

Adverse Drug Reactions in an Oncological Population: Prevalence, Predictability, and Preventability

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

Background. Our goal was to determine (a) the prevalence of multimorbidity and polypharmacy in patients with cancer and (b) the prevalence, predictability, and preventability of adverse drug reactions (ADRs) causing/contributing to hospitalization.

Materials and Methods. We conducted a 12-month prospective observational study of patients aged ≥ 16 years admitted to an oncology center. Older adults were aged ≥ 70 years.

Results. We enrolled 350 patients: 52.3% ($n = 183$) female, mean age 63.6 years (SD 12.1), 36.6% ($n = 121$) aged ≥ 70 years. Multimorbidity (≥ 2 conditions) was identified in 96.9%; 68% had ≥ 5 conditions. The median number of medications was 6 (interquartile range [IQR] 4–8); 47% were prescribed ≥ 6 medications and 11.4% ≥ 11 medications. Older adults had higher numbers of comorbid conditions (7 [IQR 5–10] vs. 5 [IQR 3–7]) and were prescribed more medications (median 7 [IQR 4–9] vs. 4 [IQR 2–7]). ADRs caused/contributed to hospitalization in 21.5% ($n = 75$): 35.8% ($n = 72$) of emergency admissions and 4.7% ($n = 3$) of elective admissions. The

most common ADRs were neutropenia with infection (25.3%), dyspepsia/nausea/vomiting (20%), and constipation (20%). Causative medications included systemic anticancer therapies (SACTs; 53.3%), opioids (17.3%), corticosteroids (6.7%), and nonsteroidal anti-inflammatory drugs (5.3%). ADR prevalence was similar in older and younger adults secondary to SACTs (8.3% vs. 13.1%), non-cancer medications (10.7% vs. 8.3%), and both (0% vs. 1.3%). ADRs were predictable in 89.3% ($n = 67$), definitely avoidable in 29.3% ($n = 22$), and possibly avoidable in 33.3% ($n = 25$). No association was identified between ADRs and age, gender, daily medication number, length of stay, or death. No ADR predictor variables were identified by logistic regression.

Conclusion. More than 21% of admissions to an oncology service are ADR-related. ADRs are caused by both SACTs and non-cancer-specific medications. The majority are predictable; $\geq 60\%$ may be preventable. Patients with cancer have high levels of multimorbidity and polypharmacy, which require vigilance for related adverse outcomes. *The Oncologist* 2019;24:e968–e977

Implications for Practice: A diagnosis of cancer often occurs in patients with multimorbidity and polypharmacy. Cancer can cause an altered physiological environment, placing patients at risk of drug-drug interactions, drug-disease interactions, and adverse drug reactions (ADRs). This study identified that ADRs caused or contributed to one in five hospital admissions of patients with cancer. ADRs were caused by systemic anticancer therapies (SACTs) in 53.3% of cases and non-cancer medications in 45.4% of cases, and a combination of both in 1.3%. ADRs occurred in similar frequencies in older and younger patients secondary to SACTs (8.3% vs. 13.1%, $p = .295$), non-SACTs (10.7% vs. 8.3%, $p = .107$), and a combination of both (0% vs. 1.3%, $p = .240$). The majority of ADRs were predictable (89.3%) and potentially preventable (62.6%). These findings support the need for increased awareness of medication-related adversity in patients with cancer and interventions to minimize their occurrence, thus supporting the American Society of Clinical Oncology guidelines that recommend adults ≥ 65 years of age receiving chemotherapy have geriatric assessment to identify medical and medication issues.

INTRODUCTION

The incidence of cancer is expected to rise significantly over the next decade [1] principally in older adults because of demographic shifts toward an aging population

[2, 3]. With advancing age comes an increase in the prevalence of comorbid illnesses including hypertension [4], postural hypotension [5], falls [6], cardiac failure [7], atrial

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fibrillation [8], stroke [9], chronic kidney disease [10], and dementia [11]. Aging and comorbidity correlate with increasing numbers of prescribed medications [12]. Although often indicated, there is evidence to show that polypharmacy (the coprescription of ≥ 6 medications) [13] is associated with inappropriate prescribing and negative outcomes including adverse drug reactions (ADRs) as well as excessive health resource use [14, 15]. ADRs cause or contribute to 7% of hospital admissions in the general adult population [16, 17] and up to 20% of hospital admissions in older patients [17, 18]. The prevalence of ADRs as a cause of hospitalization in patients with cancer is unclear.

