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Research Article

PROSPECTIVE EVALUATION OF DRUG-THERAPY PROBLEMS AND ADVERSE DRUG REACTIONS IN COLORECTAL CANCER PATIENTS

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ABSTRACT

Drug therapy problems (DTPs) are common in oncology and can compromise treatment outcomes, particularly in colorectal cancer (CRC), where complex regimens are used. This prospective observational study evaluated the prevalence, causes, and predictors of DTPs in CRC patients receiving systemic anticancer therapy. A total of 200 patients were enrolled and followed during the first two treatment cycles. Over half of the cohort experienced at least one DTP, with dose selection, drug selection, and patient-related issues being the most frequent causes. Oral anticancer agents were used in nearly half of the cohort, and their use was independently associated with increased DTP risk. The most commonly implicated drugs in adverse drug reactions (ADRs) were 5-fluorouracil and oxaliplatin, with stomatitis and neuropathy being prominent toxicities. Approximately one-third of ADRs were classified as serious, with most deemed probable in causality assessments. Predictors of DTPs included poor performance status, polypharmacy, comorbidities, and use of oral therapies. While guideline adherence was high for antiemetics and G-CSF support, venous thromboembolism prophylaxis remained underutilized. This study provides a comprehensive overview of early DTPs in CRC, identifies vulnerable subgroups, and highlights the need for improved medication safety practices, especially in oral chemotherapy management and supportive care optimization.

Keywords: Drug therapy problems, Colorectal cancer, Adverse drug reactions, Oral chemotherapy.

INTRODUCTION

Colorectal cancer (CRC) is a major global health concern, representing the third most commonly diagnosed malignancy and the second leading cause of cancer mortality worldwide (WHO, 2023). In 2020 alone, an estimated 1.9 million new CRC cases were diagnosed and about 935,000 deaths occurred globally (WHO, 2023). The burden of CRC is also rising in many lower-incidence regions; for example, India reported roughly 70,000 new CRC cases in 2022 despite historically lower incidence rates (World Cancer Research Fund, 2024). Such epidemiologic trends underscore CRC's significance both globally and in regional contexts. CRC pharmacotherapy is notably complex, involving multiple drug classes and modalities. Standard treatment regimens for advanced disease combine cytotoxic chemotherapy backbones such as FOLFOX, CAPOX, or FOLFIRI – with targeted biologic agents (e.g. anti-VEGF or anti-EGFR monoclonal antibodies) (Ohishi *et al*., 2023). These combination therapies have improved outcomes in metastatic CRC and are considered first-line standards (Ohishi *et al*., 2023). Additionally, immunotherapy has emerged for microsatellite instability-high (MSI-H) or mismatch repair-deficient tumors: immune checkpoint inhibitors like pembrolizumab can induce durable remissions and are now a first-line option in this molecular subset (Shiu *et al*., 2023). The therapeutic arsenal also includes oral anticancer drugs. Capecitabine, an oral fluoropyrimidine, is often used

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in place of infusional 5-FU, and newer oral agents have expanded later-line options in refractory disease. Notably, the multi-kinase inhibitor regorafenib and the nucleoside analog combination trifluridine/tipiracil (TAS-102) have each demonstrated modest but significant survival benefits in chemotherapy-refractory metastatic CRC (Tanaka *et al*., 2018). While these agents improve disease control, they introduce additional complexity in terms of dosing, toxicity monitoring, and patient adherence.

Several patients- and treatment-specific factors heighten the risk of DTPs in CRC therapy. Many CRC patients are older adults with multiple comorbidities, often resulting in polypharmacy (the use of multiple concomitant medications). Polypharmacy has been associated with adverse outcomes in CRC survivors, including higher all-cause mortality and increased hospitalizations (Choi *et al*., 2023). Functional status is also relevant: patients with poor performance status (ECOG ≥2) may be more vulnerable to toxicity and medication misadventures due to reduced physiological reserve. Furthermore, the incorporation of oral chemotherapy presents adherence challenges. Unlike IV therapy administered in clinics, oral regimens rely on patient compliance; one longitudinal study found that 71.4% of CRC patients had suboptimal adherence to oral chemotherapy, with adherence rates declining over the course of treatment (Chen *et al*., 2020).

