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The impact of BCR-ABL tyrosine kinase inhibitor therapy on renal function in patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A 2023 cross-sectional study

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List of acronyms/ Abbreviations

ACE: Angiotensin-converting enzyme

ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker

AKI: Acute kidney injury

ALL: Acute lymphoblastic leukemia

AOR: Adjusted odds ratio

ARE: Adverse renal event

BCR-ABL TKIs: BCR-ABL tyrosine kinase inhibitors

CCB: Calcium channel blocker

CHR: Complete hematologic response

CI: Confidence interval

CKD: Chronic kidney disease

CML: Chronic myeloid leukemia

COR: Crude odds ratio

CP: Chronic phase

CRAE: Chronic renal adverse event

DFSP: Dermatofibrosarcoma protuberans

DM: Diabetes mellitus

eGFR: Estimated glomerular filtration rate

GI: Gastrointestinal

GIST: Gastrointestinal stromal tumor

Hb: Hemoglobin

HES: Hypereosinophilic syndrome

HIV: Human immunodeficiency virus

HTN: Hypertension

IQR: Interquartile range

KIT: KIT receptor

MMR: Major molecular remission

MDS/MPN: Myelodysplastic syndromes/myeloproliferative neoplasms

N/A: Not applicable

PDGF: Platelet-derived growth factor

PO: Per os (by mouth

RBC: Red blood cell

SD: Standard deviation

UAA: Urine analysis

WBC: White blood cell

WHO: World Health Organization

EXCUTIVE Summary

Background: BCR-ABL tyrosine kinase inhibitors are effective in treating various cancers, but concerns exist regarding their potential to cause kidney damage. This study investigated the association between tyrosine kinase inhibitors and renal toxicities in patients at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia.

Methods: A hospital-based, cross-sectional study was conducted on 260 patients receiving BCR-ABL tyrosine kinase inhibitors. Data on demographics, diagnoses, treatment characteristics, and laboratory parameters were collected. The primary outcome was the development of adverse renal events, defined as a combination of factors including decreased eGFR by more than 30% from the baseline, significant proteinuria, acute kidney injury, or chronic kidney disease. Logistic regression was used to identify factors associated with AREs.

Results: The study observed a statistically significant decrease in eGFR following tyrosine kinase inhibitor treatment. However, the prevalence of adverse renal events (13.1%) was lower than reported in some previous studies. Factors significantly associated with adverse renal events included longer TKI duration, male sex (protective), hypertension, HIV infection, and achieving complete molecular remission or complete hematologic response. No significant associations were found with diabetes mellitus, age, use of ACE inhibitors, or baseline creatinine level.

Conclusions: This study suggests that tyrosine kinase inhibitors may decrease eGFR, but the observed risk of adverse renal events was lower than previously reported. However, the relatively small sample size and potential differences in demographics and comorbidities may limit the generalizability of the findings. Further studies with larger sample size along with periodic determinations of renal function, are recommended to solidify these findings.

Contents

1. Introduction

1.1 Background

BCR-ABL TKIs are drugs that mainly target the BCR-ABL1 tyrosine kinase, but they can also target other tyrosine kinases like PDGFR and KIT. It is used primarily for the management of CML. However, it also has applications in treating BCR-ABL-positive ALL, MDS/MPN with PDGFR rearrangement, hypereosinophilic syndrome and chronic eosinophilic leukemia with FIP1L1-PDGFRα rearrangement, KIT-positive GIST, and DFSP (UpToDate. (n.d.). UpToDate. https://www.uptodate.com/contents/initial-treatment-of-chronic-myeloid-leukemia-in-chronic-phase?search=CML&topicRef=4496&source=see_link#H16476226501) .

The use of TKIs has significantly improved outcomes and survival for CML patients. Currently, several TKIs are available, including imatinib, nilotinib, dasatinib, bosutinib, and ponatinib. The choice of TKI for a patient depends on various factors, such as age, disease stage, comorbidities, and individual tolerability. Imatinib is the first-line therapy for many patients, and it is effective, resulting in MMR for about 85% of patients in a 5-year period of therapy (2). When there is an intolerance or resistance to primary therapy, second-generation TKIs (dasatinib, nilotinib, and bosutinib) can be used and are generally considered to be more effective. Ponatinib, a third-generation TKI, is used for the treatment of patients who failed other TKIs or have the T315I mutation (1, 3-5).

TKIs are more effective and less toxic than conventional chemotherapy (6). However, understanding the long-term consequences of TKI exposure is important, as they are administered for prolonged periods in CML patients(7). Early complications, which can occur during the initial stages of therapy, include skin rash, fatigue, nausea, myalgia, arthralgia, and edema. Additionally, each TKI may have unique complications associated with its use. Long-term TKI use can affect various body organ systems, including the cardiovascular, bone marrow, gastrointestinal, liver, and kidney systems (8, 9).

Kidneys play a role in the pharmacokinetics of TKIs, making them susceptible to their toxicities (10). However, less attention has been paid to the renal toxicities of TKIs, despite several studies showing a possible association between TKI use and renal damage, including glomerular and tubular injuries (6, 7, 11, 12). The exact mechanism by which TKIs cause renal toxicity remains unknown, but potential mechanisms are discussed below.

The first mechanism involves the presence of abundant PDGFR and KIT receptors on podocytes, mesangial cells, and tubular epithelium, which are crucial for their survival and growth. Therefore, inhibiting tyrosine kinase signaling disrupts cellular processes, leading to oxidative stress, inflammation, and apoptosis. Ultimately, this can cause fibrosis, proteinuria, and glomerulosclerosis (13, 14). Another proposed mechanism involves endothelial damage caused by TKIs, leading to local thrombosis and resulting in thrombotic angiopathy that manifests as proteinuria(9). Additionally, TKIs can inhibit the activity of angiotensin-converting enzyme (ACE), which can lead to decreased renal blood flow and glomerular filtration (15).

