The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 7, 2025

TKI RELATED CARDIOTOXICITY IN METASTATIC SOLID ORGAN TUMORS PRESENTING IN ONCOLOGY DEPARTMENT CMH RAWALPINDI

Dr Madiha Sajjad[*1], Dr Mohammad Nadeem Piracha[2], Dr Sajid Hussain[3], Dr Mansoor Zeeshan[4] Dr Raishma[5], Dr Hafiz Mohammad Daniyal[6]

*[*1,5,6]Registrar Medical Oncology*
[2]Professor/Head of Department (HOD) Medical Oncology
[3]Consultant Medical Specialist
[4]Consultant Medical Oncologist

[1]madihasajjad24@gmail.com [2]dr_nadeempiracha@hotmail.com [3]sajidrao88@gmail.com
[4]mansoor1569@hotmail.com [5]raishmanoordad@gmail.com [6]m.daniyal0707@gmail.com

DOI: https://doi.org/10.5281/zenodo.15869130

Keywords
Cardiotoxicity, Echocardiography, Metastatic Tumors, Risk Factors, Tyrosine Kinase Inhibitors

Article History
Received: 07 April, 2025
Accepted: 27 June, 2025
Published: 12 July, 2025

Corresponding Author: *
Dr Madiha Sajjad

Abstract

Background: *Although their use is linked with great cardiotoxicity, which can affect survival results, tyrosine kinase inhibitors (TKIs) are extensively employed in the therapy of metastatic solid organ cancers.* ***Objectives:*** *The frequency, risk factors, and effects of TKI-related cardiotoxicity in patients treated at the Oncology Department, CMH Rawalpindi were examined in this work.*

Methods: *180 patients with metastatic solid organ cancers undergoing TKI treatment from April 2024 to November 2024 were included in this cross-sectional analysis. Clinical, biochemical and echocardiographic data were used to evaluate cardiotoxicity. Using multivariate logistic regression, risk factors were examined; survival results were then assessed.*

Results: *Cardiotoxicity was reported in 41.7% of individuals; the most often occurring problems were left ventricular dysfunction (17.2%) and hypertension (25%). Age >60 years (OR: 3.46, p<0.001), smoking (OR: 1.93, p=0.019), history of hypertension (OR: 2.54, p=0.004) and TKI therapy duration >8 months (OR: 4.17, p<0.001) were among the risk variables most definitely linked to cardiotoxicity. In cardiotoxic group, echocardiographic results showed lower left ventricular ejection fraction (50.4% vs. 62.7%), and higher pulmonary artery pressures. p = 0.001, strongly linked with cardiotoxicity (p<0.001 were elevated biomarker values including troponin-I and NT-proBNP). Patients with cardiotoxicity had notably reduced total survival (12.3 vs. 16.2 months, p = 0.001) and progression-free survival (8.7 vs. 12.5 months, p = 0.001).*

Conclusion*: Cardiotoxicity is a prevalent and clinically important side effect of TKI treatment that compromises cardiovascular health and survival results. Early interventions, biomarker evaluations, and regular cardiovascular monitoring help to reduce these risks and maximize therapy results for patients on TKI medication.*

INTRODUCTION

For many cancer patients, targeted therapy has transformed the management of metastatic solid organ cancers and provided better survival and quality of life. Among these treatments, TKIs have become the pillar because they can target molecular pathways vital for tumor development and spread only [1-2]. Among others, TKIs are extensively utilized for cancers including non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GAST). Their usage is not without difficulties, nevertheless, since they are linked with a range of negative consequences including cardiotoxicity [3-5].

One major risk that can compromise TKIs' therapeutic advantages is cardiotoxicity. It covers a spectrum of cardiovascular problems including left ventricular dysfunction, hypertension, arrhythmias and ischemic events that could show up either during or following treatment [6-7]. Direct myocardial damage, endothelial dysfunction and interference with signaling pathways including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) define the fundamental mechanisms of TKI-induced cardiotoxicity as complex, multifactorial events [8-9]. Apart from tumor angiogenesis, these channels are essential for preserving cardiovascular homeostasis and hence their blockage can have negative consequences on the heart and vasculature [10].