Several small studies have shown that the majority of older patients presenting to oncological services are prescribed multiple medications for treatment of coexisting conditions as well as primary and secondary prevention of disease. A British study of 100 older adults with metastatic cancer reported that patients were prescribed a median of 7 (interquartile range [IQR] 1–17) daily medications [19]. A Canadian study of 112 older adults with newly diagnosed cancer found that patients were prescribed five medications before initiation of systemic anti-cancer therapy (SACT) [20]. Cancer can result in an altered physiological status that influences the pharmacokinetic handling and pharmacodynamic sensitivity to several drugs, often with requirement for dose adjustment, particularly in the context of renal or hepatic dysfunction. Furthermore, SACTs contribute to additional drug burden in the form of chemotherapy and supportive drugs placing patients at increased risk of additive toxicity, drug-drug interactions, drug-disease interactions, and ADRs.

Comprehensive Geriatric Assessment (CGA) is a multidimensional interdisciplinary diagnosis process focused on determining an older person's medical, psychological, and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up [21]. A systematic review investigating the role of geriatric assessment in oncology patients found that geriatric assessment in this setting is feasible, takes about 10–45 minutes, and can influence treatment decisions [22]. The American Society of Clinical Oncology (ASCO) now recommends that patients ≥ 65 years of age receiving chemotherapy have specialist geriatric assessment to identify medical and medication issues that are not captured by regular oncology assessments. In addition, ASCO recommends that geriatric assessment interventions be implemented to manage nononcological problems [23].

Specific chemotherapy-related ADRs are well described, classified, and risk-stratified to enable vigilance among patients and clinicians prior to and during treatment [24]. However, the prevalence and impact of multimorbidity, polypharmacy, and non-SACT-related ADRs in patients with cancer are less well studied, particularly as contributory factors to acute hospitalization. Therefore, our goal was to determine (a) the prevalence of multimorbidity and medication use in patients attending a specialist cancer center and (b) the prevalence, causality, predictability, and preventability of ADRs causing or contributing to hospitalization.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted over a 12-month period in two academic teaching hospitals in the Republic of Ireland: Cork University Hospital and Mercy University Hospital. Together, these make up one of eight regional cancer centers in the Republic of Ireland and serve a population of 800,000 people. The study protocol was approved by the local Clinical Research Ethics Committee.

Participants and Eligibility

All patients aged ≥ 16 years, admitted under the medical or radiation oncology services, were eligible for inclusion. Older adults were defined as ≥ 70 years of age, and younger adults were defined as < 70 years of age. Participants were enrolled from three admission pathways: emergency, elective, and medical oncology day unit attendances. Emergency and elective admissions were reviewed within 72 hours of presentation to hospital, thus enabling inclusion of patients admitted over the weekend. Patients attending the day unit received repeated cycles of SACT over several weeks, with the same patients attending weekly over a defined period. A representative sample of patients attending the day units in each hospital were studied for a 1-week period to avoid repetition. Patients were not enrolled if they were deemed to be actively dying by the treating physician or if they had participated in the study on a prior admission. Written informed consent to participate was sought from each participant. Consent was obtained from the patient's legal representative in cases in which patients were unable to give consent because of reduced decision-making ability (e.g., cognitive impairment).

Sample Size Calculation

A sample of 333 patients was required to detect an ADR rate of 7% with a margin of error of 2% at 95% confidence.

Data Collection and Measurements

All participants were interviewed by a single physician researcher. The following data were collected: (a) demographic details, (b) medical comorbidities with associated Cumulative Illness Rating Scale (CIRS) [25], (c) detailed list of medications, (d) functional ability using the Barthel Index [26], (e) cognitive status using the mini-mental state examination [27], the 4 A's test (4-AT) [28], and the Diagnostic and Statistical Manual of Mental Disorders V for delirium [29], (f) hematological and biochemical laboratory values, and (g) electrocardiogram. Medication reconciliation was completed using the Structured History taking of Medication use [30] to ensure accurate identification of all medications being consumed by patients. The World Health Organization (WHO) definition of multimorbidity was employed (i.e., the co-occurrence of two or more chronic medical conditions in one person) [31].

