

Incidence and Risk Factors of Chemotherapy-Induced Hepatotoxicity: A Cross-Sectional Study

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Background: Cancer is a major global health concern, causing significant morbidity and mortality, with particularly a high burden observed in low- and middle-income countries (LMICs). While chemotherapy remains a cornerstone of cancer treatment, it often causes adverse effects, particularly hepatotoxicity. Chemotherapy-induced hepatotoxicity (CIH) can severely compromise treatment effectiveness, often leading to necessary dose reductions or discontinuation, thereby increasing patient morbidity and mortality. Despite its clinical significance, there is currently limited data available on the incidence, severity, and risk factors of chemotherapy-induced hepatotoxicity specifically within Uganda or LMIC.

Objective: This study aimed to determine the incidence, severity, and risk factors with chemotherapy-induced hepatotoxicity among adult patients with cancer at the cancer unit of Mbarara Regional Referral Hospital (MRRH).

Methods: A cross-sectional study was conducted among adult cancer patients receiving chemotherapy at MRRH. Data was collected through patient interviews, chart reviews, and laboratory assessments, including liver enzyme measurements. Statistical analysis was performed using STATA version 17 software.

Results: Out of 216 adult patients with cancer. A total of 63 (29.2%) developed chemotherapy-induced hepatotoxicity. Most cases were of grade 1 (n = 51, 81%) followed by grade 2 (n = 8, 12.7%), then grade 3 (n = 4, 6.3%). Risk factors of chemotherapy-induced hepatotoxicity included; living with HIV (adjusted odds ratio (AOR) = 2.5, 95% CI: 1.1–5.6, p-value = 0.033) and diabetes mellitus (AOR = 20.2, 95% CI: 1.7–228.5, p-value = 0.015).

Conclusion: Chemotherapy-induced hepatotoxicity affects about one in three cancer patients at MRRH, with HIV and diabetes significantly increasing risk. Routine liver function monitoring and individualized protocols, including prophylactic hepatoprotectants for high-risk patients, are essential to prevent severe hepatotoxicity and improve cancer treatment outcomes.

Keywords: incidence, risk factors, chemotherapy, hepatotoxicity, cancer, Mbarara

Introduction

Cancer is a significant threat to society, health of the public, and the economy.¹ It accounts for nearly one in six deaths (16.8%) and one in four deaths (22.8%) from noncommunicable diseases (NCDs) globally.² Cancer-associated deaths are significantly higher in LMICs (low- and middle-income countries), particularly among individuals below the age of 65 years.³ In 2015, LMICs accounted for 78% of all global deaths from noncommunicable diseases (NCDs), including cancer, with nearly half of these deaths being considered premature.⁴

Cancer treatment options may include surgery, radiation therapy, biological agents, immune mediated therapy, hormonal therapy, and chemotherapy. Among these, chemotherapy is recognized as the most effective and extensively used treatment modality for most types of cancer.⁵ Chemotherapeutic drugs used in cancer treatment are known to cause adverse reactions such as neutropenia, anemia, thrombocytopenia, diarrhea, mucositis, nausea and vomiting, neuropathy, dermatologic toxicity, and hepatotoxicity.⁶

Hepatotoxicity is a significant concern due to the liver's key role in metabolism of drugs and potential drug interactions, is often indicated by elevated liver enzyme levels.⁷ The liver is very vulnerable to chemotherapeutic agents.⁸ Chemotherapy-induced hepatotoxicity (CIH) arises from diverse aetiologies, including indirect metabolic disruptions via cytochrome P450 enzyme inhibition, direct hepatocyte injury, or immune-mediated damage.⁹ While high-grade elevations in transaminases or bilirubin can occur, they are generally transient, reversible upon drug cessation, and rarely fatal.¹⁰ CIH primarily manifests as unpredictable reactions without distinct clinical or histological features unique to chemotherapy.¹¹ CIH may be associated with several drug classes, including antimetabolites, alkylating agents, vinca alkaloids, antitumor antibiotics, topoisomerase inhibitors, platinum derivatives, taxanes, and tyrosine kinase inhibitors.^{11,12}

Chemotherapy-induced hepatotoxicity is a critical concern, as it can lead to dose reductions, treatment delays, or even discontinuation of therapy, thereby compromising the overall effectiveness of cancer treatment. Studies report an incidence of chemotherapy-induced hepatotoxicity as 30.4% in India,¹³ 22.2% in South Korea,¹⁴ 15% in Ethiopia.¹⁵ Hepatotoxicity, therefore, resulting from chemotherapeutic agents, has serious repercussions for patients, this condition complicates with liver cirrhosis or liver failure,¹⁶ significantly elevates both morbidity and mortality rates among affected individuals.¹⁷

Some of the factors reported to be associated with chemotherapy-induced hepatotoxicity among cancer patients, include; gender, age, blood transfusions, hepatic tumor involvement, genetic susceptibility, immune compromise, pre-existing liver disease, concomitant medications, and radiation. Additionally, concurrent use of cancer chemotherapeutic agents with other medications increases the risk of developing chemotherapy-induced hepatotoxicity.¹² Furthermore, pre-existing liver disease may impair drug metabolism and escalate the risk of chemotherapy-induced hepatotoxicity.¹⁸

Despite the global and regional burden of cancer and chemotherapy's central role, there is a need for regional-specific data on the incidence of hepatotoxicity due to chemotherapy since there is limited data on the incidence of chemotherapy-induced hepatotoxicity among patients with cancer in Uganda.