To guarantee best patient outcomes in clinical practice, TKI-related cardiotoxicity identification and therapy are absolutely essential. Managing advanced cancer cases, including those treated with TKIs, the oncology department at Combined Military Hospital Rawalpindi has been leading front-runner. Understanding the incidence, risk factors and effects of TKIs-induced cardiotoxicity in this population is crucial given their growing usage in the therapy of metastatic solid organ cancers. This study therefore, intended to look at the frequency and clinical features of TKI-related cardiotoxicity in patients having metastatic solid organ malignancies.

Materials and Methods

Study Design and Setting

From April 2024 until November 2024, the Oncology Department of Combined Military Hospital (CMH) Rawalpindi, a tertiary care hospital with excellent diagnostic and therapeutic facilities, conducted this cross-sectional study.

Study Population

The study comprised adult patients having treatment with tyrosine kinase inhibitors (TKIs) who had been diagnosed with metastatic solid organ malignancies. We included patients of both sexes ranging in age from eighteen years and above. To concentrate on TKI-related cardiotoxicity, patients having pre-existing major cardiovascular illnesses or those undergoing simultaneous cardiotoxic chemotherapeutic treatments were excluded.

Sample Size

Assuming an expected prevalence of TKI-related cardiotoxicity at 10%, the WHO sample size calculator helped one to determine the sample size with a 95% confidence level and a margin of error of 5%. The computed sample count came to 180 cases. Until the intended sample size was reached, suitable patients were enlisted using non-probability sequential sampling.

Data Collection

Medical records and standardized questionnaire helped to gather the data. For every participant, the following was gathered:

1. Age, gender, BMI and smoking status comprise demographic data.
2. Type of metastatic tumor, particular TKI utilized, dosage and length of treatment are among the clinical aspects.
3. Evaluation of Cardiovascular Systems including blood pressure, heart rate, symptoms including dyspnea, palpitations or chest pain, and medications [11].

Cardiotoxicity Assessment

Clinical assessment, laboratory testing and imaging techniques all helped to evaluate cardiotoxicity:

1. Echocardiography and electrocardiograms (ECGs) were used to identify left ventricular dysfunction and arrhythmias.

2. Troponins and natriuretic peptides among other serum indicators were tested to find myocardial damage.
3. Blood pressure was tracked to assess hypertension.
4. Established cardio-oncology rules helped to classify cardiotoxicity [11].

Statistical Analysis

SPSS version 26 helped to enter and examine the data. Clinical and demographic data were compiled using descriptive statistics. Calculated as percentage of the overall sample, the frequency of TKI-related cardiotoxicity was using chi-square tests and logistic regression, associations between cardiotoxicity and possible risk factors, e.g., age, tumor type and TKI dosage were investigated with the significance level set at $p = 0.05$.

Ethical Approval

Approved by CMH Rawalpindi's Institutional Review Board (IRB), the study was conducted under the Declaration of Helsinki. Every participant received written informed consent; they were guaranteed their right to withdraw at any moment without influencing their treatment. Patient data kept confidentiality by means of anonymization and safe storage. Using non-invasive techniques guarantees no damage to the subjects. Any unusual results from cardiovascular tests were sent straight for clinical management. Participation was voluntary; non-participants' care was unaffected. No conflicts of interest were declared.

Results

With the mean age of 55.3 ± 10.2 years and little male predominance, a male-to-female ratio of 1.2:1, our study comprised 180 participants. Out of all the participants, 42.8% were smokers; average BMI was 27.48 ± 4.83 kg/m². Reportedly present in 28.9% and 20.6% of patients respectively were hypertension and diabetes mellitus. NSCLC was the most often occurring cancer type (39.4%), followed by RCC at 25.6%, gastrointestinal stromal tumors (GAST) at 19.4%, and other malignancies at 15.6%). The TKI treatment lasted on average 8.3 months (IQR: 6.2–11.7). Emphasizing the variety of cancer types and related comorbidities, these features gave a complete picture of the study population (Table 1).