Adverse Drug Reactions: Definition and Process of Identification

The primary outcome measure was the proportion of patients experiencing one or more nontrivial, probable, or

Table 1. Adverse event trigger list

	Event	Definition
1	New onset fall/s	New fall
2	New onset of unsteady gait	New onset of unsteady gait that results in poor mobility and unsteady balance
3	Acute kidney injury	An increase in serum creatinine by 26.5 $\mu\text{mol/L}$ within 48 hours or an increase in serum creatinine by 1.5 baseline, which is known or presumed to have occurred within the prior 7 days
4	Symptomatic orthostatic hypotension	A systolic blood pressure drop of ≥ 20 mmHg \pm diastolic blood pressure drop ≥ 10 mmHg within 3 minutes of standing from the lying or sitting posture associated with symptoms
5	Major serum electrolyte disturbance	A sodium (Na) of < 130 mmol/L or > 145 mmol/L AND/OR a potassium (K+) < 3.5 mmol/L or > 5.2 mmol/L AND/OR a corrected calcium (Ca++) < 2.1 mmol/L or > 2.7 mmol/L
6	Symptomatic bradycardia	Heart rate of < 50 beats with symptoms
7	New major constipation	Subjective symptoms of hard stools and/or fewer than three bowel movements per week and/or supported by nursing records
8	Acute bleeding	Melena or hematuria or hematemesis or hemoptysis with or without a drop in hemoglobin level > 2 g/dL (not due to rehydration) or associated symptoms (hypotension, tachycardia, pallor) or secondary renal failure
9	Acute dyspepsia/nausea/vomiting	Subjective symptoms of acute "indigestion"/"upset stomach" or acute abdominal pain or acute refusal to eat or acute heartburn/acid reflux or acute nausea/vomiting
10	Acute diarrhea	New liquid stools reported by the patient or the nursing staff or new liquid stools detected by medical staff on physical examination or new liquid (nonsolid) stools occurring more than three times in 24 hours
11	Acute delirium	Confirmed by a reliable witness and the DSM-V criteria. Supported by a 4-AT ≥ 4 and/or MMSE $< 23/30$
12	Acute hypoglycemia	Symptoms with a blood glucose of < 3.5 mmol/L or < 63 mg/dL
13	Unspecified adverse event	For ADRs not specified above (e.g., acute liver failure, anaphylaxis)

Abbreviations: 4-AT, 4 As test; ADRs, adverse drug reactions; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MMSE, mini-mental state examination.

certain ADRs causing or contributing significantly to hospital admission. Edwards and Aronson's definition of an ADR was used (i.e., "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product") [32].

To limit potential bias from selective ADR reporting and to ensure ADRs were not missed, a "trigger list" comprising the 12 most common drug-related adverse events (AEs) was used [33]. This list was derived from previous studies within our research group and aims to standardize the identification and classification of ADRs [34]. Each potential ADR on this trigger list is initially identified by the occurrence of an AE represented by a clearly defined clinical symptom or syndrome (e.g., a fall, bleeding, delirium, or metabolic disturbance such as hyponatremia or hypoglycemia; Table 1). The identification of such AEs triggers a standardized process of medication review that investigates the precise sequence of clinical events to determine whether a medication caused or contributed to the AE. Figure 1 outlines this process. ADRs not listed in the trigger list were also studied (e.g., anaphylaxis).

ADR Causality, Severity, Predictability, and Preventability

Causality was assessed using the WHO-Uppsala Monitoring Centre criteria, whereby the likelihood of a drug causing the

AE is certain, probable, possible, unlikely, or unrelated [35] (Table 2). ADR severity was assessed using the Hartwig & Seigel scale, in which severity is graded according to clinical consequence on a scale of one to seven [36] (Table 2). A grade 1 ADR requires no medical intervention; a grade 7 ADR represents a fatal event. Preventability was evaluated using Hallas criteria (i.e., definitely avoidable, possibly avoidable, and unavoidable) [37]. ADRs were deemed predictable if they were listed in the relevant summary of product characteristics (SmPCs) as common ($\geq 1\%$ and $< 10\%$) or very common ($\geq 10\%$) occurrences. The SmPCs of medications were accessed on an online up-to-date repository of medications information (www.medicines.ie).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 22 (IBM, Armonk, NY). Descriptive data included mean and SD for normally distributed variables and median and IQR for nonparametric variables. Differences in the distribution of categorical variables were compared using the Pearson's chi-square test and continuous variables using the independent *t* test. The Mann-Whitney *U* and Kruskal-Wallis tests were employed to determine independence of two or more nonparametric variables, respectively. Logistic regression was used to determine the influence of gender, age, medication number, and burden of comorbidity on ADRs. A probability value of $< .05$ was considered statistically significant.

