Development and Validation of a Predictive Model for Severe Hematological Toxicity in Adult Colorectal Cancer Patients Taking Chemotherapy at Tikur Anbessa Specialized Hospital

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This is to certify that Wondim Ayenew's thesis, *Development and Validation of a Predictive Model for Severe Hematological Toxicity in Adult Colorectal Cancer Patients Taking Chemotherapy at Tikur Anbessa Specialized Hospital*, submitted in partial fulfillment of the requirements for the Degree of Master of Science (Pharmacoepidemiology and Social Pharmacy) complies with the regulations of the University and meets the usual standards with respect to originality and quality.

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Abstract

Development and Validation of a Predictive Model for Severe Hematological Toxicities in Adult Colorectal Cancer Patients Taking Chemotherapy at Tikur Anbessa Specialized Hospital

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Addis Ababa University, 2021

Background: Hematological toxicities are common in colorectal cancer patients taking chemotherapy. The development of a valid predictive model would go a long way in preventing for such toxicities.

Objectives: To develop and validate a prediction model for severe hematological toxicities in adult colorectal cancer patients taking chemotherapy at Tikur Anbessa Specialized Hospital

Methods: A retrospective cohort study was conducted using medical records of adult colorectal cancer patients who received chemotherapy from 2017 to 2021 at Tikur Anbessa Specialized Hospital. The model was developed using uni-variable and multivariable logistic regression analyses, and it was validated using bootstrapping. The model was developed for severe neutropenia only because of limited number of outcomes for anemia and thrombocytopenia. Discrimination and calibration were used to determine the model's prediction accuracy. All statistical tests were two-sided and P-value < 0.05 was considered statistically significant.

Results: A total of 224 colorectal cancer patients were considered for analysis. About

114 (50.9%), 25 (11.2%) and four (1.8%) patients developed severe neutropenia, anemia and thrombocytopenia respectively. Age, polychemotherapy, type of therapy, and longer duration of chemotherapy were predictors of severe neutropenia. The model had sensitivity of (71.05% versus 73.24%) and specificity of (71.82% versus 68.49%) in the derivation and validation cohorts respectively. The area under receiver operating curve was 0.7995 for the derivation and 0.7741 for the validation cohorts.

Conclusions: Neutropenia was the most common hematological toxicity. The application of the developed model could help to identify high-risk patients for severe neutropenia and to institute preventive strategies before neutropenia develops.

Key words: *Chemotherapy, Colorectal Cancer, Hematological toxicity, Predictive model, Tikur Anbessa Specialized Hospital*

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List of Abbreviations

5- FU	5- Fluorouracil
ADEs	Adverse Drug Effects
ADRs	Adverse Drug Reactions
CRC	Colorectal Cancer
FDA	Food and Drug Administration
FOLFIRI	Folinic acid, Fluorouracil and Irinotecan
FOLFOX	Folinic acid, Fluorouracil and Oxaliplatin
FU/LU	Fluorouracil and leucovorin
HSRs	Hypersensitivity Reactions
TASH	Tikur Anbessa Specialized Hospital
WHO	World Health Organization
XELOX/CAPOX	Capecitabine and Oxaliplatin

1. Introduction

1.1. Background

According to a recent report, colorectal cancer (CRC) was the third most frequent cancer in the world, with more than 1.9 million (10.0%) new cases. It is also Ethiopia's third most prevalent cancer, with 6,048 (7.8%) new cases, after breast and cervix-uterine cancers (Sung *et al.*, 2021).

Surgery, chemotherapy, radiotherapy, and targeted agents are the most used treatment options for CRC. Chemotherapy can be the mainstay of treatment choice, especially for stage III and IV CRC patients. Folinic acid, fluorouracil and oxaliplatin (FOLFOX), fluorouracil and leucovorin (FU/LU), capecitabine and oxaliplatin (XELOX) and folinic acid, fluorouracil and irinotecan (FOLFIRI) are commonly used chemotherapy agents for colorectal cancer patients (Barbounis *et al.*, 2001; Benson *et al.*, 2004).

Despite the benefits of these chemotherapeutic agents, the regimens are predictably associated with serious adverse drug effects (ADEs) (Grothey, 2006). Hematological toxicities are among the most common adverse effects that occur in CRC patients treated with chemotherapeutic agents (Hu *et al.,* 2012). These toxicities include a decreased in red blood cell production, white blood cell production and platelet production, all of which can be life threatening to the patient (Diane *et al.,* 2007). These toxicities can lead to dose reduction, treatment delay, drug discontinuation and endanger patients' treatment success (Caggiano *et al.*, 2005).

Even though there is a means to prevent or lessen the impact of hematological toxicities, patients are managed after they develop toxicities (i.e. a traditional model of management). This is because of lack of reliable and accessible method for predicting when and in whom toxicities will emerge. As such, data driven approaches based on predictive models may assist clinicians and researchers in anticipating the likelihood of hematologic toxicities in patients receiving chemotherapy agents (Steensma and Loprinzi, 2005). In fact a predictive model can be an economical method to prevent toxicities before they occur by helping to identify the higher risk patients and the time or the cycle the risk would become elevated (Coiffier and Bastit, 2001; Kosmidis and Krzakowski, 2005; Rambach *et al.*, 2014).

1.2. Statement of the problem

In cancer patients on chemotherapy, hematological toxicities occur very frequently (Tecza *et al.,* 2018). Chemotherapeutic drugs decrease white blood cells (neutropenia and leukopenia), red blood cells (anemia), and platelets (thrombocytopenia) and cause harmful effects on patients (Groopman & Itri, 1999; Tecza *et al.,* 2018; Kuilenburg *et al.,* 2002). These ADEs lead to increased morbidity and mortality. Moreover, they can also lead to dose reduction, treatment delay, drug discontinuation, and endanger patients' treatment outcome (Caggiano *et al.*, 2005).

Studies show that hematological toxicities are common in CRC patients treated with chemotherapy (Rambach, 2014; Zineb *et al.*, 2020). Many of the toxicities are preventable and reasonable action is necessary to monitor and avoid drugs that are problematic. In many cases, oncologists manage the toxicities after the patient develops them (Steensma and Loprinzi, 2005). One way to prevent ADEs is to employ a predictive model that helps to identify higher risk patients and the time or the cycle the risk would be elevated before toxicities occurred (Coiffier *et al.,* 2001; Kosmidis & Krzakowski, 2005; Rambach *et al.,* 2014).

While oncologists in some settings develop and utilize such predictive models in their practice, it is not the case in many resource poor contexts including those in Ethiopia (Vincent *et al.,* 2007; Ichikawa *et al.,* 2015). The absence of such predictive models in the Ethiopian context greatly compromises the quality of oncology services for CRC patients. At Tikur Anbessa Specialized Hospital (TASH), there is a multidisciplinary

team (MDT) for care and management of CRC patients but oncologists managed toxicities after patients develop hematological toxicities. The current study, therefore, aims to fill this gap by developing and validating a predictive model for severe hematological toxicities among adult CRC patients at TASH, the largest oncology service provider in Ethiopia.

1.3. Significance of the study

Oncologists treat cancer patients based on chemotherapy treatment guidelines but many patients develop serious hematological toxicities (Steven, 2001). After these toxicities have been developed, oncologists take efforts to combat them. Such management puts the patient in unpleasant and potentially dangerous situation, prompting them to change their chemotherapy regimen to avoid it happening again. However, clinical care could be improved if toxic effects are accurately predicted and early interventions is taken proactively to prevent them. A prediction model can help with this. Prediction models are critical tools that help healthcare providers and patients make decisions about diagnostic testing, treatment initiation and discontinuation, and life style changes. They can provide objective data regarding an individual's illness risk and help to minimize biases in clinical decision-making , but they were not used to replace clinical experience (Harrell, 2015).

As a result, our research aids oncologists in the identification of high risk and low risk individuals and the provision of primary prophylaxis of granulocyte colony stimulating factor (G-CSF) at the start of the cycle for high-risk patients and reassuring low risk

patients. Therefore, it helps to prevent severe hematological toxicities before they occur in CRC patients. It also aids oncologists in detecting and treating hematological toxicities early, allowing chemotherapy to be administered at the prescribed dose.

2. Literature Review

2.1. CRC: Epidemiology and Treatment Modalities

Cancer is a broad term that refers to any disease that is caused by uncontrolled cell growth and proliferation. Abnormal cell morphology results from uncontrolled cellular growth and proliferation. If it is metastasized, the cancerous cells able to invade and spread to other tissues and organs. Metastasis is the major contributor to death as the treatment of advanced cancer can be difficult (Alberts *et al.*, 2008; WHO, 2013).

CRC is a type of cancer which originates in colon and rectum (Mitry, 2008). It is the third most commonly diagnosed cancer in both sexes globally with 1, 931, 590 (10%) cases and the second deadly cancer with 935, 173 (9.4%) death next to lung cancer (Sung *et al.*, 2021). In Africa, reports showed the proportion of cancer death (57.3%) was higher than the incidence in 2018 (48.4%). This is because of poor cancer prognosis, limited access to timely diagnosis and treatment (Bray *et al.*, 2018). In 2020, Africa has 3.4% CRC incidence and 4.6% death in both sexes. Despite the fact that most countries' epidemiological data is of poor quality, the incidence of CRC in sub-Saharan Africa (SSA) is increasing year after year. This increase could be attributed to increased access to health care and investigation services. CRC patients are mostly young, and some have molecular and pathological characteristics that point to hereditary cancer (Katsidzira *et al.*, 2017).

In Ethiopia, cancer incidence and death is alarmingly increased. According to GLOBOCAN 2018, the incidences of cancer in the last five years were around 67,573 cases and 47,954 deaths. CRC became the third most frequent cancer in Ethiopia in both sexes, breast and cervix-uterine cancer, with about 4716(7%) new cases (Bray *et al.*, 2018). According to GLOBOCAN 2020, it was the third most prevalent cancer in Ethiopia, 6,048 (7.8%) new cases, next to breast and cervix-uterine cancers in both sexes, first 3, 121 (11.7%) in males and third 2,927 (5.8%) in females (Sung *et al.*, 2021).

There are different treatment modalities for CRC patients. The treatment depends on factors such as the stage of cancer and preference of the physician and the patient but the age of the patient shouldn't play a role in the choice of treatment (Popescu *et al*, 1999; Iwashyna and Lamont, 2002). Even though studies showed the age of the patient didn't influence the choice of treatment, the likelihood of receiving the same chemotherapy as other patients by older patients is lower (Cronin *et al*, 2006).

Surgery, radiotherapy, and chemotherapy which include biological/targeted agent therapies are the most commonly used modalities for CRC treatment (Mitry, 2008; ACC, 2016). Chemotherapy includes medications taken by patients to target and destroy cancerous cells. They act systematically to stop or slow down the growth of cancer cells. They are cell cycle-specific or nonspecific. They usually act on rapidly dividing cells but affect the healthy cells negatively. The damage incurred by healthy cells determines the side effect of the treatment (Rang and Dale, 2007).

Depending on the stage of the CRC, chemotherapy can be used to cure, ease the symptoms of the CRC, or prolong the life of the patient. They may be given after surgery as adjuvant chemotherapy or before surgery as neoadjuvant chemotherapy or as palliative chemotherapy. Adjuvant chemotherapy is used to reduce the likelihood of the CRC returning but if the cancer isn't cured palliative chemotherapy is administered to slow down metastasis or to shrink the tumor to alleviate any pain or pressure caused by them (Mitry, 2008).

A single chemotherapy drug or a combination of drugs is used for the management of cancer. Chemotherapy is also used in combination with radiation or biological therapy to improve the prognosis of cancer. Combination chemotherapy drugs are often more effective. Capcitabine, oxaloplatin, 5- fluorouracil with folinic acid, FOLFOX and CAPOX regimens were used for early CRC. Irinotecan and biological therapies weren't used as adjuvant therapy in CRC. FOLFOX, XELOX/CAPOX and FOLFIRI are the common combination chemotherapy regimens used in advanced CRC treatment (ACS, 2019).

In the treatment of CRC, active chemotherapeutic drugs are also employed in conjuction with novel targeted monoclonal antibodies such as cetuximab and panitumumab or bevacizumab. These drugs improve patient outcomes but come with a lot of severe toxicities. Furthermore, these agents may not be beneficial to all patients (Chua *et al.*, 2011).

Many chemotherapeutic drugs have a narrow therapeutic window, which means the therapeutic doses employed are dangerously close to toxic levels. These suggest that the chemotherapy treatment's adverse effects will be more severe and will affect the majority of individuals. Chemotherapy affects healthy fast dividing cells such as those present in the blood, hair, mouth, skin and nails, causing many adverse effects (ACS, 2019).

2.2. Hematological toxicity in CRC patients: Causes, prevalence and severity

Hematological toxicity in CRC patients occurs because of the drugs affect hematopoietic cells and decrease the level of erythrocytes, leukocytes and thrombocytes in the blood (ACS, 2019). The most prevalent hematological adverse effects in cancer patients receiving chemotherapy are anemia, neutropenia and thrombocytopenia. These adverse effects lead to morbidity, mortality and they can also lead to dose reduction, treatment delay, drug discontinuation, and endanger patients' treatment outcome (Caggiano *et al.*, 2005).

Most toxicity that occurs in CRC treatment is drug-specific. Nausea and vomiting are mostly observed in patients taking FOLFOX regimen even though all patients are pre-medicated with antiemetic drugs (Wiela-Hojenska *et al.*, 2015). Hand–foot syndrome has commonly occurs in CRC patients taking capecitabine regimen and neuropathy is an oxaliplatin-induced adverse drug reaction (ADR). Severe diarrhea and neutropenia are caused by Irinotecan. Hematological toxicities (leukopenia, thrombocytopenia and

neutropenia) are more frequently associated with 5-FU than with capecitabine (Saltz *et al.*, 2000; Kadoyama *et al.*, 2012).

A prospective cross sectional study in Iran revealed, the most common hematologic toxicities were anemia and leukopenia in CRC patients who had taken FOLFOX regimen. The severity levels were reported to correspond with grades 1 to 2 toxicities for anemia (76.83%) and leukopenia (26.48%) (Dehghani *et al.*, 2015).

Another cross sectional study done in Cuba showed 48 % of patients used capecitabine as a chemotherapy schedule in their treatment. This drug caused the highest hematological toxicity i.e. anemia in the group of patients ≥ 70 years. The hepatic and renal toxicity was higher in patients treated with FOLFOX regimen. Diarrhea, nausea and vomiting were mostly produced by the XELOX regimens (Soriano-lorenzo *et al.*, 2018).

The most common adverse effect linked with the administration of the FOLFOX and FOLFIRI treatment regimens, according to a study in Poland, were nausea, vomiting and neurotoxicity. The most common hematological adverse effects in the patients with FOLFRI regimen were leucopenia and granulocytopenia (Wiela-Hojeńska *et al.*, 2015).

The Hartwig and Siegel adverse drug effect assessment scale is used to determine the severity of adverse medication effects. The severity is classified as mild (level 1, 2), moderate (level 3, 4, 5), and severe (level 6, 7) (Hartwig *et al,* 1992). Hematological toxicities were also assessed and graded according to Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade refers to the severity of the toxicity. Grade 1 and 2 hematological toxicities were considered as mild.

Grade 3 and 4 hematological toxicities were considered as severe neutropenia (NCI, 2009; NCI, 2017). Table 1 shows criteria for classifying hematological toxicities based on National Cancer Institute.

Table 1:- Classification of hematological toxicity and their severity (grade) based on National Cancer Institute

Hematological toxicity	**Value**	**Grade**			
		1	**2**	**3**	**4**
Neutropenia	neutrophil(* 109 /L)	1.5 – 2.0	1.0 – 1.5	0.5 – 1.0	0 – 0.5
Anemia	hemoglobin(g/dL)	10.0-12g/dL	8.0 -9.9 g/dL	6.5-8(transfusion needed	< 6.5(life threatening)
Thrombocytopenia	platelet(/mm3)	75,000-99,000	50, 000-74,000	25,000-49,000	< 25,000

According to a study conducted in France, 71.2% of CRC patients experienced neutropenia. In the first two cycles of treatment, 36.1% of CRC patients developed mild neutropenia, and 35.1% developed severe neutropenia. Anemia struck 91.7% of patients in this study. 71.3% of those developed grade 1 and 2 anemia and 20.4% developed grade 3 and 4 anemia. Thrombocytopenia affects about 58.8% of people. About 50.7% of patients developed grade 1 and 2 and 8.1% developed grade 3 and 4 thrombocytopenia (Rambach *et al.*, 2014). Another study done in Australia showed about 70% of CRC patients who take 5-flurouracil developed hematological toxicity (grades ≥1 for neutropenia and leukopenia). From the toxicities developed, 69% were neutropenia, 58% mucositis and 46% leukopenia (Garg MB *et al.*, 2012).

