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Chemotherapy-Induced Toxicities, Clinical Outcomes and Associated Factors among Patients with Gastrointestinal Cancer in Two Tertiary Care Hospitals, Addis Ababa, Ethiopia

By

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A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirement for a Master of Science Degree in Pharmacy Practices.

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This study aims to certify that the thesis prepared by Samson Fisseha, entitled *"Chemotherapy-Induced Toxicities, Clinical Outcomes and Associated Factors among Patients with Gastrointestinal Cancer in Two Tertiary Care Hospitals, Addis Ababa, Ethiopia,"* and submitted to the Partial Fulfillment of the Requirement for a Master of Science degree in Pharmacy Practices, complies with the regulations of the university and meets the accepted standards concerning originality and quality.

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Abstract

Background: Gastrointestinal tract cancers are the leading cause of cancer-related death worldwide. Chemotherapy remains a cornerstone of treatment, and it is often associated with various toxicities. However, there is a lack of data that shows the prevalence of chemotherapy-induced toxicity, clinical outcomes, and associated factors among patients with gastrointestinal tract cancer in Addis Ababa, Ethiopia.

Objective: To assess chemotherapy-induced toxicity, clinical outcomes, and associated factors among patients with gastrointestinal tract cancer at Tikur Anbessa Specialized Hospital and St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.

Methods: A hospitalized-based prospective study design was used. Data were collected from patients and medical records from June 20, 2023 to February 15, 2024. Adverse medication events were graded via the National Cancer Institute Common Terminology version 5.0. The data were entered and analyzed using SPSS software version 26. Descriptive statistics and logistic regression analyses were used to analyze the data. A p-value <0.05 was considered as statistically significant.

Results: Out of a total of 204 patients, 105 (51.5%) were female. The mean (± SD) age of patients was 51.5 (±11.14) years. A total of 1499 adverse medication events were reported. According to the NCI-CTAE grading score, 37.15% of adverse medication event were graded 3-4. Overall, more than half (53.4%, 109) of patients had poor treatment outcomes, with significant predictors including age ≥60 years (AOR: 4.640, 95% CI: 1.201–17.933, p=0.026), poorly differentiated tumors (AOR: 5.100, 95% CI: 1.483–17.539, p=0.010), metastasis (AOR: 9.124, 95% CI: 3.477-23.947, p=0.001), grade 3-4hematological toxicity (AOR: 3.677, 95% CI: 1.286-10.513, p=0.015), and treatment delays (AOR: 2.762, 95% CI: 1.805-9.475, p=0.016).

Conclusion: The higher incidence of adverse medication event is concerning, as both the prevalence and severities among GIT cancer patients in the study settings. High grade toxicities were associated with demographic, clinical, and treatment-related characteristics. The prognosis for GI cancer patients remains poor, with treatment outcome negatively impacted by high-grade chemotherapy toxicities and patients' characteristics.

Key Terms*:* Toxicity, Chemotherapy, Gastro-intestinal tract cancer, Ethiopia, Adverse medication events, treatment outcome.

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Abbreviations and Acronyms

5-FU:	5-Fluorouracil
AAU:	Addis Ababa University
ADR:	Adverse drug reaction
AOR:	Adjusted odds ratio
ASDR:	Age- Standardized death rate
CAPEOX or CAPOX:	Capecitabine and oxaliplatin
COR:	Crud odds ratio
CRC:	Colorectal cancer
ECOG:	Eastern Cooperative Oncology Grade
FOLFIRI:	5-Fluorouracil, leucovorin and irinotecan
FOLFOX:	5-Fluorouracil, leucovorin and oxaliplatin
FOLFOXIRI:	5-Fluorouracil, leucovorin, irinotecan and oxaliplatin
GBD:	Global Burden of Diseases
GCSF:	Granulocyte Colony Stimulating Factor
GI:	Gastrointestinal
GLOBOCANO:	Global Cancer Statistics
OR:	Odds ratio
NCCN:	National Comprehensive Cancer Network
SoP:	School of Pharmacy
SPHMMC:	St. Paul's Hospital Millennium Medical College
SPSS:	Statistical Package for the Social Sciences
TASH:	Tikur Anbessa Specialized Hospital
VEGF:	Vascular endothelial growth factor
WHO:	World Health Organization

1. Introduction

1.1 Background

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths in 2018 (1). Globally, approximately one in every six deaths is due to cancer(2). During the last two decades, the incidence of cancer has increased worldwide, and approximately 70% of deaths have occurred in low and middle-income countries (3). The burden of cancer in sub-Saharan African countries is likely to increase in the new millennium (4). The number of cancer deaths and incidences is increasing globally, primarily due to aging, poor public awareness of cancer, population growth, and increased prevalence of cancer risk factors (5).

According to the Global Cancer Statistics (GLOBOCAN) 2020 report, lung cancer is the leading cause of death affecting approximately 1.8 million (18%) of all cases , followed by colorectal cancer (9.4%), liver cancer (8.3%), stomach cancer (7.7%), and breast cancer (6.9%) (6)**.** According to the World Health Organization (WHO) in 2018, colorectal cancer (1.80 million cases) is the third most common cancer, and stomach cancer (1.03 million cases) is sixth (7). Overall, common GI tract cancers accounted for 36.2% of neoplasm-related deaths (6)**.**

In Africa, the causes of cancer-related death include breast cancer (12.1%), cervical cancer (10.8%), liver cancer (9%), prostate cancer (6.6%), and lung cancer (5.8%) (1, 7)**.** Colorectal cancer (CRC) is considered the fifth most common cancer in Africa, and it is estimated to be higher in northern Africa (8.8%) than in sub-Saharan Africa (5.9%) (8, 9).

In Ethiopia in 2019, there were an estimated 53,560 new incident cases of cancer in both sexes, and the burden of cancer was 30.5% of the total population in 2019 (1, 10). The incidence of GI tract cancer in Ethiopia is rising; among the GI tract cancers, CRC accounts for 8.5 and 6.3 per 100,000 for men and women, respectively (11).

The treatment of gastrointestinal tract cancer consists of surgery, chemotherapy, radiation, and biological modulators. The most common chemotherapy regimens are 5-FU-based chemotherapy, such as oxaliplatin plus 5-fluorouracil, and leucovorin (FOLFOX); 5-fluorouracil plus irinotecan, and leucovorin (FOLFIRI); irinotecan plus oxaliplatin, 5-fluorouracil, and

leucovorin (FOLFOXIRI); capcitabine and oxaliplatin (CAPOX); and capcitabine, oxaliplatin, irinotecan (XELIRI) (8, 9).

The side effects of cancer treatment cause significant morbidity, strongly impact the quality of life, and frequently impair the delivery of optimal cancer therapy. Antineoplastic agents have side effects such as alopecia, nausea and vomiting, myelosuppression, cardiac toxicity, hemorrhagic cystitis, mucositis, hot flashes, electrolyte imbalance, neuropathy, and deep vein thrombosis (12).

The overwhelming majority of patients who are receiving chemotherapy for gastrointestinal tract (GIT) cancer are affected by treatment-related adverse events (AEs). Among the most common symptoms reported by patients are fatigue (88%), diarrhea (75%), constipation (73%), and vomiting (58%) (3, 8, 11, 13)**.** Chemotherapy-induced nausea and vomiting (CINV) is associated with a high risk of CINV (>90%) with IV cisplatin (13).

Chemotherapy-induced hematologic toxicities have the potential to be life-threatening, and chemotherapy-induced neutropenia is arguably the most dangerous due to the potential risk of developing a life-threatening infection (14). If the predicted risk of neutropenic fever is greater than 20% with a particular regimen, patients should be given granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis (1).

Treatment outcomes for gastrointestinal tract cancers are influenced by factors, including cancer type, treatment modalities, tumor stage at diagnosis, lymph node involvement, and patient characteristics significantly influence these outcomes (15). Survival rates for gastrointestinal (GI) cancers vary widely, reflecting the complexity of these diseases, For example, the five-year survival rate for localized colorectal cancer can exceed 90% (16). In addition to survival, quality of life (QoL) emerges as a critical outcome for GI cancer patients, often impacted by treatment side effects, nutritional status, and psychological well-being (17) . Recurrence rates are essential in determining long-term outcomes (18). Addressing disparities and improving early detection will be pivotal in optimizing outcomes for GI cancer patients.

1.2 Statements of the Problem

Cancer incidence data from 2019 reveals that GIT cancer is among the five most common cancers in Ethiopia (12). The increasing incidence and prevalence of GIT cancers, particularly colorectal and stomach cancers, pose a significant public health concern (19). The incidence of colorectal cancer mortality is reported at 22.5 per 100 person-years (20). From 2010 to 2019, colorectal and stomach cancers showed the highest percentage changes in death count, with increases of 56% and 12%, respectively (12). Post-2020, the incidence and prevalence of GI tract cancers have continued to rise alarmingly (11).

Chemotherapeutic agents, while effective, have a narrow therapeutic index, leading to severe toxicities that may result in treatment discontinuation, high healthcare costs, and premature death (21-23). These toxicities severely impact patients' physical, emotional, and financial well-being, affecting their quality of life and treatment adherence (24, 25). Hospital admissions due to chemotherapy toxicity are common, with a reported rate of 13.1% and a median stay of 3 days (21). Clinical outcomes are adversely affected, as patients with severe toxicities exhibit poorer prognoses and reduced survival rates (20). Toxicities can cause acute and long-term effects on various organ systems, including cardiac, neurological, renal, pulmonary, and hepatic systems (26).

Despite improvements in the outcomes of cytotoxic treatment for GI tract cancer, toxicities such as myelosuppression remain significant dose-limiting complications, particularly with FOLFOX chemotherapy (25). Treatment delays and inefficiencies due to toxicities lead to additional healthcare costs and negative clinical encounters for patients (20, 27). Chemotherapy's side effects and long-term toxicities compromise treatment compliance and efficacy, with most patients experiencing at least one adverse event during and after treatment (28). These side effects diminish health-related quality of life by affecting physical, psychological, and social functioning (21). Additionally, the impact on work productivity is substantial for both patients and caregivers (29).

Studies indicate that common chemotherapy toxicities include nausea, vomiting, infection, neutropenia, anemia, and fever, with drugs such as platinum compounds, nitrogen mustards, taxanes, and antimetabolites being frequently implicated (21, 30). In Ethiopia, neutropenia,

particularly febrile neutropenia, is a common complication of FOLFOX chemotherapy, leading to dose reductions and delays, reduced relative dose intensity, and significant morbidity, mortality, and costs (5, 21)..

The treatment burden for managing toxicity involves significant time and travel, with patients from rural areas facing additional challenges such as high treatment costs, psychological problems, and social stigmatization. Many patients lack adequate information about chemotherapy side effects and their management, contributing to treatment discontinuation and decreased quality of life (10, 26).

The increasing incidence of gastrointestinal (GIT) cancers in Ethiopia poses a significant public health challenge. Treatment toxicities not only compromise patient outcomes but also diminish quality of life and increase healthcare costs. Enhancing patient education on chemotherapy side effects and improving support, particularly for rural patients, is crucial. Addressing complications like neutropenia in FOLFOX chemotherapy is essential for better outcomes. A focused approach on toxicity management and patient support is vital for improving health outcomes for GIT cancer patients in Ethiopia.

1.3 Significance of the Study

This study is essential to advancing patient care for GI cancer patients undergoing chemotherapy in Ethiopia, where limited data exists on the safety and adverse effects of cancer chemotherapeutic agents. By identifying demographic and clinical factors linked to chemotherapy-induced toxicities, the study aims to provide healthcare providers with insights that can guide the customization of treatment, reducing adverse effects and improving patient satisfaction. Furthermore, understanding the prevalence and impact of toxicity will empower healthcare providers to develop safer, more effective chemotherapy protocols that could inform revised treatment guidelines tailored to local needs.

Evaluating clinical outcomes in the context of chemotherapy toxicity will also offer valuable insights into the long-term effects of current treatment approaches, potentially leading to increased treatment success rates. By highlighting areas where supportive care measures are needed, this study will help healthcare providers expand strategies to improve patients' health-related quality of life, thus addressing the challenges and discomforts faced by patients as they undergo treatment.

The study's results will benefit both high-risk patients and the healthcare system overall. Identifying specific risk factors for toxicity will enable interventions targeting these vulnerable populations, ultimately enhancing patient outcomes. Additionally, the findings could influence resource allocation, guiding policymakers and healthcare administrators in Ethiopia to prioritize effective toxicity management and preventive strategies that alleviate healthcare costs, reduce morbidity, and improve patient experiences.

In a healthcare system with no organized toxicity monitoring and reporting program, the insights from this study will be instrumental in filling a critical gap in chemotherapy safety. It will provide foundational data that not only addresses immediate safety concerns but also supports future academic research, paving the way for potential breakthroughs in GI tract cancer treatment. Ultimately, this study aspires to improve clinical outcomes and mitigate the toxic burden of chemotherapy on patients, thereby significantly enhancing the quality of cancer care in Ethiopia.

2. Literature Review

2.1 Burden of Gastro Intestinal Tract Cancer

Globally, in 2018, approximately 4.8 million new cases were estimated, and approximately 3.4 million deaths from GI cancer occurred. The estimated new cases and deaths in Asia are approximately 63% and 65%, respectively (31). In China, the estimated number of new cases is 38%, and the number of deaths is approximately 41% (1). North America and Europe together account for 26% and 23% of new cases and deaths, respectively. The proportion of deaths from GI cancer is greater than that of new cancer cases in Africa (5% vs. 4%) (4).

A randomized study conducted in Switzerland by Bordry et al., (2021) found that among gastrointestinal tract cancers, the most prevalent type are colon/rectum (60.0%), esophageal (7.0%), stomach (6.5%), and others (5.2%) (32). In a separate study in China by Hong et al (2022) reported that 5-FU is the main drug administered via intravenous bolus and 46-h continuous infusion (2400 mg/m² initially). Patients were treated with routinely used regimens such as FOLFOX (39.4%), and FOLFIRI (18.1%) (6).

A retrospective cohort study in Ethiopia by Hassen et al., (2018) identified esophageal cancer was the seventh most common cancer in terms of cancer morbidity and the sixth most common cause of cancer-related death in the world; this type of cancer accounted for approximately 572,000 and 508,000 new cases and deaths, respectively (33). Esophageal cancer is common in Eastern Asia (12.2%), Eastern Africa (8.3%), and Southern Africa (7.4%) (4).

A longitudinal cohort study in Sweden by Johansson et al.,(2022) found that anal cancer is a rare disease that accounts for less than 1% and less than 3% of all new cases of GIT cancer (34). In a prospective observational study conducted in India by Jain et al.,(2016-2018), gallbladder cancer (GBC) accounts for 80 to 90% of carcinomas of the biliary system. It is the most common and aggressive biliary tract cancer, with an overall 5-year survival of only 5%–10% (35).

A retrospective cohort in Germany by Teufeal et al., (2020) revealed that small Intestinal Cancer, Pancreatic, and Liver Cancer remains a rare malignancy accounting for less than 55 of all gastrointestinal tract cancers, while 555 and 82% of the cases are located in the duodenum, followed by the jejunum. Only 7-175 cases occurred in the ileum and pancreatic cancer is still

one of the most aggressive oncological diseases, with a 5-year mortality rate of less than 10% (36)

A randomized controlled trial in Germany by Michnevich et al., (2018) found that most patients received either postoperative chemotherapy (treatment applied until progression or therapy (≥ 3 months, ≤ 6 months) or palliative chemotherapy intolerability) (13). In a retrospective study conducted in China by S et al.,, (2020-2022) different treatments were received by the study population, in which most of the patients were receiving chemotherapy along with surgery 101 (77.69%). The other patients received chemotherapy with surgery and radiation: 19 (14.61%), 7 (5.38%) received chemotherapy alone, and 3 (2.30%) received chemotherapy with radiation. The common chemotherapy regimen used was CAPOX (60%) (23).