This study aimed to establish the incidence of chemotherapy-induced hepatotoxicity, assess its severity and to identify risk factors of chemotherapy-induced hepatotoxicity among adult patients at cancer unit of MRRH.

Methods and Materials

Study Design

A cross-sectional study was carried out among adult patients with cancer on chemotherapy treatment at the cancer unit of Mbarara Regional Referral Hospital.

Study Setting

The study was carried out at Mbarara Regional Referral Hospital (MRRH's) cancer unit, a government-owned regional referral hospital and a teaching facility for the Medicine faculty at Mbarara University of Science and Technology. MRRH's cancer unit has a bed capacity of 45, that is 18 adult beds, 19 beds for paediatric patients, and 8 beds in the infusion room. The unit is staffed by 22 healthcare personnel, including 4 specialist oncologists, 1 physician, 2 medical officers, 2 pharmacists, and 13 nurses.

Study Participants

The study interviewed adult cancer patients who were on chemotherapy treatment for at least a period of one week. It was conducted for a period of three months, from April 2025 to June 2025 at MRRH Cancer unit.

Inclusion Criteria

The study enrolled adult patients with cancer who fulfilled the following inclusion criteria;

- Patients aged 18 years and above.
- Patients who had a confirmed cancer diagnosis.
- Patients who had previously received chemotherapy for at least one week from the initiation date.

Exclusion Criteria

- Patients who had hepatotoxicity (elevated AST, ALT, ALP levels of 3 times the upper limit of normal) before initiation of chemotherapy.
- Underlying Liver disease.

Sample Size Calculation

The sample size was calculated using the Cochran formula; $N \geq Z^2P(1-P)/d^2$. The incidence of hepatotoxicity (15%) was adopted from the study conducted in Ethiopia.¹⁵ Adding 10% contingency for incomplete data, 216 participants were recruited for the study. A consecutive sampling technique was used to select 216 adult cancer patients who were receiving chemotherapy at the cancer unit of Mbarara Regional Referral Hospital.

Data Collection

The study site was arranged in such a way that there was organization of patient flows in the study to limit interruption to patient care and delays. A structured questionnaire (for interviews) and an appended data extraction form were used to document information from patient clinical records, especially data from the start of chemotherapy. The data collection tool was structured to include the following parts: patient socio-demographic data, medical information, drug information, and laboratory tests among the selected cancer patients. The principal investigator was assisted by four trained research assistants (an intern medicine resident and three registered nurses) in the data collection process from April 2025 to June 2025. Additionally, a pre-test was administered to 11 patients, that represented 5% of the sample size population, prior to the real data collecting for the study. This was used to improve the data collection tool. The pre-test results were not included in the final study results.

Clinical assessment for hepatotoxicity was done by a clinical pharmacist resident and the internal medicine resident to assess for signs and symptoms of hepatotoxicity. Medical information was obtained from the patient files, laboratory forms, and other investigations. Liver function enzymes (ALT, AST, and ALP) were assessed from the patient's laboratory forms in their files, both at baseline and after chemotherapy treatment cycle. Emphasis was put on patients that had previously received chemotherapy for at least a week.

Causality assessment of hepatotoxicity and the suspected chemotherapy drug was done using the Naranjo adverse drug reaction probability scale developed in 1991 by Naranjo where the score of less than 0 regarded as doubtful, score of 1–4 as possible, score of 5–8 as probable, and a score of 9 and above regarded as definite. The Naranjo scale was scored by a clinical pharmacist resident and an internal medicine resident who reached consensus on the rating of every suspected incident. The grading of hepatotoxicity was performed using the Common Terminology Criteria for Adverse Events (CTCAE) tool. Laboratory results, specifically Liver Function Enzymes, were considered for both baseline and after chemotherapy treatment cycle.

Data Analysis

The collected data was exported from Microsoft Excel version 2016 into Stata software version 17 for analysis. Descriptive statistics were used to describe the characteristics of the study group and to determine the severity of chemotherapy-induced hepatotoxicity. The incidence of chemotherapy-induced hepatotoxicity was analysed using percentages and proportions by comparing the baseline liver function tests with those taken after at least one week of chemotherapy. This was expressed as a percentage of the number of people with chemotherapy-induced hepatotoxicity out of the total number of patients receiving chemotherapy. Logistic regression was employed to determine the risk factors of chemotherapy-induced

hepatotoxicity. Univariate logistic regression was used to identify significant risk factors of chemotherapy-induced hepatotoxicity. Independent variables with p-values <0.25 were then considered for multivariate logistic regression, where the adjusted odds ratio (aOR) of developing chemotherapy-induced hepatotoxicity with the independent variables was determined at a 95% level of confidence.¹⁹ A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) before research commenced. Administrative clearance from the Hospital Director of MRRH was obtained prior to the study's commencement. Before participants' interviews for this study, they were requested for their informed consent. Participants' information was kept confidential and used solely for research purposes. Participants were assigned unique identification codes rather than names or direct identifiers, and only the research team had access to the coded data. Data was securely stored, with electronic data being password protected and paper records kept in locked cabinets. To maintain privacy, individuals were approached respectfully and in a private setting.

Results

Socio-Demographic Characteristics of the Study Participants

A total of 216 adult patients with cancer who received chemotherapy were enrolled in the study. The majority of the participants were male (55.6%, 120/216). The mean age of the participants was 57.4 years (± 15.8), with nearly half 49.1% (106/216) aged 60 years or older. The median (IQR) body surface area (BSA) was 1.6 m² (1.5 to 1.7 m²). Over half of the participants, 53.7% (116/216) had normal weight, while 25.9% (56/216) were underweight. About 26.9% (58/216) of the participants reported a history of smoking while half 50.9% (110/216) reported a history of alcohol consumption. Most participants were married 88.9% (192/216), and the majority were unemployed 59.7% (129/216) as shown in Table 1.

