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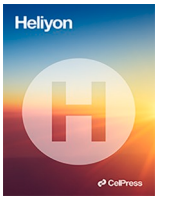

Research article

Nephrotoxic drug burden and predictors of exposure among patients with renal impairment in Ethiopia: A multi-center study

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ABSTRACT

Background: Nephrotoxic drugs may hasten the decline in kidney function and worsen the progression of renal impairment as a result; these drugs should be avoided or used with caution in patients with pre-existing renal insufficiency. The purpose of this study was to assess the burden of nephrotoxic medication use and its predictors among patients with underlying renal impairment.

Methods: A multicenter, institution-based, cross-sectional study was conducted from May 30, 2021 to July 30, 2021, at medical wards. Renal impaired patients admitted during the data collection period who took at least one medication were enrolled in the study. A simple random sampling technique was used to select the study participants. Data was collected through an interview and a medical card review. Both bivariable and multivariable binary logistic regression analyses were fitted to identify factors associated with nephrotoxic drug use.

Results: Among the 422 participants, more than half of them (53.6 %) were male. The mean patient's age was 47.5 (±16.7) years. A total of 1310 drugs were prescribed for 422 patients with renal impairment, of which 80.15 % were nephrotoxic. Nephrotoxic drugs were prescribed for 66.4 % of patients. The burden of nephrotoxic medication prescription was significantly associated with variables like the presence of comorbidity (AOR = 6.31, 95 % CI: 2.01–19.79), the number of medications prescribed (AOR = 1.43, 95 % CI: 1.05–1.93), and the age of participants (AOR = 1.12, 95 % CI: 1.07–1.17).

Conclusion: The present study demonstrated that two-third of the patients with renal impairment were exposed to nephrotoxic medications. Furosemide, Enalapril, and vancomycin were the most frequently prescribed nephrotoxic medications. The study suggests that prescribers need to give special attention to older patients who have underlying renal insufficiency, a comorbid condition, and polypharmacy regarding exposure to contraindicated nephrotoxic medication.

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1. Introduction

Renal impairment is an abnormal kidney function in which the kidney is unable to adequately eliminate or discharge hazardous substances from the body [1,2]. Many medications that are used to control and treat different diseases are nephrotoxic [3]. Nephrotoxicity can be defined as a rapid loss of kidney function caused by medications and chemical toxicity [4]. Drugs have been implicated in 26 % of all cases of in-hospital Kidney injuries [5]. Most nephrotoxic drugs cause harm to the kidney via one or more common pathogenic mechanisms, including altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy [2,6,7]. The use of nephrotoxic drugs could accelerate the decline in kidney function and worsen the progression of renal impairment.

Deterioration of kidney function is often linked to the use of nephrotoxic drugs, and patients who are at high risk of renal injury, such as those with diabetes, hypertension, and obesity, as well as individuals with chronic kidney disease (CKD) and acute kidney injury (AKI), are at greater risk for disease progression and poor outcomes when exposed to renal insults [8–10]. Moreover, nephrotoxicity of many medicines is poorly tolerated by patients with underlying renal impairment, which requires these drugs to be avoided or used with caution in such a population [11–16]. As a result, when prescribing medications for these patients, the adverse effects must be considered, and it is critical to encourage regular prescription reviews for their use [2,14]. Despite the fact that many nephrotoxic medications should be avoided or used with caution in individuals with underling kidney disease, clinicians failed to adjust doses of renally cleared medications or avoid nephrotoxic medications in standard clinical practices [16–18]. Identifying the predictors of nephrotoxic drug use among renally impaired patients is critical for reducing morbidity and mortality caused by the use of nephrotoxic medication, saving costs, and preventing drug-related toxicity.

Even though Ethiopia is one of the countries in Africa with an increasing number of renal impairment cases [19,20] no studies have been conducted in the country to investigate the nephrotoxic medication burden among patients with decreased renal function, which could be used to alert prescribers in actual clinical settings about the full picture of the use of nephrotoxic medications and the risks of inappropriately prescribing nephrotoxic medications when safer alternatives are available. Therefore, this study aimed to evaluate the burden of nephrotoxic medication use and its predictors in patients with underling renal impairment.