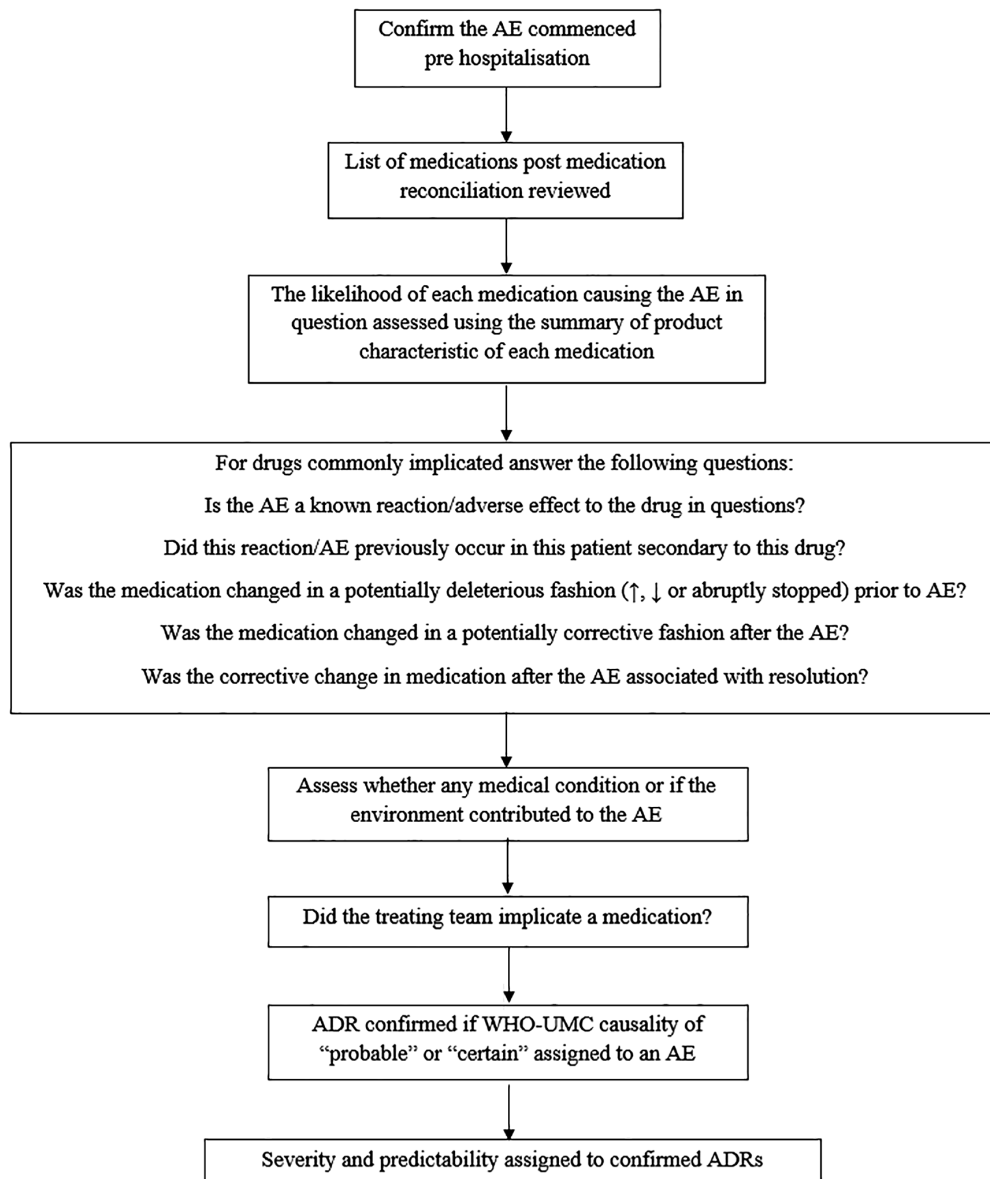


Figure 1. Standardized process to determine whether a medication caused or contributed to an AE. Abbreviations: ADR, adverse drug reaction; AE, adverse event; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

RESULTS

Baseline Demographics

Four hundred and eight oncology inpatients and 90 oncology day unit attendees were screened for study inclusion. In total, 350 patients, comprising 265 hospital inpatients and 85 oncology day unit admissions, enrolled in this study. Of the hospital inpatients, 201 were admitted emergently (57.4% of study population) and 64 electively (18.3% of study sample). Reasons for exclusion are outlined in Figure 2. Baseline characteristics are presented in Table 3. In brief, 183 patients (52.3%) were female, the mean age was 63.6 (SD 12.1) years, range 16–90, with 36.6% aged 70 years or older.

Prevalence of Multimorbidity

Multimorbidity (≥ 2 chronic conditions) was identified in 96.9% of patients, with 68% having ≥ 5 conditions. The median

number of comorbid conditions in older adults was 7 (IQR 5–10), versus 5 (IQR 3–7) in younger adults. Older adults also had a higher median CIRS score than younger adults (15 [IQR 11–19] vs. 11 [IQR 9–14.5], $p < .001$).