1.2 Statement of the problem

Studies on the renal toxicities of TKIs have increased in recent years. However, the exact cause of these toxicities remains unknown. Reports suggest that the incidence of AKI in patients taking Imatinib falls between 4 and 7%, while the incidence of CKD is even higher, ranging from 14 to 23% in these patients. When evaluating patients with TKI-associated toxicities, it is crucial to consider any existing comorbidities they might have. The development of these renal issues can negatively impact both medication adherence and overall prognosis.

Further research on this topic can not only raise awareness among healthcare professionals but also lead to the development of strategies for prevention and timely management of these complications.

1.3 The significance of the study

This study investigates the impact of BCR-ABL TKIs on renal function in Ethiopian patients taking them. Notably, the extent of this impact and the influencing factors remain underexplored in Ethiopia. To our knowledge, this is the first study in the country to address this issue. Given the growing recognition of TKI-related renal dysfunction, even though previously considered uncommon, this research aims to elucidate the burden of such toxicities in the Ethiopian patient population. By identifying the factors influencing these effects, the study can facilitate early detection and management in patients.

2 Literature review

2.1 Magnitude and patterns of TKI-associated renal toxicities

A search of the World Health Organization's (WHO) Pharmacovigilance Database identified a total of 1,409 reported events of renal failure associated with tyrosine kinase inhibitors (TKIs) from November 7,

2001, to June 2, 2021. The majority of these reports originated in Europe, the United States, and Japan. Imatinib was implicated in approximately half of all reported events. While all five investigated TKIs—imatinib, nilotinib, dasatinib, bosutinib, and ponatinib—were associated with renal failure, none were definitively linked to tubulointerstitial nephritis. Specifically, dasatinib and nilotinib were linked to nephrotic syndrome, while nilotinib and ponatinib were associated with renal artery stenosis. Additionally, dasatinib was reported to be related to thrombotic microangiopathy(1).

An observational study conducted in Brazil investigated the association between imatinib and the development of renal complications in 105 patients. The study found that 7% of the patients developed AKI and 16% developed CKD while receiving imatinib treatment(11).

Yılmaz et al. conducted a retrospective analysis of medical records from 468 patients with newly diagnosed CML at the University of Texas MD Anderson Cancer Center. The study found that 4% of the patients developed TKI-associated AKI, and 14% developed TKI-associated CKD. The incidence of AKI was significantly higher in patients treated with imatinib compared to those treated with dasatinib or nilotinib(7).

A retrospective analysis was conducted on a cohort of 397 patients with chronic myeloid leukemia (CML). Patients were categorized by the specific drug they received: Imatinib (320 patients), Dasatinib (25 patients), and Nilotinib (53 patients). During the first year of treatment, 4% of patients in the imatinib group developed acute kidney injury (AKI). The incidence of AKI was significantly lower in the dasatinib group, with only one patient experiencing the condition. None of the patients in the nilotinib group developed AKI within the first year(10).

A retrospective study by Xin et al. investigated the incidence of CRAE in patients with CML receiving TKIs. CRAE was established based on two criteria: a reduction in eGFR by 30% compared to baseline or a sustained eGFR below 60 ml/min/1.73 m2 for a minimum duration of 90 days. The study included 460 patients, with 360 receiving Imatinib and the remaining 100 receiving Nilotinib. After a median follow-up of 12 months, 44% of patients in the Imatinib group developed CRAE, while 23% developed CKD. In the Nilotinib group, the median time to develop CRAE and CKD was 21 and 6 months, respectively, with a prevalence of 20% and 8%, respectively(16).

In Africa, there is a paucity of data on renal dysfunction associated with TKI use in CML patients. There is no single study in Ethiopia that has addressed this issue.

2.2 Factors associated with TKI-related renal toxicities

Multiple studies have identified various risk factors associated with TKI-induced renal toxicities. These include pre-existing impaired kidney function, the specific type, dose, and duration of the TKI used, age, and the presence of other medical conditions like HTN and DM. Additionally, the use of certain non-TKI medications (e.g., hydroxyurea, interferon) and specific anti-hypertensive medications.

The One of the most crucial risk factors identified is age. Studies have shown that the incidence of TKI-associated renal toxicities is significantly higher in elderly patients, with the observed decline in eGFR exceeding the expected decline solely attributed to aging (6, 7, 10, 11).

Patients who developed TKI-related renal toxicities had a higher prevalence of medical comorbidities, such as DM and HTN, compared to patients who did not develop these complications (10, 11, 13, 17). Pre-existing low renal function has been associated with an increased risk of developing renal toxicities during TKI therapy (7, 10, 11, 16).

In several studies, imatinib was found to be more detrimental to kidney function compared to other TKIs. The effectiveness of switching from imatinib to alternative therapies is unclear. One study observed improvement in kidney function after switching therapies, whereas another did not find a significant benefit(14). The duration of TKI therapy has been identified as a risk factor contributing to the rapid rate of eGFR decline observed in patients with CML(18).

Non-TKI medications play a diverse role in patient care, including the management of co-existing medical conditions. Several studies have shown an association between the use of antihypertensive medications and an increased risk of TKI-associated renal toxicities compared to patients who do not use them. Notably, one study found a rapid decline in eGFR in patients taking angiotensin-converting enzyme (ACE) inhibitors(10, 19). While loop diuretics can be used cautiously for managing edema associated with TKIs or comorbidities, their use should be monitored due to the potential risk of further affecting kidney function (8, 19). Additionally, another study identified a possible association between the use of hydroxyurea, a cytoreductive agent, and TKI-related renal toxicities (6).