2. Methods

2.1. Study setting and design

An institution-based, multicenter, cross-sectional study was employed at randomly selected hospitals in Amhara Regional State from May 30, 2021, to July 30, 2021. The selected hospitals were the University of Gondar Specialized Comprehensive Hospital, Felege-Hiwot Specialized Comprehensive Hospital, and Debre Markos Specialized hospital.

2.2. Study participants and study population

All adult (age $\geq$18 years) patients admitted to medical wards at the selected hospitals were the source population, while all adult patients with SrCr levels of $\geq$1.2 mg/dl who were admitted during the data collection period to the medical wards at the selected hospitals were the study population.

2.3. Inclusion criteria

- Patients whose age was above 18 years
- Patients who had at least one estimated GFR value of $\leq$60 ml/min/1.73 m^2
- Patients admitted to medical wards with a diagnosis of renal impairment
- Patents who received at least medication

2.3.1. Exclusion criteria

- Patients who were critically ill
- Patents with incomplete medical profile and laboratory result

2.4. Sample size determination and sampling techniques

A single population proportion formula was used to calculate the sample size, in which the following assumptions were considered: 50 % prevalence, 95 % confidence interval, and 5 % margin of error.

- $n = \frac{(Za/2)^2 p(q)}{d^2}$, where Z statistics (at 95 % CI = 1.96), p (population proportion) and d (margin of error)
- $n = \frac{(1.96)^2 x 0.5 x 0.5}{0.05^2} = 384.$

Finally, we had added a 10 % non-response rate which made our final sample size 422.

A single-stage cluster sampling technique was employed to recruit the study participants. In the first step, six referral hospitals found in Amhara Regional State (University of Gondar Comprehensive Specialized Referral Hospital (UOGCSH), Felege Hiwot Comprehensive Specialized Hospital (FHCSH), Debre Markos Referral Hospital (DMRH),Tibebe Gion Referral Hospital (TGRH), Dessie Referral Hospital (DRH), and Debre Berhan Referral Hospital (DBRH) were considered as clusters, and the three of them (UOGCSH, FHCSH, and DMRH) were selected on a random basis. Following that, the first 422 patients who were eligible for inclusion and were admitted to the medical wards of the selected hospitals during the study period were all included.

2.5. Study variables

Nephrotoxic medication use was the dependent variable, whereas socio-demographic variables including age, sex, weight, marital status, residence, educational status, and occupation status, clinical characteristics like diagnosis, presence of comorbid conditions such as hypertension, diabetes mellitus, heart diseases, stroke, pneumonia, and asthma), laboratory test results such as serum creatinine, and prescriber's characteristics such as work experience and specialty were independent variables.

2.6. Operational definitions

Renal impairment: is a medical condition in which the kidneys fail to adequately filter waste products with an estimated GFR$\leq$60 mL/min/1.73 m^2 [14].

Nephrotoxic medication: A medication shown to cause nephrotoxicity [6,16] (see Supplementary Table S1).

2.7. Data collection tools and procedures

Data was collected using a pretested interviewer-administered structured questionnaire. The questionnaire was prepared by the investigators after reviewing various literatures. Six trained nurses with BSc degrees worked as data collectors during the data collection process. The patient's sociodemographic characteristics were obtained by interviewing them, and the weight of the patient was determined by measurement. The patient's clinical parameters, such as SrCr level and the lists of prescribed medications were taken from the patient's medical chart. Besides that, physicians' work experiences were obtained from the human resources department, whereas their specialty was obtained from both the patient's medical record and the human resources department of the respective hospitals. The recent SrCr value recorded prior to medication prescription with a value of $\geq$1.2 mg/dl was used as a cutoff point in the pre selection of patients; furthermore, for patients with a SrCr level of $\geq$1.2 mg/dl, GFR was calculated by using the Cockroft–Gault equation (CG formula). Finally, patients with a GFR value of $\leq$60 mL/min/1.73 m^2 were included in the study. The estimated GFR (eGFR) was calculated using the CG equation as follows [21].