Table 1 Socio-Demographic Characteristics of Adult Patients with Cancer Receiving Chemotherapy at the Oncology Unit of Mbarara Regional Referral Hospital

Characteristic	Category	Frequency (%) N=216
Age category (years) Mean $\pm$ SD= (57.4 $\pm$ 15.8)	18-39	30 (13.9)
	40-59	80 (37.0)
	≥ 60	106 (49.1)
Gender	Male	120 (55.6)
	Female	96 (44.4)
Body mass index (BMI, kg/m ²)	Underweight	56 (25.9)
	Normal weight	116 (53.7)
	Overweight	26 (12.0)
	Obesity	18 (8.3)
History of smoking	No	158 (73.1)
	Yes	58 (26.9)
Alcohol use	No	106 (49.1)
	Yes	110 (50.9)

(Continued)

**Table 1** (Continued).

Characteristic	Category	Frequency (%) N=216
Marital status	Married	192 (88.9)
	Single	5 (2.3)
	Divorced	7 (3.2)
	Widowed	12 (5.6)
Employment status	Unemployed	129 (59.7)
	Employed	63 (29.2)
	Retired	24 (11.1)

Clinical and Medication Related Characteristics of the Study Participants

The median time since cancer diagnosis among the study participants was 4.0 months, (IQR: 2.0–11.0). Regarding exposure to hepatotoxic agents other than chemotherapy drugs, 48% of participants received at least one hepatotoxic agent. Approximately 40.7% (88/216) of the study participants reported herbal medicine use alongside chemotherapy, and over half (56.0%, 121/216) had stage 4 cancer. Comorbidities were present in 29.2% (63/216) of participants (Table 2).

The most common diagnosis among the study participants was prostate cancer (20.4%, 44/216), followed by gastrointestinal cancer (16.7%, 36/216). Breast cancer and esophageal cancer were also common, comprising 13.4% (29/216) and 13.0% (28/216) of cases, respectively (Figure 1).

Table 2 Clinical and Medical Related Characteristics of Adult Patients with Cancer Receiving Chemotherapy at the Oncology Unit of Mbarara Regional Referral Hospital

Characteristic	Category	Frequency (%) N=216
Time since cancer diagnosis (months), median (IQR)		4.0 (2.0, 11.0)
Chemotherapy duration (weeks), median (IQR)		20.0 (8.0, 52.0)
Cycles received, median (IQR)		6.0 (4.0, 10.0)
Hepatotoxic agent other than chemotherapy in the last 1 month N=148	No	77 (52)
	Yes	71 (48)
Herbal medicine use in the last 1 month	No	128 (59.3)
	Yes	88 (40.7)
Cancer stage	Not staged	15 (6.9)
	Stage 1	1 (0.5)
	Stage 2	15 (6.9)
	Stage 3	64 (29.6)
	Stage 4	121 (56.0)
Comorbidity	No	153 (70.8)
	Yes	63 (29.2)

(Continued)

Table 2 (Continued).

Characteristic	Category	Frequency (%) N=216
HIV	No	182 (84.3)
	Yes	34 (15.7)
Hypertension	No	189 (87.5)
	Yes	27 (12.5)
Diabetes	No	211 (97.7)
	Yes	5 (2.3)

Notes: Herbal medicine: The use of any herbs or herbal formulations within the previous one month.

Abbreviations: HIV, Human Immunodeficiency Virus IQR, interquartile range.

Loss of appetite was the most reported symptom, affecting 80.6% (174/216) of the study participants, followed by nausea and vomiting 61.6% (133/216), fatigue 49.1% (106/216) and fever 30.1% (65/216). Less common symptoms included right upper quadrant pain (5 patients, 2.3%), dark urine (4 patients, 1.9%), and rash (3 patients, 1.4%), as shown in [Figure 2](#).

Taxanes were the most frequently prescribed class of chemotherapeutic agents for patients with cancer (50.5%, n = 109), followed by platinum analogs (37.5%, n = 81) and antimetabolites (35.6%, n = 77). Camptothecins were the least commonly used, prescribed in only two cases (0.9%), as shown in [Figure 3](#).

Incidence of Chemotherapy-Induced Hepatotoxicity

Out of 216 participants enrolled in this study, 63 (29.2%; 95% CI: 23.5–35.6) developed chemotherapy-induced hepatotoxicity ([Figure 4](#)). The causality assessment for hepatotoxicity was done using the Naranjo probability scale which showed that 66.7% of the cases were possible ADRs and 33.3% were probable cases.