All TKIs can cause gastrointestinal (GI) side effects, including nausea, vomiting, diarrhea, and abdominal pain. Bosutinib and nilotinib represent the extremes of this spectrum, with bosutinib having the highest and nilotinib having the lowest rates of GI toxicities. These side effects can contribute to dehydration, which can further complicate kidney function (9, 10, 12).

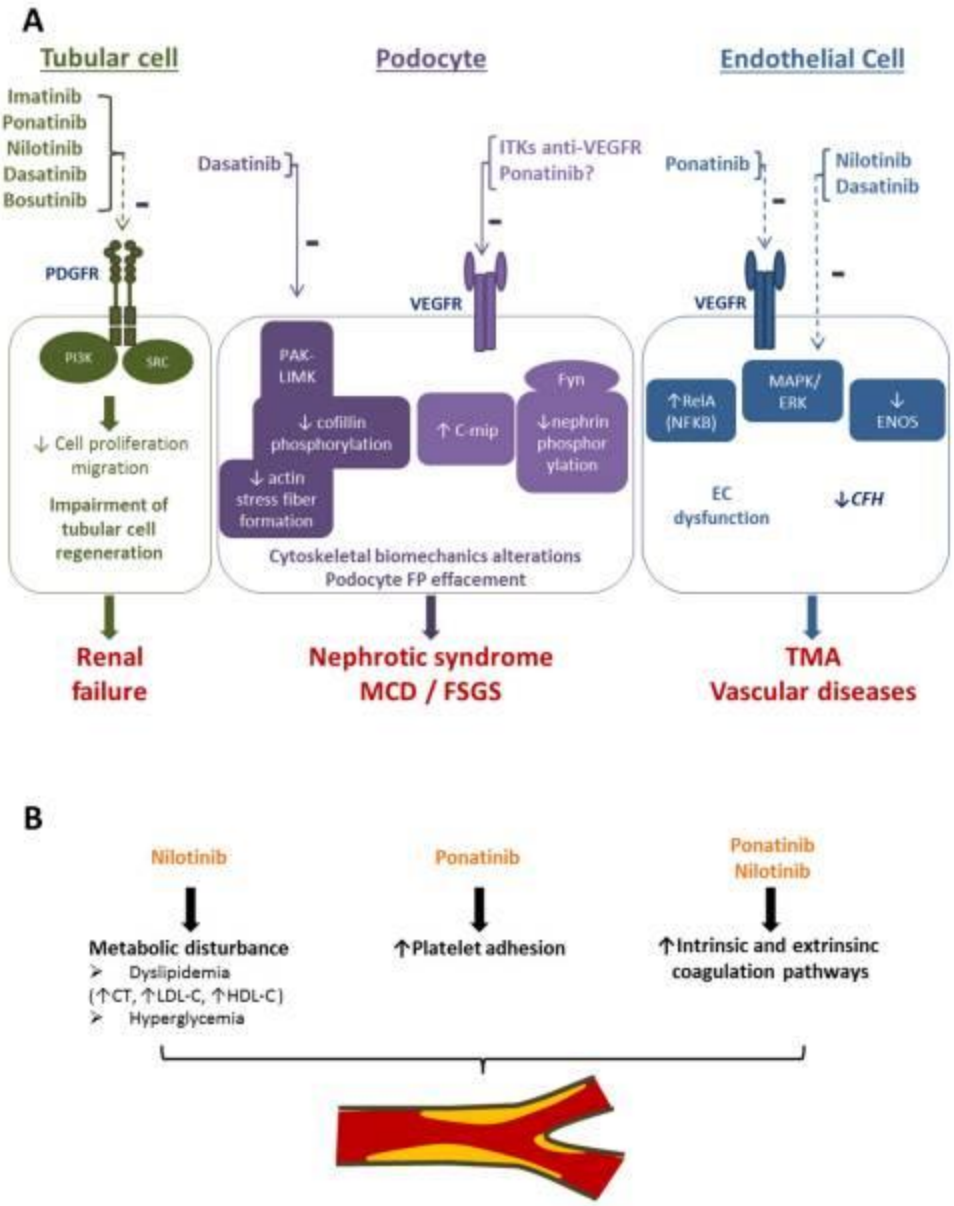

Figure 1: conceptual framework. Adopted from (Cellier M, Bourneau-Martin D, Abbara C, Crosnier A, Lagarce L, Garnier AS, Briet M. Renal Safety Profile of BCR-ABL Tyrosine Kinase Inhibitors in a Real-Life Setting: A Study Based on Vigibase®, the WHO Pharmacovigilance Database. Cancers (Basel). 2023 Mar 29;15(7):2041. doi: 10.3390/cancers15072041. PMID: 37046701; PMCID: PMC10093506.)

2. Objectives

2.3 General objective

- To determine the burden and pattern of TKI associated renal toxicities

2.4 Specific objectives

- To describe the type of renal abnormalities in patients taking BCR-ABL TKIs
- To identify factors associated with associated renal toxicities
- To evaluate the difference in renal toxicities between different TKIs
- To assess the practice of renal function assessment during the follow-up of patients taking TKIs

3 Methodology

3.1 Study Setting and Design

A hospital-based cross-sectional analytic study was conducted from January 2023 to January, 2024, at Tikur Anbesa Specialized Hospital (TASH), the only center in the country that provides TKIs to patients. These TKIs are donated by the MAX Foundation. All the TKIs are freely provided through the generous and continous support of GIPAP (Glivec international patient assistance program).

3.2 Participants

The source population included all patients who followed up at the TASH hematology unit and were taking TKIs. The study population included all patients from the source population who had at least one documented renal function test (RFT) within the past 3 months.