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	Mean ± SD / Frequency (%)
Sample Size	180
Age (years)	55.3 ± 10.2
Gender (Male:Female)	98:82 (1.2:1)
BMI (kg/m²)	27.48 ± 4.83
Smoking Status	77 (42.8%)
Hypertension History	52 (28.9%)
Diabetes Mellitus History	37 (20.6%)
Cancer Type NSCLC RCC GIST Others	 71 (39.4%) 46 (25.6%) 35 (19.4%) 28 (15.6%)
Duration of TKI Therapy (months)	Median 8.3 (IQR: 6.2-11.7)

With 41.7% (75 out of 180) individuals in the research group experiencing cardiotoxic episodes, frequency of the cardiotoxicity among them was noteworthy. Affecting 25% of the patients, hypertension was the most often noted cardiotoxicity; left ventricular failure followed in 17.2%. Less often occurring in 11.7% and 8.3% of the patients respectively were arrhythmias and myocardial ischemia. These results underlined the significant load of cardiovascular issues connected with TKI therapy in patients with metastatic solid organ

malignancies, stressing the need of careful monitoring and control of these side effects (Figure 1).

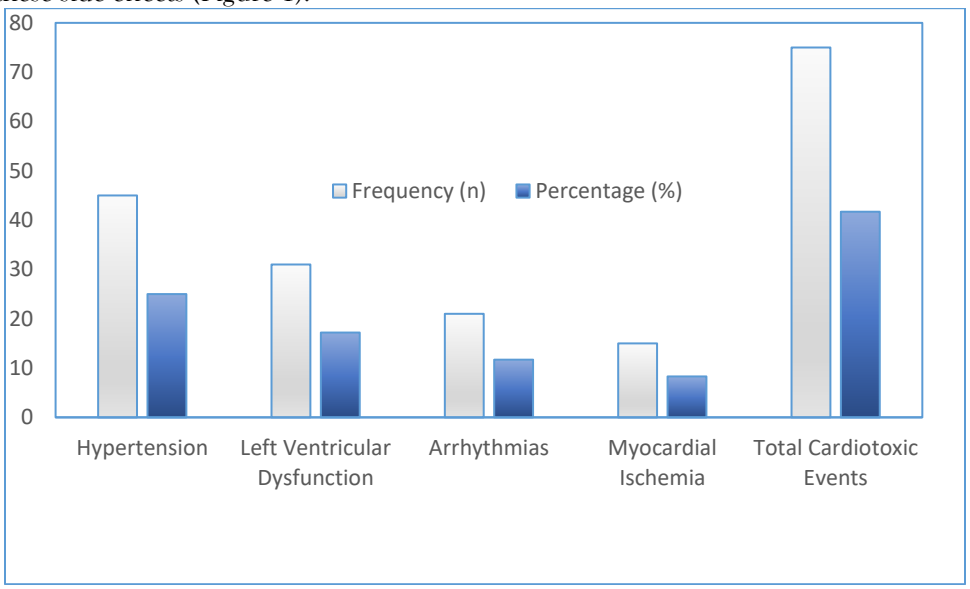

Figure 1: Prevalence and Types of Cardiotoxicities Observed

The study turned out notable relationships between some risk variables and cardiotoxicity presence. Cardiotoxicity (60% vs. 19%), was more commonly experienced by patients over 60 years of age (p<0.001). With 55% of cardiotoxic patients smokers compared to 34% in the non-cardiotoxic group (p=0.032), smoking also revealed a clear correlation. Among those with cardiotoxicity (40% vs. 21%, p=0.005), a history of hypertension was much more common; diabetes mellitus (27% vs. 16%, p=0.005) was also rather more common. Furthermore highly correlated with cardiotoxicity (67% vs. 33%, p<0.001) was prolonged TKI therapy length exceeding 8 months. These results underlined the significance of closely observing high-risk patients having TKI treatment and of customizing therapies (Table 2).

Table 2: Association of Risk Factors with Cardiotoxicity

Risk Factor	Cardiotoxicity Present (n=75)	Cardiotoxicity Absent (n=105)	p-value
Age > 60 years	45 (60%)	20 (19%)	<0.001
Smoking	41 (55%)	36 (34%)	0.032
Hypertension History	30 (40%)	22 (21%)	0.005
Diabetes Mellitus History	20 (27%)	17 (16%)	0.048
Duration of TKI Therapy > 8 months	50 (67%)	35 (33%)	<0.001

Following TKI treatment, cardiovascular values clearly deteriorated. Mean systolic BP rose from 121.6 ± 10.3 mmHg to 145.2 ± 14.8 mmHg (p<0.001) while mean diastolic BP rose from 78.1 ± 7.9 mmHg to 92.6 ± 9.7 mmHg (p<0.001). From 62.3 ± 4.7% at baseline to 50.4 ± 9.8% post-therapy (p<0.001), LVEF dropped sharply, indicating notable myocardial dysfunction. After therapy, troponin-I levels and NT-proBNP, indicators of myocardial damage and heart failure, respectively, also rose significantly (Troponin-I: 0.012 ± 0.004 to 0.084 ± 0.029 ng/mL, p = 0.001; NT-proBNP: 118.5 ± 49.3 to 453.2 ± 201.7 pg/mL, p = 0.001). These results underlined the requirement of close monitoring and quick response as well as the great cardiovascular impact of TKI treatment (Table 3).