$$\text{Male : eGFR ml} \Big/ min = \frac{[(140\text{-age(in year)}) \times \text{weight(kg)}]}{\text{SrCr(mg/dl)} \times 72}$$

$$\text{Female : eGFR ml} \Big/ min = \frac{[(140\text{-age(in year)}) \times \text{weight(kg)}] \times 0.85}{\text{SrCr(mg/dl)} \times 72}$$

2.8. Nephrotoxic drugs assessment

Nephrotoxic drug assessment was based on two types of underlying mechanisms: acute interstitial nephritis and tubular cell toxicity. The burden of nephrotoxic medications prescription for each patent was evaluated by using list of nephrotoxic medications to be used with caution and contraindicated in patients with renal impairment (see Supplementary Table S1) that were adapted from previously published literatures [6,16,22]. Medications available in Ethiopia were included in the list.

2.9. Data quality assurance

The questionnaire's completeness and readiness were pretested before the actual data collection began on 5 % of the study subjects at the Tibebe-Ghion specialized hospital. The results of the pretest were not used in the final study. The data collectors were trained on the data collection tool, questionnaire technique, and ethical issues. The questionnaire's quality was assured by having the data collectors check the questionnaire's completeness and consistency at each step of the data collection process, as well as during data entry.

2.10. Data processing and analysis

The collected data was checked for completeness, accuracy, and clarity before analysis. The data was entered into Epidata 4.6 and transferred to SPSS version 26 for analysis. Frequency and percentage were computed for categorical variables, while the mean with standard deviations was used for continuous variables. For group comparisons, chi-square and independent sample t-tests were computed. Bivariable binary logistic regression analysis was used to identify factors that were candidates for multivariable analysis at a

p-value of less than 0.2. A multivariable binary logistic regression analysis was fitted to identify factors associated with nephrotoxic drug use. Model fitness was checked with the Hosmer and Lemeshow goodness of fit test, and it was 0.1. Furthermore, to identify and avoid redundant variables that may affect our estimate, multicollinearity between the explanatory factors was assessed with the variance inflation factor (VIF). The VIF was in the acceptable range. An adjusted odd ratio (AOR) at a 95 % confidence interval (CI) with a P-value $\leq$0.05 was considered statistically significant.

3. Result

3.1. Sociodemographic and clinical characteristics of study participants

A total of 422 renally impaired patients were included in the study. The participants' age range was between 18 and 84 years, with a mean age of 47.5 ($\pm$16.7) years. More than half of the participants were men:226 (53.6 %) and 221 (52.4 %) were from urban areas. Regarding their education status, 112 (26.5 %) of the participants had joined higher education, whereas 122 (28.9 %) of the participants were government workers (Table 1).

3.2. Study participants' clinical characteristics

Of the total respondents, 248 (58.8 %) were diagnosed with CKD, while most of the patients, 352 (83.4 %) presented with comorbid illnesses. Categorically, 138 (32.7 %) of them were hypertensive; 92 (21.8 %) had diabetes mellitus; and 19 (4.5 %) had other comorbidities (such as arthritis, epilepsy or sepsis). The mean estimated CrCl value was 32.69 ml/min, with an average SrCr value of 3.04 mg/dl. On average, about four medications were prescribed for each patient (Table 2).

3.3. Prescriber's characteristics

When the characteristics of prescribers were evaluated, the majority of patients (80.6 %) received medication prescriptions from either general practitioner physicians, residents, or interns, while almost half of the study participants (47.6 %) received medications from prescribers with three years or more of work experience (Table 3).

A total of 1310 drugs were prescribed for 422 patients with renal impairment, of whom 1050 (80.15 %) of the ordered drugs were nephrotoxic. Two-thirds (66.4 %) of the study participants were prescribed nephrotoxic medications. Among them, 77 of the patients had received one nephrotoxic medication, while the majority of the patients (72.5 %) had received at least two nephrotoxic medications. Furosemide was the most commonly prescribed medication, with 210 of the study participants having received it. Overall, diuretics were prescribed 315 times, followed by antibiotics (256 times), enalapril (155 times), and cimetidine (86 times). On the evaluation of the frequency of individual nephrotoxic drugs prescribed, furosemide ranked first, followed by enalapril (Table 4).