A systematic review in Ethiopia by Awedew et al., (2022) found that the majority of patients who are receiving chemotherapy for gastrointestinal tract (GIT) cancer are affected by treatment-related adverse events (AEs). Among the most common symptoms reported by patients are fatigue (88%), diarrhea (75%), constipation (73%), and vomiting (58%) (12, 13).

2.2 Treatment Regimen Used for Gastrointestinal Tract Cancer

2.2.1 Gastric Cancer and Esophageal Cancer

A prospective study in France by Morawska et al., (2018) identified that the first-line chemotherapy used for gastrointestinal cancer is a 5-FU-based regimen (37). In a prospective observational study conducted in Boson by Finkelman et al., it was revealed that nearly 80% of patients had undergone prior gastrectomy and 5-FU, 5-FU, and cisplatin (n = 141) or 5-FU and oxaliplatin were used as first-line treatments, and the response rate was (16.0%) (38). Additionally a prospective observational study in Ethiopia by Gadisa et al., (2020) found that having there or more metastatic sites of disease (HR, 1.72), a performance status >2 (HR, 1.79), and time to progression under first-line chemotherapy ≤6 months were found to be independently associated with poor overall survival (27, 31).

A facility-based retrospective cohort study in Ethiopia by Hassen et al., (2021) revealed that among 349 patients with esophageal cancer, 183 (52.1%) were treated with a transhiatal esophagectomy surgical procedure, whereas 112 (31.9%) with transthoracic esophagectomy and

112 (31.9%) with feeding gastrostomy were treated. More than one-fourth (25.8%) of these patients received chemotherapy, whereas only 26 (7.7%) were treated with radiotherapy (33).

A retrospective study in Ethiopia by Wondimagegnehu et al., (2012-2017) found that among the 149 patients with gastric cancer, 90.9% received fewer than seven cycles of chemotherapy and the most commonly prescribed regimen was cisplatin/FU in 22 (56.4%) patients and cisplatin/paclitaxel in 15 (38.4%) patients. Among the patients in the chemotherapy follow-up, 20 (51.2%) had taken between two and five treatment cycles, whereas 15 (38.5%) completed six cycles of treatment (39).

2.2.2 Colorectal Cancer

A retrospective study in Ethiopia by Wondimagegnehu et al., (2012-2017) reported that the main treatment for colorectal cancer consists of chemotherapy, surgery, radiation, and biological modulators (39). I a retrospective study conducted in India by S et al., (2020-2022) it was found that the most common chemotherapy regimens are 5-FU-based chemotherapy, such as oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX); 5-fluorouracil, irinotecan, and leucovorin (FOLFIRI); irinotecan, oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOXIRI); capcitabine and oxaliplatin (CAPOX); and capcitabine, oxaliplatin, and irinotecan (XELIRI) (23).

A prospective patient-reported outcomes study in Ethiopia by Gadisa et al., (2020) revealed that the most common treatment for colorectal cancer was combined chemotherapy and surgery, followed by surgery, chemoradiation, and chemotherapy alone. In that study of 285 (93.35%) patients who received chemotherapy, most patients (165, 55.6%) received chemotherapy containing the FOLFOX regimen, and approximately 6 cycles of chemotherapy were used; the other patients received more than 6 cycles of chemotherapy (1, 14).

A randomized trial conducted in Italy by Aprile et al., (2015) established that three to six months of adjuvant chemotherapy, using regimens that include flouropyrimidine combination with oxaliplatin (FOLFOX or CAPOX), is currently offered as the standard of care in stage III and high-risk stage II CRC patients (40). Similarly, a retrospective study conducted in Ethiopia by Ababa et al., (2020) indicated that for patients with advanced-stage disease, FOLFOX/CAPOX or irinotecan with flour pyrimidine (FOLFIRI) with or without targeted agents are used as first-line treatment options after demonstrating a clear survival benefit in over no chemotherapy (30).

2.2.3 Anal Cancer and Gallbladder Cancer

Combinations of mitomycin C (MMC) and 5-fluorouracil (5-FU) have been established as the standard of care, leading to complete tumor regression in 80-90% of patients, and other cytotoxic agents (mainly cisplatin) can be considered if clinically indicated (41).

Curative treatment for anal cancer varies and consists of both chemoradiotherapy and radiotherapy (46–64 Gy) alone. 5-FU, mitomycin, and cisplatin are the most commonly used chemotherapeutic agents. In a Cross –sectional study conducted in Ethiopia in 2016, the five-year overall survival for patients treated with curative intent was 73%. In an adjusted analysis, 5-FU and mitomycin were associated with lower mortality than were 5-FU and cisplatin, but the association was weaker (HR 1.61 (95% CI: 0.904; 2.85) than that in the unadjusted analysis (3, 37).

A retrospective study conducted in South Korea by Young et al., (2018) found that gemcitabine plus cisplatin is widely used as a first-line chemotherapy for unresectable GBC based on the recent clinical trial showing favorable outcomes of combination chemotherapy in patients with biliary tract cancer (BTC) (42).

2.2.4 Small Intestinal Cancer, Pancreatic, and Liver Cancer

The most common chemotherapy drugs used for small intestine adenocarcinoma are fluorouracil (5-fluorouracil or 5-FU), oxaliplatin, and irinotecan (32).

The current standard treatment of pancreatic cancer is palliative chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or nab-paclitaxel with gemcitabine (43). In a Cross –sectional study conducted in Ethiopia in 2016, palliative settings and therapeutic regimens, such as FOLFIRINOX or gemcitabine and nab-paclitaxel, have been established recently and are associated with increased OS, with medians of 11 and 8.5 months, compared with 7 and 6.7 months, respectively, with the single agent gemcitabine (3)

2.3 Chemotherapy-Induced Toxicity and its Management

A retrospective cohort study in Ethiopia by Tiruneh et al., (2022) revealed that the most common types of chemotherapy-induced toxicity are neutropenia, gastrointestinal problems and

cardiovascular toxicity with hypersensitivity. The management of this toxicity involves the use of treatments such as antibiotics, antifungals, antiemetics, electrolytes, filgrastim, and analgesics (12, 19).

Fluoropyrimidines as monotherapy are the leading cause of death related to their toxicity. A prospective cohort study conducted in France by Morawsk et al., (2018) revealed that 10%–30% of patients receiving fluoro-pyrimidines experienced treatment-related toxicity, which led to death in approximately 1% of the patients and was even greater when these patients were dosed with irinotecan and/or oxaliplatin (37).

A retrospective study conducted in India by S et al., (2022) showed the incidence of chemotherapy-induced toxicity was greater in female patients (73.6%). Toxicity mostly occurred in the 41–50 year age group (27.4%). Among other chemotherapies, cisplatin (19.6%) was the most common offense drug. The most commonly reported toxicity was nausea and vomiting (23%) (23). Most toxicities required treatment, and 12.9% of the ADRs were considered serious. Assessment of causality revealed that 80% of adverse drug reactions were possible (44).

A retrospective study conducted in Ethiopia by Wondimagegnehu et al., (2020), grade I/II mucositis incidence was noted at cycle 2 (6.5%) compared with cycle 1 (5.2%). However, a study performed in India revealed that only 10 patients (6.5%) benefited from 5-FU bolus dose reduction between cycle 1 and cycle 2; due to grade 2 toxicity, 79 patients experienced adverse drug reactions, including constipation (20.56%), vomiting (19.85%), and neutropenia (19.1%). After the occurrence of adverse drug reactions, each drug treatment regimen and the occurrence of the corresponding adverse drug reactions were assessed. Among those studies, 28.6% reported neutropenia, 35.7% constipation, 7.1% diarrhea, and 21.4% vomiting. There was also an increased incidence of diarrhea, nausea, and diarrhea with capecitabine (12) (39). andomized trial

A randomized trial conducted France by Tournigand et al., (2012) identified FOLFOX as the primary adjuvant treatment regimen for colon cancer. Among 1123 patients, 237 who received FOLFOX, the incidence of neutropenia was 1.8%, and gastrointestinal adverse effects were low. However, out of the 12 colon cancer patients who received FOLFOX, two experienced neutropenia (16.66%). The incidence of gastrointestinal adverse effects was high (66.66%) (45).

A retrospective study performed in New York by Smoragiewicz et al., (2014) reported that capecitabine combined with oxaliplatin (XELOX regimen) for the treatment of metastatic CRC has similar efficacy but has a lower incidence of severe diarrhea than FOLFOX (14% vs. 24% (46). Similarly, a prospective study in Vietnam by Nguyen et al., (2022), capecitabine combined with irinotecan (XELIRI) resulted in higher rates of severe chemotherapy-induced diarrhea than FOLIRI during treatment for metastatic CRC, indicating that toxicity profiles between different forms of fluoro-pyrimidine administration cannot be automatically assumed when combined with other drugs (21, 34). However, the CAPIRI treatment regimen is associated with a high incidence of diarrhea (6.7%), neutropenia (33.3%), anemia, and abdominal pain (16.7%), whereas the CAPOX treatment regimens are associated with neutropenia (16.5%), vomiting and constipation (24.1%) and vomiting and constipation (24.1%) (23).

A prospective observational study in India by Rao et al., (2021), colorectal cancer patients treated with FOLFOX had a higher rate of peripheral neuropathy (96% versus 76.6%, $P < 0.001$), but the FOLFIRI treatment regimen was associated with a greater occurrence of hair loss (58.5% vs. 40%, $P = 0.04$). The rates of other adverse effects, including diarrhea, nausea and vomiting, were not somewhat different (35, 41). Dose-limiting toxicities occurred in 22% of the treatment cycles, and most dose-limiting toxicities were associated with treatment delays. Neutropenia accounted for 51% of all dose-limiting toxicities in this series. Granulocyte colony-stimulating factor (GCSF) was used in 10% of the patients (42)

A Cross –sectional study conducted in Ethiopia in 2016 revealed that a total of 815 ADRs were identified per 203 patients included in the study. The most commonly occurring ADRs were nausea and vomiting (18.9%), infections (16.7%), neutropenia (14.7%), fever and/or chills (11.3%), and anemia (9.3%) (3). Platinum compounds (31.4%) were the most common group of drugs causing ADRs. Among the reported ADRs, 65.8% were grade 3–4 (severe), 29.9% were grade 1–2 (mild), and 4.3% were grade 5 (toxic). A significant association was found between age, several chemotherapeutic agents, the dose of chemotherapy, and the occurrence of grade 3–5 toxicity (3).

A prospective study conducted in Ethiopia by Gadisa et al., (2021), chemotherapy-induced nausea and vomiting (CINV) is associated with a high risk of CINV (>90%) with IV cisplatin, whereas there is a low risk (<10%) with IV rituximab. 5-HT3 receptor antagonists (such as

ondansetron), NK-1 receptor antagonists (such as aprepitant), glucocorticoids (such as dexamethasone), and olanzapine, a second-generation antipsychotic, are used to treat CINV(14).

A retrospective study conducted in china by Hong et al.,(2022), hemotherapy-induced hematologic toxicity has the potential to be a life-threatening form of chemotherapy-induced neutropenia, arguably the most dangerous because of the potential risk of developing a life-threatening infection. If the predicted risk of neutropenic fever is greater than 20% with a particular regimen, patients should be given granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis (6).

2.4 Factors Associated with Chemotherapy-Induced Toxicities

A prospective study in India by Aprile et al., (2015) shows 93.0% of patients who received high-dose cisplatin who had a history of alcohol intake experienced nausea and vomiting (40). Another prospective study conducted in Italy by Mascaretti et al., (2020), reported that 17.6% of patients were referred for nutritional intervention, with a positive association with body mass index (BMI) after gaining weight (47).

A retrospective study performed in USA by Sonis et al., (2010), identified fifty-one medication errors in seventy-three patients and a total of 1215 patient days, resulting in a cumulative incidence of 69.86 medication errors per 100 patients and 25.63 medication errors per 100 (CI 1.167–24.684) admissions (48). Among the factors associated with grades 3 and 4 adverse drug reactions, the presence of comorbidities, cancer type, and the use of four or more chemotherapy drugs were associated with the risk of developing grades 3 and 4 adverse drug reactions (30, 48).

A prospective study conducted in India by Aprile et al., (2015), evaluated the associations of socio-demographic and clinical factors with chemotherapy-induced toxicity during first-line chemotherapy, Grade ≥ 3 hematological (38.6%), and non-hematological (12.9%) toxicities are common (40). Similarly, a prospective study in Vietnam by Nguyen et al., (2022), Patients diagnosed with stage II and stage III-IV disease had a lower risk of grade ≥ 3 toxicity non-hematological toxicities, with OR of 0.26; 95% CI [0.12–0.59], and OR of 0.47; 95% CI [0.20–1.10], respectively (21).

2.5 Conceptual Framework

After reviewing different literature, a conceptual framework was developed for this study. The conceptual framework depicts the predictors or risk factors of severe toxicities and treatment outcomes which may have a direct and /or indirect impact on poor treatment outcomes (21, 28, 30, 37, 48-53) .

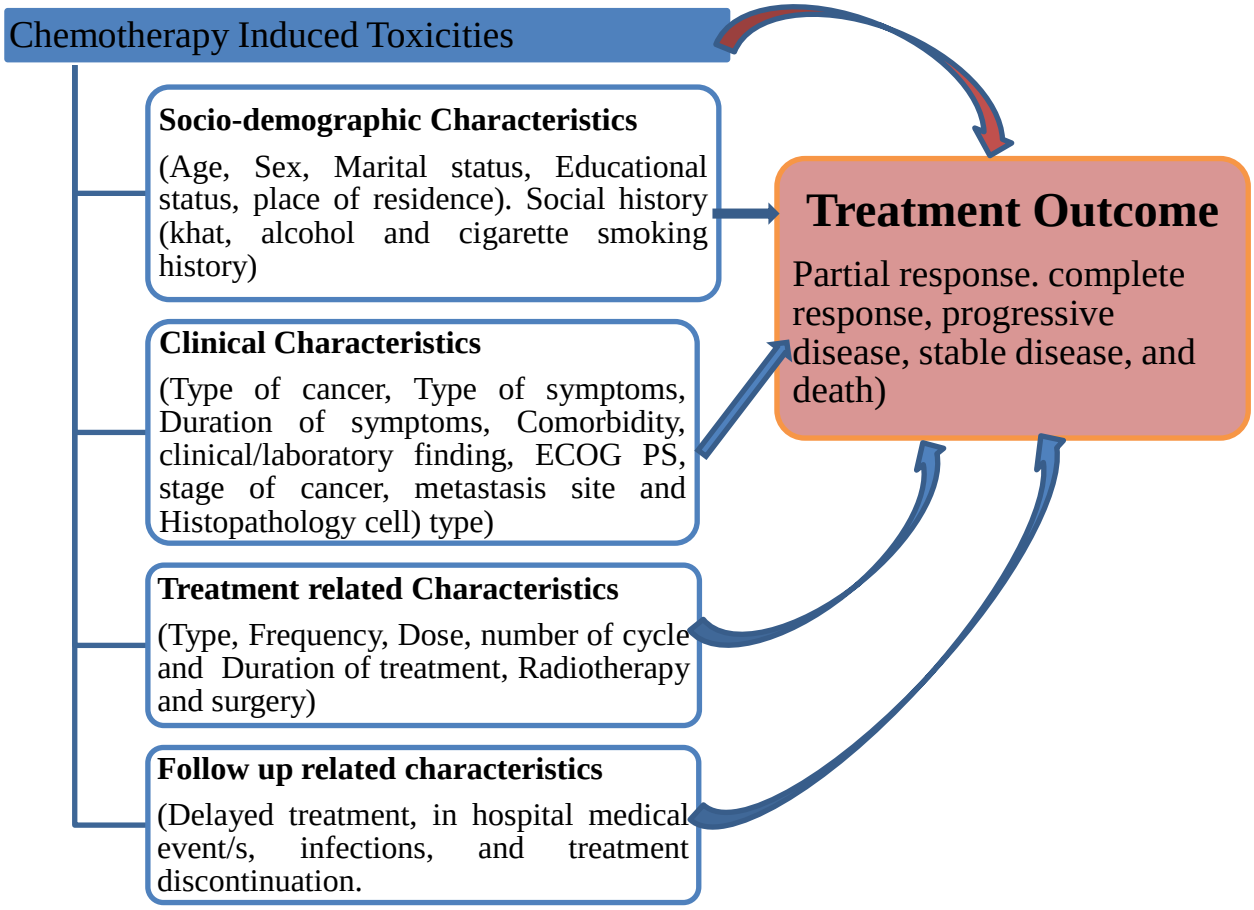

Figure 1: Conceptual framework showing the associations between treatment outcomes, and chemotherapy-induced toxicity with different factors adopted from different types of literature**.**

3. Objectives

3.1 General Objective

To assess chemotherapy-induced toxicity, clinical outcomes, and associated factors among patients with gastrointestinal tract cancer at Tikur Anbessa Specialized Hospital (TASH) and St. Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia.