Despite the clear importance of managing DTPs in oncology, there is a lack of focused prospective studies examining DTP incidence and outcomes specifically in CRC patients receiving modern systemic therapy. Most existing literature addresses medication-related problems in broader cancer populations or through retrospective analyses, leaving gaps in our understanding of how contemporary CRC treatments (including biologics and immunotherapy) impact DTP patterns (Degu *et al*., 2024). This deficit in evidence highlights the need for dedicated research to inform prevention and management of DTPs in CRC. The present study aims to evaluate the prevalence, causes, and predictors of drug therapy problems in CRC patients receiving systemic anticancer therapy.

MATERIALS AND METHODS

Study design and setting

We conducted a prospective, observational cohort study of adults with histologically confirmed colorectal cancer (CRC) initiating systemic anticancer therapy.

Participants

Inclusion criteria. Age ≥18 years; AJCC stage II–IV; starting adjuvant or metastatic systemic therapy (intravenous, oral, or combined); complete baseline medication list (prescription, OTC, and herbal). Exclusion criteria. Enrollment in interventional clinical trials with incompatible adverse-event (AE) reporting frameworks; missing baseline laboratory data precluding safety assessment; or refusal of pharmacist review.

Therapeutic regimens

Chemotherapy and biologic backbones were pre-specified as: FOLFOX, CAPOX (capecitabine/oxaliplatin), FOLFIRI, FOLFOXIRI (considered "irinotecan-containing" for some analyses), targeted biologics (anti-VEGF; anti-EGFR), immunotherapy (MSI-H/dMMR), and oral agents (capecitabine, regorafenib, TAS-102). For regimen-level cross-tabulations of drug-therapy problem (DTP) causes, FOLFOXIRI was pooled with FOLFIRI, and IO/orals aggregated pembrolizumab, regorafenib, and TAS-102.

Outcomes

Presence of ≥1 DTP during cycles 1–2, modeled at the patient level. ADR profile: type, CTCAE grade, seriousness, causality (Naranjo), severity (Hartwig & Siegel), and preventability (Schumock–Thornton). Drug Therapy Problem Classification using Pharmaceutical Care Network Europe (PCNE) vs 9.1.

Sample size rationale

The study enrolled 200 patients to estimate the prevalence of ≥1 DTP in cycles 1–2 with ~±7% precision (95% CI) under an expected prevalence near 50–60%. For multivariable modelling of ≥1 DTP, this sample yields ~110–120 events, supporting ~10–12 prespecified predictors at ~10 events-per-variable; when EPV was borderline, we planned penalization and bootstrap internal validation.

Statistical analysis

Descriptive statistics. Baseline characteristics were summarized as n (%), mean ± SD, or median (IQR). ADRs were tabulated by suspected drug, syndrome, grade, seriousness, Naranjo/Hartwig/Schumock distributions. PCNE profiles were reported as (i) Problem domain proportions and (ii) Cause domain counts with dose-selection sub codes. A regimen-level cross-tab (Cause × Regimen) was constructed for CAPOX, FOLFOX, FOLFIRI (incl. FOLFOXIRI), and IO/orals. Primary model (forest plot). We fit a multivariable logistic regression for ≥1 DTP in cycles 1–2. Prespecified predictors (with reference levels in parentheses) were: ECOG ≥2 (vs 0–1), age ≥65 (vs <65), female (vs male), comorbidity count per +1, polypharmacy ≥5 (vs <5), any oral therapy (vs none), regimen class (CAPOX, FOLFIRI, FOLFOXIRI vs FOLFOX), anti-EGFR use (vs none), emetogenic risk Moderate/High (vs ≤Low), high FN-risk regimen (yes/no), immunotherapy (MSI-H/dMMR vs no), and cycle number per +1 (to reflect early clustering). We examined collinearity (VIF <5), reported adjusted odds ratios (aORs) with 95% CIs, and displayed estimates on a log-scale forest plot with a no-effect line at OR=1. Software. Analyses

were conducted in R or Stata; graphics used matplotlib for the forest plot.

RESULTS AND DISCUSSION

The cohort was predominantly male and middle-aged, with most patients presenting with advanced disease**:** Stage III (≈44%) and Stage IV (≈31%) together comprised nearly three-quarters of cases. Tumours were more often rectal than colonic (≈60% vs 40%). Excess body weight was common (≈63% overweight/obesity), while performance status was generally preserved (ECOG 0–1 in ≈84%). Just over half were treated with metastatic intent (Table 1)**.**

Table 1. Sociodemographic and clinical characteristics of colorectal cancer patients (n=200).