Table 3: Cardiovascular Parameters Before and After TKI Therapy

Parameter	Baseline (Mean ± SD)	Post-TKI Therapy (Mean ± SD)	p-value
Systolic BP (mmHg)	121.6 ± 10.3	145.2 ± 14.8	<0.001
Diastolic BP (mmHg)	78.1 ± 7.9	92.6 ± 9.7	<0.001
Left Ventricular Ejection Fraction (%)	62.3 ± 4.7	50.4 ± 9.8	<0.001
Troponin-I Levels (ng/mL)	0.012 ± 0.004	0.084 ± 0.029	<0.001
NT-proBNP (pg/mL)	118.5 ± 49.3	453.2 ± 201.7	<0.001

Several important determinants of cardiotoxicity in patients on TKI treatment were found by multivariate logistic regression analysis. With the odds ratio of 3.46 (95% CI: 2.03-6.14, p<0.001), age >60 years was clearly linked with cardiotoxicity. With the OR of 1.93 (95% CI: 1.12-3.36, p=0.019), smoking was likewise a major risk factor. By more than two-fold (OR: 2.54, 95% CI: 1.34-4.71, p=0.004), a history of hypertension raised the chance of cardiotoxicity. With the OR of 4.17 (95% CI: 2.28-7.41, p<0.001), extended TKI therapy surpassing 8 months was the best predictor. These results showed the need of spotting and controlling these risk factors in order to reduce the cardiotoxic consequences of TKI treatment (Table 4).

Table 4: Multivariate Logistic Regression Analysis of Risk Factors for Cardiotoxicity

Risk Factor	Odds Ratio (OR)	95% CI	p-value
Age > 60 years	3.46	2.03 - 6.14	<0.001
Smoking	1.93	1.12 - 3.36	0.019
Hypertension History	2.54	1.34 - 4.71	0.004
Duration of TKI Therapy > 8 months	4.17	2.28 - 7.41	<0.001

Individuals treated with TKIs indicated the frequency of cardiotoxicity among several cancer types. Patients with NSCLC (45.1%) followed by those with GST (42.9%) and RCC (39.1%), had the highest prevalence of cardiotoxicity among the 180 total study population. Cardiotoxicity (35.7%), was less common in those with other cancer types. With 41.7% (75 out of 180) of patients suffering cardiotoxicity overall, TKI treatment clearly carried the major cardiovascular risks in this population. These results implied the necessity of tailored monitoring strategies for cancer-type specific risks to properly handle cardiotoxic hazards (Figure 2).