3.2 Specific Objectives

- To assess the prevalence of Adverse drug events
- To identify demographic and clinical factors associated with Adverse drug events
- To evaluate the treatment outcomes of chemotherapy treatment at two tertiary care hospitals
- To determine independent factors affecting treatment outcomes at two tertiary care hospitals

4. Methods and Participants

4.1 Study Setting

The study was conducted at the adult oncology unit of Tikur Anbessa Specialized Hospital (TASH) and St. Paul's Hospital Millennium Medical College (SPHMMC). TASH was founded in 1972 and serves as the primary referral center in Ethiopia and is found in Addis Ababa. TASH serves over 6,000 new cancer patients per year. The center started training in clinical oncology in 2013, and thirty-six residents are currently enrolled. The center is also used for outpatient chemotherapy administration. The hospital has around 465 physicians, 76 pharmacists, 992 nurses, and 115 other health-care professionals. It also has 950 administrative and support staff. The Hospital has about 700 beds and serves more than 500,000 patients per year in its 20 outpatient specialty clinics, inpatient, and emergency departments. Overall, the adult oncology center serves more than 850 patients per month and around 10,000 patients per year (54). The SPHMMC is the third largest tertiary teaching and referral hospital formed as a medical college in 2007, and the hospital was established in 1968 by the late Emperor Haile Selassie. The SPHMMC Oncology Unit was established on August 1, 2018. It was the second hospital offering cancer treatment in the country next to TASH. Currently, three oncologists, 12 general practitioners, 25 nurses, two medical physicist, 3 clinical pharmacists, 2 cleaners, 2 porters, and around 800 cancer patients have served in the SPHMMC oncology unit since its establishment (55).

4.2 Study Design and Study Period

Hospital-based prospective study was carried out from June 20, 2023 to February 15, 2024.

4.3 Population

4.3.1 Source Population

The source population was all patients treated for GI tract cancer at the adult oncology inpatient unit of TASH and SPHMMC.

4.3.2 Study Population

The study population was all patients treated for GI tract cancer at the adult oncology inpatient unit of TASH and SPHMMC who fulfilled the eligibility criteria.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

- All adult patients who were admitted to inpatient adult oncology ward with confirmed diagnoses of GI tract cancer
- Patients who were taking chemotherapy for GI cancer
- Aged ≥18 years old and
- Patients willing to participate in the study

4.4.2 Exclusion Criteria

- Patients with incomplete information on registration and medical charts

4.5 Sample Size and Sampling Technique

4.5.1 Sample Size Determination

All adult GI tract cancer patients attending TASH and SPHMMC during the study period were recruited for the study patients were followed until treatment completion. Most patients completed their first-line chemotherapy with six cycles, which took a minimum of six months or a maximum of eight months. Since most patients had delayed treatment; the final assessment was performed between 6 and 8 months.

4.5.2 Sampling Technique

The study patients were recruited from TASH and SPHMMC via nonprobability sampling with a consecutive sampling technique.

4.6 Study Variables

4.6.1 Dependent Variables

- ✓ Presence or absence of Adverse drug events
- ✓ Overall clinical outcome (Good or Poor response rate of chemotherapy)

4.6.2 Independent Variables

- ✓ Socio-demographic characteristics (age, sex, educational status, place of residence, and marital status) and social history (khat, alcohol, and cigarette smoking history) were recorded.
- ✓ Clinical characteristics (type of cancer, types of symptoms, duration of symptoms, comorbidities, clinical/laboratory findings, stage of cancer, histopathological cell type, and metastasis site).
- ✓ Treatment-related characteristics (type, frequency, dose, number of cycles, and duration of chemotherapy treatment)
- ✓ Follow-up related characteristics (treatment delayed, in-hospital medical event/infection, shock, treatment discontinuation, and refractory to first-line treatment).

4.7 Data Collection and Management

4.7.1 Demographics, Clinical, and Treatment-Related Data

A data abstraction form was prepared by the principal investigator after reviewing the literature on socio-demographic characteristics such as age, sex, educational status, marital status, clinical, pathological characteristics, and treatment approaches used (28, 37, 49-53)

After intensive training on the data abstraction tool and data collection techniques provided by the principal investigator to data collectors. All the demographic, clinical, and treatment-related characteristics were collected from respective patients and their medical records.

4.7.2 Chemotherapy-Induced Toxicity Assessment

Gastrointestinal cancer patients routinely undergo blood and urine tests (CBC, LFT, RFT) before each cycle of chemotherapy, and the oncologists or oncology residents routinely assess their health condition and chemotherapy-induced toxicity and record all test results and health status

in their medical records. The trained data collectors reviewed the studied patient's medical chart during all cycles of chemotherapy. Then, hematological and non-hematological chemotherapy-induced toxicities were graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI CTCAE) classification version 5.0 by the principal investigator.

Non-hematological toxicity was identified through a combination of patient self-reported side effects at each follow-up visit and the assessment recorded by nurses during each cycle of chemotherapy or hospital visit. Self-reported side effects of non-hematological toxicity, such as vomiting, diarrhea, constipation, and difficulty swallowing, were recorded during each chemotherapy cycle by data collectors. The combination of self-reported symptoms and medical chart information was graded by the NCI-CTCAE by the principal investigator.

4.8 Data Entry, Analysis, and Interpretation

The collected data were entered and analyzed via the Statistical Package for Social Sciences (SPSS) software version 26. Descriptive statistics were used to summarize the findings, whereas inferential statistics and binary logistic regression for categorical dependent variables were used to examine associated factors.

The treatment outcome was categorized into two categories according to the WHO guideline classification of cancer treatment outcomes, and to determine the factors associated with poor treatment outcome, those variables with a p-value of less than 0.25 in the bivariate logistic regression analysis were included in the final multivariable logistic regression analysis model. Variables with a p-value < 0.05 in the final model were considered statistically significant.

4.9 Data Quality Control

The quality of the collected data was maintained by appropriate training of the data collectors. The data collector was recruited by five trained data collectors (3 nurses with BSc. and 2 nurses with M.Sc. in oncology nursing), and half-day training was given by the principal investigator about the aim of the study and how to collect data from patients and medical records. Additionally, daily follow-ups were made by the supervisor to check the accuracy, completeness, and consistency of the collected data.

4.10 Operational Definitions and Definitions of Standard Terms

Stage of GI CA: diagnosis stage of cancer with pathological confirmation from stage I to stage IV.

Treatment pattern: defined as the number or frequency of patients with GI CA treated with chemotherapy or radiotherapy.

Treatment outcomes:

- **Good treatment outcome**: Characterized by increased overall survival, progression-free survival, significant tumor shrinkage or disappearance (high response rate), improved quality of life, and prolonged disease-free survival.
- **Poor treatment outcome**: Indicated by reduced overall survival, minimal or no reduction in tumor size, rapid progression of disease, diminished quality of life, and shorter disease-free survival periods.

Complete response: Disapperancrce of all target lesions**.**

Partial response: at least a 30% decreased in the sum of the longest diameter of the target lesions, taking as the reference the baseline sum longest diameter.

Progressive disease: at least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable disease: Neither sufficient shrinking to qualify for partial response nor sufficient increased to qualify for progressive, taking as the reference the smallest sum of longest diameter the treatment started.

ECOG performance status: a scale used to assess patient disease progression and how the disease affects a patient's ability to perform activities of daily living

Neutropenia is defined as an absolute neutrophil count less than 1500 from baseline.

ADR: any response to a drug, which is noxious, unintended, and occurs at doses used in man for prophylaxis, diagnosis, or therapy.

Adverse drug event (ADE) refers to any injury caused by a medicine and it encompasses all adverse drug reactions (ADRs), (including allergic or idiosyncratic reactions) as well as medication errors (MEs) that result in harm to a patient (56)

4.11 Ethical Considerations

Ethical approval for the study and study protocol was obtained from the AAU, CHS, School of Pharmacy ethical review board with protocol no. **ERB/SOP/522/15/2023** on May 04, 2023, and Institution review board (IRB) of (SPHMMC) with Ref no PM 23/212 on May 31, 2023. Before data collection, written permission was obtained from the oncology units of TASH and SPHMMC. The aims of the study were clearly explained to the study participants, and information was collected after written informed consent was obtained from each patient and taken from the participant's family. The right was given to the study patients to refuse or discontinue participation at any time they wanted and the chance to ask anything about the study objective. For privacy, the patients name was not used at the time of data collection, other personal information was kept entirely obscure, and confidentiality was assured throughout the study period.

4.12 Plan for dissemination of the results

The thesis work will be prepared both in hard and soft copy to be submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University. In addition, the findings of the study will be disseminated to TASH, SPHMMC and other key stakeholders involved in gastro intestinal cancer management. Publication of the result in scientific journals will be considered through peer review and presentation at different meetings/conferences.

5. Results

5.1 Socio-demographic characteristics of the patients

A total of 209 adults GIT cancer patients receiving chemotherapy were recruited for this study. Of these 5 (2.5%) patients were subsequently removed from the analysis. Thus, complete data available for 204 patients were included for final analysis, with a 97.6% response rate. More than two-thirds (72.5%, 148) of the patients were from TASH. Nearly half (51.5%, 105) of the patients were female. In terms of the age distribution, the mean (± SD) age of the patients at diagnosis was 51.5 (±11.14) years and nearly one-third (30.4%, 62) were ≥60 years of age. According to the residents of patients 55.2% were from urban. More than two-thirds (69.1%, 141) of the patients were married (Table 1).

Table 1: Socio-demographic characteristics of GIT cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variable		**Frequency n (%)**	**Mean ± SD**
Study site	TASH	148 (72.5)	
	SPHMMC	56 (27.5)	
Gender	Male	99 (48.5)	
	Female	105 (51.5)	
Age in year	<40	37 (18.1)	51.5 ±11.14
	40-49	44 (21.6)	
	50-59	61 (29.9)	
	60 and Above	62 (30.4)	
Marital status	Married	141 (69.1)	
	Single	20 (9.8)	
	Windowed	23 (11.3)	
	Divorced	20 (9.8)	

Educational level	No formal education	95 (46.1)
	Primary school(1-8) grade	41 (20.1)
	Secondary school(9-12) grade	31 (15.2)
	Higher education (diploma and above)	37 (18.1)
Residence	Urban	133 (65.2)
	Rural	71 (34.8)
Alcohol used	No	167 (81.9)
	Yes	37 (18.1)
Cigarette Smoker	No	169 (82.8)
	Yes	35 (17.2)
Khat	No	164 (80.4)
	Yes	40 (19.6)

Abbreviations: SD: standard division, TASH-Tikur Anbessa Specialized Hospital, SPHMMC-St. Paul's Hospital Millennium Medical College.

5.2 Clinical Characteristics of the Patients

Among the 204 patients with GI cancer, 65 (31.9%) had comorbidities. Hypertension (10.3%), diabetes mellitus (3.4%), and retroviral infection (3.4%) were the most common comorbidities.

Among histopathology cell type, the majority (93.1%, 190) of the patients had adenocarcinoma histopathology cells. More than two-thirds (72.1%, 147) of the patients had well-differentiated, and (22.5%, 46) had poorly differentiated. With respect to Eastern Cooperative Oncology Group Performance-Status (ECOG-PS), more than two-thirds (72.1%, 147) of the patients had an ECOG-PS of 0-1 during cycle 1, and 193 (94.6%) had an ECOG-PS of 0-1 during cycle 6. The means (± SD) of BSA and BMI were 1.56 (±0.014) m^2, and 20.96(± 3.6)7, respectively. Nearly two-thirds (64.7%, 132) of the patients had a clinical stage IV and metastasized to the liver accounting for 47 (35.6%) (Table 2)

Table 2: Clinical characteristics of GI tract cancer patients treated at the adult oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variables		**Frequency n (%)**
Comorbidity diseases	No-comorbidity	139 (68.1)
	HTN	21 (10.3)
	DM	7 (3.4)
	CKD	5 (2.5)
	RVI	7 (3.4)
	Asthma	6 (2.9)
	BPH	5 (2.5)
	Other*	14 (6.8)
Duration of symptoms	≤6 month	88 (43.1)
	> 6month	116 (56.9)
Histopathology cell type	Adenocarcinoma	190 (93.1)
	Squamous cell carcinoma	14 (6.9)
Pathological grading	Well differentiated	147 (72.1)
	Moderately differentiated	11 (5.4)
	Poor differentiated	46 (22.5)
Stage of cancer	Stage 3	72 (35.3)
	Stage 4	132 (64.7)
Metastasis of diseases	Yes	132 (64.7)
	No	72 (35.3)
Site of metastasis (n =132)	Lung	18 (13.6)
	Liver	47 (35.6)
	Liver and Lung	30 (22.7)
	Other*	37 (28.0)
Body surface area (m^2)	1-1.49	83 (40.7)
	1.5-1.99	116 (56.9)
	≥2	5 (2.5)

Body mass index		<18.5	84 (41.2)
		18.5-24.99	90 (44.1)
		25-29.99	17 (8.3)
		30 and above	13 (6.4)
ECOG-PS	Cycle 1	0-1	147 (72.1)
		≥2	57 (27.9)
	Cycle 2	0-1	149 (73.0)
		≥2	55 (26.96)
	Cycle 3	0-1	168 (82.35)
		≥2	36 (17.64)
	Cycle 4	0-1	188 (92.2)
		≥2	16 (7.84)
	Cycle 5	0-1	190 (93.1)
		≥2	14 (6.8)
	Cycle 6	0-1	193 (94.6)
		≥2	11 (6.4)

Abbreviations: ADC-adenocarcinoma, HTN-hypertension, DM-diabetic mellitus, RVI-retroviral infection, HF-heart failure, ECOG-PS-Eastern Cooperative Oncology Group Performance Status, GIT-gastrointestinal tract. **Note**: Other* HTN and DM = 2, HTN and RVI = 2, HF = 3, DM and asthma = 2, DM and RVI = 2, hyperthyroidism = 2, and Epilepsy =1.

5.2.1 Clinical Symptoms of the Patients

Among the GIT cancer patients, 43 (21.0%) presented with swallowing difficulty and weight loss, 33 (16.2%) with abdominal pain, 31 (15.2%) with combined epigastric pain and vomiting, and 16 (7.8%) with combined rectal bleeding and tenesmus. More than half (56.9%, 116) of the patients had an experience of symptoms for more than six months before diagnosis (Figure 2).