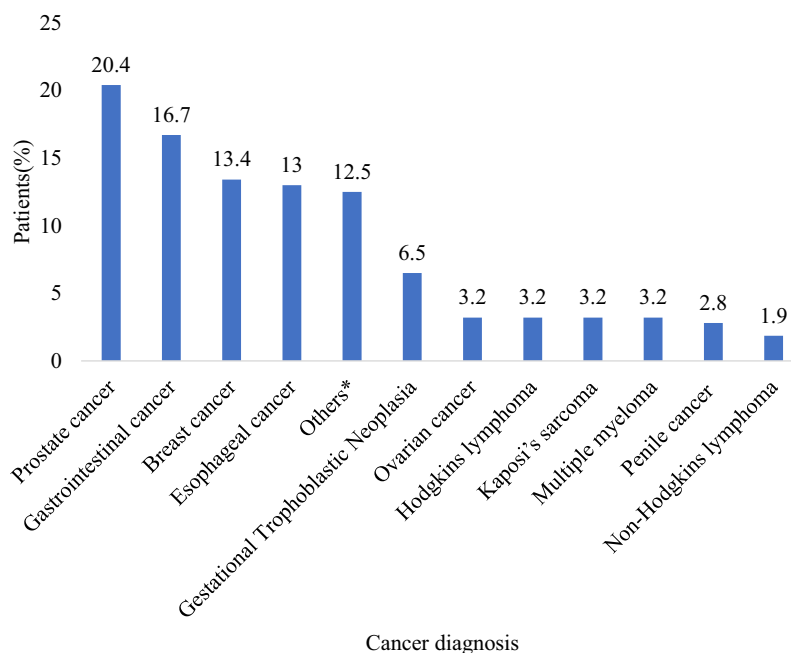


Figure 1 Common cancer diagnosis among patients attending the oncology unit of Mbarara Regional Referral Hospital. *Acute myeloid leukemia (3), bone cancer (1), chronic lymphocytic leukemia (1), dermatofibrosarcoma (1), follicular lymphoma (1), foot malignancy (1), glioma (1), high grade sarcoma (1), left iliac bone (1), lung cancer (4), mediastinal cancer (1), metastatic adenocarcinoma (1), mucinous adenocarcinoma (1), myeloid liposarcoma (1), nasopharyngeal carcinoma (1), neck cancer (1), osteosarcoma (1), parotid cancer (1), pleomorphic sarcoma (1), skin cancer (1), squamous cell carcinoma (2).

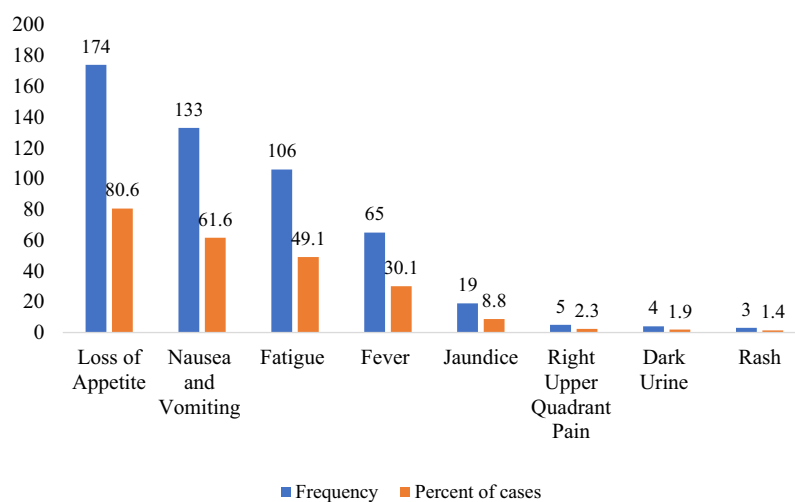


Figure 2 Signs and symptoms of hepatotoxicity of adult patients with cancer at oncology unit of Mbarara Regional Referral Hospital.

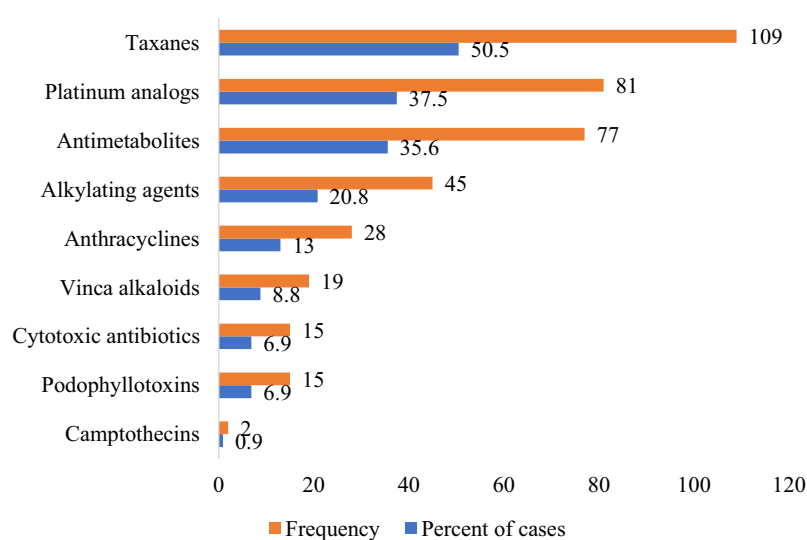


Figure 3 Common classes of anticancer drugs prescribed for patients with cancer at the oncology unit of Mbarara Regional Referral Hospital.

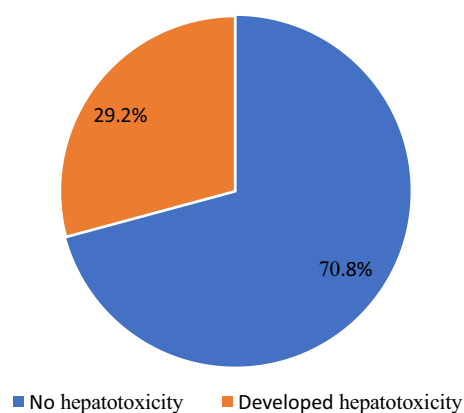


Figure 4 Incidence of chemotherapy-induced hepatotoxicity among adult patients with cancer receiving chemotherapy at Mbarara Regional Referral Hospital.