Characteristic	Statistic
Age (in years)	54.55±14.84
Gender, n (%)	
Male	149 (74.5)
Female	51 (25.5)
Educational Level, n (%)	
Uneducated	89 (44.5)
High School	52 (26.0)
Graduate	38 (19.0)
Post Graduate	21 (10.5)
Smoking, n (%)	
Smokers	39 (26.2)
Ex-Smokers	46 (30.9)
Non-Smokers	64 (42.9)
Alcohol, n (%)	
Alcoholic	49 (32.9)
Ex-Alcoholic	55 (36.9)
Non-Alcoholic	45 (30.2)
Tumor Location, n (%)	
Rectum,	119 (59.5)
Colon	81 (40.5)
Stage at Diagnosis, n (%)	
Stage I,	23 (11.5)
Stage II	29 (14.5)
Stage III	87 (43.5)
Stage IV	61 (30.5)
Body Mass Index (kg/m^2) category, n (%)	
< 18.5 (underweight)	06 (3.0)
18.5 – 24.9	68 (34.0)
25.0 –29.9	86 (43.0)
≥ 30.0	40 (20.0)
ECOG Performance Status, n (%)	
0	64 (32.0)
1	104 (52.0)
≥2	32 (16.0)
Treatment Intent, n (%)	
Adjuvant	92 (46.0)
Metastatic	108 (54.0)

Table 2. Treatment characteristics of colorectal cancer patients (n=200).

Characteristic	Statistic
Line of Therapy, n (%)	
First Line	150 (75.0)
Second Line or later	50 (25.0)
Initial regimen class, n (%)	
FOLFOX	58 (25.0)

CAPOX	46 (19.8)
FOLFIRI	32 (13.8)
FOLFOXIRI	12 (5.2))
Any anti-VEGF	52 (22.4)
Any anti-EGFR	22 (9.5)
Immune Checkpoint Inhibitor	10 (4.3)
Oral therapy Involvement, n (%)	
Any oral agent	74(48.7)
Capecitabine	49 (32.2)
Regorafenib	15 (9.9)
TAS-102	14 (9.2)
Regimen emetogenic risk, n (%)	
Low	32 (16.0)
Moderate	96 (48.0)
High	72 (36.0)
Febrile Neutropenia Risk, n (%)	
Low	47 (23.5)
Intermediate	122 (61.0)
High	31 (15.5)

First-line systemic therapy predominated (≈75%). Oxaliplatin-based backbones were most frequent (FOLFOX ≈25%; CAPOX ≈20%), followed by FOLFIRI (≈14%) and FOLFOXIRI (≈5%). Biologic use included anti-VEGF (~22%) and anti-EGFR (~10%), with a smaller proportion receiving immunotherapy (~4%). Oral therapy featured in nearly half of patients, most commonly capecitabine**,** with smaller contributions from regorafenib and TAS-102 (Table 2)**.** Across 217 adverse drug reaction (ADR) events**,** the agents most often implicated were 5-fluorouracil (~32%) and oxaliplatin (~30%). The leading clinical syndromes were stomatitis (~32%) and peripheral sensory neuropathy (~17%), alongside hypersensitivity, palmar-plantar erythrodysesthesia, and diarrhea. About one-third of ADRs were serious**,** and most were improving or resolved at reporting. Causality skewed strongly toward probable (~78%), with few definite cases. Drug-therapy problem (DTP) causes were dominated by dose-selection issues (C3) (~26%), followed by drug selection (C1) (~20%) and patient-related factors (C7) (~17%). The regimen-level pattern was intuitive: dose selection problems clustered in CAPOX/FOLFOX**;** patient-related causes were comparatively higher in the IO/oral group (adherence/knowledge/access); and monitoring gaps (C8) were modestly more prominent with FOLFOX.

Table 3. Adverse Drug Reaction (n=217) assessment for colorectal cancer patients.