3.4. Predicators of nephrotoxic medications use

Following univariate and multivariate logistic regression analysis, the COR and AOR results showed that there was no significant association between the variables like the participant's sex, weight, occupation, place of residence, educational level, serum creatine level, creatinine clearance, physician's experience, and the prescription of nephrotoxic drugs. However, the multivariable logistic regression model revealed that the burden of nephrotoxic medications was significantly associated with the type of renal impairment

Table 1
Sociodemographic characteristics of patients with renal impairment in Amhara regional state Hospitals.

	Variables	Frequency(n)	Percent (%)
Sex	Male	226	53.6
	female	196	46.4
Residence	Rural	201	47.6
	Urban	221	52.4
Education	Unable to read and write	99	23.5
	Literate with no formal education	90	21.3
	Primary Education (1–8)	72	17.1
	Secondary Education (9–12)	49	11.6
	Higher Education	112	26.5
Occupation	House wife	95	22.5
	Farmer	94	22.3
	Merchant	36	8.5
	Government employee	122	28.9
	NGO employee	65	15.4
	Other[a]	10	2.4
		Mean	$\pm$Standard deviation
Age (years)		47.5	16.7
Weight (Kg.)		60.1	8.9

[a] Pensioner, Daily laborer, Student.

Table 2
Clinical characteristics of patients with renal impairment in Amhara regional state Hospitals.

	Variables	Frequency (n)	Percent (%)
Diagnosis	AKI	169	40.0
	CKD	253	60.0
Presence of comorbid illness	Yes	352	83.4
	No	70	16.6
Type of comorbidities	Hypertension	138	32.7
	Diabetes Mellitus	92	21.8
	Heart Diseases	85	20.1
	Stroke	38	9.0
	Pneumonia	38	9.0
	Asthma	35	8.3
	Anemia	29	6.9
	Acute Glomerulonephritis	25	5.9
	Others[a]	19	4.5
		Mean	±Standard deviation
Serum creatine(mg/dl)		3.04	2.36
Creatine clearance (ml/min)		32.69	14.71
Number of medications		4	1.64

[a] Chronic obstructive pulmonary disease, Cirrhosis, Epilepsy, Depression, Visceral Leishmaniasis, Arthritis, Sepsis.

Table 3
Characteristics of physicians who were involved by prescribing medications to patients with renal impairment in Amhara regional state Hospitals.

	Variables	Frequency(n)	Percent (%)
Specialty of prescribers	Patients prescribed medications from General practitioner physicians, residents and interns	340	80.6
	Patients received medications from Internist	82	19.4
Length of service of physicians	Patients received medications from prescribers with experience of ≤ one year	99	23.5
	Patients received medications from prescribers with experience of one up to two years	122	28.9
	Patients received medications from prescribers with experience of ≥ three years	201	47.6

Burden of nephrotoxic medications among patients with renal impairment.

Table 4
Burden of nephrotoxic drugs prescribed to patients with renal impairment in Amhara regional state Hospitals.

	Variables	Frequency(n)	Percent (%)
Diuretics	Furosemide	210	20
	Spironolactone	78	7.42
	Hydrochlothazide	55	5.23
Antibiotics	Vancomycin	79	7.52
	Ciprofloxacin	69	6.57
	Ceftazidime	47	4.47
	Ceftriaxone	61	5.8
ACEs	Enalapril	155	14.76
Anti-diabetic agents	Metformin	49	4.66
Statins	Atorvastatin	50	4.76
H2 receptor antagonists	Cimetidine	86	8.19
PPI	Omeprazole	38	3.61
Anti-platelet agents	Aspirin	53	5.04
Others[a]		20	1.97
Total		**1050**	**100**

[a] Others: Diclofenac, Ibuprofen, Amphotericin B, Phenytoin.