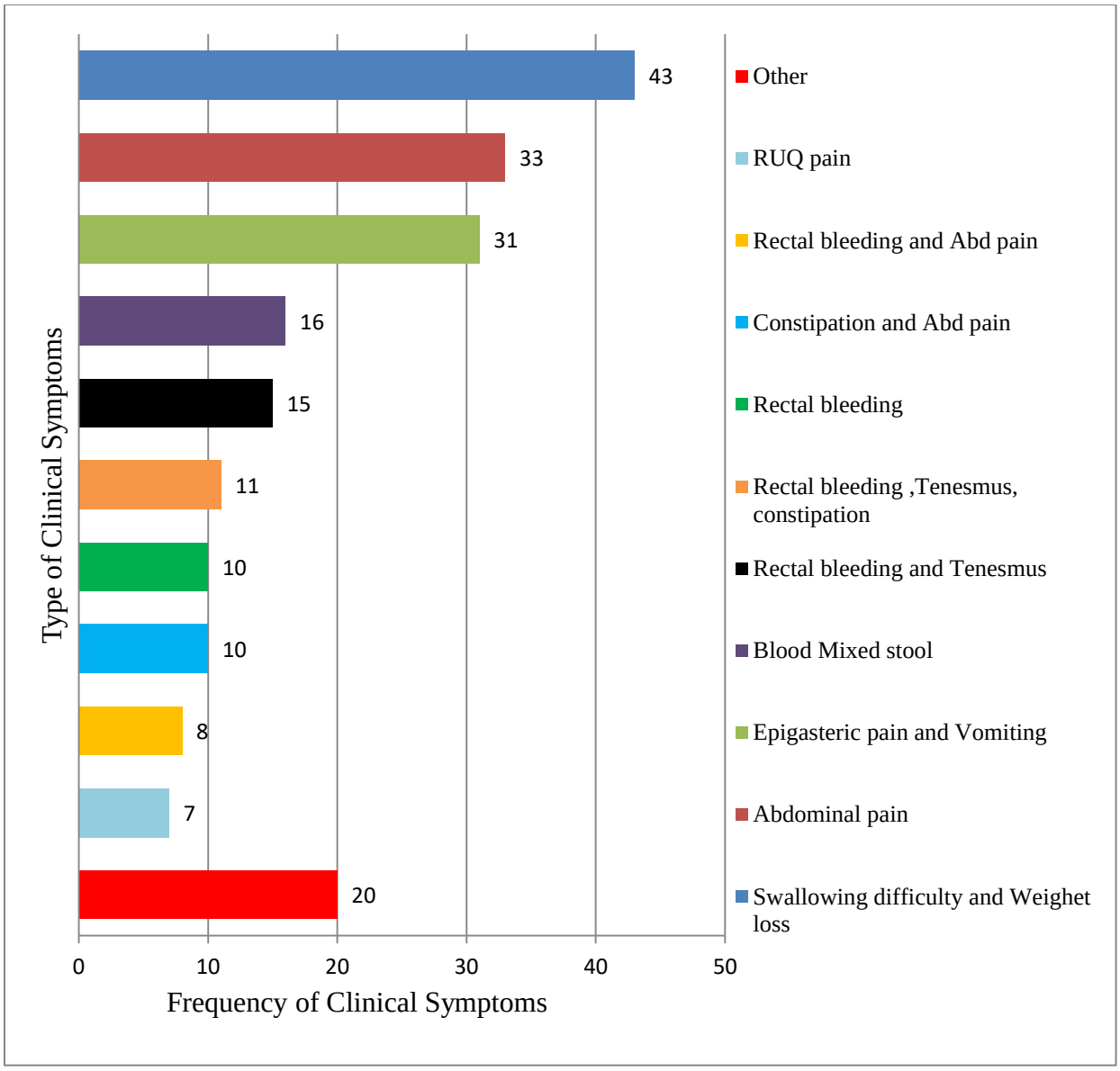

Figure 2: Clinical symptoms at the time of first diagnosis of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Note: Others*: Constipation = 4, Diarrhea = 2, Vaginal bleeding and perianal discharge = 6, Rectal bleeding, vomiting and diarrhea = 4, Tenesmus = 3, Intestinal obstruction = 1.

5.2.2 Type of Gastro Intestinal Tract Cancer

Among the types of GI tract cancers, one-fourth (25.0%-51) of the patients were diagnosed with rectal cancer, 47 (23.0%) with colon cancer, 35 (17.2%) with esophageal cancer, and 28 (13.7%) with gastric cancer (Figure 3).

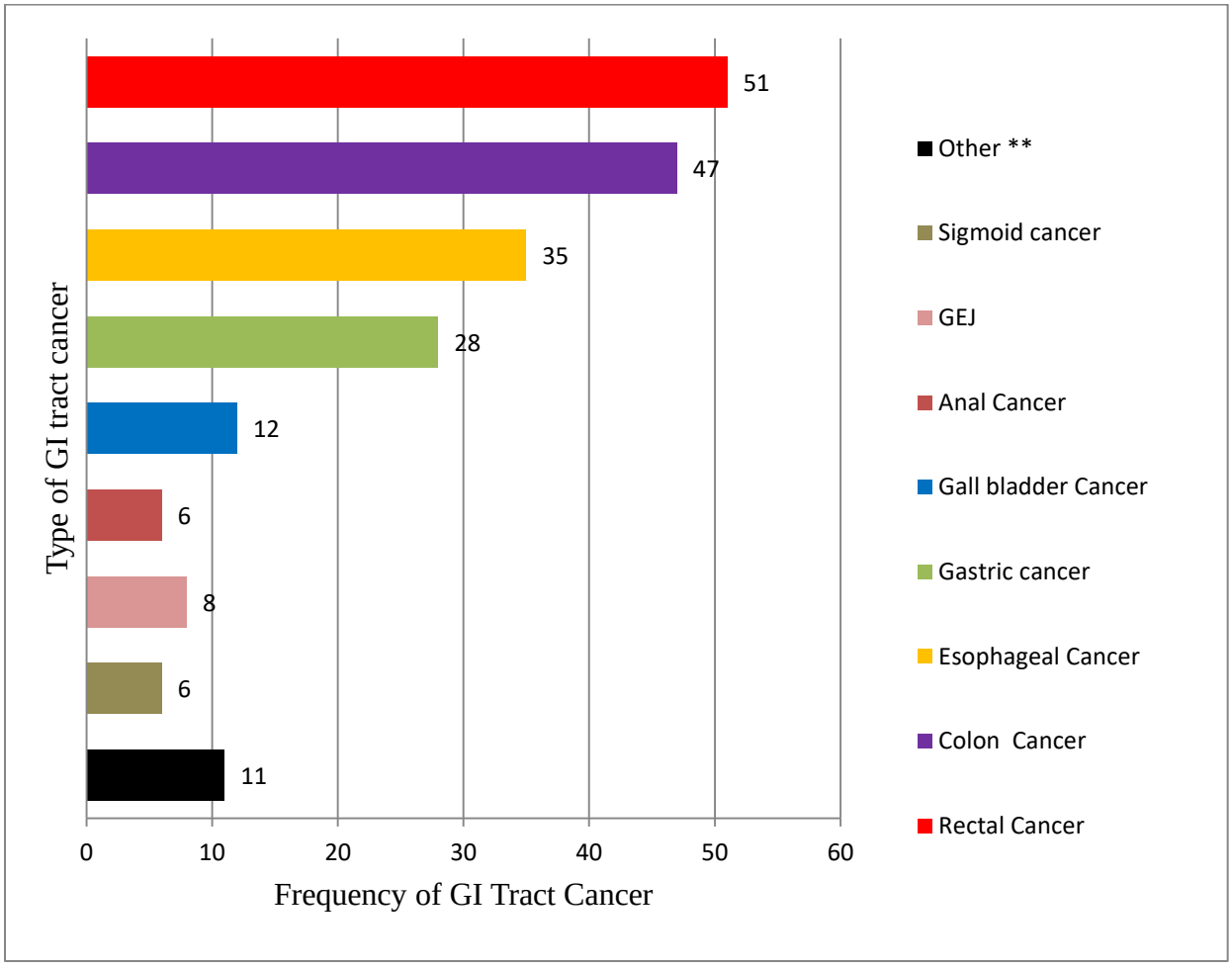

Figure 3: Frequency of GI tract cancer diagnosed at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Abbreviations: GIT: Gastrointestinal tract; GEJ: Gastro Esophageal junction cancer. **Note:** Other **: Duodenal adenocarcinoma, Ano-rectal, Liver cancer, and Pancreatic cancer.

Nearly two-thirds (64.7%, 132) of the patients had metastasized cancer, among these 47 (35.6%) had liver metastases, followed by in both liver and lung 32 (26.5%), and 12 (19.1%) peritoneum and liver (Figure 4).

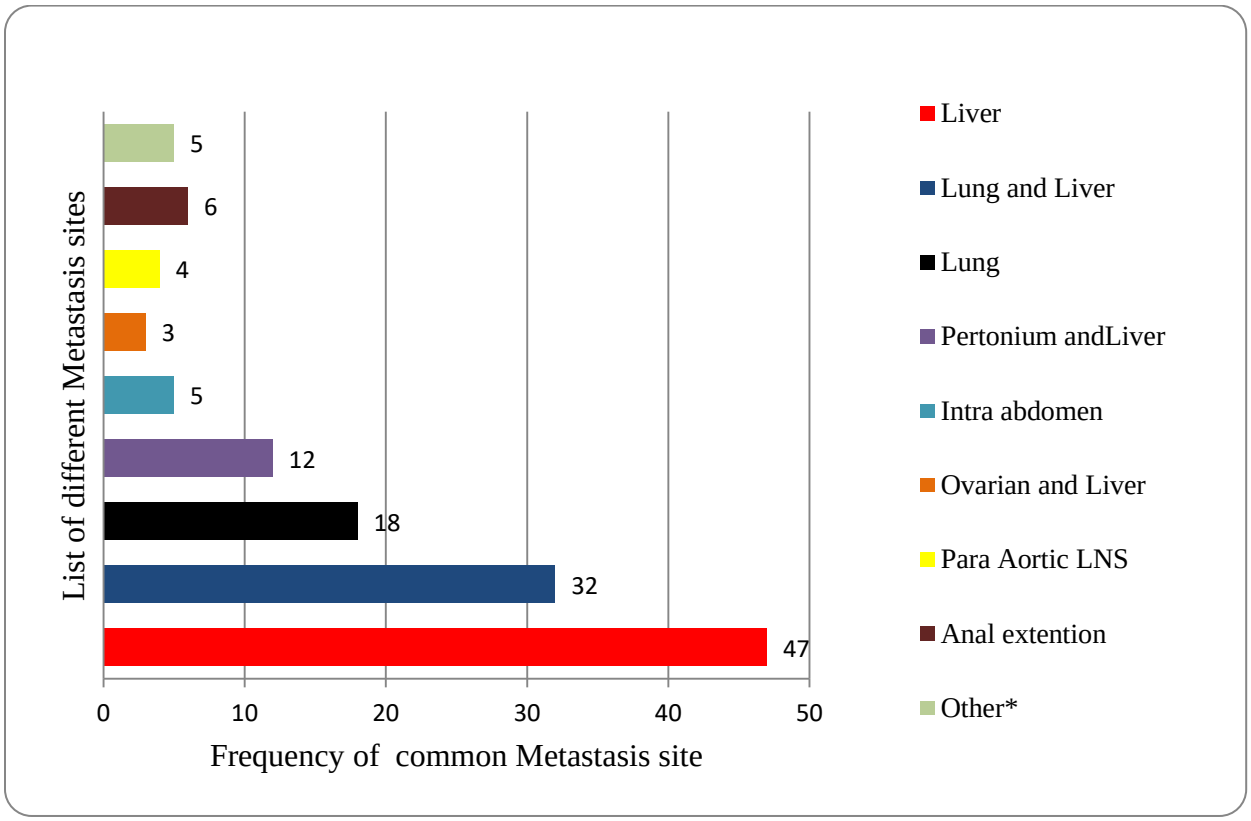

Figure 4: Metastasis characteristics of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Note: Other*: Pancreatic metastasis, Intrahepatic, Urethral, and Adjacent small bowel

5.2.3 Laboratory Findings of the Patients

The median value of baseline laboratory test at the time of diagnoses was as follows: White blood cell (WBC) count was 7.3 × 10^3/µL (IQR: 5.8–8), hemoglobin 12.6 g/dl (IQR: 12.1–13.4), absolute neutrophil count (ANC) 3.6 × 10^4/µL (IQR: 2.6–4.8), platelet count 296 × 10^3/µL (IQR: 226–345), and the median creatinine 0.7mg/dl (IQR: 0.64–0.8) (Table 3).

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Table 3: Baseline and cycle-specific median hematology and chemistry values of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Lab-value Median (IQR)	Baseline Value	1st Cycle	2nd Cycle	3rd Cycle	4th Cycle	5th Cycle	6th Cycle
WBC (10^3/uL)	7.3 (5.8-8.1)	6.5(4.6-7.1)	5.8 (3.8-6.9)	5.4 (4.1-6.7)	5.6 (4.3-6.7)	5.4 (4.5-6.9)	5.9(4.8-7.6)
Hgb (g/dl)	12.6(12.1-13.4)	12.1(10.4-13)	12(11-12.5)	11.9(11-12.3)	12.1(11.5-12.4)	12.3(12-13)	12.4(12.1-13.4)
ANC (10^3/uL)	3.6(2.6-4.8)	2.4(1.3-3.4)	1.9(0.9-2.8)	2.1(0.9-3.1)	2.3(1.37-3.3)	2.5(2.1-3.4)	2.6(2.3-3.5)
Platelets (10^3/uL)	296(226-345)	245(200-321)	234(176-321)	226(171-296)	234(189-323)	149(197-345)	234(230-345)
Creatinine (mg/dl)	0.7 (0.64-0.80)	0.71(0.6-0.89)	0.76(0.6-0.9)	0.7(0.65-0.8)	0.6(0.54-0.7)	0.6(0.5-0.7)	0.65(0.54-0.7)
AST (U/L)	24 (18-27)	25(19-28.3)	24.5(21-27)	26(23-28)	25(21-32)	25(23-32)	26(23-31)
ALT (U/L)	21(16-26)	21(17-25.5)	19(17-25)	23 (17-25.7)	18.9(16-26)	25(18-28)	25(19-31.1)
ALP (U/L)	178(120-219.7)	183(143-234)	187(123-231)	189(132.5-234)	178(123-234)	182.5(123-231)	189(134-234)

Abbreviations: IQR-interquartile range, Hgb-hemoglobin, ANC-absolute neutrophil count, AST-aspartate aminotransferase, ALP-alkaline phosphatase, ALT-alanine transaminase, WBC-white blood test, mg/dl-milligrams per deciliter, and microliter.

5.2.4 Treatment-Related Characteristics of the Patients

Out of the total GI tract cancer patients, half (50.0%, 102), and nearly one-third (31.4%, 64) of them received chemotherapy as palliative therapy and neo-adjuvant respectively. With respect to treatment modalities, nearly half (48.5%, 99) of the patients were treated with a combination of chemotherapy and surgery, followed by 74 (36.3%) with chemotherapy alone (Figure 5).