The highest occurrence of hepatotoxicity was observed with cytotoxic antibiotics and podophyllotoxins, both exhibiting an index of 53.3%. Doxorubicin causes severe oxidative damage to healthy tissue, particularly the heart, by inducing excessive reactive oxygen species (ROS) production, leading to mitochondrial dysfunction, lipid peroxidation, and cardiomyocyte apoptosis. Podophyllotoxin (PPT) causes hepatotoxicity primarily by triggering inflammation and cell death, mediated by the C5a/C5aR/ROS/NLRP3 axis and cGMP/PKG/mTOR pathway inhibition. This process induces pyroptosis, a form of inflammatory programmed cell death, and results in severe damage characterized by increased liver enzymes (ALT/AST), oxidative stress, and inflammatory infiltration. This was followed by vinca alkaloids (42.1%) and alkylating agents (40.0%), indicating a relatively high risk of hepatotoxicity. Lower hepatotoxicity indices were seen in taxanes (25.7%) and platinum analogs (24.7%) as shown in [Figure 5](#)

Severity of Chemotherapy-Induced Hepatotoxicity

Using the Common Terminology Criteria for Adverse Events (CTCAE) for grading hepatotoxicity, most cases were of grade 1 (81%) followed by grade 2 (12.7%) ([Figure 6](#)).

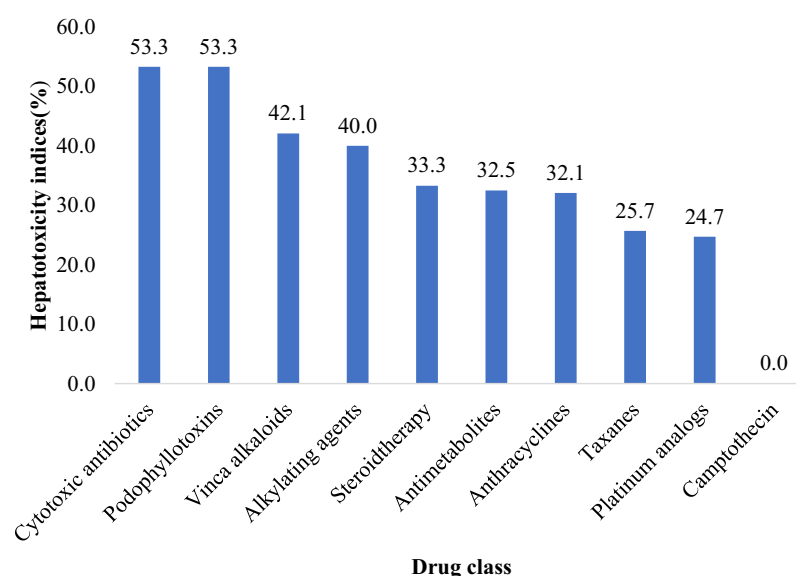


Figure 5 Hepatotoxicity indices of each class of chemotherapeutic drugs.

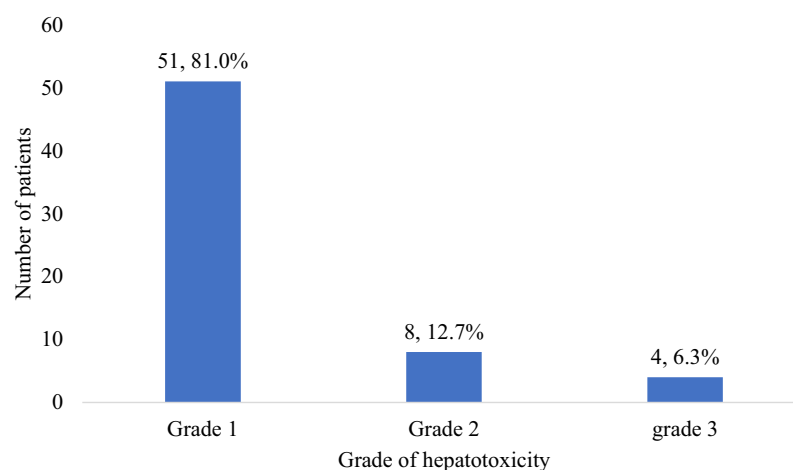


Figure 6 Grades of hepatotoxicity among adult patients with cancer receiving chemotherapy at Mbarara Regional Referral Hospital.

Risk Factors Chemotherapy-Induced Hepatotoxicity

Bivariate logistic regression analysis showed that the following variables were associated with chemotherapy-induced hepatotoxicity (all grades): having a comorbid HIV infection (COR = 2.2, 95% CI: 1.0–4.7, p-value = 0.040), having diabetes mellitus (COR = 10.3; 95% CI: 1.1–94.1; p = 0.039), cytotoxic antibiotics (COR = 3.0; 95% CI: 1.1–8.8; p = 0.040), and podophyllotoxins (COR = 3.0; 95% CI: 1.1–8.8; p-value = 0.040).

Associations between independent variables and chemotherapy-induced hepatotoxicity with a p-value <0.25 and clinical relevance at bivariate logistic regression were included in the multivariate regression model. In the multivariate logistic regression analysis, two variables remained significantly associated with chemotherapy-induced hepatotoxicity and were distributed amongst severity of all grades of hepatotoxicity. Participants living with HIV had 2.5 higher odds of experiencing chemotherapy-induced hepatotoxicity compared to those without HIV (AOR = 2.5, 95% CI: 1.1–5.6, p = 0.033). Participants with comorbid diabetes mellitus were 20 times more likely to develop chemotherapy-induced hepatotoxicity than those without DM (AOR = 20.2, 95% CI: 1.7–228.5, p = 0.015) (Table 3).