Patients with breast, lung, colorectal, ovarian cancer who started a new chemotherapy regimen suffered 28% severe neutropenia and 16% febrile neutropenia, according to a prospective research. In the first cycle of chemotherapy, almost 67% of CRC patients developed severe neutropenia and 53% develop febrile neutropenia (Crawford *et al.*, 2004).

Another study done in Morocco found that neutropenia (36%), anemia (3.2%) and thrombocytopenia (1.6%) were the most common hematological toxicities of all grades. Neutropenia (11%) was the most common severe hematological toxicity followed by anemia (1.6%). There was no evidence of severe thrombocytopenia (Zineb *et al.*, 2020).

2.3. Predictive factors of hematological toxicity in CRC patients

ADEs are caused by a variety of circumstances, although the risk factors for developing countries differ from those for rich countries. For example, African origin persons are shown to have high risk of toxicity for commonly used drugs for the treatment of disease like cancer, tuberculosis and HIV/AIDS (Aminkeng *et al.*, 2014).

Most of the risk factors associated with toxicity in patients taking anticancer drugs are polypharmacy, gender and age (Wang and Huang, 2007; Poddar *et al.*, 2009). Female patient are known to be 1.5 to 1.7 times more likely than male patients to acquire medication toxicity. This is because of gender-related differences in immunological, hormonal and pharmacokinetic factors (Franconi and Campesi, 2014; Rademaker, 2001; Rodenburg *et al.*, 2011). Despite the fact that older age and female gender have been identified as risk factor for experiencing anticancer medication toxicity (Chopra *et al.*, 2016), some studies showed male and older patients were highly predisposed to drug toxicities (Poddar *et al.*, 2009).

There are factors associated with development of toxicities due to chemotherapeutic agents in CRC patients. The first one is nongenetic factors like age, gender, organ dysfunction, comorbid disease and performance status. Secondly, genetic factors may increase risk of toxicities in CRC patients taking 5-FU, capcitabine, oxaloplatin, irinotecan and cetuximab (Cortejoso and López-Fernández, 2012). A study done in

Korean colorectal cancer patients showed that alopecia and leukopenia due to 5-FU were more frequent in females than male patients (Lim *et al.*, 2019).

Lengthen cycles and use of chemotherapy is a factor for predicting hematological toxicities in CRC patients taking chemotherapy. The number of chemotherapy cycles was found to be the most important risk factor for predicting hematological toxicities in CRC patients receiving chemotherapy in an Iranian study (Dehghani *et al.*, 2015).

A Pharmacokinetic and pharmacodynamics property of anticancer drugs determines the occurrence of adverse drug events. Advanced age, female gender, race, high performance status, decreased pretreatment neutrophil count, drug-drug interaction, drug administration schedule and bilirubinemia were the risk factors that predict the occurrence of adverse effects related to fluorouracil and irinotecan. There are no clinical and molecular risk factors that identify patients more likely to experience oxaloplatin induced adverse effects (Vincenzi *et al.*, 2008).

Predictive factors for capcitabine induced adverse effects weren't identified. From pharmacokinetic and pharmacodynamics data, capcitabine had reduced toxicity, improve response rate (Twelves *et al.*, 1996). Obese patients were shown to be considerably less likely than normal than normal weight patients to experience severe adverse effects in a study of rectal cancer patients (Meyerhardt *et al.*, 2004).

Different studies also shown factors such as gender, advanced age, performance status, pretreatment absolute neutrophil count, total bilirubin level, type of regimen, dose of chemotherapy, reduced baseline bilirubin, low hemoglobin level, metastasis, were predictors for severe neutropenia in colorectal cancer patients who take irinotecan (Boige *et al.,* 1998; Ichikawa *et al.*, 2015).

Low baseline hemoglobin, reduction in hemoglobin during the first cycle of chemotherapy, past blood transfusion, and treatment length were all predictive risk factors for anemia in a study of solid tumors, including colon cancer (Coiffier *et al.*, 2001).

Drug efficacy and the chance of toxicity are both influenced by genetic variables. Because many chemotherapeutic drugs have very narrow therapeutic index, a better understanding of pharmacogenetic connections is especially relevant in cancer chemotherapy. The 5-FU, a fluoropyrimidine, and its derivatives capecitabine is one of them chemotherapeutic agent that are most typically utilized for the treatment of solid cancer including CRCs. Genetic factors such as dihydropyrimidine dehydrogenase (DPD) gene are assumed to be responsible for a fraction of estimated 10-40% of individuals who acquire severe to life threatening conditions, and in some circumstances 5-FU and capecitabine toxicity can be fatal (Meyerhardt & Mayer, 2005). DPD, a crucial enzyme in the catabolism of 5-FU, is the leading option for pharmacogenetic investigations on 5-FU

toxicity, because decreased DPD activity is anticipated to result in a longer half-life of the medication and hence a higher risk of toxicity (Amstutz and Froehlich, 2011).

2.4. Hematological toxicity in CRC patients: Clinical and economic impact

The frequency and severity of ADEs are growing. This leads to steady rising of the costs of ADEs and imposed an economic burden on patients, care givers and healthcare institutions. They have an impact on the ability to deliver planned treatment and lead to poor clinical outcome (Bouvy et al., 2015). They also lead to dose reduction, treatment delay, drug discontinuation and endanger patients' clinical outcome (Caggiano *et al.*, 2005).

Both direct and indirect costs are included in the cost of ADEs. Direct costs are those attributed to direct medical costs which includes the medical management of toxicity, whereas indirect costs are those attributed to time away from work, caregiver costs, and so on. In health cost analysis and pharmacoeconomic research, they constitute an important part of the cost structure (Carlotto *et al.*, 2013).

ADEs associated with treatments of CRC have the potential to impact healthcare resource utilization and overall cost of patient care (Overbeek *et al.*, 2011). In the treatment of CRC, studies have shown that hematological toxicities have a higher total monthly cost than other non-hematological toxicities. The cost of dealing with these toxicities are

significant and vary depending on the severity of the toxicity. The cost of hematological toxicity in the treatment of CRC treatment has been estimated to be $1,480 in the United States (Latremouille-Viau *et al.*, 2017). Anemia costs between $22,775-$93,454 per year, while neutropenia costs between $2,632 and $49,917 every hospitalization, according to other studies (Liou *et al*, 2007).

2.5. Prevention of Hematological toxicity in CRC patients and the place of predictive models

The primary consequence of cancer treatment is chemotherapy-induced myelosuppression, which decreases the effectiveness of chemotherapy (Maxwell and Maher, 1992). The complication leads to neutropenia, anemia and thrombocytopenia (Kuhn, 2002). Infection, bleeding, fatigue, decreased quality of life, and survival are all increased by these toxicities. In subsequent chemotherapy rounds, It may also result in dose reduction, treatment delay or both (Johnston and Crawford, 1998; Cairo, 2000). As a result effective prevention and management of chemotherapy associated myelosuppression is critical for lowering cancer treatment toxicity, improving tolerability, and allowing potentially curative therapy to be provided at a predetermined dose and interval.

Treatment with granulocyte colony stimulating factor (G-CSF) treatment is used in the management of chemotherapy patients who are at risk of infection due to neutropenia (Morstyn *et al.,* 2001). Patients who get CSF when they develop neutropenia may have a

lower risk of developing neutropenia in later chemotherapy cycles. In select high-risk neutropenic patients, such as those with neutrophil count of less than 1* 109 /L, pneumonia, hypotension, sepsis syndrome or invasive fungal infection, the administration is contemplated (Ozer *et al.,* 2000). They are used as supportive and adjunct to chemotherapy to reduce the incidence, severity and duration of neutropenia and in turn to reduce hospitalizations, antibiotic usage, and enable scheduled delivery of chemotherapy (Moore and Crom, 2006).

Anemia is another hematological toxicity experienced by CRC patients. Historically, the major treatment for severe anemia in cancer patients has been red blood cell (RBC) transfusion. They immediately raise RBC and hemoglobin levels, but the benefits are only temporary, and transfusions carry the danger of infection and hemolysis. When it comes to RBC transfusion, there is no defined trigger (O'Brien *et al.,* 2000). RBC transfusion can be replaced with recombinant human erythropoietin (epoetin alfa and beta) and darbepoetin alfa. In anemic cancer patients, they raise hemoglobin levels and reduce the need for RBC transfusions requirements in anemic cancer patients (Osterborg *et al.,* 2002). For severe thrombocytopenia, patients were treated with dose reduction or delay, platelet transfusion or platelet growth factor oprelvekin (ONS, 2008).

Different studies showed models for predicting hematological toxicities have already previously developed and validated for different types of cancer. There is no general model for all types of cancers that fits for patients. They put the importance of the

application of the model to oncologists to identify cancer patients at risk of hematological toxicities during their treatment and to enhance patient centered care by the application of the model in a proactive manner (Coiffier *et al.,* 2001; Dranitsaris *et al.,* 2005; Razzaghdoust *et al.,* 2018; Vincent *et al.,* 2007).

The model could be clinically applicable when a model is developed a simplified regression model or scoring system based on regression coefficients of final multivariable logistic regression analysis (Mehta *et al.,* 2016; Moons, 2015). Studies also put the model and the risk scoring system in a website for ease use and application in chemotherapy ordering system. They recommended oncologists to use G-CSF in the clinical practice. The use of prediction models is decided by the clinical or oncologist. It does not replace the clinical judgment of the clinician or oncologist. It should be used as an additional resource for medical decision making (Dranitsaris *et al.,* 2005; Vincent *et al.,* 2007; Razzaghdoust *et al.,* 2018).

Even though the prophylactic use of G-CSF have been shown to be effective, placing all cancer patients on CSF for all cycles of chemotherapy is too expensive for most healthcare systems to sustain and increased health care costs (Dinan *et al.,* 2015; Steensma & Loprinzi, 2005).

However, reliable prediction of individuals at high risk and preventive management would be a cost effective method if we knew who was at high risk and when their cycle would become heightened. Therefore, the selective use of prophylactic G-CSF in high

risk cancer patients for hematological toxicity reduces health care expenses while improving patients quality of life (Kuderer and Lyman, 2011; Razzaghdoust *et al.*, 2020). Prophylactic use of G-CSF (either filgrastim or pegfilgrastim) at the start of the first cycle of chemotherapy was also found to be cost effective when patients at higher risk for neutropenia were targeted (Cappozzo, 2004).

2.6. Conceptual frame work

After reviewing different literatures, conceptual framework was developed for this study. The conceptual framework depicts the predictors or risk factors of severe hematological toxicities which may have a direct and/or indirect impact for the occurrence of severe hematological toxicities.

Female gender, older age, organ dysfunction, comorbid disease, high performance status, reduced pretreatment absolute neutrophil count, reduced baseline bilirubin, low hemoglobin level, metastasis, longer duration of chemotherapy taking and taking polychemotherapy were predictors for severe neutropenia in colorectal cancer patients (Boige *et al.*, 1998; Vincenzi *et al.*, 2008; Cortejoso and López-Fernández, 2012; Dehghani et al., 2015; Ichikawa et al., 2015).

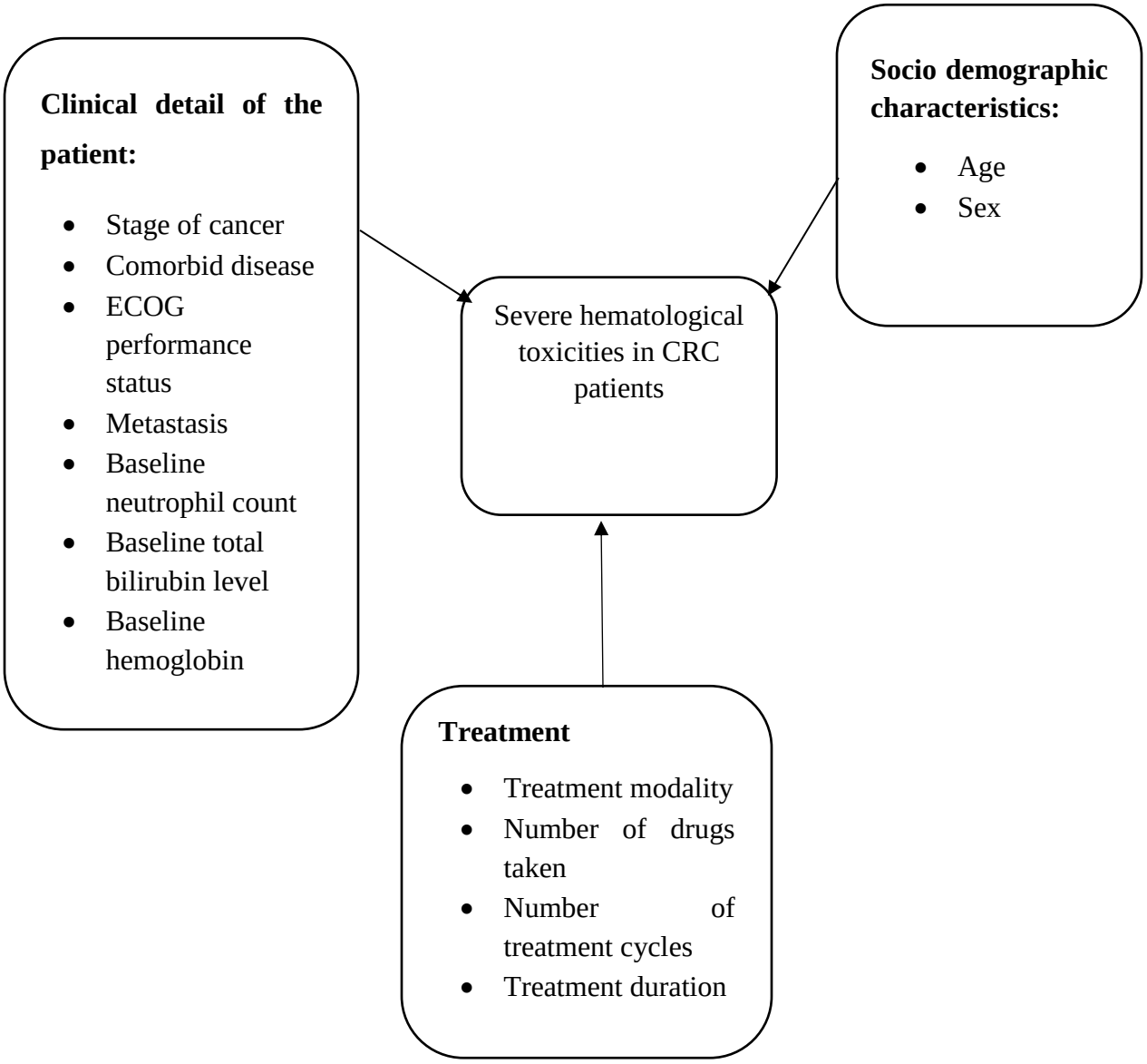


Fig 1: Conceptual framework of the study

3. Objectives

3.1. General objective

- ✓ To develop and validate a prediction model for severe hematological toxicities in adult CRC patients taking chemotherapy at TASH

3.2. Specific objectives

- ✓ To develop a prediction model for severe hematological toxicities in adult CRC patients taking chemotherapy at TASH
- ✓ To validate the prediction model for severe hematological toxicities in adult CRC patients taking chemotherapy at TASH

4. Methods

4.1. Study area

The study was conducted at the oncology department of TASH, which is a specialized hospital established in 1972. Since 1998, it has been operating under the administration of Addis Ababa University as a teaching hospital for the College of Health Sciences. It is the largest referral hospital in Ethiopia with a bed capacity of 800. The hospital provides patient care services in multiple specialty areas with annual patient volume of approximately 400,000.