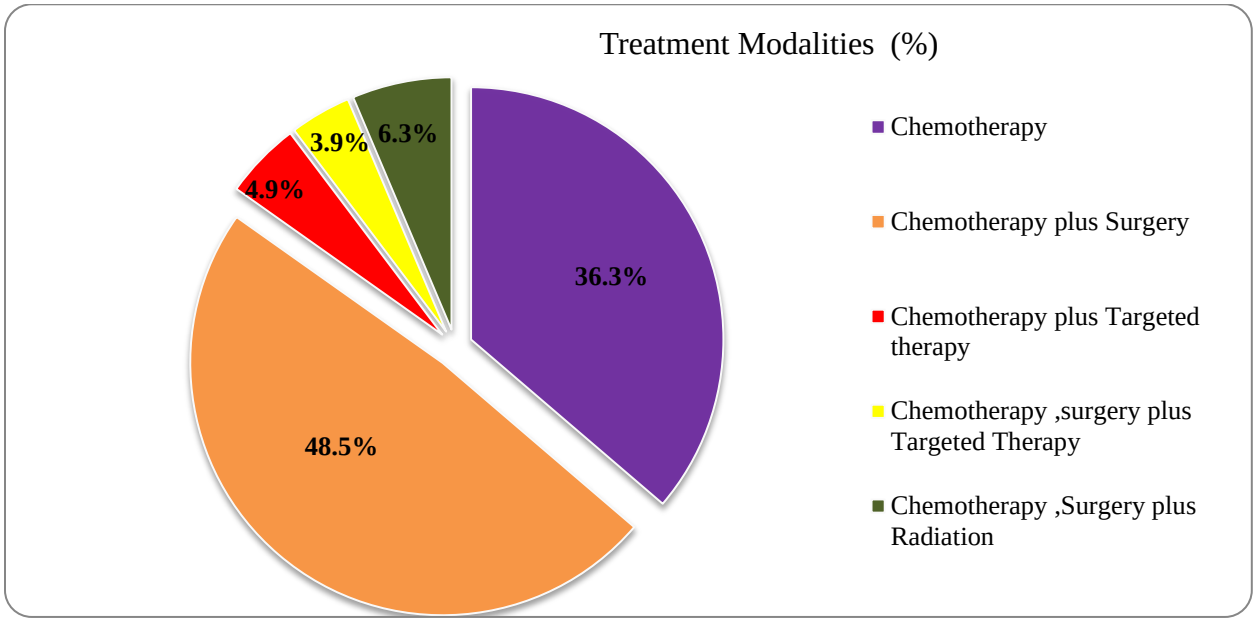

Figure 5: Treatment modalities of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Nearly four-fifths (79.9%, 163) of the patients took a fluoropyrimidine-based chemotherapy regimen, and 41 (20.1%) patients took taxanes/platinum as first-line therapy. More than half (73.5%, 150) of the patients were received FOLFOX, and 17 (8.3%) gemcitabine plus cisplatin. In addition, 61 (29.9%) patients received second-line chemotherapy.

One hundred eight (62.7%) of the patients received 5-FU and oxaliplatin, along with an additional 10% bolus dose of 5-FU. Surgery was performed on 59.3% of patients, 10 (4.9%) patients were treated with radiation, and 40 (19.6%) patients booked for radiation therapy. Nearly four-fifths (77.9%, 159) of the patients received a standard dose of chemotherapy. In comparison, 24 (11.8%) and 21 (10.3%) patients were received low and high-dose chemotherapy (Table 4).

Table 4: Treatment related characteristics of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variables	**Frequency n (%)**
Fluor-pyrimidine based used at first-line	
No	41 (20.1)
FOLFOX	150 (73.5)
Cap-OX	8 (3.9)
5-FU plus Lecuvorin	5 (2.5)
Taxanes/Platinum based used as first-line	
No	163 (79.9%)
Gemcitabine Plus Cisplatine	17 (8.3)
Carboplatin plus Paclitaxel	15 (7.4)
Cisplatine Plus Paclitaxel	6 (2.9)
Other*	3 (1.5)
Chemotherapy regimen used as the Second-line	
No	143 (70.1)
FOLFOX	17 (8.3)
FOLFIRI	32 (15.7)
Carboplatin plus paclitaxel	4 (2.0)
Cisplatin plus Paclitaxel	2 (1.0)
Other **	6 (2.9)
Targeted therapy used	
No	185 (90.7)
Yes	19 (9.3)
Chemotherapy used as	
Neo- Adjuvant	64 (31.4)
Adjuvant	38 (18.6)
Palliative	102 (50.0)
Dose of FOLFOX given	

	Not	41 (20.1)
	5-FU, Oxaliplatin plus 10% added 5-FU	128 (62.7)
	5-FU, Lecuvorin plus Oxaliplatin	35 (17.2)
Total chemotherapy dose		
	At standard dose	159 (77.9)
	Dose too high	21 (10.3)
	Dose too low	24 (11.8)

Abbreviations: FOLFOX; fluorouracil, leucovorin, and oxaliplatin; CAP-OX: capecitabine and oxaliplatin; FLOT: fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFOXIRI: fluorouracil, leucovorin, oxaliplatin and irinotecan. **Notes**: Other*: gemcitabine alone = 1; cisplatin plus etoposide = 2; other** FLOT = 2; Cap-OX = 2; gemcitabine + paclitaxel = 2.

5.3 Magnitude of Chemotherapy-Induced Toxicity

Of 204 GI tract cancer patients with completed chemotherapy cycles, a total of 1499 adverse drug reactions were detected. Out of these, 789 (52.6%) were non-hematological, and 710 (47.4%) were hematological. The highest numbers (32.2%, 482) of ADRs were observed in cycle 2, followed by cycle 3 (24.4%, 366) (Table 5).

Table 5: Chemotherapy-induced toxicity in each treatment cycles of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variables	Chemotherapy Cycle						
	Total n (%)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Overall Toxicity	1499	283(18.9)	482(32.2)	366(24.4)	169(11.3)	125 (8.3)	74(4.9)
Hematological Toxicity	710(47.4)	128(18.0)	196(27.6)	171(24.1)	93 (13.1)	80 (11.3)	42(5.9)
Non-hematological Toxicity	789(52.6)	155(19.4)	286(36.2)	195(24.7)	76 (9.6)	45(5.7)	32(4.1)

Hematological and Non-Hematological Toxicities

Hematological toxicities accounted for 710 (47.4%) of the total toxicities. Of these, anemia (40.3% 286), and neutropenia (39.0%, 277) were the most common ADRs. Whereas, more than half (52.6%, 789) of them were non-hematological toxicities. Which includes nausea/vomiting was the leading one (12.5%, 99), followed by fatigue (12.4%, 98), and then peripheral neuropathy (11.2%, 88) (Figure 6).

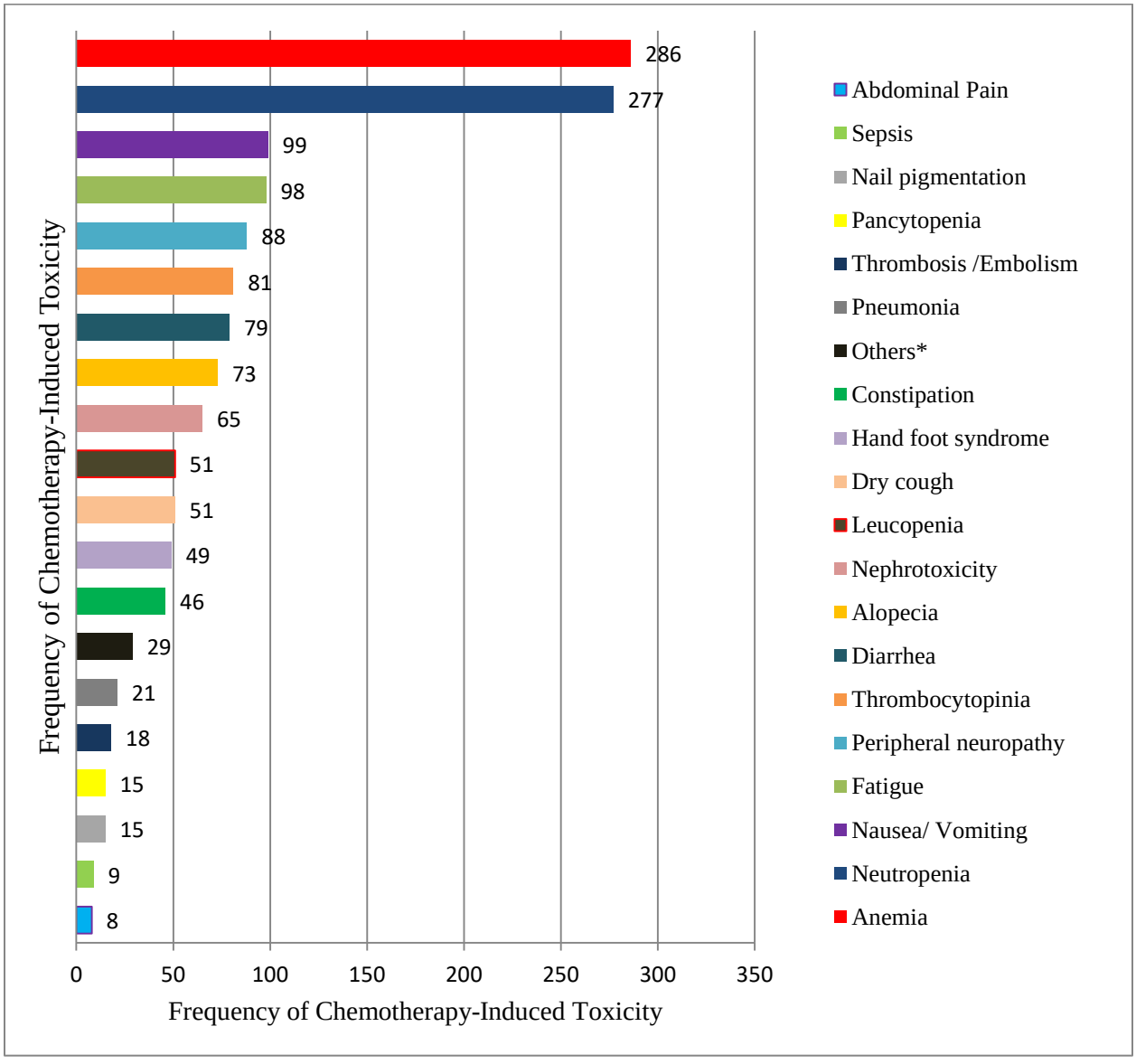

Figure 6: Type and frequency of chemotherapy-induced toxicity among GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Note: other*Mucositis = 6, headache = 4, fever = 3, photosensitivity = 3, Rash = 3 Conjunctivitis = 4, hypovolemic shock =2 urinary incontinence =2 and tooth discoloration =2.

5.4 Chemotherapy-Induced Toxicity Grading by NCI CTCAE

5.4.1 Hematological Toxicity Grading

The severity of chemotherapy-induced hematological toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Overall, 556 (37.1%) documented toxicities were grade 3-4 chemotherapy-induced toxicities. Of these, 254 (45.7%) were combined grade 3-4 hematological toxicities. Nearly four-fifth (79.9%, 203) of them attributed to neutropenia across all cycles. Among all cycles, eighty-one (40.0%) patients experienced neutropenia during cycle 3, with 63 (77.8%) of them having grade 3-4 neutropenia. Whereas, 80 (39.2%) patients had anemia during cycle 2, and the majority (92.5%, 74) of the patients experienced grade 1-2 toxicity (Table 6).

Table 6: National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for severity of toxicity assessment of hematological toxicity grading

Variable n (%)	Chemotherapy Cycle (n=204)					
	1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle
Neutropenia	55 (26.9)	66 (32.4)	81 (40.0)	24(11.7)	30 (14.7)	21(10.3)
Grade 1-2	13 (23.6)	13 (19.7)	18 (22.2)	9 (37.5)	12 (40.0)	9 (42.9)
Grade 3-4	42 (76.4)	53 (80.3)	63 (77.8)	15 (62.5)	18 (60.0)	12 (57.0)
Anemia	57 (27.9)	80 (39.2)	59 (28.9)	44 (21.6)	32 (15.7)	14 (6.8)
Grade 1-2	53 (92.9)	74(92.5)	58 (98.3)	44 (100)	32 (100)	14 (100)
Grade 3-4	4 (7.1)	6 (8.1)	1 (1.7)	__	__	__
Thrombocytopenia	10 (4.9)	25 (12.3)	16(7.8)	18 (8.8)	9 (4.4)	3 (1.5)
Grade 1-2	8 (80.0)	21 (84.0)	12 (75.0)	17 (94.4)	6 (66.7)	3
Grade 3-4	2 (10.0)	4 (16.0)	4 (25.0)	1 (5.5)	3 (33.3)	__
Pancytopenia	1 (0.5)	6 (2.9)	3 (1.5)	3 (1.5)	__	2 (2.7)
Grade 1-2	__	2 (33.3)	__	1	__	__
Grade 3-4	1	4 (66.6)	3	2	__	2

Leucopenia	5 (2.5)	19 (9.3)	12 (5.8)	4 (1.9)	9 (4.4)	2 (1.0)
Grade 1-2	4	15 (78.9)	8 (66.7)	3	7 (77.8)	__
Grade 3-4	1	4 (21.0)	4 (33.3)	1	2 (22.2)	2

Abbreviations: NCI CTCAE-National Cancer Institute Common Terminology Criteria for Adverse Events, GIT; gastrointestinal tract cancer. Note: n = 201 at cycle 6)

5.4.2 Non-Hematological Toxicity Grading

Among the grade 3-4chemotherapy-induced toxicities, more than half (54.3%, 302) of them were grade 3-4non- hematological. During cycle 2, 31 (15.2%) patients experienced nausea and vomiting, with 7 (22.6%) of patients had grade 3-4. The most prevalent non-hematological toxicity was alopecia, affecting 45 (22.1%) patients, of those 36 (80.0%) had grade 3-4toxicity. Additionally, 32 (15.7%) patients experienced diarrhea during cycle 2, with 4 (43.8%) patients had grade 3-4toxicity (Table 7).

Table 7: National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for severity of toxicity assessment of non-hematological toxicity grade

Variable N (%)	Chemotherapy Cycle (n=204)					
	1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle
Nausea/vomiting	33 (16.2)	31 (15.2)	13 (6.4)	10 (4.9)	5 (2.5)	7 (3.4)
Grade 1-2	31 (94.0)	24 (77.4)	6(46.2)	3 (30.0)	1 (20.0)	2 (28.5)
Grade 3-4	2 (6.0)	7 (22.6)	7 (53.8)	7 (70.0)	4 (80.0)	5 (71.4)
Diarrhea	18 (8.8)	32 (15.7)	22 (10.8)	3 (1.5)	3 (1.5)	1 (0.5)
Grade 1-2	15 (83.3)	18 (56.2)	5 (22.7)	__	3	__
Grade 3-4	3 (16.6)	4 (43.8)	17 (77.3)	3	__	1
Constipation	8 (3.9)	13 (6.4)	16 (7.8)	5 (2.5)	4 (1.9)	3 (1.5)
Grade 1-2	4 (1.9)	11 (5.4)	11 (5.4)	2 (1.0)	__	1 (0.5)
Grade 3-4	4 (1.9)	2 (1.0)	5 (2.5)	3 (1.5)	4 (1.9)	2 (1.0)
Abdominal pain	11 (5.4)	5 (2.5)	14 (6.9)	5 (2.5)	1 (0.5)	2 (1.0)
Grade 1-2	10 (4.9)	4 (1.9)	10 (4.9)	5 (2.5)	1 (0.5)	2 (1.0)
Grade 3-4	1 (0.5)	1 (0.5)	4 (1.9)	__	__	__
Peripheral Neuropathy	10 (4.9)	31 (15.2)	24 (11.8)	10 (4.9)	8 (3.9)	5 (2.5)
Grade 1-2	9 (4.4)	25 (12.3)	15 (7.4)	7 (3.4)	2 (1.0)	1 (0.5)
Grade 3-4	1 (0.5)	6 (2.9)	9 (4.4)	3 (1.5)	6 (2.9)	4 (1.9)
Hand Foot Syndrome	10 (4.9)	20 (9.8)	16 (7.8)	1 (0.5)	2 (1.0)	__
Grade 1-2	9 (4.4)	19 (9.3)	8 (3.9)	1 (0.5)	1 (0.5)	__
Grade 3-4	1 (0.5)	1 (0.5)	8 (3.9)	__	1 (0.5)	__
Alopecia	16 (7.8)	45 (22.1)	7 (3.4)	3 (1.5)	2 (1.0)	__
Grade 1-2	3 (18.8)	9 (20.0)	__	1	1 (0.5)	__
Grade 3-4	13 (81.2)	36(80.0)	7	2	1 (0.5)	__