3.3 Eligibility Criteria

Inclusion criteria: All patients taking BCR-ABL TKIs were included.

Exclusion criteria: Patients with no documented serum creatinine level at baseline or within the past 3 months were excluded.

3.4 Sample Size and Sampling Technique

3.4.1 Sample size:

Sample size is determined based on the following assumptions; the confidence level to be 95%, margin of error <0.05 to be significant.

n=$\frac{z^2 p(1-p)}{d^2}$where n= number of sample, z= standard score at 95% CI which is 1.96, P- the prevalence of TKI associated renal toxicities is assumed to be 25% most studies had similar findings. ‘d’ is margin of error.

n=288,

Since, the number of source of population is 2500 (which is less than 10,000). Therefore, sample size is Sample size = $\frac{n}{1+n/N}$ = $\frac{384}{1+384/2500}$=258.

3.4.2 Sampling technique:

Convenient non-probability sampling was used.

3.5 Study Variables

3.5.1 Dependent variable:

- Development of adverse drug events (ADEs)

3.5.2 Independent variables:

- Demographics: Age, sex
- Treatment characteristics: Dose of TKI, change of TKI, duration of therapy, treatment outcome
- Baseline renal function: Baseline serum creatinine or eGFR
- Comorbidities: Hypertension (HTN), diabetes mellitus (DM), cardiac diseases
- Concomitant medications: Non-TKI medication use

3.6 Operational definition

- **AKI** is an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days.
- **TKI associated AKI:** defined as the same criteria used for general AKI, but specifically linked to TKI use or documentation of AKI by a physician which was not explained by other cause.
- **CKD** is decrement of glomerular filtration rate (GFR) <60 mL/min/1.73 for three or more months.
- **CKD associated with TKI use-** defined decrement of eGFR to < 60 ml/min/1.73 m 2 ≥90 days after initiation of TKI.
- **TKI associated Adverse Renal Event** is defined as a 30% eGFR reduction from baseline or eGFR < 60 ml/min/1.73 m 2 which occurred for more than 90 days or the development of AKI or development of significant proteinurea after initiation of TKI
- **Non TKI medication use** defined as use of any anti hypertensive drugs, loop diuretics or Hydroxyurea
- **Significant proteinuria**-defined as having more than 500 milligrams of protein in urine over a 24-hour period**.**
- **Significant associated with TKI use:** Specific occurrence of significant proteinuria after starting TKI therapy.

3.7 Data Collection and Statistical analysis

Data were collected using a structured data collection tool developed by reviewing relevant scientific literature and tailored to meet the study objectives. Trained medical interns conducted the data collection. Information on sociodemographic characteristics, comorbidities (HTN, DM, cardiac disease), laboratory investigations (urine analysis, serum creatinine, CBC), non-TKI medications, and treatment outcomes were extracted from medical records.

The data were coded and entered into the KoBo Collect tool. They were then exported to SPSS version 26 for analysis. Descriptive statistics were used to summarize and present the data, including frequencies, percentages, and tables.

Initially, the association between the outcome variable and the predictor variables was assessed using a bivariate logistic regression model. All variables with a p-value less than or equal to 0.25 in the bivariate analysis were retained and included in the final multivariable logistic regression model. This approach aimed to control for potential confounding factors. The Hosmer-Lemeshow test was employed to assess the model's goodness of fit. The model was deemed to have a good fit due to the non-significant Hosmer-Lemeshow statistic (p = 0.256). The model explained 23.7% of the variance (Nagelkerke R-squared).

The multicollinearity test results showed no significant correlation between the independent variables. This finding was supported by the variance inflation factor (VIF) being less than 10, indicating no multicollinearity concerns.

The association between the independent and outcome variables was assessed using adjusted odds ratios (AORs) with 95% confidence intervals (CIs). A p-value less than 0.05 was considered statistically significant.

3.8 Data Quality Assurance

To ensure data quality, the following measures were undertaken:

- A well-designed data collection tool was used.
- The tool's format and clarity of language were reviewed before data collection.
- Collected data were reviewed weekly for completeness and consistency.
- The principal investigator randomly selected a sample of collected data and compared it to the corresponding medical charts for accuracy.

3.9 Ethical Considerations

Ethical clearance was obtained from the Addis Ababa University, College of Health Sciences, School of Medicine Institutional Review Board before starting the study. Privacy and confidentiality of collected information were maintained throughout the process.

3.10 Dissemination of Results

The research findings will be submitted to the Department of Internal Medicine, College of Health Sciences, Addis Ababa University. We also plan to submit the results for publication in reputable journals.

4 Results

4.1 Sociodemographic characteristics

A total of 260 patients were included in the study. Among them, 142 (54.6%) were male. The mean age of the patients in the study was 45.15 years (SD ± 14.03).

Table 1: Sociodemographic characteristics of patients

		Mean + SD	Frequency	Percentage
Age (Years)		45+ 14.03		
Sex	Male		142	54.6%
	Female		118	45.4%

4.2 Disease characteristics

The study population primarily consisted of patients with CML, with 86.5% falling into this category. Notably, 92% of these CML patients were in the chronic phase of the disease, while only a small percentage (4.9% and 3.1%, respectively) were in the accelerated phase or blast crisis. Table 2 summarized the diagnosis.

Table 2: Diagnosis of the patients

		Frequency	Percentage (%)
Diagnosis	CML	225	86.5
	GIST	31	11.9
	DFSP	3	1.2
	HES	1	.4
	Total	260	100.0

4.3 Baseline hematologic and renal parameters

The median creatinine level was 0.7 mg/dL (IQR 0.6-0.8). Similarly, the median eGFR, was 115 mL/min/1.73m² (IQR 101-123). However, only a small percentage (6.5%) of patients underwent a urine analysis at baseline. Among those who did, the majority (10) had no abnormalities detected. However, a smaller group (7 patients) exhibited varying levels of proteinuria, ranging from +1 to +3. 90% of patients was GFR stage 1 at the time of diagnosis. Hematologic and renal function parameters are summarized in Table 3.