diagnosis, the presence of comorbidity, the number of medications prescribed, the age of participants, and the specialty of the physicians. Regarding the type of renal impairment, patients with the diagnosis of CKD were 22 times more likely to receive nephrotoxic drugs as compared to patients diagnosed with AKI [AOR = 22.0, 95 % CI: (9.04–53.78)]. A one-year increment in age of the patients increased the prescription of nephrotoxic medications by 88 % (AOR = 1.12, 95 % CI: 1.07–1.17, P < 0.001). Moreover, the presence of underling comorbidity increased the odds of having been prescribed nephrotoxic medications by a factor of 6.31 (AOR = 6.31 (2.01–19.79), P < 0.001). As the number of prescribed medicines increases by one, the odds of exposure to a nephrotoxic agent increase by 1.43 times (AOR = 1.43, 95 % CI: 1.05–1.93, P = 0.02). In addition to this, the burden of nephrotoxic medications was 19.5 times higher among renally impaired patients who were prescribed drugs by unspecialized prescribers as compared to specialized internists (AOR = 19.5, 95 % CI: 5.57–68.51, P < 0.001). (Table 5).

Table 5
Univariate and Multivariate analysis to identify factors associated with nephrotoxic drug burden among patients with renal impairment in Amhara regional state Hospitals.

Variable		Patients received nephrotoxic medications		Bi-variable analysis		Multi-variable analysis	
		Yes(n)	No(n)	P value	COR (95%CI)	P value	AOR (95%CI)
Sex	Male	152	74	0.67	1.09 (0.72–1.63)		
	Female	128	68		1		
Place of Residence	Rural	147	54	0.00	1.80 (1.19–2.72)	0.86	1.13 (0.25–5.08)
	Urban	133	88		1		
Occupation	House wife	83	12	0.05	2.25 (0.98–5.16)	0.64	1.62 (0.20–12.71)
	Farmer	69	25	0.77	0.90 (0.43–1.86)	0.70	1.50 (0.18–12.48)
	Merchant	14	22	0.00	0.20 (0.87–0.49)	0.41	0.40 (0.04–3.59)
	Government employee	58	64	0.00	0.29 (0.15–0.57)	0.53	0.54 (0.08–3.71)
	NGO employee	7	3	0.71	0.76 (0.17–3.29)	0.45	3.04 (0.16–56.32)
	Others	49	16		1		
Level of Education	Unable to read and write	83	16	0.00	3.75 (1.95–7.21)	0.15	0.25 (0.03–1.70)
	Literate with no formal education	73	17	0.01	3.10 (1.62–5.93)	0.38	0.49 (0.10–2.42)
	Primary(1–8)	41	31	0.88	0.95 (0.52–1.74)	0.57	1.61 (0.29–8.69)
	Secondary (9–12)	18	31	0.14	0.42 (0.21–0.83)	0.89	0.89 (0.15–4.99)
	Higher(Diploma & higher)	65	47		1		
Presence of comorbidity	Yes	262	90		1		
	No	18	52	0.00	8.41 (4.67–15.12)	<0.001*	6.31 (2.01–19.79)
Diagnosis	AKI	53	116		1		
	CKD	227	26	0.00	19.10 (11.3–32.1)	<0.001*	22.0 (9.04–53.78)
Length of service	≤1 year	79	20	0.00	3.61 (2.05–6.34)	0.34	0.57 (0.18–1.81)
	2 years	96	26	0.00	3.37 (2.01–5.64)	0.45	0.67 (0.23–1.89)
	≥3 years	105	96		1		
Specialty	GP/Resident/Intern	271	69	0.00	31.8 (15.1–66.8)	<0.001*	19.5 (5.57–68.51)
	Internist	9	73		1		
Age		54.9 + 13.37	32.73 + 12.25	0.00	1.12 (1.10–1.15)	<0.001*	1.12 (1.07–1.17)
Weight		62.29 + 8.79	55.82 + 7.60	0.00	1.10 (1.07–1.13)	0.84	1.00 (0.94–1.06)
Serum creatinine		2.91 + 2.31	3.27 + 2.46	0.14	0.94 (0.86–1.02)	0.09	0.86 (0.72–1.02)
Creatinine clearance		32.8 + 14.6	32.4 + 14.8	0.83	1.00 (0.98–1.01)		
Number of medications prescribed		4.35 + 1.64	3.27 + 1.39	0.00	2.01 (1.68–2.40)	0.02*	1.43 (1.05–1.93)

1 = indicate for the reference group, * Statistically significant.

4. Discussion

The current study evaluated nephrotoxic medication prescriptions in hospitalized patients with renal impairment. To our knowledge, this is the first study exploring the pattern of nephrotoxic medication prescriptions in patients with renal impairment in Ethiopia.