Fatigue	18 (8.8)	31 (15.2)	22 (10.8)	13 (6.4)	10 (4.9)	4 (1.9)
Grade 1-2	18 (8.8)	25 (12.3)	18 (8.8)	9 (4.4)	10 (4.9)	3 (1.5)
Grade 3-4	_	6 (2.9)	4 (1.9)	4 (1.9)	__	1 (0.5)
Dysphagia	__	4 (1.9)	3 (1.5)	__	__	1 (0.5)
Grade 1-2	__	3 (1.5)	2 (1.0)	__	__	1 (0.5)
Grade 3-4	__	1 (0.5)	1 (0.5)	__	__	__
Nail Pigmentation	5 (2,5)	7 (3.4)	3 (1.5)	__	__	__
Grade 1-2	5 (2.5)	7 (3.4)	3 (1.5)	__	__	__
Grade 3-4	__	___	__	__	__	__
Dry Cough	7 (3.4)	13 (6.4)	15(7.4)	10 (4.9)	5 (2.5)	1 (0.5)
Grade 1-2	3 (1.5)	8(3.9)	9 (4.4)	4 (1.9)	5 (2.5)	__
Grade 3-4	4 (1.9)	5 (2.5)	6 (2.9)	6 (2.9)	__	1 (0.5)
Nephrotoxicity	6 (2.9)	20 (9.8)	21 (10.3)	8(3.9)	5 (2.5)	4 (1.9)
Grade 1-2	5 (2.5)	19 (9.3)	19 (9.3)	8(3.9))	5 (2.5)	4 (1.9)
Grade 3-4	1 (0.5)	1 (0.5)	2 (1.0)	__	__	_-
Thrombosis/Embolism	3 (0.2)	5 (2.5)	9 (4.4)	__	__	1 (0.5)
Grade 1-2	__	__	__	__	__	__
Grade 3-4	3 (1.5)	5 (2.5)	9 (4.4)	__	__	1 (0.5)
Sepsis	2 (1.0)	3 (1.5)	__	1 (0.5)	__	3 (1.5)
Grade 1-2	____	__	__	__	__	__
Grade 3-4	2 (1.0)	3 (1.5)	__	1 (0.5)	__	3 (0.2)
Pneumonia	2 (1.0)	10 (4.9)	3 (1.5)	6 (2.9)	__	__
Grade 1-2	__	__	__	__	__	__
Grade 3-4	2 (1.0)	10 (4.9)	3 (1.5)	6 (2.9)	__	__
Other*	6 (2.9)	15(7.4)	7 (3.4)	1 (0.5)	__	__
Grade 1-2	5 (2.5)	10 (4.9)	4 (1.9)	__	__	__
Grade 3-4	1 (0.5)	5 (2.5)	3 (1.5)	1 (0.5)	__	__

Note: Other* Mucositis, headache, fever, photosensitivity, rash, conjunctivitis, hypovolemic shock, urinary incontinence, and tooth discoloration.

5.5 Chemotherapy-Induced Toxicity Evaluation

5.5.1 Distribution by Patient Characteristics

The associations between patient characteristics and the occurrence of highest toxicity was evaluated by using Pearson Chi-square test, accordingly significant association was found between Age, Comorbidity, 5-FU, ECOG-PS, baseline Hemoglobin and ANS. For combined hematological toxicity, males, and females presented similar incidences of moderate to severe (grade 3-4) toxicity (59.6% vs. 64.8%, p=0.447). The incidence of grade 3-4 hematological toxicity was 69.3% in patients aged ≥60 years with a p-value of 0.042, and there was a significant difference in the distribution of grade 3-4hematological toxicity between TASH

(62.8%), and SPHMMC (60.1%) patients (p=0.780). TASH had a slightly greater proportion of patients with Grade 3-4hematological toxicity.

Among patients with comorbidities, (58.5%, 38) patients experienced significant grade 3-4 hematological toxicity, with a p-value of 0.024. In addition, a higher ECOG-PS score (≥ 2) was associated with grade 3-4 non-hematological toxicity (73.6%), with a p-value of 0.048. One hundred sixty three (79.9%) of patients received a fluoropyrimidine-based regimen, of these (68.7%, 112) of patients experienced grade 3-4 hematological, and (71.2%, 116) experienced grade 3-4 non-hematological toxicity. Notably, grade 3-4 toxicity was common in patients who received FOLFOX (Table 8).

Table 8: Association between patient characteristics and occurrence of highest grade of ADRs According to NCI CTCAE version 5.0 of GIT cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

		Combined hematological Toxicity			**Combined Non-hematological Toxicity**		
Variables	n	Low/ Mild	Moderate to Severe	P’	Low/ Mild	Moderate to Severe	P’
Study Settings							
TASH	148	55 (37.2)	93 (62.8)	0.780	49 (33.1)	99 (66.9)	0.708
SPHMMC	56	22 (39.2)	34 (60.1)		17 (30.4)	39 (69.6)	
Gender							
Male	99	40 (40.4)	59 (59.6)	0.447	32 (32.3)	67 (67.7)	0.994
Female	105	37 (35.2)	68 (64.8)		34 (32.4)	71 (67.6)	
Age (years)							
<40	37	13 (35.1)	24 (64.9)	0.042	13 (35.1)	24 (64.9)	0.080
40-49	44	20 (45.5)	24 (54.5)		14 (31.8)	30 (68.1)	
50-59	61	25 (41.0)	36 (59.0)		26 (9.8)	35(90.2)	
≥60	62	19 (30.6)	43 (69.3)		13 (21.0)	49 (79.0)	
Body Weight							
<18.5	84	27 (32.1)	57 (67.8)	0.508	27 (32.1)	57 (67.8)	0.203
18.5-24.99	90	38 (42.2)	52 (57.8)		34 (37.7)	56 (62.2)	
25-29.99	17	6 (35.3)	11 (64.7)		14 (82.4)	3 (17.6)	
30 and above	13	2 (15.4)	11 (84.6)		2 (15.4)	11 (84.6)	
Education Status							
No formal education	95	36 (37.9)	59 (62.1)	0.975	32 (33.7)	63 (66.3)	0.674
Primary school	41	15 (36.6)	26 (63.4)		10 (24.4)	31 (75.6)	

Secondary school	31	11 (35.5)	20 (64.5)		11 (35.5)	20 (64.5)	
Higher education	37	15 (40.5)	22 (59.5)		13 (35.1)	24 (64.8)	
Histopathology							
ADC	190	73 (38.4)	117(61.6)	0.463	63 (33.2)	127(66.8)	0.365
SCC	14	4 (28.6)	10 (71.4)		3 (21.4)	11 (78.6)	
Pathological grading							
WD	147	62 (42.2)	85(57.8)	0.111	45 (30.6)	102(69.4)	0.235
MD	11	3 (27.7)	8 (72.7)		2(18.2)	9 (81.8)	
PD	46	12(26.1)	34 (73.9)		19 (41.3)	27 (48.7)	
Main Diagnosis							
Rectal cancer	51	19(37.3)	32(62.7)	0.481	15 (29.4)	36(70.6)	0.464
Colon cancer	47	21(44.7)	26(55.3)		13 (27.7)	34(72.3)	
Gastric cancer	28	10 (35.7)	18(64.3)		7(25.0)	21(75.0)	
Esophageal	35	9(25.7)	26(74.3)		15 (42.8)	20(57.1)	
Other*	43	18(41.8)	25(58.1)		16(37.2)	27(62.8)	
Comorbidity							
No	139	50 (36.0)	89(64.0)	**0.024**	50 (36.0)	89(64.0)	0.106
Yes	65	27 (41.5)	38(58.5)	*****	16 (24.6)	49 (75.4)	
Metastasis							
No	72	24 (33.3)	48 (67.7)	0.337	28 (38.9)	44 (61.1)	0.141
Yes	132	53 (40.1)	79 (59.9)		38 (28.8)	94 (71.2)	
ECOG PS 0-1	94	38(40.4)	56(59.6)	0.465	37(39.4)	57(60.6)	**0.048***
≥2	110	39(35.5)	71(64.5)		29(26.4)	81(73.6)	
Fluorpyrimidine							
Used No	41	26(63.4)	15(36.6)	**0.000***	19(46.3)	22(53.7)	**0.032***
Yes	163	51(31.3)	112(68.7)		47(28.8)	116(71.2)	
Fluorpyrimidine							
FOLFOX	150	54(36.0)	96(64.0)	0.169	46(30.6)	104(69.0)	0.513
Cap-OX	8	4(50.0)	4(50.0)		2(25.0)	6(75.0)	
5-FU plus Leucovorin	5	0	5		1	4	
Taxanes/Platinum							
GC*	17	11(64.7)	5(35.3)	**0.049***	5(29.4)	12(70.5)	**0.023***
PC*	15	7(46.7)	8(53.3)		10(66.7)	5(33.3)	

CP*	7	1(14.3)	6(85.7)		1(14.3)	6(85.7)	
FOLFOX Given as							
5-FU.Oxaliplatin plus 10% added 5-FU	129	44(34.1)	85(65.8)	0.335	35(27.1)	94(72.8)	0.098
5-FU,Lecuvorin plus Oxaliplatin	34	14(41.2)	20(58.8)		13(38.2)	21(61.7)	
Chemotherapy dose							
At Standard dose	159	63(39.6)	96(60.4)	0.373	52(32.7)	107(67.3)	0.632
Dose To High	21	5(23.8)	16(76.2)		8(38.1)	13(61.9)	
Dose To Low	24	9(37.5)	15(62.7)		6(25.0)	18(75.0)	

Abbreviations: ECOG PS- Eastern Cooperative Oncology Group performance status. BMI-body mass index, ADC-adenocarcinoma, WD-well differentiated, MD-moderately differentiated, PD-poorly differentiated, SCC-Squamous Cell Carcinomas, GC*- Gemcitabine plus Cisplatin, PC*-Paclitaxel plus Carboplatin, CP*- Cisplatin plus Paclitaxel, F-Female, M-Male**,** Low/Mild-grade 1-2, Moderate to Severe-Grade 3-4, Note *****significant at $p < 0.05$.

A total of 753 supportive measures were administered, with (33.6%, 253) were G-CSF, (13.0%, 98) multivitamins, (11.4%, 86) antimicrobial, and (10.2%, 77) blood transfusions. More than half (53.4%, 109) of the patients used G-CSF at least once, with 50 (24.5%) using it during cycle 2. Throughout the treatment, (41.7%, 85) of patients received antimicrobial agents at least once. In addition eighty (39.2%) patients used multivitamins at least once during the entire cycle, with 24 (11.8%) receiving it during cycle 2 (Table 9).

Table 9: G-CSF, antibiotics, antiemetics, and other supportive measures used among GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variable N (%)	Chemotherapy cycle						Over all supportive measure
	1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6thcycle	
G-CSF Use	17 (8.3)	50(24.5)	37(18.1)	22 (10.8)	24(11.8)	3 (1.5)	253 (33.6)
Anti-Emetics	6 (2.9)	17 (8.3)	7 (3.4)	5 (2.5)	5 (2.5)	4 (2.0)	44 (5.8)
Blood Transfused	14 (6.9)	17 (8.3)	17 (8.3)	16 (7.8)	9 (4.4)	4 (2.0)	77(10.2)
Multi-Vitamins	21(10.3)	24(11.8)	17 (8.3)	14 (6.9)	14 (6.9)	8 (3.9)	98 (13.0)

Anti-Microbial	14 (6.9)	33(16.2)	22(10.8)	8 (3.9)	4 (2.0)	5 (2.5)	86 (11.4)
Laxative	2 (1.0)	10 (4.9)	7 (3.4)	3 (1.5)	0	3 (1.5)	25 (3.3)
Anti-Diarrhea	5 (2.5)	10 (4.9)	12 (5.9)	6 (2.9)	2 (1.0)	1 (1.0)	36 (4.8)
Analgesics	18 (8.8)	16 (7.8)	13 (6.4)	3 (1.5)	6 (2.9)	4 (2.0)	60 (7.9)
Atropine	3 (1.5)	8 (3.9)	3 (1.5)	2 (1.0)	2 (1.0)	__	18(2.4)
Diphenhydramine	1 (1.0)	3 (1.5)	6(3.0)	4 (2.0)	2 (1.0)	__	16 (2.1)
Amitriptyline	__	__	2 (1.0)	__	2 (1.0)	1 (1.0)	5(0.7)
Anti-coagulant	3 (1.5)	4 (2.0)	5 (2.5)	__	__	__	12(1.6)
Pregabaline	__	2 (1.0)	2 (1.0)	__	__	__	4 (0.5)
Anti-viral/Anti-fungal	__	2 (1.0)	2 (1.0)	__	__	__	4 (0.5
Other *	4 (2.0)	5 (2.5)	2 (1.0)	3 (1.5)	1 (1.0)	__	15 (1.9)

Abbreviations: *G-CSF: granulocyte colony stimulating factor.

More than four-fifths (81.9%, 167) of the patients experienced treatment delay, of these nearly half (48.5%) of them had two or more treatment delays. Nearly half (47.5%, 97) of the patients were admitted hospital due to toxicity. In addition (9.3%, 19) patients discontinue their medication. Furthermore, More than four-fifths (83.3%, 170) of the patients had adherence to the chemotherapy schedule (Table 10).

Table 10: Impact of chemotherapy induced toxicity on GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024 Addis Ababa, Ethiopia (n=204).

Variable		**Frequency n (%)**
Treatment delay	No delay	37 (18.1)
	One time	68 (33.3)
	Two times or above	99 (48.5)
Hospital admission due to toxicity	No admission	107 (52.5)
	One times	73 35.8)
	Two times or above	24 (11.8)

Medication discontinuation	No	185 (90.7)
	Yes	19 (9.3)
Adhere to their chemotherapy schedules	No	34 (16.7)
	Yes	170 (83.3)
Chemotherapy changed	No	135 (66.2)
	Yes	69 (33.8)

5.6 Treatment Outcomes of the Patients

The treatment outcomes for patients with GIT cancer revealed that during the mid-cycle assessment, More than half (53.4%, 109) of the patients who achieved a partial response, while one-third (33.8%, 69) of them had progressive disease. Patients who were treated at TASH had a higher percentage of partial response (75.2% vs. 24.8%), and progressive disease (68.1% vs. 31.9%) compared to patients from SPHMMC.

In the end-cycle assessment, 90 (44.1%) patients achieved a partial response, which was higher in the TASH group as compared to SPHMMC (76.7% vs. 23.3%). Overall, 95 (46.6%) patients had good outcomes (partial or complete response), while 109 (53.4%) had poor outcomes (stable diseases, progressive diseases, or death). Patients treated with TASH had significantly good treatment outcomes (75.8% vs. 24.2%) than those treated with SPHMMC (Table 11).

Table 11: Treatment outcomes of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 and February 2024, Addis Ababa, Ethiopia (n = 204).

Variable	**Treatment Outcome**	n (%)		
		Total	TASH	SPHMMC
Mid Cycle Assessment	Partial response	109 (53.4)	82(75.2)	26(24.8)
	Stable diseases	26 (12.7)	19(73.1)	7(26.9)
	Progressive Disease	69 (33.8)	47(68.1)	22(31.9)
	Death	0	0	0

End cycle Assessment	Complete response	3 (1.5)	2	1
	Partial response	90 (44.1)	69(76.7)	21(23.3)
	Stable diseases	24 (11.8)	19(79.1)	5(20.8)
	Progressive Disease	84 (41.2)	56(66.7)	28(33.3)
	Death	3 (1.5)	2	1
Over All Treatment Outcome	Good Outcome	95 (46.6)	72(75.8)	23 (24.2)
	Poor Outcome	109 (53.4)	76(24.2)	33 (75.8)

5.7 Predictors of Poor Clinical Outcomes

Variables having a p-value ≤ 0.25 in the bivariate logistic regression model were included in the multivariable logistic regression model. A total of twelve (12) variables passed the bivariate logistic regression, including patient age, body mass index, pathological grading, ECOG performance status, metastasis diseases, comorbidities, FOLFOX dose, grade ≥3 toxicity (both hematological and non-hematological), treatment delays, total chemotherapy dose, G-CSF usage and adherence to treatment schedule.