The most common cancer sites were breast (18.3%), lung (16.6%), and colorectal (13.1%), with lung cancer being more prevalent in older patients (22.3% vs. 13.5%, $p = .036$), and breast cancer being more prevalent in younger patients (21.4% vs 12.4%, $p = .038$). The most common non-cancer diagnoses were hypertension (39.7%), dyslipidemia (38%), and gastroesophageal reflux disease (27.1%). Older adults had a higher prevalence of hypertension (62.8% vs. 27.5%, $p < .001$), dyslipidemia (51.2% vs. 31%, $p < .001$), ischemic heart disease (26.4% vs. 8.7%, $p < .001$), atrial fibrillation (22.3% vs. 4.8%, $p < .001$), diabetes mellitus (19.8% vs. 10%, $p = .011$), cardiac failure (5.1% vs. 0.9%, $p = .015$), osteoarthritis (24% vs. 12.2%, $p = .005$), and hypothyroidism (18.2% vs. 10.5%, $p = .043$).

Table 2. WHO-UMC causality criteria and Hartwig and Siegel Severity Scale

WHO-UMC criteria		Hartwig and Siegel Severity Scale	
Causality	Conditions (All conditions need to be complied with for each causality criteria)	Grade	Explanation
Certain	Event/laboratory test abnormality with plausible time relationship to intake of a drug Cannot be explained by disease or other drugs Response to withdrawal plausible Event definitive pharmacologically or phenomenologically Rechallenge satisfactory, if necessary	1	An ADR occurred but no change in treatment with suspected drug
		2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in length of stay
Probable	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required	3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, or an antidote or other treatment. No increase in length of stay
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear	4	Any level 3 ADR that increases length of stay by at least 1 day or the ADR was the reason for admission
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable Disease or other drugs provide plausible explanations	5	Any level 4 ADR that required intensive medical care
		6	Any ADR causing permanent harm to the patient
Conditional/ Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination	7a	The ADR was indirectly linked to the death of the patient
Unassessable/ Unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified	7b	The ADR was directly linked to the death of the patient

Abbreviations: ADR, adverse drug reaction; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

Prescribed Medications

A total of 2,575 medications were prescribed regularly to 326 (93.1%) of 350 patients, and a further 491 medications were prescribed “as required” to 280 (80%) patients. The median number of medications was 5 (IQR 3–8), range 0–24. Polypharmacy (≥ 6 medications) was identified in 47.1% of patients and major polypharmacy (≥ 11 medications) in 11.4%. Older patients were prescribed more medications than younger patients (median 7 [IQR 4–9] vs. 4 [IQR 2–7], $p < .001$). Older patients had higher rates of polypharmacy (63% vs. 38.4%, $p < .001$) and major polypharmacy (19% vs. 7.4%, $p = .001$).

Proton pump inhibitors (58.3%), opioids (30.9%), and statins (29.1%) were the most common non-cancer prescriptions. Older patients were more commonly prescribed antiplatelet therapy (32.2% vs. 11.8%, $p < .001$), statins (43.8% vs. 21.4%, $p < .001$), beta blockers (37.2% vs. 16.2%, $p < .001$), and angiotensin receptor blockers (23.1% vs. 7.9%, $p < .001$). 5-fluorouracil (18.2%), doxorubicin (12.4%), and oxaliplatin (12%) were the most commonly prescribed SACTs, with older patients less likely to receive SACTs than younger patients (56.2% vs. 75%, $p < .001$).

Adverse Events and Adverse Drug Reactions

A total of 274 AEs were identified in 166 (47.4%) patients, of which 139 were specifically categorized as ADRs in 90 (25.7%)

patients (Table 4). Of these, an ADR caused or contributed significantly to hospitalization in 75 patients (21.5% of the study sample and 28.3% of oncology patients requiring hospitalization); 72 of 201 emergency admissions (35.8%) and 3 of 64 (4.7%) elective admissions were related to ADRs (Fig. 3). ADRs did *not* cause or contribute significantly to admission in 15 patients. Rather, these were incidental and were categorized as trivial. Clinically significant ADRs were not identified in patients attending the oncology day unit.

ADR Causality, Severity, Predictability, and Preventability

The most common ADRs were neutropenia with infection (25.3%), dyspepsia/nausea/vomiting (20%), and constipation (20%). The 12-point ADR trigger list identified 64% ($n = 48$) of all ADRs that caused or contributed to hospitalization. Older and younger adults were equally likely to experience the same ADR type ($p = .493$), as were men and women ($p = .142$).