Table 3: baseline hematologic and renal function parameters

	Diagnosis	

	CML	Others(DFSP, GIST, HES)	Percentage (%)
	Median	Median	
WBC (Cells/uL)	229000	5230	
Hemoglobin (g/dl)	10.00	13.00	
Platelet (Cells/uL)	349000	267000	
Baseline creatinine (mg/dl)	.70	.70	
Baseline eGFR (mL/min/1.73m^2)	116	103	
Baseline eGFR stage 1	NA	NA	90
Baseline eGFR stage 2	NA	NA	7.7
Baseline eGFR stage 3a	NA	NA	2.3
Baseline eGFR stage 3b	NA	NA	0
Baseline eGFR stage 4	NA	NA	0
Baseline eGFR stage 5	NA	NA	0

4.3.1 Co morbidities affecting renal functions

The most common comorbidities were DM and HTN, found in 5.5% and 5.1% of patients, respectively. Similarly, the most frequently used non-TKI medications were CCBs and ACEis, used in 3.5% and 3.0% of patients, respectively. Table 4 summarizes other comorbidities and medications.

Table 4 : Co morbidities

		Median	Frequency	Percentage (%)
Total duration of TKI (months)		35		
DM	No		245	94.2%
	Yes		15	5.8%
HTN	No		246	94.6%
	Yes		14	5.4%
HIV	No		254	97.7%
Cardiac	No		256	98.5%
	Yes		4	1.5%
Thiazide diuretics	No		256	98.5%
	Yes		4	1.5%
CCB	No		251	96.5%
	Yes		9	3.5%
ACEi/ARB	No		252	96.9%
	Yes		8	3.1%

4.4 Treatment and Outcomes

Initially, all patients received imatinib. The daily dosing regimen varied, with 240 patients receiving 400mg PO, 17 receiving 600mg PO, and 3 receiving 800mg PO daily or in divided doses. For CML patients, hydroxyurea was used initially to manage high white blood cell counts and reduce them below 20,000 Cells/uL, followed by the initiation of imatinib. The median duration of treatment was 34.5(IQR 16-79.5) months. Approximately 19% of patients required a switch to second or third-line therapy due to resistance or treatment failure. Among these patients, Nilotinib was the most common alternative TKI (57.4%), followed by Bosutinib and Dasatinib (around 18.5% each). A smaller number (5.6%) received Ponatinib.

To assess treatment effectiveness, molecular testing was performed on 104 patients. Notably, 63.5% achieved major molecular remission (MMR). However, among all 260 patients, only 63.5 patients achieved either MMR or complete hematologic response (CHR). The remaining 36.5% of patients experienced either hematologic/molecular failure or disease progression.

4.5 Magnitude of Adverse Renal Events

TKI treatment led to a statistically significant decrease in eGFR, as measured by the Wilcoxon Signed-Ranks test (mean difference: -6.365, p-value < 0.001). AREs were defined as any of the following: presence of acute kidney injury (AKI), significant proteinuria, development of chronic kidney disease (CKD), or a decrease in eGFR by at least 30%. The overall prevalence of AREs was 13.1%. Four patients developed AKI, all of whom recovered but did not receive nephrologist's follow-up. Seven patients developed CKD after the initiation of TKI: four with stage 3a, two with stage 3b, and one with stage 4 diseases. Only four of these patients were linked to nephrology follow-up. Additionally, one patient developed significant proteinuria (2 g/24 hours) within the first year of follow-up. This patient's baseline eGFR was 56 mL/min/1.73 m² and progressed to stage 3b CKD within 50 months. It could be undiagnosed renal disease before treatment initiation. From the seven patients who developed CKD only 4 of them received nephrologist care. Only thirty-four patients had a recent urinalysis, with results showing protein levels ranging from +1 to +3. 27 patients had protein +1, 4 patients had protein +2 and 3 patients had protein +3. However, only one of these patients underwent a 24-hour urine protein test. Only four of those patients had AREs.

The following 2 tables summarized characteristics of patients who develop AKI and CKD.

Table 5: Characteristics of patients who developed AKI

patient	Age (Year)	Sex	Diagnosis	Baseline eGFR	Last eGFR	Time to AKI development (in months)	Comorbidity	Non TKI medications
1	58	Female	CML (AP)	58	74	12	None	None
2	36	Male	CML (CP)	119	73	60	None	None
3	83	Male	GIST	75	60	1	DM, HTN	CCB, Metformin
4	52	Male	CML (CP)	108	91	1	None	None

Table 6: Characteristics of patients who develop CKD

Patient	Age (Year)	Sex	Diagnosis	Baseline eGFR	Last eGFR	Stage of CKD	Duration of TKI	Comorbidity	Non TKI medication	UAA result
1	63	Female	GIST	64	20	4	19	DM, HTN	ACEi/ARB, insulin	Protein +1 24 hour-175mg
2	55	Female	CML (CP)	95	36	3b	169	None	None	NA
3	60	Female	CML (CP)	76	40	3b	86	DM	Metformin	NA
4	50	Female	CML (CP)	111	55	3a	103	None	None	NA
5	61	Female	CML (CP)	77	52	3a	109	HTN	Thiazide, ACEi/ARB	NA
6	71	Male	CML (CP)	73	54	3a	31	None	None	NA
7	66	Female	CML(CP)	62	55	3a	93	None	None	NA

4.6 Factors associated with ARE

Upon binary regression, age, sex, baseline creatinine, total duration of TKI treatment, DM, HIV infection, HTN, use of ACEi, and treatment outcome were associated with AREs using a p-value of 0.25 as a cutoff. These variables were then included in a multivariate logistic regression analysis, which revealed that five variables were statistically significantly associated with the development of AREs. These variables were: total duration of TKI treatment (AOR: 1.009, 95% CI: 1.00-1.017, P = 0.034), HTN (AOR: 7.651, 95% CI: 1.483-39.479, P = 0.015), HIV (AOR: 7.599, 95% CI: 1.184-48.770, P = 0.033), male gender (AOR = 0.366, 95% CI = 0.154-0.918, P = 0.032), and the combined variable of MMR and CHR (AOR: 2.822, 95% CI: 1.032-7.714, P = 0.043).