Characteristic	**n (%)**
Suspected Drug	
5-Fluorouracil	69 (31.8)
Oxaliplatin	64 (29.5)
Capecitabine	23 (10.5)
Regorafenib	21 (9.6)
Irinotecan	14 (6.4)
TAS-102	14 (6.4)
Pembrolizumab	12 (5.5)
CTCAE term	
Stomatitis	69 (31.8)
Peripheral sensory neuropathy	37 (17.1)
Hypersensitivity Reaction	27 (12.4)
Palmar-plantar erythrodysesthesia	25 (11.5)
Diarrhea	24 (11.1)
Neutropenia	14 (6.5)
ALT increased	13 (6.0)
Colitis	8 (3.7)
Seriousness	
Yes	68 (31.3)

No	149 (68.7)
Outcome	
Recovering	82 (37.8)
Recovered	72 (33.2)
Improved	42 (19.4)
Ongoing	21 (9.6)
Naranjo Category	
Probable	169 (77.9)
Possible	46 (21.2)
Definite	02 (0.9)

Table 4. Regimen wise drug therapy problems in the colorectal cancer patients.

PCNE Cause	CAPOX	FOLFOX	FOLFIRI (incl. FOLFOXIRI)	IO/Orals *	Row total (n)	Row total (%)
C1 - Drug selection	18	20	22	22	82	19.5
C2 - Drug form/route inappropriate	2	1	1	3	7	1.7
C3 - Dose selection	36	34	28	12	110	26.2
C4 - Treatment duration inappropriate	6	6	6	10	28	6.7
C5 - Dispensing/supply/labelling	3	2	2	8	15	3.6
C6 - Drug use/administration process	10	10	16	9	45	10.7
C7-Patient-related (adherence/knowledge/access)	16	10	12	32	70	16.7
C8 -Monitoring (labs/parameters insufficient/absent)	13	17	16	12	58	13.8
C9 - Other / not classifiable	0	1	1	3	5	1.2

***** IO/Orals pooled: pembrolizumab (MSI-H/dMMR), regorafenib, TAS-102, and any oral-only maintenance if present. FOLFOXIRI merged under FOLFIRI for "irinotecan-containing" grouping.

Patients with ECOG ≥ 2 had over two-fold higher odds of a DTP (aOR ≈ 2.10; 95% CI 1.32–3.33). Polypharmacy ≥ 5 (aOR ≈ 1.72; 1.12–2.62), any oral therapy involvement (capecitabine/regorafenib/TAS-102; aOR ≈ 1.55; 1.01–2.39), and higher comorbidity burden (per +1 condition; aOR ≈ 1.18; 1.05–1.32) were also independently associated with increased DTP risk.

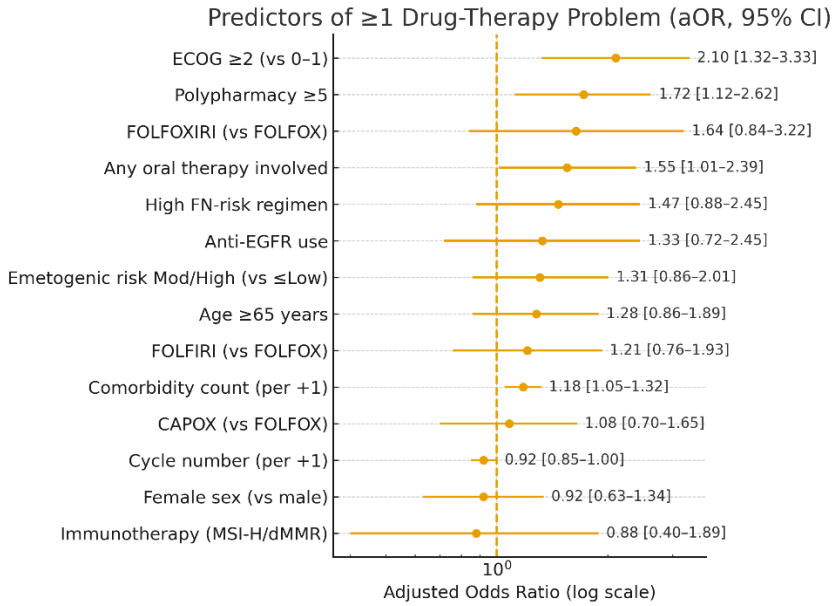

Figure 1. Predictors of experiencing ≥1 drug-therapy problem within the first two treatment cycles in colorectal cancer (adjusted odds ratios with 95% confidence intervals).