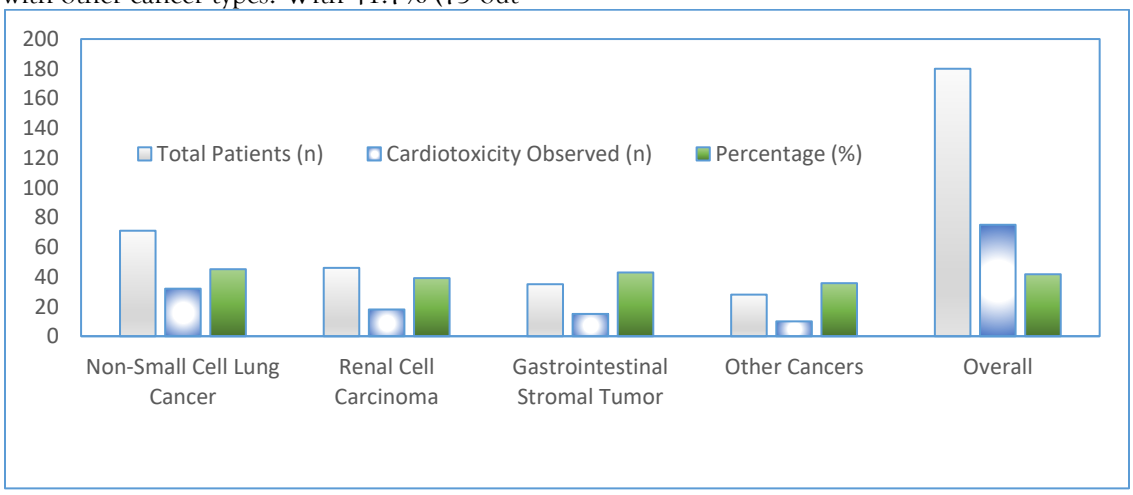

Figure 2: Prevalence of Cardiotoxicity by Cancer Type

The study found notable increases in biomarker levels between cardiotoxicity sufferers and non-suffering subjects. Indicator of myocardial damage, troponin-I levels were much greater in the cardiotoxic group (0.084 ± 0.029 ng/mL) than non-cardiotoxic group (0.015 ± 0.006 ng/mL, p=0.001). Likewise, measure of heart failure, NT-proBNP, revealed a significant rise in the cardiotoxic group (453.2 ± 201.7 pg/mL vs. 132.4 ± 58.6 pg/mL, p = 0.001). Cardiotoxic individuals (12.4 ± 3.6 mg/L vs. 4.7 ± 2.1 mg/L, p = 0.001) had significantly high-sensitivity CRP, indicating inflammation. Reflecting tissue injury, LDH levels were likewise much greater in the cardiotoxic group (225 ± 45 U/L vs. 185 ± 40 U/L, p=0.003). These results implied that these indicators are highly linked with cardiotoxicity and may be useful for early identification and control of cardiovascular problems in patients on TKI treatment (Table 5).

Table 5: Correlation between Biomarker Levels and Cardiotoxicity

Biomarker	Cardiotoxicity Present (Mean ± SD)	Cardiotoxicity Absent (Mean ± SD)	p-value
Troponin-I Levels (ng/mL)	0.084 ± 0.029	0.015 ± 0.006	<0.001
NT-proBNP (pg/mL)	453.2 ± 201.7	132.4 ± 58.6	<0.001
High-Sensitivity CRP (mg/L)	12.4 ± 3.6	4.7 ± 2.1	<0.001
LDH (U/L)	225 ± 45	185 ± 40	0.003

The length of TKI treatment seemed to be correlated with the degree of cardiotoxicity. Of patients with the therapeutic duration of ≤6 months, 22.7% suffered cardiotoxicity; most of them were mild (10 cases), followed by moderate (5 cases) and severe (2 case). With more moderate (12 cases) and severe (5 case) occurrences, cardiotoxicity prevalence rose to 42.7% in individuals treated for 7–12 months. 34.6% of patients on TKI treatment for more than 12 months experienced cardiotoxicity; occurrences of mild (12 cases), moderate (9 cases), and severe (5 cases) very equal distribution. 75 individuals in all suffered cardiotoxicity; mild instances were most common (37 cases, 49.3%), followed by moderate (26 cases, 34.7%) and severe (12 cases, 16%). These results highlighted the link between longer therapy duration and higher degree of cardiotoxicity, therefore stressing the importance of continuous observation in patients receiving protracted TKI treatment (Figure 3).