The oncology department of TASH has outpatient and inpatient units. It provides chemotherapy, surgery and radiation treatment to the patients. The outpatient unit treats both new and follows up patients and it has 12 beds. The inpatient unit has 36 beds and provides treatment services for patients with cancer currently hospitalized and receiving chemotherapy. The oncology department has also two radiotherapy machines (cobalt-60) and two computed tomography scans and one magnetic resonance imaging unit. Six clinical oncologists, two colorectal surgeons, three palliative care specialists, six pharmacists, and 26 nurses provide service in the oncology department.

4.2. Study design and Period

The study design was a retrospective cohort study. Adult colorectal cancer patients (age ≥ 18 years) who were taking chemotherapy drugs from January 1, 2017 to January 1, 2021 in TASH were included.

4.3. Population

4.3.1. Source population

- ✓ All adult CRC patients at the oncology department of TASH during the study period

4.3.2. Study population

- ✓ All adult CRC patients who were taking chemotherapy in the oncology department of TASH during the study period

4.4. Sampling design and Sample size determination

All CRC patients receiving chemotherapy during the study period were included in the study. The medical records of patients who received chemotherapy for colorectal cancer in the four years were reviewed. Sample size i.e. number of events per predictor variable greater than or equal to 10 was used to obtain a robust predictive performance for severe hematological toxicity.

4.5. Inclusion and Exclusion criteria

The following inclusion and exclusion criteria were used in this study:

4.5.1. Inclusion criteria

- ✓ CRC patients treated with chemotherapy in the inpatient and outpatient setting during the study period

- ✓ Patients who were on one up to six treatment cycles
- ✓ Patients who had complete medical records

4.5.2. Exclusion criteria

- ✓ Patients who developed hematological toxicity because of accidental overdose
- ✓ Patients who received a prophylactic colony stimulating factor like filgrastin/epoetin alpha before treatment initiation

4.6. Study variables

4.6.1. Dependent variables

- ✓ Severe hematological toxicities

4.6.2. Independent variables

- ✓ Socio demographic characteristics: age, sex, weight, height, body surface area and body mass index
- ✓ Disease history/Clinical detail of the patient: Disease status, stage of cancer, comorbid disease, baseline laboratory values
- ✓ Treatment-related factors: treatment modality, number of drugs taken (monochemotherapy or polychemotherapy), number of treatment cycles and treatment duration

4.7. Data collection and management

4.7.1. Data collection techniques and instruments

Two nurses, who worked in the oncology department, collected all the data. They collected the data from patient's medical records by using a data collection checklist (Annex 1). The checklist was used to collect data regarding socio-demographic and patient characteristics, clinical details of the patients, and chemotherapy treatment. Hematology (hemoglobin, hematocrit, red blood cell, white blood cell and platelet count) and chemistry laboratory data at baseline and during each cycle of chemotherapy regimen were recorded. Hematology and chemistry data before the start of cycle one was considered as baseline. Data collectors also recorded the data of patients who developed hematological toxicity.

4.7.2. Data quality assurance

The data collectors were trained for half day about the objectives, methods and data collection of the research. The data collection was developed after reading different literatures and the checklist was confirmed by this research teams. The quality of the data was assured by pre-testing 10 of the study records. After reviewing the pre-test result, appropriate modifications were made. This pretest helped to check the validity of the questioners of this research. During data collection, data were checked for completeness, missing information at each point and consistency by the investigator. In addition, the data were checked before the data analysis.

4.8. Operational definitions

Calibration: - is the agreement between the observed and expected severe hematological toxicities

Discrimination: - is the ability of a prediction model to identify the risk level (high or low risk) of CRC patients for the occurrence of severe hematological toxicities. It is presented as the area under the ROC. The area under the ROC of 0.70 is considered to have good discrimination whereas area under the ROC of 0.5 is regarded as the equivalent of a coin toss (Krupp *et al.*, 2003).

Hematological toxicity: are those adverse effects such as neutropenia, anemia and thrombocytopenia that are always detected by laboratory tests and developed in CRC patients. A patient was considered to have developed neutropenia, anemia and thrombocytopenia if the neutrophil, hemoglobin and platelet values are less than 12g/dL, $2.0 * 10^9$ /L and 99,000 /mm^3 respectively.

Negative predictive value: - the probability of that severe hematological toxicity is present given a positive test result

Positive predictive value: - the probability of that severe hematological toxicity is absent given a negative test result

Sensitivity: - is the ability of the model to correctly identify CRC patients which developed severe hematological toxicity

Specificity: - is the ability of the model to correctly identify CRC patients which did not develop severe hematological toxicity

Severe hematological toxicity was defined as grade 3 and/or 4 toxicities.

Severe anemia is when hemoglobin level < 8 g/dL in patients treated with chemotherapy (NCI, 2017).

Severe neutropenia is when neutrophil count < $1*10^3$/uL in patients treated with chemotherapy (NCI, 2017).

Severe thrombocytopenia is when platelet count < 50,000/mm^3 in CRC patients undergoing chemotherapy (NCI, 2009).

4.9. Data analysis

Descriptive analyses were employed to describe patient's demographic, clinical, treatment characteristics and frequency of hematological toxicity. Categorical variables were reported as percentage. Continuous variables were tested for normality by Shapiro Wilk test and presented as mean with standard deviation (SD) if the data is normally distributed or median with interquartile range (IQR) if the data is not normally distributed. Wilcoxon signed-rank test/paired sample t-test was employed to compare the median/mean of laboratory values across chemotherapy cycles and to determine if there were significant changes in hematological toxicities at each cycle compared to baseline laboratory values. All statistical analyses were performed by STATA version 16 statistical software. P-value < 0.05 was considered statistically significant. All statistical tests were two-sided.

Development of the prediction model (model derivation) and scoring system

The association between the primary outcome (i.e. the occurrence of severe hematological toxicity) at any time during all cycles of chemotherapy regimen and the

independent variables was analyzed by univariable logistic regression analysis for initial model inclusion. The remaining significant risk factors and variables that had known clinical relevance with p-value less than 0.25 were included in the multivariable logistic regression analysis. P-value less than 0.25 is supported and recommended to screen variables at univariable analysis (Hosmer and Lemeshow, 1989). Multicollinearity tests were performed for categorical, continuous and binary variables. Multicollinearity was measured by variance inflation factor (VIF) and tolerance. When a VIF was below five and tolerance was above 0.1, variables were forwarded to multivariable logistic regression analysis. Variables with a VIF score of $\geq$ 5 to 10 and tolerance below 0.1 were excluded from the final model (Belsley, 1991). A multivariable logistic regression analysis was applied to determine the final predictive factors for retention in the model.

The likelihood ratio test was used in a backward elimination process with p-value < 0.05 for a final predictor. The final predictor variables were assigned a statistical weight based on regression model coefficients. The model regression coefficients were then rounded to the nearest integer to assign weights. Then, a risk scoring system was developed from the regression coefficients and the intercept. The intercept of final predictors were minus four and there was negative predictors. Therefore, the scoring system was adjusted to ensure that none was below zero by adding a constant five across all scores. A risk score was assigned for every patient by the addition of points for every risk factor they had (Mehta *et al.,* 2016).

Each patient risk score was calculated as weighed sum of regression coefficients and intercept. The individual risk of developing hematological toxicity (predicted risk) was estimated as the inverse logit of the risk score (Xu and Long, 2005).

$$\text{Predicted risk} = \frac{\exp(\text{risk score})}{1+\exp(\text{risk score})} * 100\%$$

A higher risk score is associated with a greater predicted risk of hematologic toxicity.

Validation of the prediction model and model performance

The predictive accuracy of the developed model and the risk scoring system was quantified by discrimination and calibration measures both in the derivation cohort and the internal validation cohort. The derivation cohort was the original samples obtained from patients' medical records. The internal validation cohort was the bootstrapped samples drawn with replacement from the original data set using a bootstrapping technique. The discrimination and calibration of the significant predictors were assessed by using receiver operating curve (ROC) and Hosmer Lemeshow goodness of fit respectively (Steyerberg *et al.*, 2010).

Discrimination is the ability of a prediction model to identify the risk level (high or low risk) of patients accurately for the event under investigation or a prediction model can discriminate between those who do or do not experience the event. Calibration is the agreement between the observed and expected outcomes (Krupp *et al.*, 2003). The developed model was validated internally by a bootstrapping technique. Bootstrapping is a computer in depth resampling technique. It is far the most efficient internal validation

technique which presents stable estimate with low bias (Efron and Tibshirani, 1997). It generates samples from the population by drawing samples with replacement from the original data with equal size as the original data set (Efron and Tibshirani, 1993).

The bootstrapped samples were drawn from the original data using a “bsample”. Then, ROC and goodness of fit of the bootstrapped sample was done by “lroc” and “estat gof” command on STATA 16.

To compare the scoring system performance with the model, performance characteristics such as sensitivity, specificity, negative and positive predictive values, and ROC were assessed.

4.10. Ethical consideration

Ethical clearance was obtained from Addis Ababa University, School of pharmacy, Ethical Review Committee (Ref. No. ERB/SOP/209/03/2020) (Annex 2). After receiving ethical clearance, permission to conduct the research and to review the medical records of patients were obtained from the Oncology Department of TASH. Then, participant identification number was selected from the patient registration book to easily identify CRC patients. Patient card record staffs selected CRC patients who were taking chemotherapy based on the identification number. The name of the participant was omitted from the data collection checklist; instead, study assigned identification number was used to ensure confidentiality. The confidentiality was also assured by placing the

daily collected data in a lockable cabinet. After data collection, the data were entered to password-protected computer.

5. Results

5.1. Background characteristics of patients

5.1.1. Socio-demographic characteristics of CRC patients

From January 1, 2017 to January 1, 2021, a total of 268 CRC patient medical records were reviewed for the study. Of these, 44 CRC patients were excluded from the study for the following reasons: 39 patients had incomplete/missing information, three patients started chemotherapy at another institution in Ethiopia and didn't have complete information, one patient started chemotherapy abroad and had incomplete information, and one patient died. After excluding patients with missing data, information from 224 CRC patients were included for the final analysis and development of the prediction model.

Regarding socio-demographic characteristics, a larger proportion of CRC patients were males 130 (58.1%). Fifty-one (22.8%) were 41-50 years old. The mean body surface area (BSA) (m^2) and weight (Kg) of patients were 1.59 ± 0.18 and 56.75 ± 10.87 respectively. The median height (m^2) and body mass index (BMI) (Kg/ m^2) of patients were 1.65 (1.57, 1.72), 20.51 (18.69, 23.17) respectively (Table 2).

Table 2:- Socio-demographic characteristics of adult CRC patients taking chemotherapy at TASH from 2017-2021

Characteristics	No. of patients with at least one HT n (%)	Total n (%) (n=224)	Hematological toxicity					
			Neutropenia (n=157) n (%)		Anemia (n=116) n (%)		Thrombocytopenia (n=41) n (%)	
Sex, no. (%)								
Male	107 (82.3)	130 (58.1)	84 (64.6)	46 (35.4)	63 (48.5)	67 (51.5)	26 (20.0)	104 (80.0)
Female	81 (86.2)	94 (41.9)	73 (77.6)	21 (22.4)	53 (56.4)	41 (43.6)	15 (16.0)	79 (84.0)
Age (years)								
18-30	29 (85.3)	34 (15.2)	23 (67.6)	11 (32.4)	15 (44.1)	19 (55.9)	10 (29.4)	24 (70.6)
31-40	36 (80.0)	45 (20.1)	29 (64.4)	16 (35.6)	26 (57.8)	19 (42.2)	7 (15.6)	38 (84.4)
41-50	46 (90.2)	51 (22.8)	36 (70.6)	15 (29.4)	31 (60.8)	20 (39.2)	7 (13.7)	44 (86.3)
51-60	41 (85.4)	48 (21.4)	36 (75.0)	12 (25.0)	24 (50.0)	24 (50.0)	11 (22.9)	37 (77.1)
≥ 61	36 (78.3)	46 (20.5)	33 (71.7)	13 (28.3)	20 (43.5)	26 (56.5)	6 (13.0)	40 (87.0)
BSA (m^2) mean ± SD	1.59 ± 0.18							
Weight (Kg) mean ± SD	56.75 ± 10.87							
Height (m^2) median (IQR)	1.65 (1.57, 1.72)							
BMI (Kg/m^2) median (IQR)	20.51 (18.69, 23.17)							

5.1.2. Disease history/clinical condition of the patients

Most 189 (84.4%) of the participants had an ECOG performance status of I (one) when they started their treatment. About 35 (15.6%) of patients had a comorbid disease, with diabetes being the most common condition in 11 patients (31.4%). 116 (51.8%) of patients had stage IV cancer at the start of their treatment, and 117 (52.2%) had rectal cancer. 115 (51.3%) of CRC patients had a metastasized cancer, with the liver being the main site of metastasis in 57 (49.6%) of patients (Table 3).

Table 3:- Clinical condition of adult CRC patients taking chemotherapy at TASH from 2017-2021

Characteristics	No. of patients with at least one HT n (%)	Total n (%) (n=224)	Hematological toxicity					
			Neutropenia (n=157) n (%)		Anemia (n=116) n (%)		Thrombocytopenia (n=41) n (%)	
ECOG performance status								
0	6 (100.0)	6 (2.6)	5 (83.3)	1 (16.7)	6 (100.0)	0 (0.0)	0 (0.0)	6 (100.0)
I	156 (82.5)	189 (84.4)	133 (70.4)	56 (29.6)	93 (49.2)	96 (50.8)	39 (20.6)	150 (79.4)
II	26 (89.6)	29 (13.0)	19 (65.5)	10 (34.5)	17 (58.6)	12 (41.4)	2 (6.9)	27 (93.1)
Patients with comorbid disease								
Yes	29 (82.8)	35 (15.6)	25 (71.4)	10 (28.6)	18 (51.4)	17 (48.6)	5 (14.3)	30 (85.7)
No	159 (84.1)	189 (84.4)	132 (69.8)	57 (30.2)	98 (51.9)	91 (48.1)	36 (19.0)	153 (81.0)

Type of comorbid disease								
Diabetes	9 (81.8)	11 (31.4)	8 (72.7)	3 (27.3)	7 (63.6)	4 (36.4)	1 (9.1)	10 (90.9)
Hypertension	7 (70.0)	10 (28.57)	6 (60.0)	4 (40.0)	2 (20.0)	8 (80.0)	1 (10.0)	9 (90.0)
Hypertension and diabetes	6 (85.7)	7 (20.0)	4 (57.1)	3 (42.9)	5 (71.4)	2 (28.6)	0 (0.0)	7 (100.0)
Asthma	4 (100.0)	4 (11.4)	4 (100.0)	0 (0.0)	1 (25.0)	3 (75.0)	2 (50.0)	2 (50.0)
HIV/AIDS	2 (100.0)	2 (5.7)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
Rheumatoid arthritis	1 (100.0)	1 (2.9)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Cancer stage								
Stage II	10 (71.4)	14 (6.3)	10 (71.4)	4 (28.6)	4 (28.6)	10 (71.4)	1 (7.1)	13 (92.9)
Stage III	74 (78.7)	94 (42.0)	62 (66.0)	32 (34.0)	41 (43.6)	53 (56.4)	19 (20.2)	75 (79.8)
Stage IV	104 (89.7)	116 (51.8)	85 (73.3)	31 (26.7)	71 (61.2)	45 (38.8)	21 (18.1)	95 (81.9)
Primary tumor location								
Colon	91 (85.1)	107 (47.8)	71 (66.4)	36 (33.6)	49 (45.8)	58 (54.2)	23 (21.5)	84 (78.5)
Rectum	97 (82.9)	117 (52.2)	86 (73.5)	31 (26.5)	67 (57.3)	50 (42.7)	18 (15.4)	99 (84.6)

Cancer								
metastasize	103 (89.6)	115 (51.3)	84 (73.0)	31 (27.0)	71 (61.7)	44 (38.3)	21 (18.3)	94 (81.7)
Yes	85 (77.9)	109 (48.7)	73 (67.0)	36 (33.0)	45 (41.3)	64 (58.7)	20 (18.3)	89 (81.7)
No								
Metastatic tumor								
site	57 (49.6)	57 (49.6)	41 (71.9)	16 (28.1)	35 (61.4)	22 (38.6)	13 (22.8)	44 (77.2)
Liver	28 (24.4)	28 (24.4)	20 (71.4)	8 (28.6)	13 (46.4)	15 (53.6)	4 (14.3)	24 (85.7)
Lung	20 (17.4)	20 (17.4)	13 (65.0)	7 (35.0)	15 (75.0)	5 (25.0)	1 (5.0)	19 (95.0)
Lung and liver	6 (5.2)	6 (5.2)	6 (100.0)	0 (0.0)	4 (66.7)	2 (33.3)	1 (17.0)	5 (83.0)
Peritoneum	1 (0.9)	1 (0.9)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Brain	1 (0.9)	1 (0.9)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Bladder	2 (1.7)	2 (1.7)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
Bone								
Baseline laboratory values								
Hgb(g/dL) mean ± SD			12.9 ± 1.9					
Hematocrit (%) median (IQR)			38.9 (35.4, 42.3)					
WBC(10^3/uL) median (IQR)			7.7 (5.9, 9.3)					
Platelets(10^3/uL) median (IQR)			289.5 (220.0, 403.0)					
Neutrophil (10^3/uL) median (IQR)			4.2 (2.6, 5.7)					
Lymphocyte(10^3/uL) median (IQR)			2.1 (1.4, 2.7)					

Alkaline phosphatase (U/L) median (IQR)	170.5 (125.0, 231.0)
ALT(U/L) median (IQR)	17.0 (13.0, 27.0)
AST (U/L) median (IQR)	23.0 (19.0, 31.0)
Creatinine (mg/dL) median (IQR)	0.8 (0.6, 1.0)
BUN(mg/dL) median (IQR)	18.0 (15.7, 26.0)

5.1.3. Treatment history of the patients

In this study, 119 (53.1%) of CRC patients underwent surgery and chemotherapy and two (0.9%) had taken both chemotherapy and radiation therapy. Most CRC patients (92.0%) had taken polychemotherapy, with the FOLFOX regimen being the most common type, with 163 (79.1%) patients found to have received the regimen. Adjuvant chemotherapy was given to 136 (60.7%) patients. A complete of 224 CRC patients taken 1,069 cycles of chemotherapy with a median of six cycles and 6.25 months duration. About 156 (69.6%) of patients were still under their physician's follow-up care and one died (Table 4)**.** All patients had taken premedications (ondasteron, metoclopramide, dexamethasone, cimetidine or omeprazole) before each cycle of chemotherapy.