The forest plot displays adjusted odds ratios (aOR) with 95% confidence intervals from a multivariable logistic regression modelling the probability of at least one drug-therapy problem (DTP) during cycles 1–2 (N = 200). Point estimates are plotted on a logarithmic x-axis; the vertical dashed line denotes the null (aOR = 1). Reference categories: ECOG 0–1; age <65 years; male sex; FOLFOX backbone; no oral therapy; no anti-EGFR; not high FN-risk; ≤Low emetogenic risk. Continuous predictors are scaled per indicated unit (comorbidity count per +1; cycle number per +1). Our prospective study demonstrated a high prevalence of drug therapy problems (DTPs) in colorectal cancer patients receiving systemic therapy. Well over half of the cohort experienced at least one DTP within the first two treatment cycles. This finding is consistent with prior research showing that 50–60% or more of oncology patients encounter DTPs during chemotherapy (Kefale *et al*., 2022; Degu *et al*., 2024). Our observed average of ~2 DTPs per patient aligns with multiple studies reporting 2–3 DTPs per patient (Sah *et al*., 2025), underscoring the substantial medication burden in this population. In characterizing DTP types, issues related to dose selection (26%) and drug selection (20%) were most frequent in our cohort, followed by patient-related factors (~17%). This profile suggests that suboptimal dosing (e.g. non-individualized starting doses, or needed adjustments) and regimen choices (e.g. drug omitted or not ideal for the indication) are primary contributors to DTPs. A similar pattern has been documented in other oncology settings – for example, among hospitalized cancer patients with pain, inappropriate drug choice and dosing were implicated in roughly 41% and 24% of DTP causes respectively. Likewise, an analysis of cancer pain management found that insufficient pain control was often due to analgesic selection and dosing problems**,** which pharmacists could successfully identify and resolve (Su *et al*., 2021).

While our study focused on a comprehensive oncology pharmacotherapy review, other settings have identified additional DTP categories. For example, a study in Kenya reported that among gastrointestinal cancer patients, the "need for additional drug therapy" (e.g. omission of a needed supportive medication) and ADRs were the most prevalent DTP types (Degu *et al*., 2024), a contrast to our finding of dose/drug selection issues predominating. Such differences may reflect variations in practice patterns and resource availability; in some settings, under-treatment (missing adjunct therapies) is common, whereas in others optimization of chosen therapies is the bigger challenge. The treatment regimens observed in our study were in line with standard colorectal cancer therapy worldwide. The vast majority of patients received combination cytotoxic chemotherapy backbones such as FOLFOX, CAPOX**,** or FOLFIRI**.** These three regimens accounted for the bulk of first-line and second-line treatments, reflecting their status as global standards (Tang *et al*., 2016). Indeed, infused 5-fluorouracil plus oxaliplatin (FOLFOX) and 5-FU plus irinotecan (FOLFIRI) are the two most commonly used cytotoxic regimens for metastatic CRC (Tang *et al*., 2016).

CAPOX (capecitabine plus oxaliplatin) was also prominent in our cohort, consistent with its role as an alternative to FOLFOX – especially in adjuvant therapy or when an oral approach is preferred. In our study, approximately half of patients received an oral anticancer agent at some point (either capecitabine in combination or oral targeted therapies like regorafenib and TAS-102). This proportion underscores the growing integration of oral chemotherapy in colorectal cancer management. Real-world data from other settings support this trend: for example, an Ethiopian study reported that about 74% of CRC patients received fluoropyrimidine-based combination regimens (infusional 5-FU or capecitabine) (Kefale *et al*., 2022), demonstrating the predominance of those backbones, and about one-quarter were on biologic or oral agents. Our finding of ~50% oral agent use likely reflects both the use of CAPOX in first-line therapy and the adoption of newer oral drugs (regorafenib, trifluridine-tipiracil) in later lines for metastatic disease. The high use of oral agents in our cohort is clinically significant, as it ties into the increased DTP risk we observed with oral therapy. Oral chemotherapy shifts more responsibility to patients (for adherence, proper administration, and monitoring of side effects), which can in turn generate DTPs related to patient behavior and monitoring. Our multivariable analysis identified "any oral therapy" as an independent predictor of having ≥1 DTP (aOR ~1.55). This aligns with the notion that oral regimens, while convenient, require robust patient education and follow-up to ensure safe use. Other studies have similarly cautioned that oral oncolytics are associated with adherence problems and medication errors if not managed carefully (Sah *et al*., 2025).