Our study found that 66.4 % of patients received nephrotoxic medications; among these, 72.5 % received at least two nephrotoxic medications. Previous studies also revealed the presence of a higher prevalence of nephrotoxic medication administration among patients with renal impairment [23–25]. However, the findings of these studies differed from one another. This disparity could be explained first by a variation in how prescription error is defined. In our study, prescription error was defined as administering a drug that is contraindicated at a given stage of renal impairment, whereas other studies defined error as a combination of contraindicated

drug administration and/or administration of an inappropriate dose. Secondly, the drug information sources used by the systems in these various studies differ significantly [26]. Some drugs that are listed as contraindicated in one source are not listed as such in another. Third, there are differences in how these sources define and categorize renal impairment; some sources divide renal function into three categories, while others divide it into five stages, which causes some drugs to be considered contraindicated in some studies but not in others [27,28].

The burden of nephrotoxic medication use in our study was lower than a study done in Nigeria [16]. The disparity between our findings and the study in Nigeria could be explained through variations in the study settings, system, and practice. However, in our findings the burden of nephrotoxic medication was much higher than the findings in Italy, Sweden, the USA, and Saudi Arabia [15,22,29]. The good practice of collaborating clinical pharmacists with physicians in the care of patients with renal impairment [30] and a clinical decision support system implementation that had the potential to improve kidney-related drug prescribing by supporting the appropriate initiation, modification, monitoring, discontinuation of drug therapy, and alerting on nephrotoxicity [31,32] might have resulted in a decrease in the use of nephrotoxic medications in developed countries. Diuretics like Furosemide, ACEIs like Enalapril, and antibiotics like vancomycin were the most frequently prescribed nephrotoxic medications in our study, which was in line with prior studies [13,14,16].

Despite the ability of diuretics to manage fluid overload in patients with renal impairment, their use is associated with adverse renal outcomes, as evidenced by a decrease in estimated glomerular filtration rate, worsening of the disease, and an increased risk of initiating renal replacement therapy [33–36]. For example, spironolactone-induced hyperkalemia and renal impairment are very common negative outcomes in renally impaired patients [37]. On the other hand, ACE-inhibitors are known for their importance in decreasing morbidity and mortality in patients with various heart diseases, and the intensive advertising for ACE-inhibitors in the treatment of hypertension has increased their use [38–40]. However, they are the second leading cause of drug-induced renal failure after antibiotics [41]. They primarily affect elderly patients with underlying chronic renal impairment and sometimes result in severe irreversible renal damage [42]. Co-prescription of ACEI with diuretics results in renal adverse effects in high-risk populations [43]. Likewise, aminoglycoside beta-lactams and fluoroquinolones are also well recognized nephrotoxins, causing a reduction in approximately 50 % of kidney function and a high risk for renal impairment [44–46].

Metformin and omeprazole were among the nephrotoxic medications used by patients in our study.High doses of metformin result in nephrotoxicity and are potentially clinically relevant to guide dose adjustments in the setting of chronic kidney disease [47]. Whereas, a study done at the nephrology ambulatory clinic in Brazil revealed that regular use of Omeprazole could deteriorate renal impairment progression [48].

There were slight differences in the types of medications prescribed in our study compared to other studies conducted in Sweden, the United States, and Italy; the most frequently prescribed medications in the studies were bisphosphonates, immunosuppressant agents, antiviral agents, and NSAIDs [22,29]. The possible reason for this difference might be that there were variations in the availability and prescription trends of medications in different settings, as well as differences in the prevalence and types of comorbid illnesses.