Table 3 Univariate and Multivariate Logistic Regression of Risk Factors of Chemotherapy-Induced Hepatotoxicity Among Adult Patients with Cancer Receiving Chemotherapy at Mbarara Regional Referral Hospital

Variable	Category	Hepatotoxicity		COR (95% C.I.)	P-value	AOR (95% C.I.)	P-value
		No n (%)	Yes n (%)				
Age	18–39 years	17(56.7)	13(43.3)	1		1	
	40–59 years	57(71.2)	23(28.8)	0.5(0.2–1.3)	0.150*	0.5(0.2–1.2)	0.129
	≥60 years	79(74.5)	27(25.5)	0.4(0.2–1.0)	0.061*	0.7(0.3–1.8)	0.500
Gender	Male	82(68.3)	38(31.7)	1			
	Female	71(74)	25(26)	0.8(0.4–1.4)	0.367		
BSA	Small	78(72.9)	29(27.1)	0.8(0.4–1.5)	0.498		
	Normal	70(68.6)	32(31.4)	1			
	Large	5(71.4)	2(28.6)				
History of smoking	No	109(69)	49(31)	1			
	Yes	44(75.9)	14(24.1)	0.7(0.4–1.4)	0.326		
Alcohol use	No	72(68)	34(32)	1			
	Yes	81(73.6)	29(26.4)	0.8(0.4–1.4)	0.356		
Herbal medicine use [#]	No	84(66.1)	43(33.9)	1		1	
	Yes	68(77.3)	20(22.7)	0.6(0.3–1.1)	0.080*	0.6(0.3–1.2)	0.146
Cancer stage	Early stage	54(67.5)	26(32.5)	1			
	Advanced stage	89(73.6)	32(26.4)	0.7(0.4–1.4)	0.354		
HIV	No	134(73.6)	48(26.4)	1		1	
	Yes	19(55.9)	15(44.1)	2.2(1.0–4.7)	0.040*	2.5(1.1–5.6)	0.033
Hypertension	No	130(68.8)	59(31.2)	1		1	
	Yes	23(85.2)	4(14.8)	0.4(0.1–1.2)	0.089*	0.3(0.1–1.2)	0.083
Diabetes	No	152(72)	59(28)	1		1	
	Yes	1(20)	4(80)	10.3(1.1–94.1)	0.039*	20.2(1.7–228.5)	0.015

(Continued)

Table 3 (Continued).

Variable	Category	Hepatotoxicity		COR (95% C.I.)	P-value	AOR (95% C.I.)	P-value
		No n (%)	Yes n (%)				
Time of chemotherapy from initiation (weeks)	≤12 weeks	59(70.2)	25(29.8)	1			
	>12 weeks	94(71.2)	38(28.8)	1.1(0.5–1.7)	0.878		
Other hepatotoxic agents other than chemotherapy	No	55(71.4)	22(28.6)	1			
	Yes	45(63.4)	26(36.6)	1.4(0.7–2.9)	0.297		
Taxanes	No	72(67.3)	35(32.7)	1			
	Yes	81(74.3)	28(25.7)	0.7(0.4–1.3)	0.257		
Platinum analogs	No	92(68.2)	43(31.8)	1			
	Yes	61(75.3)	20(24.7)	0.7	0.263		
Antimetabolites	No	101(72.7)	38(27.3)	1			
	Yes	52(67.5)	25(32.5)	1.3(0.7–2.3)	0.427		
Alkylating agents	No	126(73.7)	45(26.3)	1		1	
	Yes	27(60)	18(40)	1.8(0.9–3.7)	0.075*	1.8(0.7–4.3)	0.197
Anthracyclines	No	134(71.3)	54(28.7)	1			
	Yes	19(67.9)	9(32.1)	1.2(0.5–2.8)	0.711		
Vinca alkaloids	No	142(72.1)	55(27.9)	1		1	
	Yes	11(57.9)	8(42.1)	1.9(0.7–4.9)	0.199*	0.7(0.2–3.1)	0.661
Cytotoxic antibiotics	No	146 (72.64)	55(27.4)	1		1	
	Yes	7(46.7)	8(53.3)	3.0(1.1–8.8)	0.040*	1.7(0.3–9.1)	0.559
Podophyllotoxins	No	146(72.6)	55(27.4)	1		1	
	Yes	7(46.7)	8(53.3)	3.0(1.1–8.8)	0.040*	2.6(0.5–13.6)	0.257

Notes: #Herbal medicine use with in the last four weeks * Variables included in multivariate regression analysis. Bold, statistically significant variables at multivariate regression.

Abbreviations: BSA, body surface area. HIV, Human Immunodeficiency Virus COR, crude odds ratio AOR, adjusted odds ratio C.I., confidence interval.

Discussion

The incidence of chemotherapy-induced hepatotoxicity among cancer patients at the MRRH Oncology unit was 29.2%. This is comparable to findings in India that reported closely similar results, 30.4%.¹³ These similarities suggest that hepatotoxicity is a common adverse drug reaction across various chemotherapy regimens. On the other hand, it should be carefully interpreted as we did only a baseline and one-time LFT after chemotherapy, which may have resulted in the underreporting of chemotherapy-induced hepatotoxicity due to missed cases of delayed toxicity. Delayed CIH can occur any time between 1 and 12 months after chemotherapy. Thus, the actual incidence of CIH might be higher than what has been reported if sequential LFTs could be done every week at least for 1 month following chemotherapy.