An ADR probably or certainly caused or contributed significantly to hospitalization in 75 patients (21.5%). ADRs occurred in similar frequencies in older and younger patients secondary to SACTs (8.3% vs. 13.1%, $p = .295$), non-SACTs (10.7% vs. 8.3%, $p = .107$), and a combination of both (0% vs. 1.3%, $p = .240$). Females were more likely to experience

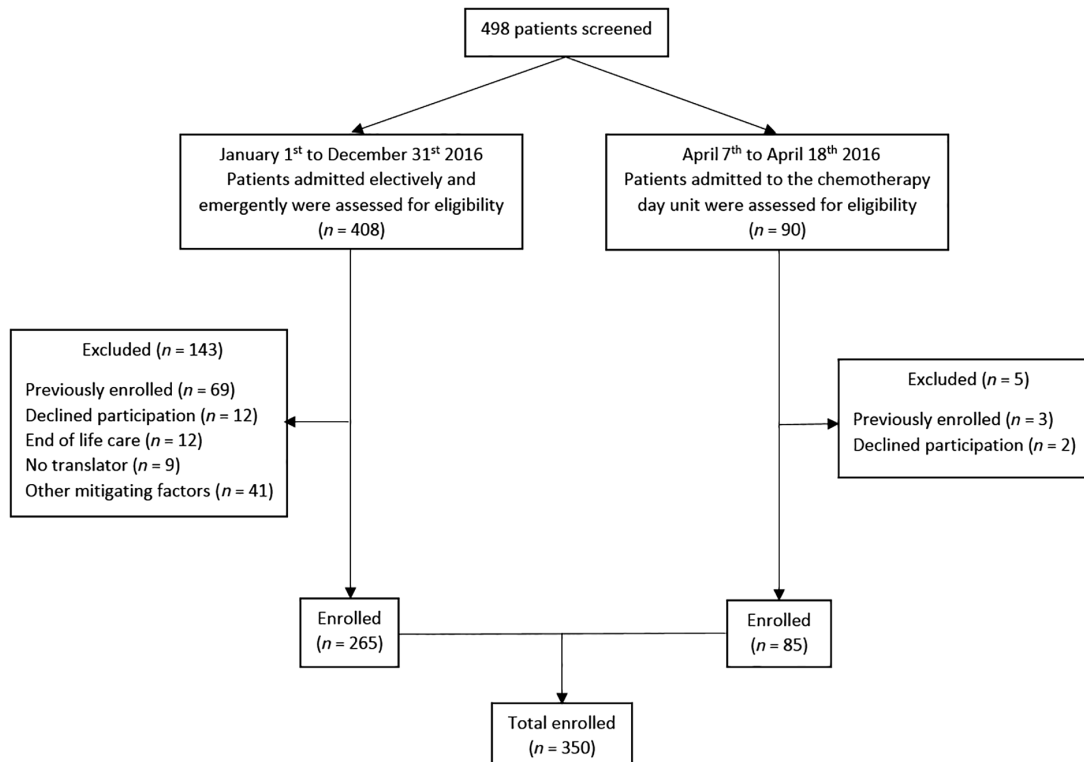


Figure 2. Participant screening, exclusion, and enrollment.

an ADR secondary to SACT (15.8 vs. 6.6%, $p = .005$). Males were more likely to experience ADRs secondary to non-cancer-specific treatment (10.8 vs. 7.7%, $p = .040$). Drugs implicated in ADRs are listed in Table 3; the most common were SACTs ($n = 40$), opioids ($n = 13$), corticosteroids ($n = 5$), and nonsteroidal anti-inflammatories ($n = 4$).

Of the 75 ADRs, 73 (97.3%) were categorized as the principal reason for admission using the Hartwig and Siegel severity scale (grade 4). Two ADRs (2.7%) required intensive medical input (grade 5). Sixty-seven ADRs (89.3%) were categorized as predictable. Twenty-two ADRs (29.3%) were definitely avoidable, 25 (33.3%) possibly avoidable, and 28 (37.4%) unavoidable using Hallas criteria.

ADR Predictor Variables

When day unit admissions were removed from the analysis, all of whom had no clinically significant ADR, it was identified that ADRs were more common in patients prescribed SACT than those not (73.3% vs. 54.7%, $p = .005$). Otherwise, there was no difference between those who experienced ADRs and those who did not (Table 5). No variables were significantly associated with ADRs. Logistic regression examined the influence of age, gender, SACT, number of comorbidities, and number of medications on the risk of ADR. No predictor variables were identified.

DISCUSSION

This is the first study to rigorously assess ADRs as a cause of hospitalization in an oncological population using a standardized methodology of evaluating adverse clinical events to determine ADRs.

