dosage Adjustment	72 (19.9)	127 (17.2)	82 (11.6)	281 (15.5)
Contraindications	11 (3.0)	39 (5.3)	45 (6.4)	95 (5.2)
Interactions	736 (203.3)	827 (111.8)	252 (35.6)	1,815 (100.3)
Possible Recommendations	813 (224.6)	993 (134.2)	379 (53.5)	2,185 (120.7)
Average cost of drugs per encounter (NGN) [b]	10,101.5	9,749.8	8,145.5	9,192.6
Possible cost savings for drugs per encounter (NGN) [b]	918.5	879.5	675.0	807.3
Percentage cost savings for drugs per encounter (NGN) [b]	9.1	9.0	8.3	8.8
* the proportions are based on the respective total number of encounters; E = total number of encounters; NGN = Nigerian Naira; [b] 1 NGN = 415.7 USD as at 11/03/2022; USD = United State Dollar				

Table 5: Factors associated with the pharmaceutical care needs among patients managed with renal insufficiencies in the hospitals, N = 688

Variables	Dosage Adjustment r (*p* – value)	Contraindications r (*p* – value)	Interactions r (*p* – value)	No of Recommendations r (*p* – value)	eGFR r (*p* – value)
Number of Dosage Adjustments	-	0.551 (<0.001*)	0.168 (<0.001*)	0.410 (<0.001*)	- 0.195 (<0.001*)
Number of Contraindications	0.551 (<0.001*)	-	0.006 (0.877)	0.219 (<0.001*)	- 0.187 (<0.001*)
Number of Interactions	0.168 (<0.001*)	0.006 (0.877)	-	0.962 (<0.001*)	0.079 (0.041*)
Number of Recommendations	0.410 (<0.001*)	0.219 (<0.001*)	0.962 (<0.001*)	-	0.016 (0.668)
Duration of Admission (Days)	0.052 (0.174)	0.086 (0.023*)	0.090 (0.018*)	0.100 (0.009*)	0.085 (0.026*)
eGFR	- 0.195 (<0.001*)	- 0.187 (<0.001*)	0.079 (0.041*)	0.016 (0.668)	-
* significant association at $p < 0.05$					

Table 6: Predictors of number of recommendations, N = 688

Variables		β – coefficient	95% CI of β – coefficient	t – value	R	R^2 (Adj. R^2)	p – value
Recommendations (LN)							
	(Constant)	0.107	0.052 – 0.162	3.823	0.937	0.879 (0.878)	< 0.001*
	Number of Interactions Present	0.217	0.209 – 0.225	54.107			< 0.001*
	Number of Dosage Adjustments	0.280	0.239 – 0.320	13.442			< 0.001*
	Number of Contraindications	0.317	0.249 – 0.385	9.151			< 0.001*
	Duration of Admission (Days)	0.004	0.000 – 0.007	2.036			0.042*

CI = confidence interval; LN = natural logarithm; eGFR = estimated glomerular filtration rate * significant predictors at $p < 0.05$

Pharmaceutical care needs of the patients

In this three-year retrospective study, a total of 1,810 prescriptions were audited in the three tertiary hospitals of which 15% (281) potentially required either dose adjustments or increased administration intervals for the maintenance dose (Table 4). This could be due to lack of compliance to guidelines and/or physicians' subjective understanding of risk-benefit ratio. This finding is in contrast to other similar findings that reported lower percentages (10.21%) [12] and at the same time significantly higher percentages (39%) were equally reported in another study[2]. Similarly, the quantum of drugs that should be completely avoided (contraindications) based on creatinine clearance of individual patients was potentially observed to be 5.2% (95). This type of scenario was reported in a similar study in conducted Denmark [17].

Potential drug-drug interactions (DDIs) were the most prevalent drug therapy problems observed in this study. The potentially very high level of DDIs 100.3% (1,815) identified in our work is not unconnected with the number of comorbidies most of the patients had that required multiple drugs (polypharmacy) for effective management. The prevalence of potential DDIs (100.3%) found in this present study is significantly higher than many studies from Malaysian, Mexican, Indian, Pakistanian and Denmark hospitals that reported a range of between 27.5-89.9% [18–22]. These variations as reported in different studies could be due to differences in the definitions of clinically significant interactions, methods employed for DDIs identification and patients 'sample sizes among other reasons. Likewise, possible recommendations 2,185(120.7%) were aggregated based on the observed potential drug therapy problems.

The present study reported average cost of drug per encounter to be NGN 9,192.6 which after possible implementation of the recommendations was found to reduce by NGN 807.3 translating into 8.3% as percentage cost savings for drugs per encounter. This has aligned with some studies that reported both reduction in direct cost of medications after drug dosage modification in similar manner and reduction in indirect tangible cost in the disease burden[23,24].

This reinforces the importance of such findings especially in a developing country like Nigeria where out of pocket expenditure is the norm. Because lack of affordability in the majority of renally impaired patients who belong to lower socioeconomic class is a common reason for nonadherence to treatment [25].

Association between potential drug therapy problems, possible recommendations and eGFR

The results of Pearson correlation analysis revealed various factors associated with indicators of pharmaceutical care needs (Table 5). eGFR was found to be significantly associated with number of drug dosage adjustments and number of contraindications. This study has aligned itself with a report from study conducted in south eastern Nigeria by Adibe *et al* that inappropriate drug selection/dosing and drug interactions were the main sources of drug therapy problems [10]. It is also similar to a study from south western Nigeria that reported significant association between number of prescribed medications and eGFR (staging for chronic kidney disease) [13]. This, by implications, justifies the suspicion that the higher the number of drug therapy problems the more likely the condition of patients with impaired renal functions continue to deteriorate. This underscores the importance of being more vigilant in drug selection and dosing by the use of appropriate laboratory data in order to minimize negative health outcomes.

Finally, regression analysis result (Table 6) shows number of DDIs and number of dosage adjustments as the significant predictors of number of possible recommendations. This, in part, is contrary to a study done in Pakistan where duration of hospital stay was not associated with number of drug therapy problems but the same study reported number of prescribed medications, number of comorbid conditions as well as eGFR as significant predictors of drug therapy problems[19].

These findings have indicated greater need for collaboration between physicians and clinical pharmacists as well as all other members of the healthcare delivery team in order to minimize the risks of drug toxicities and to improve overall patients' health outcomes.

CONCLUSION

The current study revealed a potentially high drug therapy problems in patients with renal impairment. This is a demonstration that dosing considerations are still necessary for the majority of medications in patients with renal impairment, but physicians are still not paying enough attention to this issue. A key factor in raising the standard of care for patients with renal impairment is the physicians' ongoing medical education and their collaboration with clinical pharmacists.

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