Table 4:- Treatment history of adult CRC patients taking chemotherapy at TASH from 2017-2021

Characteristics	No. of patients with at least one HT n (%)	Total n (%) (n=224)	Hematological toxicity					
			Neutropenia (n=157) n (%)		Anemia (n=116) n (%)		Thrombocytopenia (n=41) n (%)	
Treatment modality								
Chemotherapy only	8 (80.0)	10 (4.4)	6 (60.0)	4 (40.0)	4 (40.0)	6 (60.0)	1 (10.0)	9 (90.0)
Surgery and chemo	94 (79.0)	119 (53.1)	76 (63.9)	43 (36.1)	61 (51.3)	58 (48.7)	20 (16.8)	99 (83.2)
Chemo, surgery and radiation	85 (91.4)	93 (41.5)	74 (79.6)	19 (20.4)	51 (54.8)	42 (45.2)	20 (21.5)	73 (78.5)
Chemotherapy and radiation	1 (50.0)	2 (0.9)	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)
Chemotherapy treatment								
Monochemotherapy	11 (61.1)	18 (8.0)	11 (61.1)	7 (38.9)	6 (33.3)	12 (66.7)	0 (0.0)	18 (100.0)
Polychemotherapy	177 (85.9)	206 (92.0)	146 (70.9)	60 (29.1)	110 (53.4)	96 (46.6)	41 (19.9)	165 (80.1)

Monochemotherapy								
5-FU/LU	3 (60.0)	5 (27.8)	3 (60.0)	2 (40.0)	2 (40.0)	3 (60.0)	0 (0.0)	5 (100.0)
Capecitabine	8 (61.5)	13 (72.2)	8 (61.5)	5 (38.5)	4 (30.8)	9 (69.2)	0 (0.0)	13 (100.0)
Polychemotherapy								
FOLFOX	144 (88.3)	163 (79.1)	120 (73.6)	43 (26.4)	87 (53.4)	76 (46.6)	38 (23.3)	125 (76.7)
FOLFIRI	9 (81.8)	11 (5.3)	8 (72.7)	3 (27.3)	7 (63.6)	4 (36.4)	1 (9.1)	10 (90.9)
XELOX/CAPOX	16 (69.6)	23 (11.2)	11 (47.8)	12 (52.2)	14 (60.9)	9 (39.1)	2 (8.7)	21 (91.3)
(FOLFOX/Capecitabine)	3 (100.0)	3 (1.5)	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)	0 (0.0)	3 (100.0)
FOLFOX/FOLFIRI	3 (100.0)	3 (1.5)	3 (100.0)	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	3 (100.0)
FOLFOX/CAPOX	2 (66.7)	3 (1.5)	2 (66.7)	1 (33.3)	0 (0.)	3 (100.0)	0 (0.0)	3 (100.0)
Treatment intent								
Neoadjuvant	14 (58.3)	24 (10.7)	11 (45.8)	13 (54.2)	8 (33.3)	16 (66.7)	4 (16.7)	20 (83.3)
Adjuvant	117 (86.1)	136 (60.7)	97 (71.3)	39 (28.7)	73 (46.3)	63 (53.7)	25 (18.4)	111 (81.6)
Palliative	57 (89.06)	64 (28.6)	49 (76.6)	15 (23.4)	35 (54.7)	29 (45.3)	12 (18.8)	52 (81.2)
Cycle of chemotherapy taken (Cycles) median 6 range (1-6)								
Duration of chemotherapy taken (Months) median 6.25 range (1-8)								

Treatment outcomes								
Cured	1 (33.3)	3 (1.3)	0 (0)	3 (100.0)	1 (33.3)	2 (66.7)	0 (0.0)	3 (100.0)
Recurrence	59 (92.2)	64 (28.6)	52 (81.2)	12 (18.8)	40 (62.5)	24 (37.5)	10 (15.6)	54 (84.4)
Follow up	127(81.4)	156 (69.6)	105 (67.3)	51 (32.7)	74 (47.4)	82 (52.6)	31 (19.9)	125 (80.1)
Death	1(100.0)	1 (0.5)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)

Pretreatment and treatment laboratory values

Based on paired sample t-test, there was a significant decrease in the mean hemoglobin value in chemotherapy treatment cycles 1, 2 and 5 compared with the baseline hemoglobin value (P value < 0.05). Based on Wilcoxon signed-rank test, there has been significant decrease in the median neutrophil and thrombocyte value in each consecutive chemotherapy cycles compared with the baseline neutrophil and thrombocyte value (P value < 0.05). The sample pretreatment and cycle specific mean laboratory values of CRC patients were shown in fig 2, 3, 4 and table 5.

Table 5:- Pretreatment baseline hematology and chemistry value of adult CRC patients taking chemotherapy at TASH from 2017-2021

Hematology and chemistry values	**Baseline value (n=224)**	**Value in each cycle of chemotherapy**					
		1st cycle (n=224)	**2nd cycle (n=210)**	**3rd cycle (n=195)**	**4th cycle (n=155)**	**5th cycle (n=141)**	**6th cycle (n=141)**
Hgb(g/dL) Mean ± SD	12.9 ± 1.9	12.7 ± 2.1	12.8 ± 2.6	13.1 ± 7.8	13.3 ± 7.7	12.7 ± 1.8	13.5 ± 10.1
Hematocrit (%) Median (IQR)	38.9 (35.4, 42.3)	38.9 (34.6, 41.9)	37.4 (33.9, 41.2)	37.1 (33.9, 40.9)	38.0 (34.0, 41.4)	37.4 (33.9, 41.3)	37.6 (34.7, 40.3)
WBC(10^3/uL) Median (IQR)	7.7 (5.9, 9.3)	5.6 (3.9, 7.4)	4.5 (3.3, 6.4)	4.6 (3.2, 6.4)	4.8 (3.5, 6.7)	4.7 (3.2, 6.2)	4.7 (3.4, 5.7)
Platelets(10^3/uL) Median (IQR)	289.5 (220.0, 403.0)	249.0 (200.0, 329.0)	229.5 (173.0, 308.0)	184.0 (126.0, 267.0)	200.0 (138.0, 247.0)	182.0 (147.0, 237.0)	206.0 (135.0, 257.0)
Neutrophil (10^3/uL) Median (IQR)	4.2 (2.6, 5.7)	2.5 (1.94.0, 3.64.0)	2.1 (1.0, 3.1)	2.0 (1.0, 2.80)	2.3 (1.4, 3.4)	2.1 (1.1, 2.9)	2.1 (1.4, 2.8)
Lymphocyte(10^3/uL) Median (IQR)	2.1 (1.4, 2.7)	1.9.0 (1.4, 2.4)	1.8 (1.3, 2.3)	1.8 (1.2, 2.4)	1.8 (1.3, 2.4)	1.7 (1.2, 2.4)	1.8 (1.2, 2.2)
Alkaline phosphatase (U/L) Median (IQR)	170.5 (125.0,	173.5 (121.5,	174.0 (123.0,	193.0 (124.0,	190.0 (121.0,	173.0 (110.0,	184.0 (121.0,

		231.0)	233.5)	236.0)	270.0)	267.0)	271.0)	271.0)
ALT(U/L) Median (IQR)		17.0 (13.0, 27.0)	17.0 (13.0, 25.0)	18.0 (13.0, 25.0)	20.0 (14.0, 27.0)	18.0 (14.0, 29.0)	19.0 (14.0, 28.0)	20.0 (13.0, 27.0)
AST (U/L) Median (IQR)		23.0 (19.0, 31.0)	23.0 (18.0, 31.0)	23.0 (18.0, 32.0)	27.0 (19.0, 36.0)	28.0 (20.0, 35.0)	28.0 (21.0, 40.0)	25.0 (19.0, 36.0)
Creatinine (mg/dL) Median (IQR)		0.8 (0.6, 1.0)	0.9 (0.7, 1.0)	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)	0.9 (0.70, 1.0)	0.8 (0.7, 1.0)	0.9 (0.8, 1.0)
BUN(mg/dL) Median (IQR)		18.0 (15.8, 26.0)	19.0 (15.0, 25.5)	19.0 (15.0, 27.0)	20.0 (15.0, 24.0)	19.0 (15.0, 23.0)	20.0 (15.0, 25.0)	17.0 (13.0, 21.0)

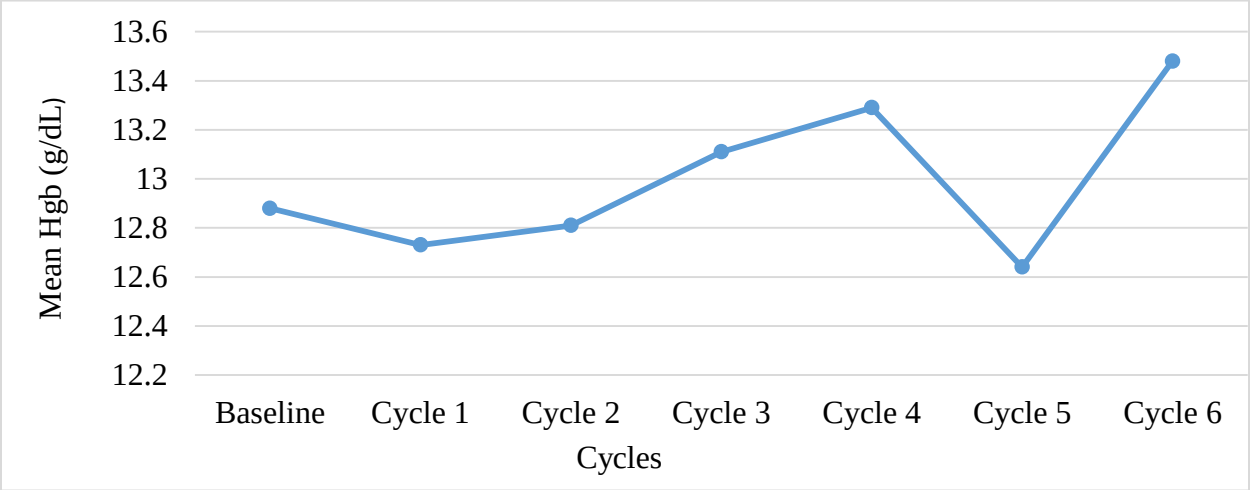


Fig 2:- Pretreatment and cycle specific mean Hgb value of adult CRC patients taking chemotherapy at TASH from 2017-2021

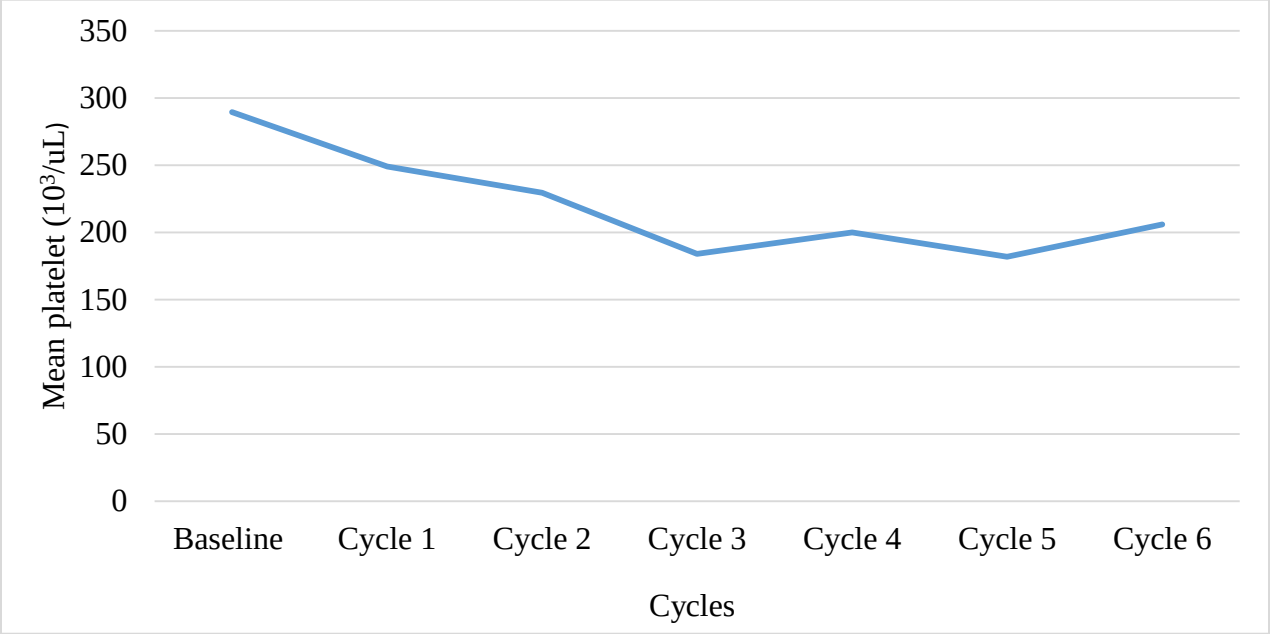


Fig 3:- Pretreatment and cycle specific median platelet value of adult CRC patients taking chemotherapy at TASH from 2017-2021