Cancer is often one of several diagnoses in patients. Accordingly, many experience high levels of polypharmacy and major polypharmacy, putting them at an increased risk of developing ADRs, as identified in this study. Many medications involved in cancer treatment regimens have the potential to worsen other conditions (e.g., corticosteroid use in diabetes mellitus). In addition, some commonly prescribed drugs have the potential to interact with chemotherapy (e.g., 5-fluorouracil increases the anticoagulant effect of warfarin). During treatment with many chemotherapeutic agents, up to 30% will experience nausea, vomiting, or diarrhea. This can have implications for other medications, specifically antihypertensive agents, which when volume depleted could provoke dizziness and falls. Additionally, ongoing diuretic use in this context could increase the risk of a patient developing an acute kidney injury. Older adults in this study were more likely to have a diagnosis of diabetes mellitus, atrial fibrillation, and hypertension, putting them at a higher risk of such medication-related adversity.

The vast majority of cancer drugs, as expected, are prescribed by oncologists, but the majority of other drugs are prescribed by patients' general practitioners (GPs) or other hospital specialists. An extensive knowledge of chemotherapeutic agents and medications required to treat non-cancer conditions is required to assess risk and adjust medications accordingly. At present, this does not appear to be the sole responsibility of any one doctor. Once a cancer diagnosis is made, patients and other doctors often defer to the treating oncologist for treatment of *all* ailments, despite many patients having complex non-cancer multimorbidity. This highlights the need for specialist geriatric assessment, as recommended by ASCO, as it has the potential to identify and manage complex

Table 3. Characteristics of study population according to age category (*n* = 350)

Variable	<70 years (<i>n</i> = 229) (65.5%)	≥70 years (<i>n</i> = 121) (34.5%)	<i>p</i> value
Multimorbidity			
Conditions, median (IQR)	5 (3–7)	7 (5–10)	<.001 ^a
≥ 2 conditions	218 (95.2)	121 (100)	.0014 ^a
≥ 5 conditions	139 (60.7)	90 (81.8)	<.001 ^a
CIRS, median (IQR)	11 (9–14.5)	15 (11–19)	<.001 ^a
Medications, median (IQR)	4 (2–7)	7 (4–9)	<.001 ^a
≥ 6 medications	88 (38.4)	77 (63.6)	<.001 ^a
≥ 11 medications	17 (7.4)	23 (19)	<.001 ^a
Functional ability			
Barthel Index, median (IQR)	20 (20–20)	20 (18–20)	<.001 ^a
Independent (≥20)	191 (83.4)	80 (66.1)	<.001 ^a
Low dependency (16–19)	32 (14)	31 (25.6)	.007 ^a
Moderate dependency (11–15)	6 (2.6)	8 (6.6)	.070
High dependency (6–10)	0 (0)	0 (0)	.017
Maximum dependency (0–5)	0 (0)	0 (0)	
Driving			
History of driving	187 (82.4)	92 (77.3)	.257
Current driving	130 (57.3)	68 (57.1)	.982
Cognitive ability			
MMSE, median (IQR)	28 (26–30)	27 (25–29)	.029 ^a
Number of patients completed MMSE (≥65 years)	56 (86.2)	109 (90.1)	.420
Normal cognition (25–30)	49 (87.5)	89 (81.7)	.336
Mild cognitive impairment (20–24)	4 (7.1)	15 (13.8)	.207
Moderate cognitive impairment (10–19)	3 (5.4)	5 (4.6)	.827
Severe cognitive impairment (0–10)	0 (0)	0 (0)	
Alcohol and smoking			
Consumes alcohol weekly	62 (27.7)	27 (22.3)	.277
Consume greater than or equal to recommended weekly limit	14 (6.3)	10 (8.3)	.483
History of smoking	129 (56.3)	66 (54.5)	.749
Current smokers	30 (13.1)	5 (4.1)	.008 ^a

Data are presented as *n* (%) unless otherwise noted.

^a*p* value is statistically significant.

Abbreviations: CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; MMSE, mini-mental state examination.

multimorbidity and associated polypharmacy in older patients with cancer, thus impacting treatment decisions and potentially improving outcomes.

Interestingly, many ADRs in patients with cancer in this study were *not* caused by toxic SACTs, with the most commonly implicated non-SACT medications being opioids, corticosteroids and NSAIDs, medications that commonly cause ADRs in the general population [9, 24, 28]. Both older and younger adults experienced ADRs at similar frequencies secondary to both SACTs and non-SACTs, highlighting the need for vigilance for potential ADRs in oncological patients of all ages. The adverse event trigger list used in this study may prove useful in this regard (i.e., if a patient presents with a new clinical event such as a fall, worsening confusion, major bleeding, metabolic disturbance, or major constipation, then this should prompt the treating clinician to evaluate all prescribed medications as being potentially causative). This