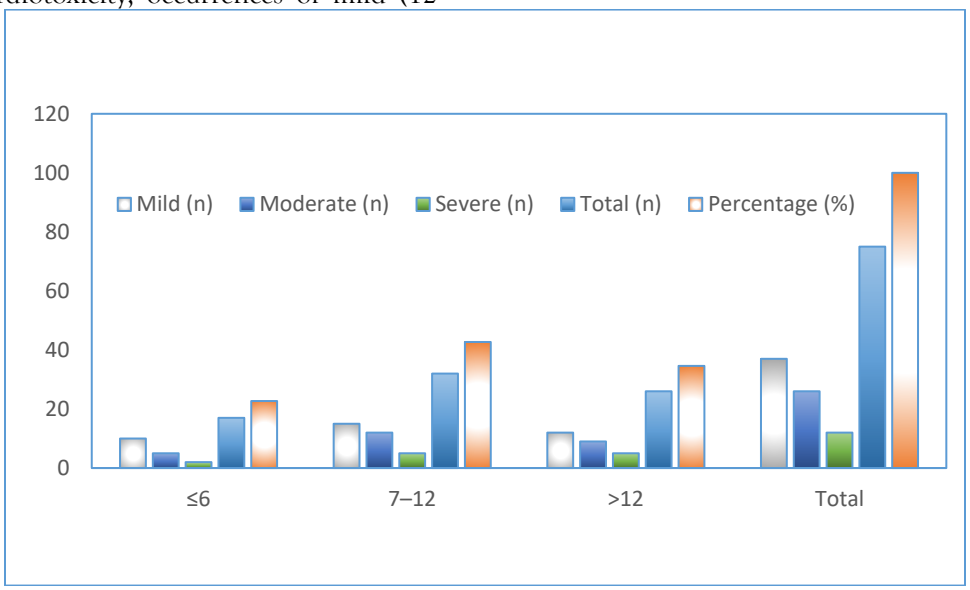

Figure 3: Severity of Cardiotoxicity by TKI Therapy Duration

Patients with and without cardiotoxicity showed appreciable variations in the echocardiographic results. Significantly lower LVEF in the cardiotoxic group (50.4 ± 9.8%) than in non-cardiotoxic group (62.7 ± 4.2%, p = 0.001), therefore showing considerable MI. Suggesting ventricular remodeling, LVEDD was notably higher in the cardiotoxic group (56.2 ± 4.1 mm) than in non-cardiotoxic group (50.3 ± 3.8 mm, p=0.001). Cardiotoxic individuals (38.7 ± 7.4 mmHg) had higher Pulmonary Arterial Systolic Pressure (PASP) than those without cardiotoxicity (28.9 ± 5.3 mmHg, p< 0.001), therefore emphasizing higher pulmonary vascular pressure. Furthermore, in cardiotoxic individuals (1.7 ± 0.6 grade) mitral regurgitation degree was much higher than in non-cardiotoxic group (0.5 ± 0.2 grade, p< 0.001. These results highlighted the significant effects of TKI therapy on cardiac structure and function calling for echocardiographic monitoring for early cardiotoxicity management and identification (Table 6).

Table 6: Echocardiographic Findings in Cardiotoxic Patients

Parameter	Cardiotoxicity Present (n=75)	Cardiotoxicity Absent (n=105)	p-value
Left Ventricular Ejection Fraction (%)	50.4 ± 9.8	62.7 ± 4.2	<0.001
Left Ventricular End-Diastolic Diameter (mm)	56.2 ± 4.1	50.3 ± 3.8	<0.001
Pulmonary Artery Systolic Pressure (mmHg)	38.7 ± 7.4	28.9 ± 5.3	<0.001
Mitral Regurgitation Severity (grade)	1.7 ± 0.6	0.5 ± 0.2	<0.001

Treatment outcome analysis exposed considerable variations between patients with and without cardiotoxicity. Although the cardiotoxic group (73.3%) had a somewhat lower treatment response rate (half either partial or complete) than non-cardiotoxic group (81%), this difference was not statistically significant (p=0.28). Still, there were clear differences in survival measures. With the p = 0.001, overall survival was much shorter in cardiotoxic group (12.3 ± 4.1 months) than in non-cardiotoxic group (16.2 ± 5.3 months. In patients with cardiotoxicity (8.7 ± 3.8 months), similarly, progression-free survival was considerably lowered compared to those without (12.5 ± 4.2 months, p<0.001). These results underlined the negative effect of cardiotoxicity on survival results, stressing the need of policies to reduce cardiotoxic risks in patients receiving TKI treatment (Table 7).

Table 7: Treatment Outcomes and Cardiotoxicity

Treatment Outcome	Cardiotoxicity Present (n=75)	Cardiotoxicity Absent (n=105)	p-value
Treatment Response (Partial/Complete)	55 (73.3%)	85 (81%)	0.28
Overall Survival (Months)	12.3 ± 4.1	16.2 ± 5.3	<0.001
Progression-Free Survival (Months)	8.7 ± 3.8	12.5 ± 4.2	<0.001

Discussion

The assessed the metastatic solid organ malignancies, its frequency, risk factors and effects of cardiotoxicity linked with TKI treatment. With the prevalence of 41.7%, our results showed considerable burden of cardiotoxicity and exposed important correlations between cardiotoxicity and clinical features, treatment duration and echocardiographic parameters. The findings emphasized the need of careful cardiovascular monitoring and control for individuals on TKI treatment [12].