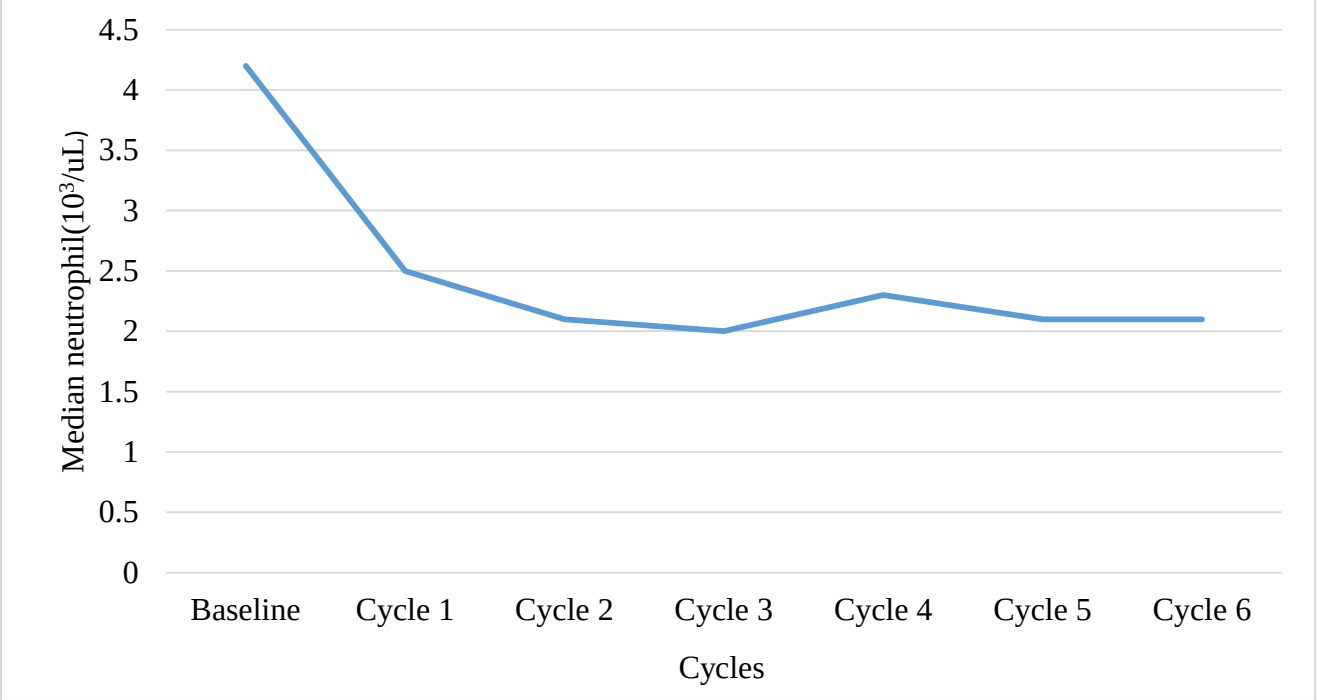


Fig 4:- Pretreatment and cycle specific median neutrophil value of adult CRC patients taking chemotherapy at TASH from 2017-2021

5.2. The extent of hematological toxicity among patients

In this study, hematological toxicity was present in all cycles. From 224 CRC patients who were taking chemotherapy, 188 (83.9%) developed at least one hematological toxicity at some stage of their course of chemotherapy treatment. Moreover, 157 (70.1%), 116 (51.8%), and 41 (18.3%) of the patients developed neutropenia, anemia and thrombocytopenia, respectively. Forty-four (69.8%) patients developed grade 1 anemia and one (1.6%) patient had grade 3 anemia before treatment initiation. Eighteen (75.0%) and one (4.2%) of patients had grade 1 and grade 4 neutropenia before starting their treatment. Two (100.0%) patients had grade 1 thrombocytopenia before treatment initiation. At cycle six, from 188 patients who developed hematological toxicity, 25.5%,

20.2%, and 5.8% of patients were neutropenic, anemic, and thrombocytopenia respectively. The prevalence of severe neutropenia, anemia and thrombocytopenia in study population were 114 (50.9%), 25 (11.2%) and four (1.8%), respectively (Fig 5, 6 and 7).

In this study, a total of 142 (63.4 %) patients needed G-CSF injections so they can continue their chemotherapy cycles. Of these patients, 89 (62.7%) had taken filgrastim (Neupogen) and 53 (37.3%) had taken both Neupogen and ciprofloxacin during different chemotherapy cycles. Thirty-eight (16.9 %) patients were transfused with whole blood at some point during their course of chemotherapy. Twenty-one (9.4%) had taken 'HEAM UP' syrup (a syrup product containing iron, folic acid, and several minerals), one (0.5) had taken ferrous fumarate and one (0.5%) of patients both HAEM UP syrup and blood transfusion. Twelve patients had transfusion with cross-matched platelets.

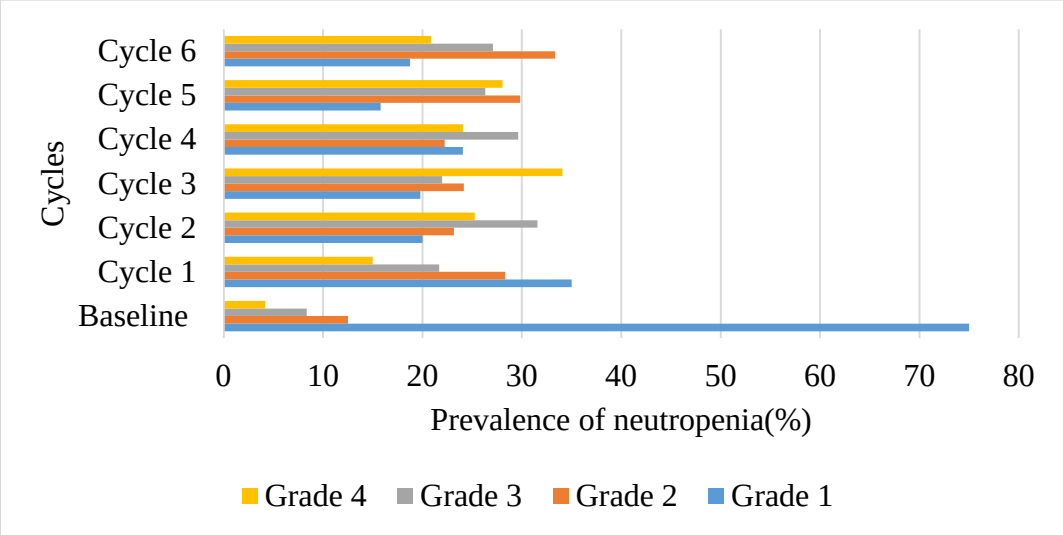


Fig 5: - Prevalence and severity of neutropenia in adult CRC patients taking chemotherapy at TASH from 2017-2021

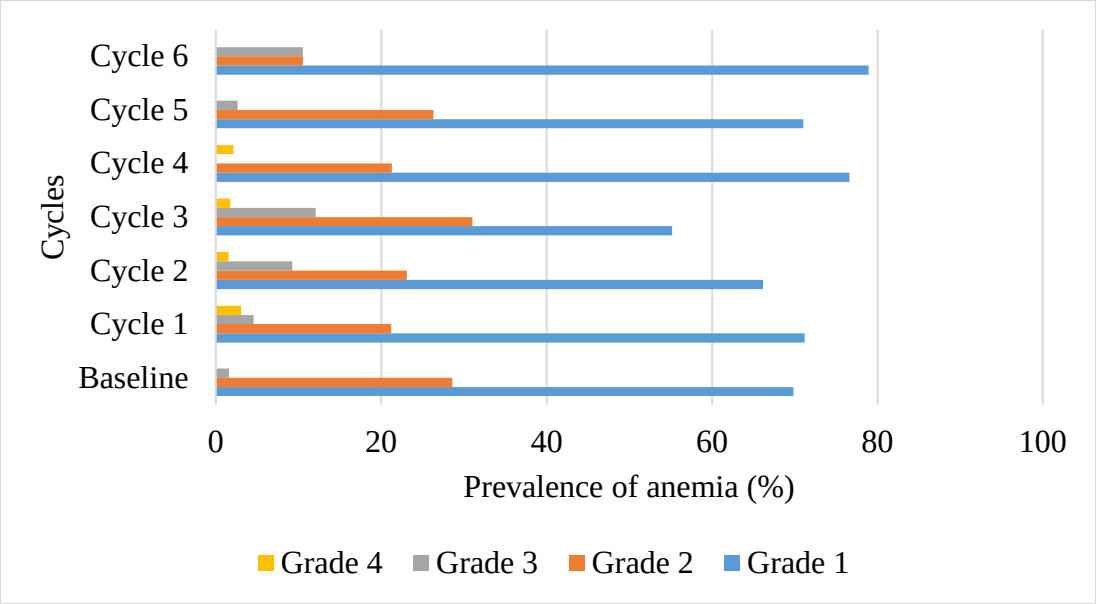


Fig 6: - Prevalence and severity of anemia in adult CRC patients taking chemotherapy at TASH from 2017-2021

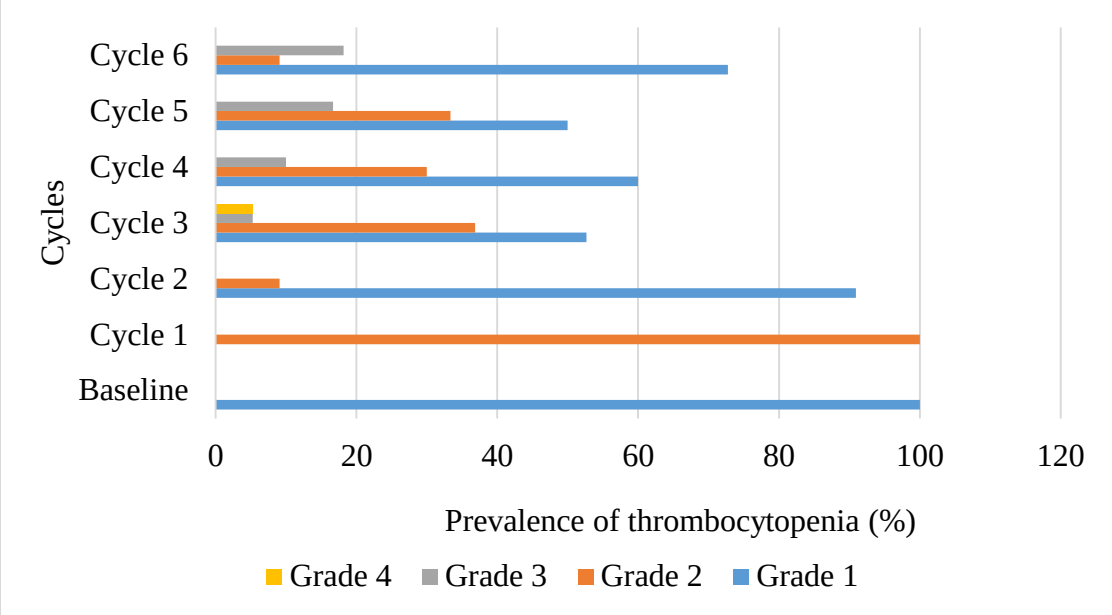


Fig 7: - Prevalence and severity of thrombocytopenia in adult CRC patients taking chemotherapy at TASH from 2017-2021

5.3. Model development

This study has three primary outcomes: occurrence of severe neutropenia, anemia, and thrombocytopenia but a prediction model was developed only for severe neutropenia because of a limited number of CRC patients and/or the number of events per predictor variable was below 10 for severe anemia and severe thrombocytopenia toxicities.

About 31 independent variables were included in the univariable logistic regression analysis. Five variables (chemotherapy treatment, polychemotherapy (FOLFOX, FOLFRI and CAPOX), treatment intent, cycle and duration of chemotherapy) was significantly associated with severe neutropenia (P value < 0.05) in a univariable logistic regression analysis. These variables together with nine other variables (age, BMI, comorbid disease, cancer stage, treatment modality, neutrophil, ALT, creatinine, and BUN) with a p-value < 0.25 were identified for inclusion in multivariable logistic regression analysis (Table 6 and 7).

Table 6:- Univariable association of independent variables with severe neutropenia of adult CRC patients taking chemotherapy at TASH from 2017-2021

Variables	**Univariable logistic regression analysis**		
	B coefficient	**OR (95% CI)**	**P-value**
Sex			
Female (Ref)			
Male	0.08	1.08 (0.64-1.85)	0.753
Age (Years)			
18-30 (Ref)			
31-40	-0.92	0.40 (0.16-0.99)	0.050
41-50	-0.49	0.61 (0.25-1.50)	0.284
51-60	-0.52	0.59 (0.24-1.46)	0.257
≥ 61	-0.78	0.46 (0.18-1.14)	0.093
BSA	0.71	2.02 (0.45- 8.95)	0.350
Weight	0.01	1.01 (0.98-1.03)	0.397
Height	-0.91	0.40 (0.02-8.34)	0.556
BMI	0.046	1.05 (0.97-1.13)	0.241
ECOG Performance			
0 (Ref)			
I	-0.66	0.52 (0.09-2.88)	0.451

II	-0.76	0.46 (0.07-2.96)	0.419
Comorbid disease			
No (Ref)			
Yes	0.52	1.68 (0.81-3.51)	0.163
Type of comorbid disease			
Hypertension (Ref)			
Diabetes	-0.57	0.56 (0.08-3.52)	0.538
Asthma	1.50	4.5 (0.33-60.15)	0.256
Hypertension and diabetes	-1.38	0.25 (0.02-2.94)	0.271
Cancer stage			
II (Ref)			
III	1.04	2.84 (0.83-9.70)	0.096
IV	0.98	2.67 (0.79-9.03)	0.112
Tumor location			
Rectum (Ref)			
Colon	0.03	1.03 (0.61-1.74)	0.903
Cancer metastasize			
No (Ref)			

Yes	-0.034	0.96 (0.57-1.63)	0.899
Metastatic site			
Liver (Ref)			
Lung	0.04	1.04 (0.42-2.55)	0.939
Liver and lung	-0.16	0.85 (0.30-2.35)	0.751
Peritoneum	0.73	2.07 (0.35-12.22)	0.421
Treatment modality			
Chemotherapy (Ref)			
Surgery and chemo	0.76	2.14 (0.53-8.69)	0.285
Chemo, surgery and radiation	1.13	3.09 (0.75-12.70)	0.118
Chemo and radiation therapy	0.85	2.33 (0.11-50.98)	0.590
Chemotherapy treatment			
Mono (Ref)			
Poly	1.07	2.92 (1.00-8.49)	0.049
Monochemotherapy			
5-FU bolus+leucovorin (Ref)			
Capecitabine	-0.79	0.45 (0.05- 4.08)	0.478
Polychemotherapy			
FOLFOX (Ref)			

FOLFRI	-1.88	0.15 (0.03-.72)	0.018
XELOX/CAPOX	-1.42	0.24 (0.09-.64)	0.004
Mixed (FOLFOX/Capecitabine)	-1.07	0.34 (0.03-3.82)	0.383
Mixed (FOLFOX/FOLFRI)	-0.38	0.68 (0.04-11.07)	0.787
Mixed (FOLFOX/CAPOX)	0.31	1.36 (0.12-15.31)	0.803
Treatment intent			
Neoadjuvant (Ref)			
Adjuvant	1.54	4.67 (1.64-13.23)	0.004
Palliative	1.46	4.30 (1.43-12.95)	0.009
Cycle of chemotherapy taken	0.19	1.21 (1.03-1.41)	0.017
Duration (Months)	0.28	1.33 (1.15-1.54)	<0.001

Table 7: - Univariable association of baseline laboratory values with severe neutropenia of CRC patients who were taking chemotherapy at TASH oncology center from 2017-2021

Variables	Univariable logistic regression analysis		
	B coefficient	**OR (95% CI)**	**P-value**
Hgb (g/dL)	0.03	1.032 (0.90-0.18)	0.638
Hematocrit (%)	0.02	1.02 (00.97-1.07)	0.437
WBC (10^3/uL)	-0.03	0.96 (0.88-1.054)	0.459
Platelets (10^3/uL)	-0.00	0.99 (0.99-1.00)	0.961
Neutrophil (10^3/uL)	-0.071	0.93 (0.83-1.05)	0.236
Lymphocyte (10^3/uL)	-0.12	0.89 (0.67-1.17)	0.413
Alkaline phosphatase (U/L)	-0.00	0.99 (0.99-1.00)	0.412
ALT (U/L)	-0.02	0.98 (0.96-1.00)	0.142
AST (U/L)	-0.00	0.99 (0.98-1.00)	0.564
Creatinine (mg/dL)	1.04	2.84 (0.97-8.26)	0.055
BUN (mg/dL)	0.02	1.03 (0.99-1.05)	0.106

Multicollinearity tests were performed for categorical, continuous and binary variables. For one predictor variable (cycle of chemotherapy), multicollinearity tests found the

variance inflation factor (VIF) was greater than ten, and tolerance was below 0.1. So it was removed from the analysis. For the other 13 predictors, multicollinearity tests found no significant correlation. Thus, 13 independent variables/predictors were taken forward to the multivariable logistic regression analysis stage. The final prediction model was developed from a multivariable logistic regression analysis and a backward stepwise selection process. Then, four predictor variables (age, polychemotherapy treatment, type of therapy and duration of chemotherapy) were retained after the likelihood ratio test (LR $chi^2 = 59.65$) with p-value 0.0001, four degrees of freedom and $R^2 = 0.6592$ (Table 8).