In the multivariable logistic regression, a significant association with eight (8) variables was identified. A statistically significant association was found between treatment outcomes and independent variables. Age was associated with poor treatment outcomes, the likelihood of having poor outcomes among patients aged 60 years and above was 4.64 times (AOR:4.640, 95% CI:1.201-17.933, P=0.026) higher as compared to those under 40 years. The odds of having poor outcomes among patients with an ECOG score of ≥ 2 was nearly four times (AOR: 4.064, 95% CI: 1.699-9.724, P=0.002) higher than their counterparts. Other factors associated with poor treatment outcomes were, patients with poorly differentiated tumors (AOR: 5.10, 95% CI:1.483–17.539, P=0.010), patients with metastasis disease (AOR: 9.124, 95% CI: 3.477-23.947, P<0.001), patients receiving a dose lower than the standard (AOR:4.917, 95% CI:1.007-24.007, P=0.049), patients who experienced grade 3 or higher hematological toxicity two or more times (AOR:3.677 (95% CI: 1.286-10.513, p=0.015) and treatment delay (AOR: 2.762, 95% CI: 1.805-9.475, p=0.016). For a patient who adhered to the schedule, the odds of having poor treatment outcomes were reduced by 75% (AOR: 0.250, 95%CI 0.065-0.969, p=0.045) as compared to those who were none-adherent to their treatment (Table 12).

Table 12: Bivariate and multivariable logistic regression analyses of the treatment outcomes of GI tract cancer patients treated at the oncology unit of TASH and SPHMMC between June 2023 to February 2024 Addis Ababa, Ethiopia (n = 204).

Variables	**Good**	**Poor**	**COR(95% C.I)**	**P value**	**AOR (95%C.I)**	**P-value**
Age (Year)						
< 40 (Ref)	21	16	1		1	
40-49	26	18	0.909 (0.375-2.203)	0.832	1.046 (0.271-4.039)	0.948
50-59	31	30	1.270(0.559-2.888)	0.568	1.688 (0.490-5.813)	0.406
60 and Above	17	45	3.474(1.475-8.185)	**0.004***	4.640 (1.201-17.933)	**0.026***
BMI (kg/m2)						
18.5–24.99 (Ref)	51	39	1		1	
<18.5	32	52	2.125(1.159-3.897)	**0.015***	2.355(0.917-6.065)	0.076
25–29.99	6	11	2.397(0.815-7.050)	0.112	3.054(0.657-14.197)	0.154
30 and Above	6	7	1.526(0.475-4.903)	0.478	1.920(0.361-10.213)	0.445
ECOG-PS						
ECOG 0-1 (Ref)	64	30	1		1	
ECOG ≥2	31	79	5.437(2.982-9.911)	**0.000***	4.064(1.699-9.724)	**0.002***
Pathological Grading						
Well differentiated (Ref)	79	68	1		1	
Moderate differentiated	4	7	2.033(0.571-7.243)	0.274	2.128(0.266-17.103)	0.476
Poor differentiated	17	46	3.292(1.581-6.855)	**0.001***	5.100(1.483-17.539)	**0.010***
Comorbidity						

No (Ref)	71	24	1			
Yes	24	41	1.784(0.975-3.262)	0.060	1.575(0.592-4.188)	0.363
Metastasis						
No (Ref)	50	22	1			
Yes	45	87	4.394(2.370-8.145)	**0.000***	9.124(3.477-23.947)	**0.000***
FOLFOX dose given						
Not used (Ref)	22	21	1		1	
5-FU,Lecuvorin plus Oxaloplatin	26	8	0.322(0.119-0.870)	**0.025***	0.263(0.050-1.391)	0.116
5-FU,Oxaloplatin +10% added 5 FU	47	80	1.783(0.887-3.584)	0.104	2.304(0.726-7.318)	0.157
Total chemotherapy dose						
At standard dose (Ref)	83	76	1		1	
Dose to high	7	14	2.184(0.837-5.700)	0.110	1.127(0.266-4.784)	0.871
Dose to low	5	19	4.150 (1.477-11.66)	**0.007***	4.917(1.007-24.007)	**0.049***
Grade 3-4 Hematological Toxicity						
No (Ref)	43	34	1		1	
One times	27	22	1.031(0.501-2.118)	0.935	0.817(0.261-2.558)	0.729
Two times and above	25	53	2.681(1.393-5.159)	**0.003***	3.677(1.286-10.513)	**0.015***
Grade 3-4 Non- hematological Toxicity						
No (Ref)	38	28	1		1	
One times	29	26	1.217(0.592-2.500)	0.592	1.162(0.379-3.560)	0.793
Two times and above	28	55	2.666(1.368-5.196)	**0.004***	1.205(0.444-3.271)	0.714

Cumulative treatment delay						
No delay(Ref)	22	15	1		1	
One times	36	32	1.304(0.579-2.933)	0.521	1.052(0.312-3.543)	0.935
Two Times and above	37	62	2.458(1.135-5.320)	**0.022***	2.762(1.805-9.475)	**0.016***
Adhere to chemotherapy schedule						
No (Ref)	6	28	1		1	
Yes	89	81	0.195 (0.077-0.495)	**0.001***	0.250(0.065-0.969)	**0.045***
G-CSF Injection used						
No (Ref)	38	57	1		1	
Yes	67	52	0.080(0.608-1.061)	0.080	0.617(0.237-1.608)	0.324

*Variable that showed a significant association with poor treatment outcome. COR: Crude odds ratio, AOR: Adjusted odds ratio, CI: Confidence interval, ADC: Adenocarcinoma, G-CSF: Granulocyte colony-stimulating factor, ECOG: Eastern Cooperative Oncology Group. 5-FU: 5-Flurouracil, Ref-References.

6. Discussion

This study provides a comprehensive analysis of 204 patients with GIT cancer treated at two tertiary care hospitals in Ethiopia. It highlights key demographic, clinical, and treatment-related aspects crucial for understanding and improving cancer care. Chemotherapy often causes side effects that challenge patients and healthcare providers, negatively impacting quality of life (57). Effective management strategies can alleviate these issues and enhance patient well-being by documenting and reporting adverse drug reactions (58).

This study found that the gender distribution of GIT cancer was nearly equal, with a slight female predominance of 51.5%. This finding is consistent with studies conducted in Nigeria, which reported a 50.0% (59). In contrast, research from India (60.5%), Italy (77.0%), and the Netherlands (75.0%), showed a male predominance (60-62). The male predominance observed in these studies may be related to increased exposure to risk factors such as occupational hazards, smoking, alcohol consumption and dietary habits (63). The mean (±SD) age at diagnosis was 51.5 (±11.4) years, with 30.4% aged 60 and above. This age distribution is in line with studies from Turkey, Nigeria, India, and Germany (7, 59, 64, 65). This is due to multiple genetic mutation and accumulation of genetic alteration over time in older patient (66). This age distribution informs healthcare planning, ensuring tailored services, targeted support, and earlier screening for those high-risk patients.

Adenocarcinomas (AC) were the predominant histopathological cell type, in 93.1% of cases. This is consistent with other studies elsewhere (67-70). Notably, 72.1% of patients exhibited well-differentiated carcinomas, consistent with results from Egypt (85.0% well-differentiated), and Turkey (70.0% well-differentiated) (71, 72). Nearly one-third (31.9%) of patients had comorbidities, including hypertension (10.3%), diabetes mellitus (3.4), and retroviral infection (3.4%). This finding is comparable to studies in the Netherlands (33.4%), China (35.11%), and Austria (40.5%) (73-76). The increased in comorbidities among patients may be linked to aging, as multimorbidities rise with age and socio-economic status is also associated with comorbid condition in cancer patient (77, 78). These findings emphasize GIT cancer patients have a high prevalence of comorbidities.

Around 64.7% of the patients had metastatic cancer at presentation, similar to a report from Turkey (65.7%), and India (50.1%) (7, 23). In Ethiopia, issues like distance from medical centers prolonged waiting times, and limited oncology centers may contribute to high rates of metastatic cancer at diagnosis. The high rate of metastatic cancer at presentation highlights the urgent need for improving screening programs and enhancing awareness campaigns to facilitate earlier detection, intervention and potentially improve patient symptoms.

The most common type of gastrointestinal GIT cancer in this study was rectal cancer (25.0%), colon cancer (23.0%), esophageal (17.2%), and gastric cancer (13.7%). These findings were mainly lower than or inconsistent with studies done in India, Nigeria, Turkey, and France (7, 11, 25, 64). The diversity in GIT cancer distribution highlights the impact of genetic, environmental, and lifestyle factors on cancer prevalence. Understanding these differences is crucial for investigating the factors that contribute to these disparities and the occurrence of GIT cancer.

In this study, 50.0% and 31.4% of patients received chemotherapy as palliative therapy and neo-adjuvant, respectively. Treatment modalities involved a combination of chemotherapy and surgery for 48.5% of patients, while 36.3% received chemotherapy alone. This is consistent with a previous study done in Ethiopia at TASH (79). Whereas somewhat inconsistent with studies from Egypt and China (23, 28). The consistency of these finding with previous studies in TASH highlights local treatment approaches. It may also reflect that more patients are presenting with advanced cancer due to lack of screening in our setting and it's crucial to improve early detection strategies.

In the current study, 79.9% of patients received fluoropyrimidine-based chemotherapy, with FOLFOX regimen (73.5%). A previous study in TASH showed FOLFOX was predominantly used at 55.6% (1). These findings were mainly lower than or inconsistent with studies done in Germany, India, and Egypt (6, 64, 80). These regional variations in chemotherapy selections highlight diverse treatment preferences influenced by factors such as drug availability, healthcare infrastructure, treatment costs, guidelines or protocols, and demographics. Recognizing and addressing these differences can result in personalized and effective cancer treatment strategies, ultimately improving patient care and outcomes.

The incidence and severity of reported toxicity varied widely in previous studies. This present study identified 1499 adverse drug reactions, with 789 (52.6%) being non-hematological, and 710 (47.4%) hematological. The highest incidence of ADRs (32.2%, 482) was observed in cycle 2. Notable non-hematological toxicities included nausea/vomiting (12.5%), and fatigue (12.4%), while hematological toxicities comprised anemia (40.3%) and neutropenia (39.0%). These results highlighted both similarities and differences in the prevalence and type of ADRs compared to studies conducted in Nepal, Ireland, Morocco, and France (22, 81-83).

Hematological toxicity is this study due to cytotoxic chemotherapy, which suppress hematopoietic system and leads to myelosuppression (3). Nausea/ vomiting arise from drugs that simulate the chemoreceptor trigger zone, while fatigue may result from other side effects or increased body energy to combat the these side effects (83). In Ethiopia, the insufficient availability of newer antiemetics and other supportive medication such as myelopoietics growth factors contributes to a higher prevalence of these ADRs. Regional variations ADRs types and frequencies may result from differences in treatment protocol, patient demographics, and reporting practices. Improved awareness and reporting can optimize treatment strategies and enhance safety.

As per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), in this study, 37.1% of toxicities were grade 3-4 chemotherapy-induced, with hematological toxicities at 45.7% and non-hematological at 54.3%. Notably, neutropenia was the most prevalent grade 3-4 hematological toxicity (79.9%), while nausea/vomiting among grade 3-4 non-hematological toxicity (32.0%). Comparatively, previous studies in Gondar, showed nausea/vomiting (18.9%), neutropenia (14.7%), fever and/or chills (11.3%), and anemia (9.3%), with (65.8%) classified as severe (grade 3–4) (3). Other studies done in Bangladesh, Vietnam, Italy, and France reported somewhat similar findings with the current study (21, 25, 28, 83). The higher percentage of grade 3-4 toxicities emphasized the need for vigilant monitoring and tailored intervention to mitigate severe side effects, consistency of these findings with previous studies, indicate a global pattern of chemotherapy-induced toxicities. Effectively addressing these toxicities can improve patient safety and reduce treatment interruption throughout chemotherapy treatment.

Identifying patients at higher risk of ADRs before chemotherapy using demographic and clinical characteristics have significant clinical impacts (11). This current study found that the incidence of grade 3-4 hematological toxicity was similar between males (59.6%) and females (64.8%), with a p-value of 0.44, as well as non-hematological toxicity (67.7% in males vs. 67.6% in females; 0.994). In contrast, a study in India reported a higher prevalence of ADRs in females (73.6%) (50). In our study, the incidence of Grade 3-4 toxicity was notably high at 69.3% among patients aged ≥60 years. This finding was consistent with other studies (22, 33). The incidence of ADRs is higher in elderly patients, likely due to natural decline in metabolism and excretory function, leading to drug accumulation and increased vulnerability to ADRs (13). This highlights the need of dosage adjustment, personalized treatment plans and further research on drug pharmacokinetics in older adults.

In this study, most patients received fluoropyrimidine-based regimens, with 68.7% experienced grade 3-4 hematological and 71.2% experienced grade 3-4 non-hematological toxicity, specifically, FOLFOX-treated patients had rates of 64.0% and 69.0%, respectively. This finding was higher than a study done in France (37). The higher rates observed in our study may be attributed to differences in patient age, BSA, plasma clearance, treatment protocols, and supportive care measures.

In the present study, 58.5% of patients with comorbidities experienced grade 3-4 hematological toxicity, with a p-value of 0.024. These findings are consistent with studies done by Li et al. (2017), who reported 55.2% of patients with comorbidities, with a p-value of 0.002 (84). Additionally, a meta-analysis by Tan et al. (2017) found a higher risk of severe toxicity associated with comorbidities (p =0.001) (85). Due to factors like impaired organ function and compromised immune function, which can impair the body's ability to tolerate and recover from the myelosuppressive effect of chemotherapy.

In this study, 81.9% of patients experienced chemotherapy-induced treatment delays, with 48.5% facing two or more dose delays over six cycles. Similarly, a study in the Canada and USA reported that 47.0% and 43.0% of patients had one or more treatment delays, respectively (46, 86). In contrast, studies from France and South Korea reported lower rates of delays, at 35.8% and 30.0%, respectively (87, 88). These findings highlight the significant variability of treatment

delay due to toxicity. It underscores the need for closer monitoring, proactive measures to reduce toxicity and minimize interruptions in the chemotherapy schedule.

Around 47.5% of patients were admitted to the hospital due to toxicity, while 9.3% discontinued their medication and 16.7% did not adhere to their schedule. In comparison, a study from Taiwan found a higher discontinuation rate of 37.8% with side effects, while a study from Japan reported lower rates of medication discontinuation (18.3%) and treatment Interruptions (10.3%) (88, 89). These findings highlight higher rates of non-adherence to treatment schedules, as patients often worry about worsening symptoms and the burden of managing the side. The comparative analysis emphasizes the importance of closely monitoring and addressing chemotherapy-related toxicity and enhancing adherence to treatment schedules.

In this study, 53.4% of GIT cancer patients had poor treatment outcomes, while 46.6% achieved good outcomes. Notable, TASH had a higher good outcome rate of 75.8% compared to SPHMMC at 24.2%. These findings are somewhat similar to studies from Egypt (52.0%) with poor outcomes, Germany (31.8%), Japanese (43.5%), and Arizona (49.5%) (90-93). Additionally a systematic review and meta-analysis by Puccini et al. (2017) noted poor treatment outcome rates ranging from 11.8% to 90% (88, 94). These findings underscore the heterogeneity in treatment outcomes seen across different settings, suggesting variation in treatment protocols and resources may affect patient treatment outcomes.

The logistic regression analysis identified several significant predictors of treatment outcomes in patients with GIT cancer. Notably, Age is a significant predictor of treatment outcomes. Those aged 60 and older had a higher likelihood of poor outcomes than those under 40, with an adjusted odds ratio (AOR) of 4.640, (95% CI [1.201-17.933], P=0.026). This finding is consistent with a study in Kazakhstan, which reported a 1.35-fold increased likelihood of poor treatment outcomes in older patients, and aligns with other studies identifying older age as an independent predictor of poor treatment outcomes (7, 92-95). These finding highlights the need for age-specific care strategies for those aged 60 and older. The underlying mechanism contributing to the poorer outcomes in older cancer patients is a higher burden of comorbidities, reduced organ function, and decreased physiological reserve, all of which limit their tolerance to chemotherapy toxicity.