The general frequency of cardiotoxicity in our sample (41.7%) fits earlier studies showing rates ranging from 20% to 45% in patients treated with TKIs including sunitinib, sorafenib and imatinib [12-13]. Among the noted forms of cardiotoxicity, hypertension (25%), left ventricular dysfunction (17.2%), arrhythmias (11.7%), and myocardial ischemia (8.3%) were the most often occurring. A well-documented negative impact of TKIs is hypertension, which results from blockage of VEGFR, hence upsetting nitric oxide-mediated vasodilation [14]. As indicated by other

research, left ventricular dysfunction may also arise from direct myocardial damage and oxidative stress brought on by TKI treatment [14].

Our results showed as major predictors of cardiotoxicity age >60 years, smoking, history of hypertension and prolonged TKI therapy (>8 months). With OR value of 3.46, older age was the largest independent risk factor; this is in line with earlier studies stressing the higher sensitivity of elderly individuals to TKI-induced cardiovascular effects. Pre-existing hypertension and smoking also greatly raised the likelihood of cardiotoxicity, therefore supporting results from research pointing to these as aggravating cardiovascular stress in cancer patients [15]. Emphasizing the whole cardiotoxic potential of TKIs, as Sayegh et al. (2023) have already shown, extended therapy (>8 months) was notably linked with the highest risk (OR: 4.17) [16].

There was cardiotoxicity linked to notable changes in cardiovascular parameters. While LVEF dropped from 62.3% to 50.4% post-TKI therapy, suggesting MI, systolic and diastolic blood pressure rose significantly. Further confirming myocardial damage and heart failure in cardiotoxic patients were raised troponin-I and NT-proBNP levels. These results complement research by Skubitz, (2019), which showed in TKI-treated patients' comparable echocardiographic alterations and biomarker increases. Furthermore, demonstrating negative hemodynamic consequences, cardiotoxic individuals had notably greater PASP and mitral regurgitation severity [17].

With generally shorter survival and progression-free survival in cardiotoxic group, cardiotoxicity negatively affected survival results. Our results lined up with earlier studies showing that cardiovascular problems can compromise therapy tolerance and efficacy, hence producing less than ideal oncologic results [18]. Although the treatment response rate did not vary much between groups, lower rate of survival emphasized the need of early identification and control of cardiotoxicity.

Our incidence of cardiotoxicity (41.7%) is higher than that recorded by Chu et al. (2019) [19], who observed a prevalence of 30% in patients treated with VEGFR-targeted TKIs. Comparatively to similar studies, this is Variations in patient demographics and inclusion criteria could help to explain this disparity since our study concentrated only on metastatic cancers, which might include longer treatment times and greater TKI doses. Moreover, our results on biomarker correlations (elevated troponin-I and NT-proBNP) complement studies by Chu et al. (2017) [19], hence highlighting the part biomarkers play in early cardiotoxicity identification [20].

Our data emphasized how urgently combined cardio-oncology treatment is needed to reduce TKI therapy's cardiovascular hazards. Standard practice for patients on continuous TKI treatment should involve regular cardiovascular examinations comprising blood pressure monitoring, echocardiography and biomarker studies. Early intervention programs including lifestyle changes and antihypertensive medication could help to lower the incidence and degree of cardiotoxicity.

The single-center setting of this study may restrict generalizability and its cross-sectional design, which forbids causal inference, may have various limits. Furthermore lacking assessment were long-term cardiovascular results. Multicenter, longitudinal designs should be the main emphasis of future research to investigate the processes of TKI-induced cardiotoxicity and assess preventive measures.

Conclusion

The significant burden of cardiotoxicity linked with TKI therapy in metastatic solid organ cancers is highlighted in this study. The most often occurring consequences were left ventricular dysfunction and hypertension. Important risk factors having major effects on cardiovascular function and survival outcomes were age >60 years, smoking, pre-existing hypertension and prolonged TKI therapy (>8 months). Reduced LVEF, raised pulmonary artery pressures and higher biomarker levels (troponin-I and NT-proBNP) shown by patients with cardiotoxicity underlined the need of early diagnosis. Our results highlighted the need of integrated cardio-oncology treatment combining timely measures to reduce cardiotoxicity and maximize oncologic outcomes with regular cardiovascular monitoring and biomarker assessments.

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