Table 8:- Final predictor variables of severe neutropenia based on multivariable logistic regression analysis

Variables	**Multivariable logistic regression analysis**			**Risk score**
	B coefficient	**OR (95% CI)**	**P-value**	
Age (years)				
18-30 (Ref)				
31-40	-1.56	0.21 (0.07-0.65)	0.007	3
51-60	-1.84	0.16 (0.06-0.45)	<0.001	3
≥61	-1.31	0.27 (0.08-0.91)	0.034	4
Poly chemotherapy				
FOLFOX	2.86	17.43 (3.29-92.21)	<0.001	8
FOLFOX/CAPOX	3.48	32.48 (1.93-54.59)	0.016	8

Type of therapy				
Neoadjuvant (Ref)				
Adjuvant	1.22	3.39 (1.22-9.48)	0.02	6
Palliative	1.26	3.52 (1.09-11.34)	0.035	6
Duration of chemotherapy (months)	0.35	1.42 (1.19-1.68)	<0.001	5

5.4. Scoring system

Finally a risk scoring system was developed from the intercept and weights of regression coefficients in the multivariable logistic regression analysis. Each of the regression coefficients of the variable in the final model provided a statistical weight to the overall risk of severe neutropenia. Then, adjustment was done for the scoring system by adding a constant five across each scores. The final risk score ranges from 0 to 23 (Table 9) and high scores were associated with increased risk of severe neutropenia.

The risk score assigned to each predictor variable is stated as follows.

The risk score= -4.00 + (-1.56* age 31-40/-1.84* age 51-60/-1.3* age ≥ 61) + (2.86*FOLFOX/3.48*FOLFOX and CAPOX + (1.22*adjuvant/1.26*palliative chemotherapy) + 0.35* duration of chemotherapy

A risk score was assigned to every patient and compared to the probability of developing severe neutropenia. The probability of developing severe neutropenia was significantly

and positively correlated with the risk scores in the derivation cohort with p-value< 0.001 (Fig 8).

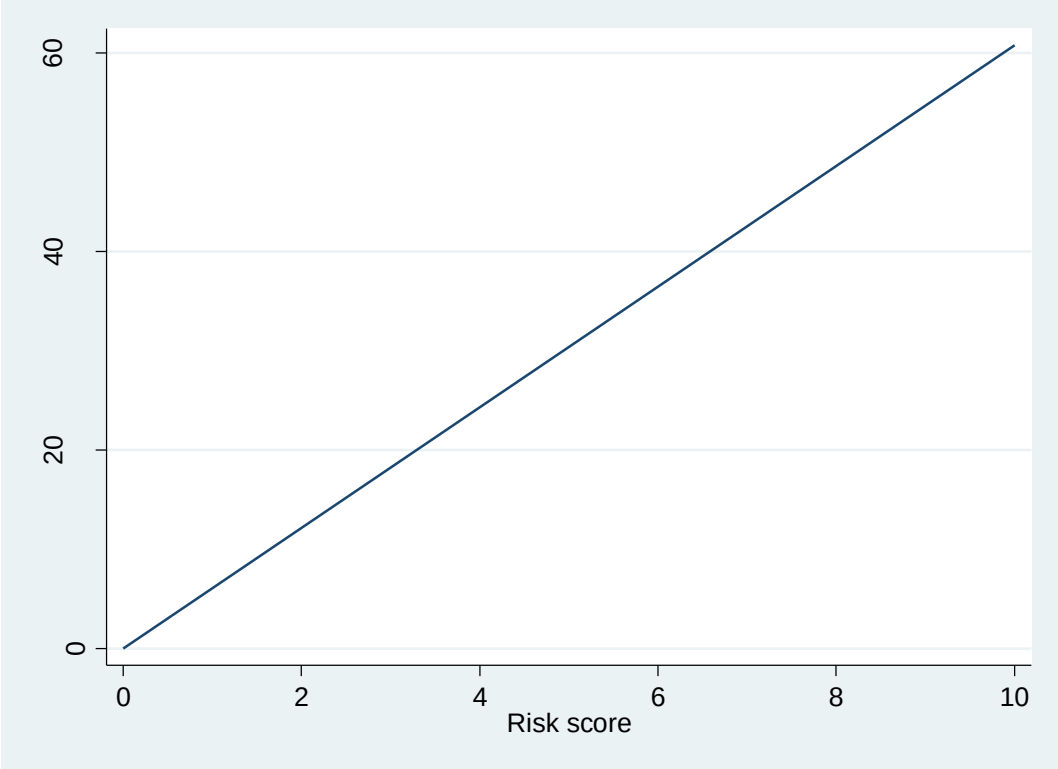


Fig 8: - Relationship between the probability of severe neutropenia and risk score of adult CRC patients taking chemotherapy at TASH from 2017-2021

5.5. Internal model validation and performance

Bootstrapping was used for internal validation of the multivariable logistic regression model of the derivation cohort. To obtain the final bootstrapped model, 100 bootstrap samples were drawn with replacement from the original sample.

To validate the clinical usefulness of the model, accuracy, sensitivity and specificity was performed. In the derivation cohort, the model had a sensitivity of 71.05% and a

specificity of 71.82% and positive predictive value (PPV) of 72.73% and a negative predictive value (NPV) of 70.54% where as in the validation cohort, the model had a sensitivity of 73.24% and a specificity of 68.49% and PPV of 69.33% and a NPV of 72.24%. This indicates the model is very good in predicting the presence of neutropenia compared to predicting the absence of neutropenia in CRC patients taking chemotherapy both in the derivation and validation cohort. The predictive capacity of the model is 71.43% and 70.83% both in the derivation and validation cohort respectively (Table 9).

Table 9:- Model performance and predictive value of the derivation and validation cohorts of adult CRC patients taking chemotherapy at TASH from 2017-2021

Model performance and predictive value	Derivation cohort	Validation cohort
Sensitivity	71.05%	73.24%
Specificity	71.82%	68.49%
PPV	72.32%	69.33%
NPV	70.54%	72.46%
Correctly classified	71.43%	70.83%

ROC analysis revealed that area under ROC is acceptable for both derivation cohort (95%CI) and internal validation cohort (95%CI).

Area under ROC (C statistic) was 0.7995 in derivation cohort and 0.7741 in the validation cohort (Fig 9 and 10). This indicates that the model can predict the presence or

absence of neutropenia about 79.95% and 77.41% both in derivation and validation cohort, respectively. The fit of the model was tested with Hosmer-Lemeshow test. The goodness of fit test showed the model adequately fits the data since p value of the Hosmer-Lemeshow goodness of fit test results were insignificant (P value= 0.0829 for derivation cohort and P value= 0.1917 validation cohort respectively).

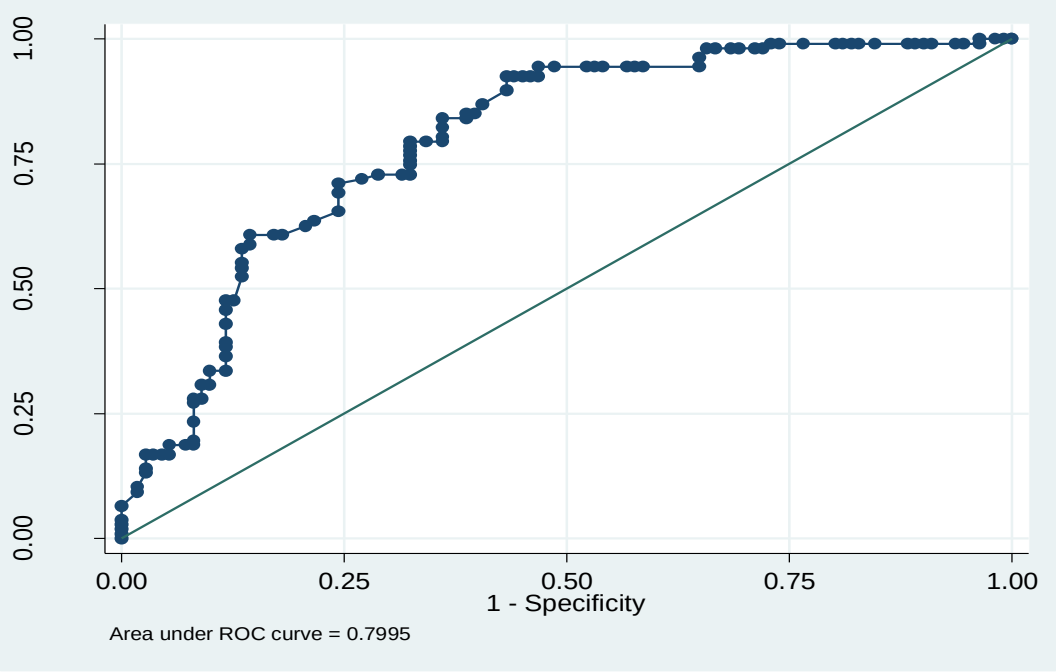


Fig 9: - AUROC curve for derivation cohort of adult CRC patients taking chemotherapy at TASH from 2017-2021

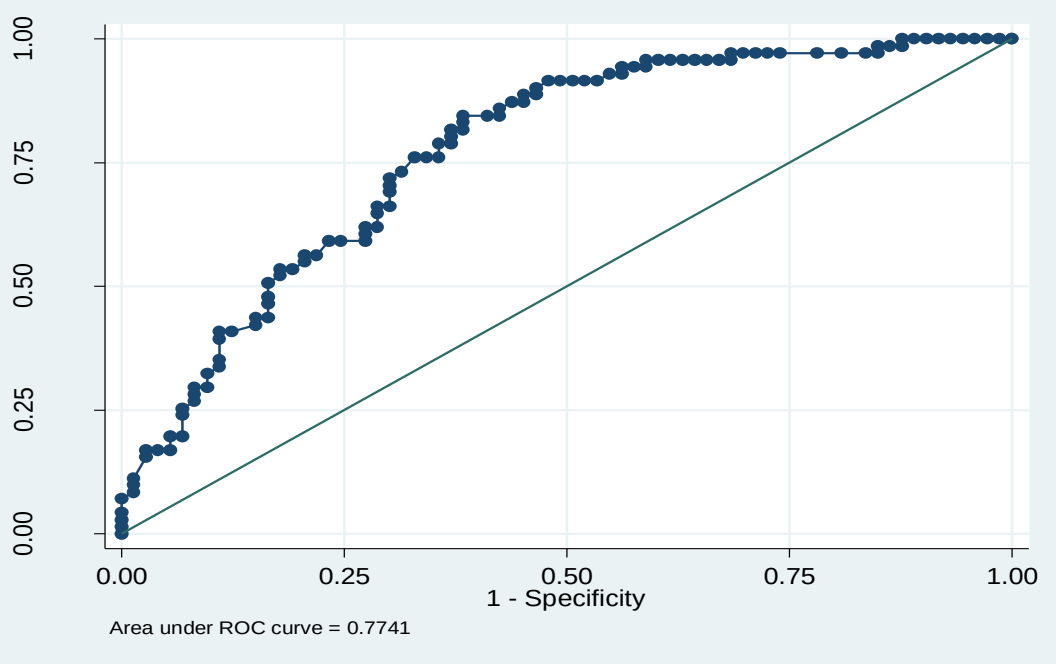


Fig 10: - AUROC curve for validation cohort of adult CRC patients taking chemotherapy at TASH from 2017-2021

To assess the calibration ability of the model to classify CRC patients who developed severe neutropenia, classification performance (sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios) for each possible risk threshold were calculated.

Three (high, intermediate and low) risk categories were identified in order to classify a risk score threshold. CRC patients classified at high risk category had 68.7% severe neutropenia prevalence with 53.3% sensitivity and 50.0% specificity. At low risk category cut off point, the model had a NPV of 100.0% and a PPV of 14.3%, a sensitivity of 100.0% and a specificity of 50.0%. High risk category threshold had 2.3 positive likelihood ratio. This result showed increased evidence for severe neutropenia in CRC patients in high risk category than intermediate and low risk categories (Table 10).

Table 10: - Risk category for severe neutropenia of adult CRC patients taking chemotherapy at TASH from 2017-2021

Risk category	Neutropenia prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified/Accuracy (%)	Positive LR	Negative LR
0-3 (low)	7.7	100.0	50.0	14.3	100.0	53.8	0.2	0.0
4-7 (intermediate)	27.3	43.6	46.4	25.0	70.3	46.7	0.3	0.4
8-10 (high)	68.7	53.3	50.0	70.0	32.8	52.3	2.3	2.1

6. Discussion

This study assessed the prevalence and severity of hematological toxicities (neutropenia, anemia and thrombocytopenia) in CRC patients taking chemotherapy from January 2017 to January 2021. Hematological toxicity was present in all cycles. Majority (83.9%) of CRC patients developed at least one hematological toxicity at some point during their course of chemotherapy. Different studies in Iran, France and Australia also supported these study (Garg MB *et al.,* 2012; Rambach *et al.,* 2014; Dehghani *et al.,* 2015). The toxicities occurred because of the drugs affect hematopoietic cells and decrease the level of erythrocytes, leukocytes and thrombocytes in the blood (ACS, 2019).

Consistent with other studies done outside Ethiopia, the current study identified neutropenia, anemia and thrombocytopenia to be common hematological toxicities. However, the severity of neutropenia (50.9%) reported in the current study appeared to be higher than studies from Morocco (11%) and France (35.1%) (Rambach *et al.,* 2014; Zineb *et al.,* 2020). The differences may be explained by the fact that patient tolerance and response to chemotherapy may differ due to genetic variability of metabolic enzymes and the differences in the study setting too (Sim *et al.,* 2013).

For personalized clinical decision making, risk prediction models are important. They provide a risk estimate which is specific to a patient based on a set of measurements for an individual patient (Steyerberg & Vickers, 2008)). This study describes the development and validation of a predictive model for severe neutropenia in CRC patients taking chemotherapy at TASH. Researches also showed that the development of a

comprehensive, clinically available and unique predictive model for patients with neutropenia with different tumor type is strongly recommended (Smith *et al.*, 2015).

In our study CRC patient's age from 31-40 years and greater than 50 years old is significantly associated with severe neutropenia. Different studies also supported the present study in which older patients were highly predisposed to anticancer drug toxicities and aging was considered as a risk factor (Poddar *et al.*, 2009; Chopra *et al.*, 2016). Aging increases the risk of complications related to bone marrow suppression due to chemotherapy and related to decreased bone marrow reserve (Bates and Leape, 2000; Hanlon *et al.*, 2002).

Polychemotherapy, oxaloplatin based regimens (FOLFOX and both FOLFOX/CAPOX regimen) were significant predictors for the occurrence of severe neutropenia in CRC patients in the current study. The occurrence of severe neutropenia toxicity was low in CRC patients who had taken oxaloplatin alone (De Gramont *et al.*, 2000) but it was more frequent in oxaloplatin based regimen that include combination therapy especially evident with FOLFOX regimen (Becouarn *et al.*, 1998). Studies indicated that the effect could be explained in part by pharmacokinetic interaction of oxaloplatin with 5-Fluorouracil (Gamelin *et al.*, 1997). Both FOLFOX and FOLFIRI result in similar outcomes when used as first line treatment therapy. The choice between the two regimens is often based on expected toxicities (Goldberg *et al.*, 2006; Tournigand *et al.*, 2014). As a result, oncologists could change FOLFOX regimen to FOLFIRI or other alternative

regimen when high risk patients developed severe neutropenia when they were taking oxaloplatin based treatment regimen.

Phase III clinical trials also showed that severe neutropenia occurred in 41.7% CRC patient's taking FOLFOX regimen compared with 5.3% of patient's monochemotherapy alone. Higher frequency of toxicity was observed in oxaloplatin based regimen than monotherapy alone but the study also showed that oxaloplatin plus 5-FU/leucovurin combination provided a significant improvement of disease control than 5-FU/leucovurin alone (De Gramont *et al.*, 2000).