The adverse drug reaction (ADR) profile in our patients reflects well-known toxicities of the backbone chemotherapies, particularly 5-FU (and capecitabine) and oxaliplatin. Stomatitis/mucositis emerged as one of the most frequent ADRs attributed to 5-FU, while peripheral neuropathy was commonly linked to oxaliplatin – observations that are consistent with the established toxicity patterns of these drugs (Tang *et al*., 2016). Fluoropyrimidines are well known to cause mucositis, stomatitis, and diarrhea due to their effects on rapidly dividing mucosal cells. Oxaliplatin, meanwhile, is among the most neurotoxic anticancer agents, causing cumulative sensory neuropathy in a majority of patients by the end of a typical course (Selvy *et al*., 2020). Our findings corroborate these patterns: many patients experienced oral soreness or ulceration (often requiring dose adjustments or supportive care), and neuropathy symptoms were prevalent during and after oxaliplatin therapy. In fact, the long-term implications of oxaliplatin neuropathy are substantial – a French multicenter study found that about 31% of colon cancer survivors still had persistent chemotherapy-induced peripheral neuropathy (CIPN) five years after adjuvant FOLFOX therapy (Selvy *et al*., 2020). Neuropathy not only

impacts functionality but also was associated with anxiety, depression, and poorer quality of life in that survivor population (Selvy *et al*., 2020). Thus, the ADR burden observed in our first-line treatments (e.g. acute mucositis, cumulative neuropathy) aligns with both clinical trial data and survivorship research, underlining the need for vigilant toxicity monitoring. Around one-third of ADRs in our study were classified as serious (31.3% met seriousness criteria, such as requiring hospitalization, being life-threatening, or causing significant disability). This is a notable proportion indicating that many patients experienced severe toxicities despite prophylactic measures. By comparison, general oncology pharmacovigilance data have reported somewhat variable rates of serious ADRs. For example, an Indian survey of chemotherapy toxicity found that ~13% of ADRs were serious (Chopra *et al*., 2016), while a population-based estimate noted that up to 44% of patients may experience a serious complication from chemotherapy (Ingrand *et al*., 2020).

The most frequent serious ADRs in our cohort corresponded to those high-incidence toxicities (e.g. Grade 3/4 stomatitis requiring IV fluids or hospitalization, Grade 3 neuropathy necessitating treatment breaks, febrile neutropenia, etc.). This burden underscores the importance of preventive and early mitigation strategies. We observed excellent implementation of some supportive measures (as discussed below, e.g. antiemetics, growth factors) which likely helped limit certain toxicities. However, our findings suggest that more can be done to anticipate and manage predictable ADRs like mucositis and neuropathy. For instance, routine oral cryotherapy or palifermin can be considered for high-risk mucositis settings, and dose-limiting strategies or neuroprotective interventions (though limited in efficacy) could be explored for neuropathy (Tang *et al*., 2016; Selvy *et al*., 2020). We observed that venous thromboembolism (VTE) prophylaxis was a clear gap in guideline adherence – very few of our ambulatory chemotherapy patients received pharmacologic thromboprophylaxis, even among those with additional risk factors. Current guidelines (e.g. ASCO, NCCN) do recommend considering prophylactic anticoagulation in high-risk outpatients (such as those with a Khorana risk score ≥2) after weighing bleeding risk. However, this guidance is relatively recent and has seen slow uptake in practice. Our findings reflect this: oncology teams were diligent about antiemetics and neutropenia prophylaxis, but routine VTE prophylaxis was seldom implemented, suggesting it is not yet ingrained in practice. This mirrors published data indicating low adherence to VTE prevention recommendations in ambulatory cancer care (Martin *et al*., 2024).