While the study did not find a statistically significant association between switching to second/third-line therapy and developing AREs, it's only 4 out of 49 patients who switched therapy experienced AREs. Table 7 summarizes these factors associated with AREs.

Table 7: Factors associated with ARE

Variables		ARE		COR (95% CI)	P- value	AOR (95% CI)	P- value
		Yes	No				
Age (mean + SD)				1.043 (1.015-1.07)	0.002	1.0309 (0.997-1.064)	1.03
Sex	Male	14	128	0.536 (0.258 -1.114)	0.095	0.376 (0.154-0.918)	0.032*
	Female	20	98				
Baseline creatinine (mean)		0.78	0.72	4.722 (0.859 -25.947)	0.074	5.45(0.577-51.495)	0.139
total duration of TKI treatment in months (mean)		66.5	45.9	1.009 (1.002-1.016)	0.014	1.009 (1.00-1.017)	0.034*
DM	Yes	4	11	0.384 (0.115-1.282)	0.12	0.708 (0.170- 2.951)	0.636
	No	30	215				
HTN	Yes	7	7	8.111 (2.643- 24.892)	<0.0001	7.651 (1.483-39.479)	0.015*
	No	27	219				
HIV	Yes	2	4	3.469 (0.61-19.711)	0.161	7.599 (1.184-48.77)	0.033*
	No	32	222				
use of ACEi	Yes	4	4	7.4 (1.756-31.152)	0.006	1.519 (0.17- 13.592)	0.709
	No	30	222				
treatment outcome	MMR + CHR	26	139	2.034 (0.881- 4.695)	0.096	2.822 (1.032-7.714)	0.043*
	In hematologic/molecular failure + progression	8	87				

* Variables that showed significant association with ARE upon multivariate logistic regression.

5 Discussion

This study was done to assess the effect of BCR-ABL TKIs associated renal toxicities and associated factors in a patients taking those medications for various reasons. The gender distribution showed slightly male predominant it can be because of both CML are more common in men(20).

Our study observed a statistically significant decline in eGFR of 6.365 mL/min/1.73 m² over a median follow-up of 34.5 months in patients receiving Imatinib treatment. This finding aligns with previous research demonstrating the impact of Imatinib on kidney function (7, 11, 14). Yilmaz et al. reported a steeper initial decline in their study, with a mean decrease of 8 and 10 mL/min/1.73 m² at 3 and 6 months, respectively, before stabilizing after 4 years. Conversely, dasatinib, showed a smaller initial decline (3 and 4 mL/min/1.73 m² at 3 and 6 months) and potentially stabilized after 1 year. Interestingly, Nilotinib even showed an increase in eGFR in similar study, highlighting the varying effects of different TKIs on kidney function. Marcolino et al. observed a significant decrease in eGFR with longer Imatinib treatment duration (2.77 mL/min/1.73 m² per year on average). Additionally, a meta-analysis of nine studies revealed a significant eGFR decline in patients taking Imatinib in six of the studies (21).

In our study, the incidence of acute kidney injury (AKI) was 1.5%, lower than the reported rates in other studies (Molica et al. and Yilmaz et al.: 4%, Marcolino etal.: 7%)(7, 10, 11). This disparity may be attributed to our study population being younger (median age: 45 years) and having a lower comorbidity burden compared to Molica et al. (median age: 57.5 years) and Yilmaz et al. (median age: 48 years at initiation, followed for 52 months)(7, 10). Additionally, only 5.8%, 5.4%, and 1.5% of our patients had diabetes mellitus, hypertension, and chronic kidney disease, respectively, while the Yilmaz et al. study reported a baseline prevalence of 25% hypertension, 7% diabetes mellitus, 9% coronary artery disease, and 11% chronic kidney disease(7). Similarly, Marcolino et al. found a prevalence of 28% hypertension, 7% diabetes mellitus and 5% CKD. These findings may explain the low incidence of AKI in our patients. Importantly, all AKI cases in our study resolved without requiring discontinuation of the TKI therapy. This contrasts with Marcolino's study, where only 1 out of 7 patients with AKI recovered(11).

Our study observed a significantly lower incidence of adverse renal events (AREs) at 13.1% compared to the 44% prevalence of CRAEs reported by Xin et al. in their imatinib cohort. In the study CRAE was established based on two criteria: a reduction in eGFR by 30% compared to baseline or a sustained eGFR below 60 ml/min/1.73 m² for a minimum duration of 90 days. Similarly, the prevalence of chronic kidney disease (CKD) was substantially lower in our study (2.7%) compared to 23% in Xin et al.'s imatinib group (17). Several factors may explain these differences. Firstly, Xin et al.'s study population had a higher baseline burden of kidney-related comorbidities (16% vs. 11.2% in our study), including hypertension and diabetes. Secondly, a larger proportion of patients in their study (20%) were using medications like antihypertensives and diabetes treatments, which can potentially affect kidney function. Additionally, the median baseline eGFR was significantly lower in Xin et al.'s study (94 vs. 115 in our study), indicating a potentially more compromised kidney function at baseline in their cohort(16). These findings are consistent with other studies reporting a higher incidence of CKD in patients treated with imatinib. For instance, one study observed a 14% CKD rate among 468 newly diagnosed CML-CP patients receiving TKIs, with 82% of these patients taking imatinib (7). Similarly, another study found CKD in 16% of 105 patients on imatinib therapy(11).