In this study, longer duration of chemotherapy is the strongest predictor of severe neutropenia among other predictors included in the final prediction model. Taking chemotherapy for longer period of time could increase the probability of developing neutropenia. Even though whether or not shortening the duration of adjuvant treatment of CRC patients ought to compromise efficacy is debated, decreasing the adjuvant treatment period may ameliorate the toxicity effect of oxaloplatin and fluoropyrimidine(5-FU, capcetabine) regimens. The toxicity of these regimens is cumulative (Pachman *et al.*, 2015).

Randomized clinical trials also established that neutropenia turned into one of the maximum common severe toxicity stated in CRC patients receiving oxaloplatin and fluoropyrimidine regimens. This toxicity was statistically significant in severity for six-month treatment group compared to six-month treatment group. This randomized clinical trial confirmed the six-month chemotherapy treatment was associated with a tremendous

high degree of toxicity but the efficacy of three-months of oxaloplatin based adjuvant chemotherapy regimen is non-inferior to six-months of the same regimen (Iveson *et al.*, 2019).

The predictive overall performance of the model was assessed by discrimination-ROC, calibration-goodness of fit and clinical usefulness through accuracy, sensitivity and specificity(Steyerberg *et al.,* 2010). The accuracy of the model for predicting severe neutropenia is 71.43% and 70.83% in the derivation and validation cohorts respectively. The resulting prediction model demonstrated acceptable discrimination for predicting severe neutropenia in CRC patients and the C-index (AUROC) both in the derivation and validation cohorts are comparable (0.7995 versus 0.7741). Studies also showed when C-index is between 0.7 and 0.8, the model is considered to have an acceptable discrimination (Hosmer and Lemeshow, 1989). In each derivation and validation cohorts, the model is very good in predicting the presence of severe neutropenia compared to predicting the absence of severe neutropenia in CRC patients taking chemotherapy (a sensitivity of 71.05% versus 73.24% and a specificity of 71.82% versus 68.49%). Therefore, the model could be helpful for oncologists to identify CRC patients who are at elevated risk of severe neutropenia. This again helps them to put on an effective preventive program for the patient in a proactive manner.

A simplified regression model or scoring system based on regression coefficients of final multivariable logistic regression analysis can be used to broaden a clinically applicable model (Moons *et al.*, 2015; Mehta *et al.*, 2016). In this study a risk score was assigned to

every patient and a risk scoring system was developed to identify high risk patients. Oncologists could apply the scoring system to discriminate between high and low risk CRC patients at TASH. This enables them to offer an individual decision to every patient and to improve the prevention of severe neutropenia.

7. Limitations of the study

Despite the fact that we followed robust analysis techniques in its development and validation, the model developed in this study was based on the medical records of CRC patients. As such the variables included in the model development were those that can be extracted from the records with reasonable completeness. This might have excluded critical variables that would have been easily caught had the study been done as a prospective cohort. For example most patients had taken a combination of chemotherapy, and our data were based on medical records, so the study didn't identify which specific drug causes the hematological toxicity.

We are unable to develop and validate a prediction model for severe anemia and thrombocytopenia because the number of events per predictor variable was less than 10. This is just another flaw in our research. Moreover, external validation is useful to demonstrate the generality and utility of the model in the whole CRC patients but our study was in a single center. This was also another limitation of the study.

8. Conclusions

Hematological toxicities were present in each cycle of chemotherapy. So monitoring of patients in each consecutive cycle of chemotherapy is important. Severe neutropenia is the most common hematological toxicity that occurred in CRC patients taking chemotherapy at TASH.

Age, polychemotherapy, type of therapy and duration of chemotherapy were predictors of severe neutropenia. The developed and validated model is unique to CRC patients. The application of this model could help oncologists to identify high risk patients for severe neutropenia and to prevent toxicity before severe neutropenia developed in a proactive way in addition to their clinical judgment. It also helps to identify patients with a minimal risk of neutropenia complications and to provide reassurance and to save cost in the hospital and patients where more aggressive customized supportive care is not required.

9. Recommendations

Based on the finding of this study, the following recommendations are forwarded:

- Older CRC patients are prone to the risk of severe neutropenia, so clinicians should modify the dose and/or provide a primary prophylaxis of G-CSF for such patients.
- Oxaloplatin based combination regimens (such as FOLFOX) were significant predictors for the occurrence of severe neutropenia. As a result, oncologists could change FOLFOX regimen to FOLFIRI or other alternative regimen when high risk patients developed severe neutropenia.
- For patients taking chemotherapy for longer duration, oncologists may provide G-CSF to lower risk of developing severe neutropenia in later chemotherapy cycles.
- The model can identify low and high risk CRC patients so oncologists could provide a primary prophylaxis of G-CSF for patients identified as high risk for severe neutropenia.
- Researchers would do a prospective cohort studies to explicit which specific drug causes the hematological toxicity. External validation in independent patients and settings are required before the clinical application of the model to demonstrate the generality and utility of the model in the whole CRC patients.

References

American Cancer Society (ACS) (2019). Cancer.org/cancer/colon-rectal-cancer. Accessed 3.6.2020.

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (2008). The cell cycle. In: Anderson M and Granum S eds, Molecular biology of the cell, 5th edn, Garland Science, New York, p 1053.

Aminkeng F, Ross C, Rassekh S, Brunham L, Sistonen J, Dube M, Hayden M (2014). Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent. Pharmacogenomics J 14(2): 160-170. https://doi.org/10.1038/tpj.2013.13

Amstutz U, Froehlich T (2011). Dihydropyrimidine dehydrogenase gene as a major predictor of severe 5-fluorouracil toxicity Review. Pharmacogenomics 12: 1321-1336.

Barbounis V, Koumakis G, Vassilomanolakis M, Demiri M, Efremidis A (2001). Control of irinotecan-induced diarrhea by octreotide after loperamide failure. Support Care in Cancer 9(4) 258-260. https://doi.org/10.1007/s005200000220

Barrett-Lee P, Bailey N, O'Brien M (2000). Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. Br J Cancer 82(1): 93-97

Bates D, Leape L (2000). Melmon and Morreli's Clinical Pharmacology, 4th edn, McGraw-Hill, USA.

Becouarn Y, Ychou M, Ducreux M (1998). Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol 16: 2739-2744.

Belsley D (1991). Conditioning diagnostics: Collinearity and weak data in regression, John Wiley and Sons, New York.

Benson A, Ajani J, Catalano R, Engelking C, Kornblau S, Martenson J, Wadler S (2004). Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. J Clin Oncol 22(14): 2918-2926.

Boige V, Raymond E, Armand J (1998). Irinotecan: various administration schedules, study of drug combinations, phase I experience. Bull Cancer 26-32.

Bouvy J, De Bruin M, Koopmanschap M (2015). Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Safety 38(5): 437-453. https://doi.org/10.1007/s40264-015-0281-0

Bray F, Ferlay J, Siegel R, Soerjomataram I, Torre L, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimate of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6): 394-424.

Caggiano V, Weiss R, Rickert T, Linde-Zwirble W (2005). Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 103(9): 1916-1924. https://doi.org/10.1002/cncr.20983

Cairo M (2000). Dose reductions and delays: limitations of myelosuppressive chemotherapy. Oncology 14: 21-31.

Cappozzo C (2004). Optimal use of granulocyte-colony-stimulating factor in patients with cancer who are at risk for chemotherapy-induced neutropenia. Oncol Nurs Forum 31(3): 569-574.

Carlotto A, Hogsett V, Maiorini E, Razulis J, Sonis S (2013). The economic burden of toxicities associated with cancer treatment: Review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. PharmacoEconomics 31:753-766. https://doi.org/10.1007/s40273-013-0081-2

Chopra D, Rehan H, Sharma V, Mishra R (2016). Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. Indian J Med Paediatr Oncol 37(1): 42.

Chua W, Kho P, Moore M, Charles K, Clarke S (2011). Clinical, laboratory and molecular factors predicting chemotherapy efficacy and toxicity in colorectal cancer. Crit Rev in Oncol 79(3): 224-250. https://doi.org/10.1016/j.critrevonc.2010.07.012

Coiffier B, Guastalla J, Pujade-Lauraine E, Bastit P (2001). Predicting cancer-associated anaemia in patients receiving non-platinum chemotherapy. Eur J Cancer 37(13): 1617-1623.

Cortejoso L, Lopez-Fernandez L (2012). Pharmacogenetic markers of toxicity for

chemotherapy in colorectal cancer patients. Pharmacogenomics 13(10):1173-1191.

Crawford J, Wolff D, Culakova E, Poniewierski M, Selby C, Dale D, Lyman G (2004). First Cycle Risk of Severe and Febrile Neutropenia in Cancer Patients Receiving Systemic Chemotherapy: Results from a Prospective Nationwide Study. Blood 104(11): 2210-2210.

Cronin D, Harlan L, Potosky A, Clegg L, Stevens J, Mooney M (2006). Patterns of Care for Adjuvant Therapy in a Random Population-Based Sample of Patients Diagnosed with Colorectal Cancer. The Am J Gastroentrol 101(10): 2308-2318.

De Gramont A, Figer A, Seymour M (2000). Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938-2947.

Dehghani M, Hafezi N, Vojdani R, Ramzi M, Karimi M, Nourani H, Bahador Z (2015). Hematologic toxicities in colorectal cancer patients who received FOLFOX4. Middle East J Cancer 6(3): 171-177.

Diane T, Pascal G, Benoit Y, Gilles F, Christian P, Brigitte T (2007). Contribution of modelling chemotherapy-induced hematological toxicity for clinical practice. Crit Rev Oncol (63): 1-11.

Dinan M, Hirsch, B, Lyman G (2015). Management of chemotherapy-induced neutropenia: measuring quality, cost, and value. J Natl Compr Cancer Netw 13(1): e1-e7.

Dranitsaris G, Clemons M, Verma S, Lau C, Vincent M. (2005). Chemotherapy-induced anaemia during adjuvant treatment for breast cancer: development of a prediction model. Lancet Oncol 6: 856-863.

Efron B, Tibshirani R (1993). An introduction to the bootstrap. Monographs on statistics and applied probability, 1st edn, Chapman & Hall, New York.

Efron B, Tibshirani R (1997). Improvements on cross-validation: the 0.632+ bootstrap method. JASA 92: 548-560.

Franconi F, Campesi I (2014). Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women. Bri J Pharmacol 171(3): 580-594.

Gamelin E, Boisdron-Celle M, Allain P (1997). Pharmacokinetic interference between oxaliplatin (L-OHP) and fluorouracil (5-FU): delayed 5-FU metabolism inhibition by LOHP. Proc Am Assoc Cancer Res 38: A1500.

Garg M, Lincz L, Adler K, Scorgie F, Ackland S, Sakoff J (2012). Predicting 5-fluorouracil toxicity in colorectal cancer patients from peripheral blood cell telomere length: a multivariate analysis. Bri J Cancer 107(9): 1525-1533.

Goldberg R, Tabah-Fisch I, Bleiberg H (2006). Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol 24: 4085-4091.

Groopman J, Itri L (1999). Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. J Natl Cancer Inst 91(19):1616-1634.

Grothey A (2006). Recognizing and managing toxicities of molecular targeted therapies for colorectal cancer. Oncology (Williston Park) 20(14): 21-28.

Hanlon J, Ruby C, Artz M (2002). Geriatrics. In: DiPiro J, Talbert G, Yee G, Matzke B, Wells, Posey L eds, Pharmacotherapy. A Pathophysiologic Approach, 5th edn, McGraw Hill Inc, McGraw Hill Inc, pp 79-89.

Harrell F (2015). Regression Modeling Strategies, 2nd edn, Springer Science and Business Media, New York.

Hartwig S, Siegel J, Schneider P (1992). Preventability and severity assessment in reporting adverse drug reactions. AJHP 49(9): 2229-2232.

Hosmer D, Lemeshow S (1989). Assessing the fit of the model in applied logistic regression. In: Noel A and David G eds, Applied logistic regression, 2nd edn, Wiley, New York, pp 135-175.

Hu C, Chan W, Delclos G, Du X (2012). Adjuvant Chemotherapy and Risk of Gastrointestinal, Hematologic, and Cardiac Toxicities in Elderly Patients With Stage III Colon Cancer. Am J Clin Oncol 35(3) 228-236.

Ichikawa W, Uehara K, Minamimura K, Tanaka C, Takii Y, Miyauchi H, Sakata Y (2015). An internally and externally validated nomogram for predicting the risk of irinotecan-induced severe neutropenia in advanced colorectal cancer patients. Br J Cancer 112(10): 1709-1716. https://doi.org/10.1038/bjc.2015.122

Iveson T, Boyd K, Kerr R, Robles-Zurita J, Saunders M, Briggs A (2019). 3-month versus 6-month adjuvant chemotherapy for patients with high-risk stage II and III colorectal cancer: 3-year follow-up of the SCOT non-inferiority RCT. Health Technol Assess 23(64).

Iwashyna T, Lamont E (2002). Effectiveness of Adjuvant Fluorouracil in Clinical Practice: A Population-Based Cohort Study of Elderly Patients With Stage III Colon Cancer. J Clin Oncol 20(19): 3992-3998. https://doi.org/10.1200/JCO.2002.03.083

Johnston E, Crawford J (1998). Hematopoietic growth factors in the reduction of chemotherapeutic toxicity. Semin Oncol 25: 552-561.

Kadoyama K, Miki I, Tamura T, Brown J, Sakaeda T, Okuno Y (2012). Adverse Event Profiles of 5-Fluorouracil and Capecitabine: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS, and Reproducibility of Clinical Observations. Int J Med Sci 9(1): 33-39. https://doi.org/10.7150/ijms.9.33

Katsidzira L, Gangaidzo I, Thomson S, Rusakaniko S, Matenga J, Ramesar R (2017). The shifting epidemiology of colorectal cancer in sub-Saharan Africa. Lancet Gastroenterol Hepatol 2: 377-383.

Kosmidis P, Krzakowski M (2005). Anemia profiles in patients with lung cancer: What have we learned from the European Cancer Anaemia Survey (ECAS)? Lung Cancer 50(3): 401-412. https://doi.org/10.1016/j.lungcan.2005.08.004

Krupp N, Weinstein G, Chalian A, Berlin J, Wolf P, Weber R (2003). Validation of a Transfusion Prediction Model in Head and Neck Cancer Surgery. AOHNS 129(12): 1297. https://doi.org/10.1001/archotol.129.12.1297

Kuderer N, Lyman G (2011). Personalized medicine and cancer supportive care: appropriate use of colony-stimulating factor support of chemotherapy. J Natl Cancer Inst 103(12): 910-913.

Kuhn J (2002). Chemotherapy-associated hematopoietic toxicity. Am J Health Syst Pharm 59(4): S4–S7.

Kuilenburg V, Andre B, Meinsma R, Zoetekouw L, Albert H, Gennip V (2002). Increased risk of grade IV neutropenia after administration of 5-fluorouracil due to a dihydropyrimidine dehydrogenase deficiency : high prevalence of the IVS14+1g >a

mutation. Int J Cancer 101(3): 253-258.

Latremouille-Viau D, Chang J, Guerin A, Shi S, Wang E, Yu J, Ngai C (2017). The economic burden of common adverse events associated with metastatic colorectal cancer treatment in the United States. J Med Econ 20(1); 54-62.

Lim H, Kim S, Lee E, Lee S, Oh S, Jung J, Moon A (2019). Sex-Dependent Adverse Drug Reactions to 5-Fluorouracil in Colorectal Cancer. Biol Pharm Bull 42(4): 594-600. https://doi.org/10.1248/bpb.b18-00707

Liou S, Stephens J, Carpiuc K (2007). Economic burden of hematological adverse effects in cancer patients: a systematic review. Clin Drug Investig 27 381-396.

Maxwell M, Maher K (1992). Chemotherapy-induced myelosuppression. Semin Oncol Nurs 8: 113-123.

Mehta H, Mehta V, Girman C, Adhikari D, Johnson M (2016). Regression coefficient based scoring system should be used to assign weights to the risk index. J Clin Epidemiol 79: 22-28.

Meyerhardt J, Tepper J, Niedzwiecki D, Hollis D, McCollum A, Brady D, Fuchs C (2004). Impact of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients With Stage II and III Rectal Cancer: Findings From Intergroup Trial 0114. J Clin Oncol 22(4): 648-657. https://doi.org/10.1200/JCO.2004.07.121

Meyerhardt J, Mayer R (2005). Systemic therapy for colorectal cancer. N Engl J Med 352(5): 476-487.