Studies have noted that only a small minority of eligible patients actually receive prophylactic anticoagulants outside of clinical trials (Martin *et al*., 2024). Reasons may include fear of bleeding complications, uncertainty about patient selection, and the lack of strong mandates compared to CINV/FN guidelines. Indeed, a narrative review of guideline implementation for CINV and thrombosis found that adherence to antiemetic protocols is good, but adherence to thromboprophylaxis guidelines is poor in current practice (Kennedy *et al*., 2024). Our multivariable analysis yielded several independent predictors of patients experiencing one or more DTPs, offering insight into which patients are most vulnerable. Notably, ECOG performance status ≥2 was associated with over double the odds of having a DTP (aOR ~2.1). This suggests that patients who are frailer or debilitated (poor PS) tend to encounter more medication-related issues. Such patients might have organ dysfunction affecting drug metabolism, greater sensitivity to side effects, or difficulty adhering to complex regimens, all of which can manifest as DTPs. Although performance status has not been explicitly examined in many prior DTP studies, it aligns conceptually with findings that advanced disease stage and patient frailty correlate with more drug problems (Degu *et al*., 2024).

Patients with polypharmacy (≥5 concomitant medications) were another high-risk group in our analysis. Polypharmacy is a well-known risk factor for drug-related problems in both general and oncology populations (Kefale *et al*., 2022). Each additional medication introduces potential for drug–drug interactions, medication errors, and additive side effects. Our results showed a roughly 1.7-fold increase in DTP risk with ≥5 medications, which resonates with previous studies: for example, Kefale *et al*. (2022) in Ethiopia reported that patients on ≥5 medications had significantly higher odds of DRPs (p=0.002). This study has several strengths. To our knowledge, it is among the first prospective analyses focusing on DTPs in colorectal cancer patients receiving contemporary systemic regimens in our region. We employed a comprehensive and standardized framework (PCNE v9.1) to classify DTPs and their causes, which enhances the rigor and reproducibility of our findings. The prospective design with active pharmacist involvement allowed for thorough detection of issues (including potential problems), rather than relying on spontaneous reporting. We also captured detailed ADR data (with causality and severity assessments), providing a nuanced view of the safety profile in routine practice. Furthermore, our sample size (n=200) was substantial for a single-center study and powered to perform multivariable risk factor analysis with internal validation, which strengthens the validity of the identified predictors of DTPs. The diversity of regimens (covering chemo, biologics, oral drugs) and inclusion of both curative and metastatic settings improve the generalizability of our results to a wide CRC population. Finally, the high guideline adherence observed for CINV and neutropenia prophylaxis in our setting might serve as a “best practice” benchmark for other centers aiming to improve supportive care quality.

Our study has important limitations. Generalizability may be limited by the single-center design at a tertiary care oncology hospital – practices and patient populations (e.g. comorbidity burden, supportive care resources) may differ in community settings or other countries. The study

observation window was confined to the first two treatment cycles, which, while capturing the initial acute DTPs, may have missed problems that manifest later in therapy (such as cumulative toxicities beyond cycle 2 or issues arising in maintenance phases). Another limitation is the potential for observer bias in identifying and classifying DTPs – although we used a standardized tool, the assessments were made by clinical pharmacists, and some judgments (e.g. what constitutes an "inappropriate" dose) have subjective elements. We tried to mitigate this by having defined criteria and, where possible, physician confirmation, but some misclassification is possible. Moreover, while we identified DTPs and their causes, our study did not formally evaluate the outcomes of pharmacist interventions on these DTPs. In practice, pharmacists likely resolved many issues as they were found (for ethical patient care), so the true frequency of uncorrected DTPs might be lower – however, we did not quantify intervention acceptance or patient outcomes (e.g. prevention of harm), which would be valuable in future research. Despite these limitations, our study provides a detailed snapshot of DTPs in real-world CRC chemotherapy and offers actionable insights. Future multicenter studies and longer follow-up would be beneficial to confirm our findings and to assess the impact of interventions on improving medication safety in oncology.

CONCLUSION

This prospective study demonstrates a high burden of early drug therapy problems in colorectal cancer patients receiving systemic therapy, primarily driven by dose selection, drug choice, and patient-related factors. Oral anticancer agents, polypharmacy, comorbidities, and poor performance status emerged as key predictors. One-third of adverse drug reactions were serious, underscoring the need for proactive toxicity monitoring. While antiemetic and G-CSF guideline concordance was strong, venous thromboembolism prophylaxis was underutilized. These findings highlight the critical role of pharmacist-led reviews and individualized care strategies in reducing preventable medication-related harm and optimizing therapeutic outcomes in colorectal cancer management.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

The study was approved by the institutional review board (VIPT/IEC/271/2025). We obtained a written informed consent from participating patients.

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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