Performance status measured by the Eastern Cooperative Oncology Group (ECOG) scale was a significant predictor. Patients with an ECOG-PS score of ≥ 2 had a higher likelihood of poor outcomes, with an AOR of 4.064 (95% CI [1.699-9.724], P=0.002). This finding is supported by multiple studies (96-99). These consistent findings underscore the importance of assessing ECOG-PS as part of the comprehensive evaluation of GI cancer patients, as it can help identify high-risk individuals who may require more tailored and supportive care approaches to optimize their treatment outcomes. Pathological grading significantly influences treatment outcomes, with poorly differentiated tumors linked to worse outcomes, with an adjusted odds ratio (AOR) of 5.100 (95% CI [1.483–17.539], P=0.010) compared to well-differentiated tumors. This is similar to a study done in China, and USA (100, 101). Tumor characterization in GIT cancer allows for personalized treatment plans based on tumor aggressiveness, and improving patient outcomes.

This current study showed that metastasis is a strong predictor of poor treatment outcomes, with an AOR of 9.124 (95% CI [3.477-23.947], P<0.001). This finding was comparable to the study conducted by Wang et al. (2022) with an AOR of (8.6), and Thng et al. (2018) (9.8) (102, 103). Additionally, Zhang et al. (2019) noted that both liver and lung metastases are significantly associated with poor outcomes (98). Patients having metastatic profiles often have limited treatment options and face a significantly worse prognosis, assessment of metastatic patterns early can help to identify high-risk patients, allowing for close monitoring and the provision of supportive care to optimize their clinical outcome.

Patients received low dose of chemotherapy more likely to have poor treatment outcomes with an adjusted odds ratio of (AOR) 4.917 (95% CI [1.007-24.007], P=0.049) as compared with standard chemotherapy dose. This finding aligns with a study done by Neill et al. (2020), who reported an AOR of 5.2 for worse outcomes (104). Similarly, a retrospective cohort study by Fujitani et al. (2021), and Xu et al. (2016) reported that low-dose chemotherapy was associated with significantly poorer treatment outcomes (105, 106). Collectively, these studies emphasize the importance of maintaining appropriate chemotherapy doses to optimize clinical benefits for GIT cancer patients. Reducing the chemotherapy dose can significantly compromise treatment efficacy and lead to poorer outcomes for these patients, underscoring the need for clinicians to adhere to standard dosing chemotherapy protocol to improve patients' prognosis.

Patients experiencing two or more treatment delays were significantly more likely to have poor treatment outcomes, with an adjusted odds ratio (AOR) of 2.762 (95% CI [1.805-9.475], p=0.016). This aligns with studies by Smoragiewicz et al. (2014), Kogan et al. (2019), and Kim et al, (2021), which found that treatment delays due to hematological toxicities lead to poorer outcomes (46, 86, 107). Conversely, adherence chemotherapy schedule was linked to better outcomes, with an AOR of 0.250 (95%CI [0.065-0.969], p=0.045). In contrast, a Study in Spain by Carrasco-Pena et al. (2020) similarly reported that adherence was associated with lower disease progression (AOR) of 0.28, with a p-value of 0.004 (108). These findings suggest that minimizing treatment delay to optimize clinical outcomes and delays in treatment can compromise the effectiveness of the therapy, lead to suboptimal outcomes, and emphasize the importance of adherence to recommended treatment regimen schedules.

Patients who experienced grade 3 or higher hematological toxicity two or more times were significantly more likely to have poor treatment outcomes, with an adjusted odds ratio (AOR) of 3.677 (95% CI [1.286-10.513], p=0.015). This finding is consistent with studies conducted by Degu et al. (2024), and Han et al. (2018) (52, 109). The result of this study highlights the importance of proactive management and mitigation of chemotherapy–induced toxicities to optimize treatment outcomes. Clinicians should closely monitor patients for the development of severe adverse events and be prepared to implement appropriate supportive care measures by focusing on toxicity management.

The present study found no association between G-CSF injection and reduced risk of poor treatment outcomes, with the adjusted odds ratio (AOR) of 0.61 (95% CI [0.237-1.608], p=0.324). This may be influenced by other confounded factors such as other patient or treatment-related factors. In contrast, a retrospective study by Smoragiewicz et al. (2017), and Zhang et al.(2020), reported better outcomes and longer progression-free survival with G-CSF (46, 110). Furthermore, a meta-analysis by Tan et al.(2017) also indicated improved overall response rates (pooled OR =1.75, 95% CI [1.27-2.42],p<0.001) (85). These findings suggest that G-CSF used may benefit chemotherapy delivery in GIT cancer patients by reducing the risk of chemotherapy-induced neutropenia. This could improve treatment outcomes and response rates, supporting G-CSF role as a supportive care measure in managing GI tract cancer.

7. Strengths and Limitations of the Study

7.1 Strengths of the study

Our study used prospective methodology for gathering both subjective and objective data about chemotherapy-induced toxicity experienced in all cycles of chemotherapy (6 cycles) is one of its major key strengths. This methodology allows the collection of data in the context of an actual setting, which increases the external validity of the result. By assessing the patient status across all cycles in a specific period, the study was able to capture the longitudinal course of chemotherapy-induced toxicity, which will provide valuable insight into the severity of as well as the natural history of those side effects. An additional strength of our study is two major cancer centers included: one largest referral hospital (TASH) and one teaching hospital (SPHMMC).

7.2 Limitations of the study

Our study does not provide information on long-term treatment outcomes, such as overall survival or disease-free survival, which would be essential for a comprehensive understanding of the impact of chemotherapy on GIT cancer patients. The maximum period was eight months was used to recruit the study patients due to the sample size was small and it was difficult to generalize the whole Ethiopian cancer population health-related quality of life and Long-term complications of chemotherapy were not assessed in this study.

8. Conclusion and Recommendation

8.1 Conclusion

This study provided valuable insight into chemotherapy-induced toxicities, and clinical outcomes of gastrointestinal tract (GIT) cancer in Ethiopia. The results of this study suggest that ADRs are common in the gastrointestinal tract (GIT) cancer in two study settings. The findings emphasize the necessity of active patient monitoring to identify and manage ADRs promptly, ensuring patient safety. High-grade hematological and non-hematological toxicities were linked to various demographic, clinical, and treatment-related characteristics. Moreover, the prognosis for GI cancer patients remains poor in two study settings, Poor treatment outcomes were significantly predicted by age ≥60, ECOG score ≥2, poorly differentiated adenocarcinoma, metastasis, low chemotherapy dose, frequent treatment delays, and occurrence of high-grade hematological toxicities. These insights highlight the importance of efficient management of chemotherapy-induced toxicity, practical screening policies, and personalized treatment approaches to enhance patient outcomes.

8.2 Recommendation

Based on the key findings of this study, the following recommendations are forwarded.

Recommendation for TASH and SPHMMC

1. Implement robust toxicity monitoring and management protocol:
   - ✓ Develop standardized guidelines for the prevention, early detection, and management of chemotherapy-induced toxicities, particularly high-grade hematological and non-hematological adverse events
2. Optimize chemotherapy dosing and supportive care
   - ✓ Adopt a personalized approach to chemotherapy dosing, accounting for patients factors such as age, and comorbidities to minimize the risk of high-grade toxicities
   - ✓ Ensure the timely provision of supportive care intervention, including growth factors, antiemetics, and antimicrobials to mitigate the impact of adverse drug events in each cycle of chemotherapy.

- ✓ For patients taking chemotherapy for a longer duration, oncologists may provide G-CSF to lower the risk of developing severe neutropenia in mild and later chemotherapy cycles.

3. Strengthen cancer registry and data management:
   - ✓ Enhance the national cancer registry system and electronic medical record systems to capture comprehensive data on GIT cancer incidence, treatment patterns, and outcomes.

Recommendation for Researchers and other stack holders

- ✓ Further larger multi-center long prospective and interventional studies on chemotherapy dosing, targeted therapy, and FOLFOX regimen (FOLFOX -6, modified FOLFOX-6, and FOLFOX -7).
- ✓ It is recommended that more research be conducted using large sample sizes and research designs.

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Appendix

Appendix I: Information Sheet

Title of the study: Chemotherapy-Induced Toxicities, Clinical Outcomes and Associated Factors among Patients with Gastrointestinal Cancer in Two Tertiary Care Hospitals, Addis Ababa, Ethiopia.

Hello! I am _____ a member of the research team of the Department of Clinical Pharmacy and Pharmacology, AAU, CHS, SOP. I will carry out a study on Chemotherapy-Induced Toxicities, Clinical Outcomes and Associated Factors among Patients with Gastrointestinal Cancer Patients. Chemotherapy drugs are not always safe; however, these medications have side effects, such as nausea, vomiting, diarrhea, constipation, peripheral neuropathy, anemia, neutropenia and others. Another type of medication is administered to treat those side effects. We wanted to know the severity of those toxicities and the outcomes of those added medications. This will assist clinicians in treating any side effects after they take chemical medications such as you.

Therefore, I am requesting that you participate in this research. This study included at least 6 months of follow-up. Your participation in this study is voluntary, so you had the choice to participate or discontinue the interview at any time.

Appendix II: Consent Form

Addis Ababa University, CHS, SoP, Department of Clinical Pharmacy and Pharmacology, consent form: Chemotherapy-Induced Toxicities, Clinical Outcomes and Associated Factors among Patients with Gastrointestinal Cancer in Two Tertiary Care Hospitals, Addis Ababa, Ethiopia. You have already received in-depth information about the research and its purpose. Therefore, would you kindly let me know if you consent to take in the study?

I voluntarily agreed to participate in the research program. Yes: _____ No:_____

I was informed regarding the study, and I was able to comprehend its objective as well as advantage. I was aware that no data about my privacy, including my name and any response I provided, might be shared with someone else. I am willing to participate in the research.

You have consented to take part in the research by signing here

Sign of the Participant _____

Name of the interviewer: _____ Sign: _____

Name of the Supervisor: _____ Sign:_____

Principal Investigator: Samson Fisseha Melaku Phone Number: 0922918549

Advisor: Minyahil Alebachew (B. Pharm, MSc, PhD)

Coadvisor: Alemseged Beyen (B. Pharm, MSc, Associate Professor)

Atalay Mulu (B. Pharm, RPh,MPharm)

Purpose of the study: To assess chemotherapy-induced toxicity, clinical outcomes and associated factors in hospitalized patients diagnosed with gastrointestinal tract cancer at Tikur Anbessa Specialized Hospital (TASH) and St. Paul's Hospital Millennium Medical College (SPHMMC, Addis Ababa, Ethiopia.

Duration of participation: Your participation in the study will last for 6 months in each chemotherapy cycle.

Possible benefits: The findings of this study can help improve the care of patients with GIT cancer by identifying effective treatments and minimizing medication side effects through the selection of appropriate supportive measures.

Possible risk and discomfort: There is no risk association with this study. There are no psychological, economic or social risks.

Confidentiality: the information you provide will be kept private. The study team will not share your information with anyone outside of the study team without your permission**.**

Person to contact: You have the right to ask information that is not clear about the context before and during the time of data collection; anyone can contact the principal investigator**.**

If you have/will have any questions, you can contact the principal investigator by

Phone number: - 0922918549/0976079040 Email: samifmust@gmail.com

Appendix III: Data collection instrument

Part I: Basic Socio-demographic

Items	Answer
Card No/ I-care	
Name of health facility:	TASH □ SPHMMC □
Gender	Male □ Female□
Age in year	
Region	
Martial statues	Married □ Single □ Windowed □ Divorced □
Educational level	1. No formal education □ 2. Primary school(1-8 grade) □ 3. Secondary school(9-12 grade) □ 4. Higher education (diploma and above) □
Social history	**1.** Alcohol use **Yes** □ **No** □ **2.** Cigarette smoking **Yes** □ **No** □ **3.** khat use **Yes** □ **N** □ **4.** other specify ----------

Part II: Clinical characteristics

Comorbidity YES □ No □ If yes ; √	1. DM □ 2. HTN □ 3.HF □ 4. Asthma □ 5. CKD □ 6.RVI □ 7.***Autoimmune diseases*** □ 8. BPH ***9.others*** _____-
Main diagnosis	1. Rectal cancer □ 4. Anal cancer □ 2. Gastric cancer □ 5. Liver Cancer □ 3. Esophageal cancer □ 6.Colon cancer □ 7.pancreatic cancer □ 8.Gall bladder cancer □ 9.other _____
ECOG performance	**At diagnoses. 0** □ **1** □ **2** □ **3** □ **4** □
Stage of cancer	One □ Two □ Three □ Four □
	If its stage 4 specify The metastasis detected to 1._____ 2._____

Part III: Treatment related characteristics

Date of treatment started	._____
Treatment Modality's	1. Chemotherapy only 2. Radiation (EBRT) only 2. Surgery only 3. Chemotherapy and EBRT 4. Surgery and ERBT 5. Chemotherapy and surgery 6. chemotherapy ,surgery and EBRT
Chemotherapy used as yes (□√) No (□ X)	**Adjuvant** □ **Neo adjuvant** □ **Palliative** □ Other.___ _____
Surgery was done	yes □ No

	Fluoropyrimidines Base	Cycle
Chemotherapy Regimen taken Height_____ Weight_____ BSA _____ BMI_____	**1.** FOLFOX □	
	2. FOLFIRI □	
	3. FOLFOXIRI □	
	4. CapOX □	
	5. Others :	
	Taxanes / Platinum	
	1. Cisplatin plus Paclitaxel □	
	2. Cisplatin plus 5 FU □	
	3. Carboplatin plus Paclitaxel □	
	4. Gemcitabine and cisplatin □	
	5. Docetaxel and cisplatin □	
	6. Capcitabine alone □	
	7. Other :	
	Targeted therapy	
	1. VEGF (Bevacizumab)	
	2 EGFR(panitumumab or cetuximab)	
	3; Other	
	Other class : 1.	
If the treatment is change specify the Reason	1._____ 2._____	

Part IV: Baseline laboratory test

Lab test was done		Results in subsequent cycle						Reference range
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	
CBC	WBC							
	RBC							
	HGB							
	ANC							
	PLT							
RFT	Creatinine							
	BUN							
LFT	AST							
	ALT							
	ALP							

Part V: National Cancer Institute Common Terminology Criteria For Adverse Event (CTCAE) Version 5.0 For severity of Toxicity Assessment

ADR/ADE	YES	Toxicity assessment from Grade 1-5					
Hematological	✓	Cycle 1/Grade	Cycle 2/Grade	Cycle 3/Grade	Cycle 4/Grade	Cycle 5/Grade	Cycle 6/Grade
Anemia							
Neutropenia							
Thrombocytopenia							
Pancytopenia							
Other							
Non-Hematological	yes	Toxicity assessment from Grade 1-5					
		Cycle	Cycle	Cycle	Cycle	Cycle	Cycle

		2/Grade	2/Grade	2/Grade	2/Grade	2/Grade	2/Grade
Nausea/vomiting							
Diarrhea							
Constipation							
Gastritis/Stomatitis							
Mucositis							
Abdominal pain							
Peripheral neuropathy							
Hand foot syndrome							
Nephro toxicity							
Neurotoxicity							
Alopecia							
Others							

Any History of Hospital/clinic admission due to chemotherapy toxicities	**YES** □ NO □

Clinical finding	Grade???	remark
Febrile neutropenia		
Thrombosis/embolism		
Sepsis		

Part VII: premedication /antibiotic prophylactic

		Yes	No	cycle			yes	No	cycle
1	Metoclopramide				3	Promethazine			
1.	Dexamethasone				4	Acetaminophen			
2.	Ondansteron				5	Omeprazole / cimetidine			
3.	Other								

Part VIII: Therapeutic classes used in ADRs Management

Class	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Anti-emetics						
Analgesics						
Laxative						
Antimicrobial agent						
Inj. Granulocyte colony stimulating factor						
Proton pump inhibitors						
Corticosteroid						
Multivitamin /V-12/Iron tablet						