Mitry E (2008). Colorectal cancer. In: Heggenhougen H and Quah S eds, International Encyclopedia of Public Health, Academic Press-Elsevier, Waltham, pp 765-772.

Moons K, Altman D, Reitsma J, Ioannidis J, Macaskill P, Steyerberg E, Collins G (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 162(1) W1-73.

Moore K, Crom D (2006). Hematopoietic support with moderately myelosuppressive chemotherapy regimens: a nursing perspective. Clin J Oncol Nurs 10(3): 383-388.

Morstyn G, Foote M, Walker T, Molineux G (2001). Filgrastim (r-metHuGCSF) in the 21st century: SD/01. Acta Haematol 105: 151-155.

National Cancer Institute(NCI) (2009). Common Terminology Criteria for Adverse Events. Available from:https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009 05-29_QuickReference_8.5x11.pdf. https://doi.org/10.1080/00140139.2010.489653

National Cancer Institute(NCI) (2017). Common Terminology Criteria for Adverse Events (CTCAE).v.5.0. Cancer Therapy Evaluation Program (CTEP) 183. Retrieved from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctc_index terms_7-99.pdf

Oncology Nursing Society (ONS) (2008). Putting Evidence into Practice.

Osterborg A, Brandberg Y, Molostova V (2002). Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin Beta, in hematologic malignancies. J Clin Oncol 20(10): 2486-2494.

Overbeek J, Zhao Z, Van Herk-Sukel M, Barber B, Gao S, Herings R (2011). Costs of hospital events in patients with metastatic colorectal cancer. J M Econ 14(5): 656-661. https://doi.org/10.3111/13696998.2011.610394

Ozer H, Armitage J, Bennett C (2000). Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. J Clin Oncol 18 3558-3585.

Pachman D, Qin R, Seisler D, Smith E, Beutler A, Ta L (2015). Clinical course of oxaliplatin induced neuropathy: results from the randomized phase III trial N08CB (Alliance). J Clin Oncol 33: 3416-3422.

Poddar S, Sultana R, Sultana R, Akbor M, Azad M, Hasnat A (2009). Pattern of Adverse Drug Reactions Due to Cancer Chemotherapy in Tertiary Care Teaching Hospital in Bangladesh. Dhaka Univ J Pharm Sci 8(1): 11-16.

Popescu R, Norman A, Ross P, Parikh B, Cunningham D (1999). Adjuvant or Palliative Chemotherapy for Colorectal Cancer in Patients 70 Years or Older. JCO 17(8): 2412-2412. https://doi.org/10.1200/JCO.1999.17.8.2412

Rademaker M (2001). Do Women Have More Adverse Drug Reactions? Am J Clin Dermatol 2(6): 349-351. https://doi.org/10.2165/00128071-200102060-00001

Rambach L, Bertaut A, Vincent J, Lorgis V, Ladoire S, Ghiringhelli F (2014). Prognostic value of chemotherapy-induced hematological toxicity in metastatic colorectal cancer patients. World J Gastroenterol: 20(6): 1565.

Rang H, Ritter J, Flower R, Henderson G (2007). Rang and Dale's Pharmacology, 8th edn, Elsevier, USA.

Razzaghdoust A, Mofid B, Peyghambarlou P (2020). Predictors of chemotherapy-induced severe anemia in cancer patients receiving chemotherapy. Supportive Care Cancer 28(1): 155-161. https://doi.org/10.1007/s00520-019-04780-7

Razzaghdoust R, Mofid B, Moghadam M (2018). Development of a simplified multivariable model to predict neutropenic complications in cancer patients undergoing chemotherapy. Supportive Care Cancer 26(11): 3691-3699.

Rodenburg E, Stricker B, Visser L (2011). Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands. Br J Clin Pharmacol 71(1): 95-104. https://doi.org/10.1111/j.1365-2125.2010.03811.x.

Saltz L, Cox J, Blanke C, Rosen L, Fehrenbacher L, Moore M, Miller L (2000). Irinotecan plus Fluorouracil and Leucovorin for Metastatic Colorectal Cancer. NEJM 343(13): 905-914. https://doi.org/10.1056/NEJM200009283431302

Sim S, Kacevska M, Ingelman-Sundberg S (2013). Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. Pharmacogenomics J 13 (1): 1-11.

Smith T, Bohlke K, Lyman G, Carson K, Crawford J, Cross S, Armitage J (2015). Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 33(28): 3199-3212.

Soriano-lorenzo J, Zaldivar-blanco K, Fabian P, Arguelles R, Pena A, Perez M, Garca S (2018). Chemotherapy adverse events in patients with colorectal and anal cancer treated in ambulatory setting. 16 de Abril 57(270): 260-269.

Steensma D, Loprinzi C (2005). Erythropoietin Use in Cancer Patients: A Matter of Life and Death? J Clin Onco 23(25): 5865-5868.

Steven A (2001). Pharmacology of cancer chemotherapy: pharmacokinetics and pharmacodynamics. In: Vincent T, Samuel H, Steven A eds, Cancer: principles and

practice of oncology, 6th edn, Lippincott Williams & Wilkins, Philadelphia, pp 335-344.

Steyerberg E, Vickers A (2008). Decision curve analysis: a discussion. Med Decis Making 28(1): 146-149. https://doi.org/10.1177/0272989X07312725.

Steyerberg E, Vickers A, Cook N, Gerds T, Gonen M, Obuchowski N, Kattan M (2010). Assessing the Performance of Prediction Models. Epidemiology 21(1): 128-138.

Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021). Global Cancer Statistics 2020 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71(3): 209-249.

Tecza K, Pamula-pilat J, Lanuszewska J, Butkiewicz D (2018). Pharmacogenetics of toxicity of 5-fluorouracil , doxorubicin and cyclophosphamide chemotherapy in breast cancer patients. Oncotarget 9(10): 9114-9136.

Tournigand C, Andre T, Achille E, Lledo G, Flesh M (2014). FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer : A Randomized GERCOR Study. J Clin Oncol 22(2): 229-237.

Twelves C, Budman D, Creaven P (1996). Pharmacokinetics and pharmacodynamics of capecitabine in two phase I studies. Proc Am Soc Clin Oncol 15: 479.

Vincent M, Dranitsaris G, Verma S, Lau C, Gascon P, Belle S, Van, Ludwig H (2007). The development and validation of a prediction tool for chemotherapy-induced anemia in patients with advanced nonsmall cell lung cancer receiving palliative chemotherapy. Support Care Cancer 15: 265-272.

Vincenzi B, Schiavon G, Pantano F, Santini D, Tonini G (2008). Predictive factors for chemotherapy-related toxic effects in patients with colorectal cancer. Nat Clin Pract Oncol 5(8): 455-465. https://doi.org/10.1038/ncponc1137.

Wang J, Huang Y (2007). Pharmacogenomics of Sex Difference in Chemotherapeutic Toxicity. Curr Drug Discov Technol 4(1): 59-68.

Wiela-Hojenska A, Kowalska T, Filipczyk-Cisarz E, Lapinski L, Nartowski K (2015). Evaluation of the Toxicity of Anticancer Chemotherapy in Patients with Colon Cancer. Adv Clin Exp Med 24(1): 103-111. https://doi.org/10.17219/acem/38154.

World Health Organization (WHO) (2013). Cancer factsheet, Geneva, Switzerland.

Xu J, Long J (2005). Confidence intervals for predicted outcomes in regression models for categorical outcomes. Stata J 5(4): 537-559.

Zineb A, Aoullay Z, Slaoui M, Razine R, Er-raki A, Meddah B, Cherrah Y (2020). Therapeutic Characteristics, Chemotherapy-Related Toxicities and Survivorship in Colorectal Cancer Patients. Ethiop J Health Sci 30(1): 65.

Annexes

Annex 1: Data collection checklist

Addis Ababa University

School of Pharmacy, Department of Pharmaceutics and Social Pharmacy

Code No._____

Part-I: Socio- Demographic Characteristics of the patient

1.1. Gender:

Male ☐ Female ☐

1.2. Age in years_____

1.3. BSA(m^2)_____

1.4. Weight(Kg)_____

1.5. Height (m^2)_____

1.6. BMI(Kg/ m^2)_____

Part II: - Disease history/clinical condition of the patient

2.1. ECOG performance status

☐ 0 ☐ 2 ☐ 4

☐ 1 ☐ 3 ☐ 5

2.2. Did the patient had comorbid disease? ☐ 1. Yes 2. ☐ No

2.3.Type of comorbid disease_____

2.4.Cancer stage

☐ 1. Stage I ☐ 3. Stage III

☐ 2. Stage II ☐ 4. Stage IV (Metastatic)

2.5. Primary tumor location

☐ 1. Colon ☐ 2. Rectum

2.6.Did the cancer metastasize? ☐ 1.Yes ☐ 2.No

2.7.Metastatic tumor site

☐ 1. Liver ☐ 2. Lung

☐ 3. Liver and lung ☐ 5. Brain

☐ 4. Peritoneum

Part III: - Treatment history of the patient

3.1. Treatment modality

☐ 1. Chemotherapy only

☐ 2. Surgery and chemotherapy

☐ 3. Chemotherapy, surgery and radiation therapy

☐ 4. Other (Specify) _____

3.2. Chemotherapy treatment 1.monochemotherapy 2. Poly chemotherapy

3.3. Monochemotherapy

☐ 1. 5-Fluorouracil bolus+leucovorin ☐ 4. Irinotecan

☐ 2. 5-Fluorouracil infusion+leucovorin ☐ 5. Oxaliplatin

☐ 3. Capecitabine

3.4.Polychemotherapy

☐ 1. FOLFOX ☐ 2. FOLFIRI

☐ 3. XELOX/CAPOX ☐ 5. Other (specify) _____

☐ 4. IROX

3.5. Premedication/ prophylactic taken

☐ 1. Ondasteron ☐ 4. Dexamethasone

☐ 2. Plasil ☐ 5. Other (specify) ____

☐ 3. Cimetidine or omeprazole

3.6. Cycle of chemotherapy taken

☐ 1st ☐ 4th

☐ 2nd ☐ 5th

☐ 3rd ☐ 6th

3.9. Duration of chemotherapy (in months) _____

3.10. Treatment outcomes of CRC patients based on physician's assessment

☐ 1. Cured

☐ 2. Recurrence occurred

☐ 3. Lost from follow up

☐ 4. Death 5. Others (specify) ___

Part IV: - Laboratory tests performed

Table 1: Pretreatment and treatment laboratory values of colorectal cancer patients taking chemotherapy

Hematology and Chemistry	**Pretreatment Baseline value**	**Value in each cycle of chemotherapy**					
		1st cycle	**2nd cycle**	**3rd cycle**	**4th cycle**	**5th cycle**	**6th cycle**
Hgb, g/dL							
Hematocrit (%)							
WBC, $\times 10^9$ cells/l							
Platelets ×109 cells/l							
Neutrophil ×109 cells/l							
Lymphocyte×109 cells/l							
Alkaline phosphatase (U/L)							
ALT							
AST							

Creatinine							
BUN							

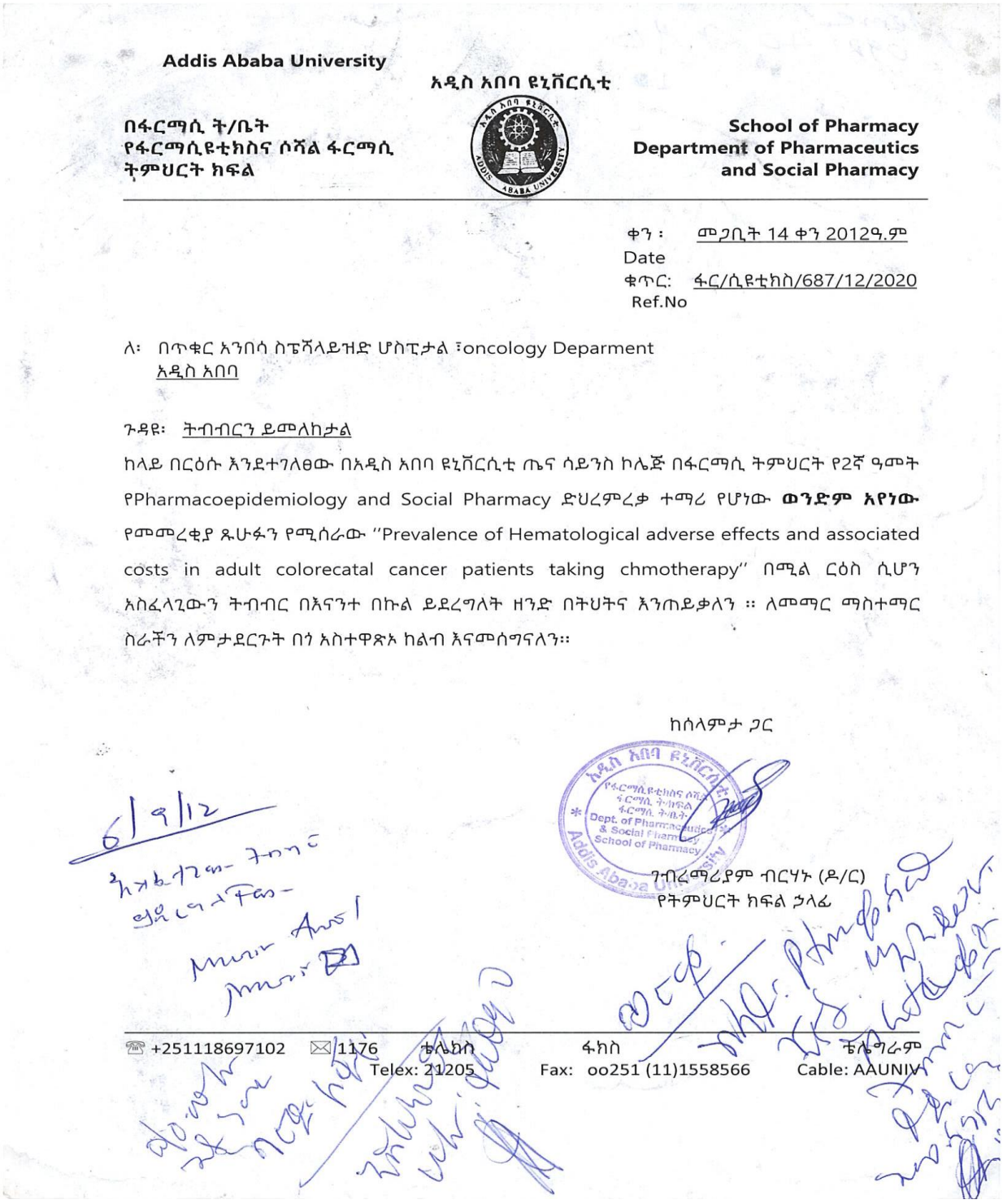
Part V: - Hematological toxicity developed

Table 2: Hematological toxicity developed in each cycle of chemotherapy

Hematological toxicity developed	**Cycle of chemotherapy**	**Severity based on CTCAE**	**Type of chemotherapy which cause hematological toxicity**	**Toxicity management**
Hematological				
1. Anemia				
1. Neutropenia				
2. Neutropenic fever				
3. Thrombocytopenia				
4. Leukopenia				
5. Increased ALT				
6. Increased AST				

7. Proteinurea				
8. **Others**				

Annex 2: Ethical Clearance of the study



Addis Ababa University

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School of Pharmacy
Department of Pharmaceutics
and Social Pharmacy

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ከላይ በርዕሱ እንደተገለፀው በአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ በፋርማሲ ትምህርት የ2ኛ ዓመት የPharmacoepidemiology and Social Pharmacy ድህረምረቃ ተማሪ የሆነው **ወንድም አየነው** የመመረቂያ ጹሁፉን የሚሰራው ''Prevalence of Hematological adverse effects and associated costs in adult colorectal cancer patients taking chmotherapy'' በሚል ርዕስ ሲሆን አስፈላጊውን ትብብር በእናንተ በኩል ይደረግለት ዘንድ በትህትና እንጠይቃለን ። ለመማር ማስተማር ስራችን ለምታደርጉት በጎ አስተዋጽኦ ከልብ እናመሰግናለን።

ከሰላምታ ጋር

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