This study investigated the predictors of nephrotoxic medication use in patients with renal impairment. Age, diagnosis with CKD, presence of comorbid illness, number of medications, and specialty of the physicians were significantly associated with nephrotoxic medication use. Older people were at a higher risk of receiving nephrotoxic medications, which was in line with a study done in a Saudi Arabian tertiary hospital [15]. The possible reason might be due to the fact that older individuals appear to have more comorbid conditions, and kidney function declines with age, which increases vulnerability to nephrotoxic medications [49,50]. The presence of comorbid illness increases nephrotoxic medication exposure [10,51]. The majority of patients in our study had comorbidities and complications, which are associated with a higher pill burden; four medications were prescribed on average, with a range of one to nine, which may explain why more medications were administered. In various related studies, polypharmacy in patients with renal impairment has been found [12–14,52]. As a result, patient-related risk factors such as age and comorbid conditions must be considered, as well as general preventive measures such as using alternative non-nephrotoxic medications, managing comorbid illness, assessing baseline renal function, adjusting the therapeutic dose, monitoring renal function during therapy, and avoiding nephrotoxic drugs [53,54].

Moreover, prescription by general practitioners/interns/residents exposes the majority of patients to nephrotoxic medications compared to prescription by specialists, which was in line with other studies done in Saudi Arabia and Italy [15,22]. In a qualitative study, general practitioners explained that infection diagnosis is typically not based on microbial culture and that the use of potentially nephrotoxic medications may be contributing to the worsening of renal impairment [55]. The introduction of clinical guidelines and safety signs may assist physicians in recognizing risky prescriptions and reduce the frequency of adverse effects [56]. However, according to one previous study, the prescription pattern does not reflect the quality of the physician order but rather the fact that the same medication order that is considered nephrotoxic in patients with severe renal impairment is considered appropriate in patients with mild or moderate renal impairment [57]. We believe that more studies are needed to back up this claim.

4.1. Limitations of the study

The diagnosis recorded by general practitioners or interns may be inaccurate; we cannot rule out the possibility of acute kidney injury (AKI) being misclassified as chronic kidney disease (CKD). Some of the drugs are specifically contraindicated in patients with severe renal disease (creatinine clearance, 30 ml/min) only. We could not get the recent serum creatinine test for some patients; for this reason, the rate of contraindicated nephrotoxic drug use may have been overestimated. Furthermore, the cross-sectional study design takes only single point in-time data, which makes it difficult to establish a cause- and -effect relationship. We recommend future studies

address the limitations by using a prospective follow-up study design that encompasses more hospitals.

Generally, the current study highlights the nephrotoxic drug burden and predictors of exposure among patients with renal impairment in Ethiopia. Indeed, the findings of this study may have significant implications for focusing on patients' underling renal impairment in order to reduce exposure to nephrotoxic medications, particularly for older patients who have underlying renal insufficiency, a comorbid condition, and polypharmacy. Additionally, it also examined the association of certain socio-demographic and clinical characteristics with nephrotoxic drug exposure. The findings may be helpful for tailored interventions considering patients' underling renal impairment in conjunction with their medication use. Furthermore, the study may be a benchmark for future researchers in the area with a prospective approach and a large sample population.

5. Conclusion

The present study demonstrated that two-third of the patients with renal impairment were exposed to nephrotoxic medications. Prescribers need to be cautious about the safety issues of nephrotoxic drug use; special consideration should be given to drugs such as furosemide, enalapril, and vancomycin when prescribing for patients with pre-existing renal impairment. According to this study, prescribers should pay close attention to older patients with underlying renal insufficiency, a comorbid condition, and polypharmacy in order to avoid exposing them to nephrotoxic drugs that are contraindicated. Our findings offer important insights for halting the progression of renal impairment brought on by the use of nephrotoxic drugs, which may result in unfavorable patient outcomes and increase the burden of the disease.

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Ethical considerations

The study protocol was reviewed, and ethical approval was granted by the Research and Ethics Committees of the clinical pharmacy department at the University of Gondar College of Medicine and Health Sciences with reference number, SoP/065/2020. The nature of the study was fully explained to the study participants, and informed consent was obtained. Furthermore, to maintain the confidentiality of the responses, no personal identifiers were included in the questionnaire.

CRediT authorship contribution statement

Tirsit Ketsela Zeleke: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Leila Kenzu Kemal:** Writing – original draft, Visualization, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eden Abetu Mehari:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Faisel Dula Sema:** Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Abdulwase Mohammed Seid:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Investigation, Formal analysis, Conceptualization. **Gizework Alemnew Mekonnen:** Writing – review & editing, Visualization, Supervision, Software, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Rahel Belete Abebe:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24618.

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