The current incidence is higher than 22.2% reported in South Korea¹⁴ and 21.8% observed in China.²⁰ The difference could be explained by differences in the study populations. For example, the study by Kim et al (2019) had a strict exclusion criterion that omitted patients with comorbidities, such as diabetes and hypertension. This likely reduced the pool of individuals at a higher risk for chemotherapy-induced hepatotoxicity, unlike our study, which included patients with comorbidities. Additionally, the studies in South Korea and China included patients with double and single chemotherapeutic regimen, respectively, while our study included multiple chemotherapeutic drug classes which have greater potential for

hepatotoxicity. Furthermore, these studies focused on specific patient populations (those with head and neck cancer and liver cancer), unlike our study, which included all patients with cancer. The current incidence emphasizes the clinical significance of hepatotoxicity as a frequent complication of chemotherapy, ultimately affecting cancer outcomes.²¹ The findings highlight the need for routine liver function assessment during chemotherapy, to enable timely interventions and improve safety.

The hepatotoxicity indices across various classes of chemotherapeutic drugs demonstrated that cytotoxic antibiotics and podophyllotoxins exhibited the highest rates of hepatotoxicity, each at 53.3%, signifying that more than half of patients on these drug classes experienced hepatotoxicity. Vinca alkaloids followed with a rate of 42.1%, whereas taxanes (25.7%) and platinum analogs (24.7%) showed comparatively lower hepatotoxicity indices. These findings were comparable with a study that reported the proportion of the clinical significance of hepatotoxicity of each chemotherapeutic drug agents.²² Furthermore, previous studies also reported various chemotherapy drugs as evident cause of hepatotoxicity.^{11,23–29} Our findings were in line with a study that demonstrated that combined chemotherapy agents increase the risk of hepatotoxicity in cancer patients.²⁴ Many chemotherapy agents are metabolized through cytochrome P450 (CYP) enzyme pathways, and their co-administration with CYP inhibitors may reduce metabolic clearance, resulting in increased systemic exposure. Because chemotherapy-induced hepatotoxicity is frequently dose-dependent, elevated serum drug concentrations secondary to such interactions may potentiate the risk of hepatotoxicity.⁹ The current findings suggest that all chemotherapeutic drug classes carry some risk of hepatotoxicity, there is need for careful monitoring and risk assessment of hepatotoxicity when prescribing these chemotherapeutic drugs.

The Common Terminology Criteria for Adverse Events (CTCAE) was used to grade the severity of chemotherapy-induced hepatotoxicity among cancer patients. The most prevalent hepatotoxicity cases were grade 1 (81%), followed by grade 2 (12.7%), and then grade 3 (6.3%). Moderate cases of chemotherapy-induced hepatotoxicity in our findings were consistent with a study done in Ethiopia which reported 15% moderate cases.¹⁵ The current findings were comparable with a study done in USA which reported 6.8% of the cases were severe.²⁵ The current findings are consistent with previous research findings which indicated that chemotherapy-induced hepatotoxicity is predominantly mild to moderate, and severe grades (3–4) constituted less than 10%. A study in China reported similar findings, grade 1 (82.7%) and grade 2 (13.5%), <10% for severe cases (grade 3–4).²⁶ Other studies similarly reported predominance of mild and moderate cases compared to severe cases of hepatotoxicity.^{24,27–29} The predominance of grade 1 and 2 hepatotoxicity suggests that, for most patients, chemotherapy-induced hepatotoxicity is mild and manageable, rarely necessitating treatment interruption. However, even mild hepatotoxicity warrants attention, as it can progress to clinically significant hepatotoxicity or complicate treatment in vulnerable patients. Additionally, severe cases of chemotherapy-induced hepatotoxicity can not only compromise treatment effectiveness and patient survival but also necessitate chemotherapy dose reductions, delays, or discontinuation. Therefore, there is a need for implementing risk adapted protocols, including prophylactic use of hepato-protectants such as silymarin and S-adenosylmethionine, particularly among patients with pre-existing liver dysfunction or those receiving potentially hepatotoxic chemotherapy regimens. These agents have been suggested to possess antioxidant and hepatocellular membrane-stabilizing properties, which may help mitigate liver injury.^{21,30}

At multivariate regression analysis, living with HIV and having a comorbid diabetes mellitus were significantly associated with chemotherapy-induced hepatotoxicity. Patients with cancer living with HIV were 2.5 times more likely to develop chemotherapy-induced hepatotoxicity. Similar findings were reported in a multicentre study in Italy, where patients with HIV receiving cancer chemotherapy drugs had a greater risk of developing hepatotoxicity.³¹ Additionally, a study done in USA found that HIV-infected patients with breast cancer receiving chemotherapy had higher rates of adverse events, including hepatotoxicity.³² This could be explained by the overlapping hepatotoxic effects of antiretroviral (ART) medication and chemotherapy drugs, which potentiate the risk of chemotherapy-induced hepatotoxicity. A study in Cameroon reported that the ART regimen (AZT+3TC+NVP) is a risk factor ($p < 0.05$) for hepatotoxicity among patients living with HIV.³³ Furthermore, a systematic review and meta-analysis in Ethiopia reported a higher pooled incidence of hepatotoxicity among HIV patients taking HAART (23.63%).³⁴ This indicates that patients with cancer living with HIV while receiving concurrent chemotherapy and antiretroviral drugs are at a high risk of developing chemotherapy-induced hepatotoxicity. These findings highlight the need for careful management of ART and chemotherapy regimens to minimize the risk of hepatotoxicity. Early identification of hepatotoxicity in this group is also critical to prevent progression to severe hepatotoxicity and to optimize cancer treatment outcomes.