The duration of TKI treatment was found to have a statistically significant associations with ARE with an AOR of 1.001 (95% CI: 1-1.017, P value: 0.034). Similar associations found in several studies (11, 17, 18). A study by Yimaz et al. found that CCyR and MMR were associated more frequently with CKD, but

not AKI. However, their multivariate analysis did not reveal any significant associations with either AKI or CKD(7). Conversely, our study found a significant association with an odds ratio (AOR) of 2.822 (CI: 1.032-7.714, p-value: 0.043).

A previous study found an association between male sex and the development of chronic renal injury in 564 patients with CML-CP(16). Conversely, our study found that male sex was associated with a protective effect, with an AOR of 0.376 (95% CI: 0.154-0.918; P value = 0.032). One study reported an association with females during multivariate analysis, which supports our findings(22).

HTN found to have association with the development of ARE with AOR (7.651; 95% CI, 1.483-39.479; P= 0.015). And it is consistently demonstrated in various studies (7, 11). A previous study retrospectively analyzed 142 patients with CML and found a decline in eGFR in patients taking anti-hypertensive medication which is rapid in patients taking ACEi compared to those not taking it. In contrast, our study did not identify a significant association between ACEi use and AREs. This difference may be attributable to the limited sample size of patients taking ACEi in our study (19).

Our study found that HIV is significantly associated with ARE with AOR of 7.599, (95% CI: 1.184-48.770, P = 0.033). No other studies have reported this association. Diabetes found association with the development of AREs (7, 10, 17). But our study did not find strong association.

While age was as an independent risk factor for developing TKI-associated renal toxicities in the literature, our study did not identify a significant association between these factors (7, 10, 11, 14, 16, 17). Use of standard dose imatinib with decreased dose does not result in significant difference in mean eGFR(17). We also observed eGFR no difference between patients receiving standard-dose and lower-dose imatinib.

Use of previous non-TKI treatment (such as hydroxyurea, interferon, and chemotherapy) were found to be associated with TKI associated renal toxicities. In our case almost all patient received hydroxyurea and it was difficult to assess the effect(16).

There is mixed evidence regarding whether changing imatinib to second or third-line therapy, or discontinuing imatinib, improves renal dysfunction. In our case, there is no increased risk in patients taking imatinib compared to those switched to second or third-line therapy. One study found that changing imatinib to second-line therapy improves renal dysfunction, even in patients with new-onset CKD(14). Another studyshowed no significant difference in eGFR after TKI discontinuation in patients who are in treatment-free remission or molecular relapse (18).

6 Limitation of the study

It has small sample size which make it difficult for generalization of the result. **C**onvenience sampling and the variable timing of these measurements of serum creatinine raise concerns about the generalizability and accuracy of our findings.

7 Recommendations

In this study, we found an association between TKI use and renal dysfunction. Physicians should regularly monitor serum creatinine in patients receiving these medications, especially those with comorbid medical conditions like HTN and HIV. Timely referral to nephrologists is recommended. A larger sample size and regular monitoring of serum creatinine would be necessary in future studies to increase generalizability.

8 Reference

1. Cellier M, Bourneau-Martin D, Abbara C, Crosnier A, Lagarce L, Garnier AS, et al. Renal Safety Profile of BCR-ABL Tyrosine Kinase Inhibitors in a Real-Life Setting: A Study Based on Vigibase(®), the WHO Pharmacovigilance Database. Cancers. 2023;15(7).
2. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. The New England journal of medicine. 2017;376(10):917-27.
3. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer cell. 2009;16(5):401-12.
4. Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. The New England journal of medicine. 2012;367(22):2075-88.
5. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. The New England journal of medicine. 2010;362(24):2251-9.
6. Ren X, Qin Y, Huang X, Zuo L, Jiang Q. Assessment of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase receiving tyrosine kinase inhibitors. Ann Hematol. 2019;98(7):1627-40.
7. Yilmaz M, Lahoti A, O'Brien S, Nogueras-González GM, Burger J, Ferrajoli A, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. 2015;121(21):3894-904.
8. Caldemeyer L, Dugan M, Edwards J, Akard L. Long-Term Side Effects of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. Current hematologic malignancy reports. 2016;11(2):71-9.
9. Shyam Sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. Signal Transduction and Targeted Therapy. 2023;8(1):262.
10. Molica M, Scalzulli E, Colafigli G, Fegatelli DA, Massaro F, Latagliata R, et al. Changes in estimated glomerular filtration rate in chronic myeloid leukemia patients treated front line with available TKIs and correlation with cardiovascular events. Annals of Hematology. 2018;97(10):1803-8.
11. Marcolino M, Boersma E, Clementino N, Macedo A, Marx-Neto A, Silva M, et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. 2011;22(9):2073-9.
12. Kantarjian HM, Cortes JE, Kim DW, Khoury HJ, Brümmendorf TH, Porkka K, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood. 2014;123(9):1309-18.
13. Emadi E, Abdoli N, Ghanbarinejad V, Mohammadi HR, Mousavi Mobarakeh K, Azarpira N, et al. The potential role of mitochondrial impairment in the pathogenesis of imatinib-induced renal injury. Heliyon. 2019;5(6):e01996.
14. Hino A, Yoshida H, Tada Y, Koike M, Minami R, Masaie H, et al. Changes from imatinib mesylate to second generation tyrosine kinase inhibitors improve renal impairment with imatinib mesylate in chronic myelogenous leukemia. International Journal of Hematology. 2016;104(5):605-11.
15. Sayitoglu M, Haznedaroğlu IC, Hatirnaz O, Erbilgin Y, Aksu S, Koca E, et al. Effects of imatinib mesylate on renin-angiotensin system (RAS) activity during the clinical course of chronic myeloid leukaemia. The Journal of international medical research. 2009;37(4):1018-28.
16. Ren X, Qin Y, Huang X, Zuo L, Jiang Q. Assessment of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase receiving tyrosine kinase inhibitors. Annals of Hematology. 2019;98(7):1627-40.
17. Sakurai M, Kikuchi T, Karigane D, Kasahara H, Matsuki E, Hashida R, et al. Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia. International Journal of Hematology. 2019;109(3):292-8.
18. Okamoto S, Ureshino H, Kawaguchi A, Miyazono M, Ikeda Y, Kimura S. Assessment of estimated glomerular filtration rate in patients with chronic myeloid leukemia following discontinuation of tyrosine kinase inhibitors. International Journal of Hematology. 2020;112(1):41-5.
19. Tsuda M, Hirata A, Tokunaga S, Masuda T, Haji S, Kimura D, et al. Rapid decrease in eGFR with concomitant use of tyrosine kinase inhibitors and renin–aldosterone–angiotensin system inhibitors in patients with chronic myelogenous leukemia. International Journal of Hematology. 2022;116(6):863-70.

20. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). Best Practice & Research Clinical Haematology. 2009;22(3):295-302.
21. Singh AK, Hussain S, Ahmed R, Agrawal N, Bhurani D, Klugar M, et al. Impact of imatinib treatment on renal function in chronic myeloid leukaemia patients. Nephrology (Carlton, Vic). 2022;27(4):318-26.
22. Motohashi T, Kamata H, Hayama K, Michishita Y, Horigome Y, Tadera N, et al. Changes in estimate glomerular filtration rate associated with long-term tyrosine kinase inhibitor treatment in patients with chronic myelogenous leukemia. 2021;51(1):32-41.

9 Annex

9.1 Data collection sheet

Patient I care ----------

I. Demographic data
   1. Age----------
   2. Sex Male ☐ Female ☐
   3. Address:
   4. Occupation:

II. Baseline clinical characterstics
   1) Intial diagnosis iagnosis
      a. Chronic phase CML
      b. Accelerated pahse CML
      c. Blast crisis phase CML
      d. Other idiagnosis with indication for BCR-ABL TKI
   2) Bseline hematologic parameters
      a. WBC count
      b. Hemoglobin
      c. Platelet
      d. Blast (%)
   3) Baseline renal investigation investigations
      a. Serum Creatinine : Available---------, Unavailable--------
      b. eGFR (CKD-EPI without race)--------
      c. UAA available----------unavailable----------
         - If available (Protein----, Blood-----, Cast------)
         - 24 hour urine protein----------

III. TKI related
   1) Type of TKI initiated
      - Imatinib
      - Nilotinib
      - Dasatinib
      - Bosutinib
      - Ponatinib
   2) Duration of TKI therapy---------
   3) Change in TKI? Yes----- No.--------
      a. If yes what was the change---------- .
      b. If yes, what was the reason for change ----------

IV. renal function determination in the first 12 months of follow up
   1) Number of serum creatinine determinations in the first year of TKI treatment----------
      ----

2) If serum creatinine is deterimed at least once in the first 12 months of follow up, what is the difference between the basleine serum creatinine and the last creatinine determined in within the 12 months follow up period:
    a) In absolute numbers
    b) In percentage changes
    c) Does the patient have CKD by GFR criteria (GFR<60ml/min)?
    d) If there is CKD
        - what is the stage?----------
        - Was the diagnosis of CKD documented? ----------
        - Was the patient linked to nephrology care? ----------
3) Number of urinalysis done in the first 12 months of follow up----------
    a) If there is a urinalysis done, what was the urinalysis finding in the last urinalysis done within the first 12 months
        - Urine protein---------
        - Urine blood/hematuria---------
4) Does the patient have a documented AKI?

V. Follow up tests after 12 months of follow up
1) Number of serum creatinine determinations per year----------
2) Number of urinalysis determinations per year----------
3) Last serum creatinine and eGFR----------
4) Does the patient have CKD by GFR criteria? Yes No
    - If yes, what is the stage of CKD-------
    - If yes, was the diagnosis of CKD documented? Yes No
    - If yes, was the patient linked to nephrology care? Yes No

VI. Documented AKI, CKD, significant proteinuria at any point in time during the follow up period
- AKI? Yes No
  If yes, when is the time from initiation of therapy?
- CKD? Yes No
- Proteinuria? Yes No

VII. CML treatment outcome
1. Remission
    a) Hematologic
    b) Molecular
2. Refractory
3. Relapse

VIII. Other comorbities
1) DM
2) HTN
3) Cardiac disease
4) Liver disease
5) Other comorbdities: specify----------

IX. Non TKI medication for chronic illness comorbities

1. Diuretics
2. ACEI/ARB
3. Other Anti HTN,---------
4. Other medications---------

9.2 Investigators Signature Form

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission of Department of Internal Medicine, except when necessary to protect the safety, rights, or welfare of study participants. I agree to personally conduct or supervise this study. I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and are met. I agree to maintain adequate and accurate study records and to make those records available for inspection by the department or unit heads, hospital administrators, and/or other applicable regulatory entities. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Signature: ____ Date: ___