Diabetes mellitus increased the odds of developing chemotherapy-induced hepatotoxicity by 20.2 times. A study by Iryna et al (2015) in Russia identified diabetes as the most significant risk factor for hepatic dysfunction in patients receiving methotrexate, positively correlated with both levels of ALT ($r = 0.837$) and ALP ($r = 0.756$).³⁵ Similarly, studies in China,³⁶ USA³⁷ and France,³⁸ identified diabetes mellitus as an independent risk factor for hepatotoxicity. This may be explained by chronic hyperglycemia and insulin resistance among patients with diabetes, which promote a state of increased oxidative stress and inflammation throughout the body, including the liver.³⁹ Chemotherapy agents often induce oxidative stress as part of their mechanism of action.⁴⁰ Therefore, an additive effect of pre-existing oxidative stress from diabetes and chemotherapy-induced stress can overwhelm the liver's protective mechanisms, leading to greater cellular damage. Furthermore, insulin resistance and high insulin levels in people with diabetes frequently result in non-alcoholic fatty liver disease (NAFLD).⁴¹ This can advance to non-alcoholic steatohepatitis (NASH), marked by liver inflammation and cell death.⁴² The current findings mandate a more personalized treatment approach, involving careful chemotherapy drug selection and dosage adjustments, alongside stringent glycemic control to mitigate risks. This necessitates increased vigilance and rigorous monitoring of liver function tests (LFTs) in patients with cancer and pre-existing diabetes undergoing chemotherapy. Early detection of hepatotoxicity is crucial for timely intervention and prevention of progression to more severe grades.

Limitations of the Study

Liver function was assessed at only one point after chemotherapy, which may have led to the underreporting of chemotherapy-induced hepatotoxicity due to missed cases of delayed toxicity. Second, the Naranjo scale, used for causality assessment, may not fully capture drug-related hepatotoxicity in patients with cancer, as some domains may not have been captured. Moreover, the estimates on the effect of diabetes on CIH should be interpreted carefully as it is not adequately powered and a larger adequately powered study should be conducted to establish this association. Finally, the study was conducted at a single site, which may limit the generalizability of the findings to other populations or settings.

Strengths of the Study

The study had a relatively large sample size (216 cancer patients), which provided sufficient statistical power, improved precision of estimates, and allowed meaningful subgroup analyses (eg, comorbidities such as HIV and diabetes).

The study provided first local data to assess chemotherapy-induced hepatotoxicity among patients with cancer at Mbarara Regional Referral Hospital, South Western Uganda. This adds novelty and local relevance to the research.

Conclusion

Chemotherapy-induced hepatotoxicity was found to be a common complication among adult patients with cancer who are on chemotherapy, with nearly one-third of patients developing liver enzyme abnormalities. Most cases were mild to moderate in severity. The observed incidence of 29% is comparable to reports from other low- and middle-income countries. HIV infection and diabetes mellitus were identified as significant predictors of hepatotoxicity, underscoring the importance of comorbidity driven risk stratification. Cytotoxic antibiotics and podophyllotoxins showed significant association with CIH at bivariate logistic regression although the significance of the association was lost at multivariate regression. Future studies should be adequately powered to determine the association of different chemotherapy classes with CIH. These findings highlight the need to strengthen routine liver function monitoring within oncology care, particularly among patients with underlying comorbidities. Integration of structured pharmacovigilance practices, targeted staff training, and context-specific clinical guidelines incorporating individualized risk assessment may improve early detection and management of hepatotoxicity. Such measures are essential to optimizing treatment outcomes and enhancing the safety of cancer care in Uganda.

Abbreviations

ADRs, Adverse Drug Reactions; ALP, Alkaline Phosphatase; ALT, Alanine transaminase; AOR, Adjusted odds ratio; ART, Antiretroviral therapy; AST, Aspartate aminotransferase; AZT, Zidovudine; BSA, Body Surface Area; CI, Confidence Interval; CIH, Chemotherapy-induced hepatotoxicity; COR, Crude odds ratio; CTCAE, Common

Terminology Criteria for Adverse Events; DM, Diabetes mellitus; HAART, Highly Active Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; IQR, Interquartile range; LFTs, Liver Function Tests; LMICs, Low- and Middle-Income Countries; MRRH, Mbarara Regional Referral Hospital; MUST, Mbarara University of Science and Technology; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic Steatohepatitis; NCDs, Noncommunicable Diseases; NVP, Nevirapine; REC, Research Ethics Committee; 3TC, Lamivudine.

Data Sharing Statement

The datasets used and analysed during this study shall be availed by the corresponding author on request.

Ethical Approval and Consent to Participate

Ethical approval for this study was obtained from the Research Ethics Committee at Mbarara University of Science and Technology as the Institutional review board for authorization to conduct the research (MUST-2025-229). Permission to conduct the study was also granted by the hospital administration. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Written informed consent was obtained from all participants prior to enrolment in the study. Participants were informed about the purpose of the study, procedures involved, potential risks and benefits, and their right to withdraw at any time without affecting their care. Confidentiality of participant information was strictly maintained throughout the study.

Consent for Publication

All authors agreed to the submission of this manuscript for publication.

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Author Contributions

All authors made significant contributions to conception and design, acquisition of data, analysis, and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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