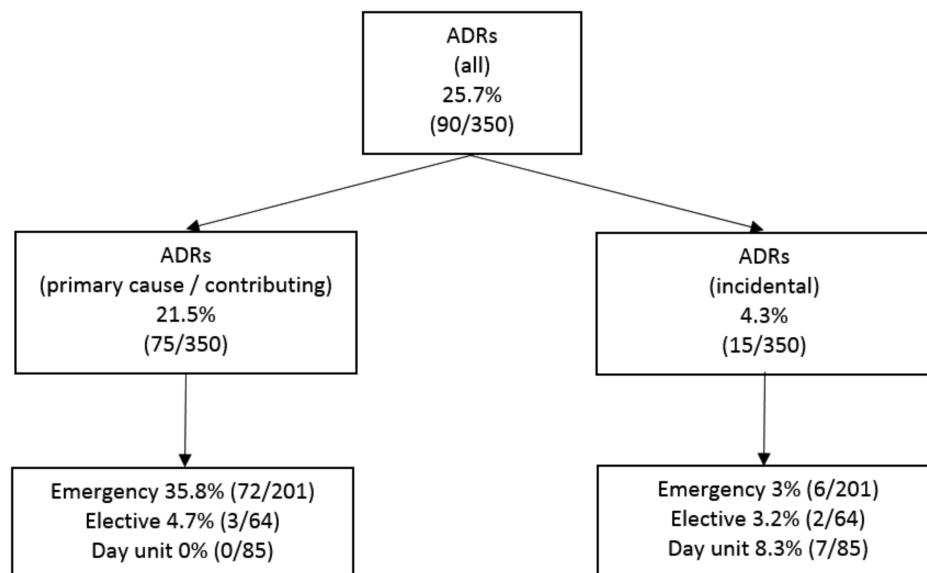
offers an opportunity to intervene in prescribing practices early and thus either avoid ADRs or improve their recognition so that they can be identified early and adverse consequences minimized or avoided. This could be achieved through specialist geriatric assessment, which encompasses (a) dose adjustment or deprescribing where appropriate because of age-related and cancer-related changes in pharmacokinetic and pharmacodynamic responses to commonly prescribed medications and (b) therapeutic goal setting where stringent targets for primary or secondary prevention of illness may no longer be a priority. Deprescribing of potentially futile medications could reduce the risk of potential ADRs in such cases. In the present study, 39.1% of patients died within 6 months of their hospital admission, many of whom continued to receive preventive therapies such as statins during their final months. Deprescribing of such medications could be negatively viewed by patients and clinicians. However, discussions regarding appropriate

Table 4. Adverse events, adverse drug reactions, and causative drug classes

AE type	AE	All ADRs	ADRs (causing/ contributing to admission)	Drug class implicated	Total (n = 75)
New onset fall/s	16 (4.6)	6 (1.7)	5 (1.4)	1 SACT	40 (53.3)
New onset unsteady gait	9 (2.6)	3 (0.9)	2 (0.6)	2 Opioids	13 (17.3)
Acute kidney injury	26 (7.4)	5 (1.4)	5 (1.4)	3 Steroids	5 (6.7)
Symptomatic orthostatic hypotension	4 (1.1)	3 (0.9)	3 (0.9)	4 Nonsteroidal anti-inflammatories	4 (5.3)
Major serum electrolyte disturbance	49 (14)	13 (3.7)	12 (3.4)	5 Antibiotics	2 (2.7)
Symptomatic bradycardia	1 (0.3)	1 (0.3)	1 (0.3)	6 Diuretics	2 (2.7)
New major constipation	30 (8.6)	19 (5.4)	14 (4)	7 Thyroid hormone	1 (1.3)
Acute bleeding	13 (3.7)	6 (1.7)	6 (1.7)	8 DMARD	1 (1.3)
Acute dyspepsia/nausea/vomiting	52 (14.9)	30 (8.6)	29 (8.3)	9 Anticholinergic	1 (1.3)
Acute diarrhea	25 (7.1)	17 (4.9)	10 (2.9)	10 Alpha blocker	1 (1.3)
Acute delirium	21 (6)	8 (2.3)	8 (2.3)	11 Proton pump inhibitor	1 (1.3)
Symptomatic hypoglycemia	0 (0)	0 (0)	0 (0)	12 Laxative	1 (1.3)
Other	28 (8)	28 (8)	28 (8)	13 SACT and antiemetic	1 (1.3)
				14 Benzodiazepine and opioid	1 (1.3)
Total number	274	139	123	15 Warfarin and DOAC	1 (1.3)
Patients involved	166 (54)	90 (25.7)	75 (21.5)		

Data are presented as n (%).

Abbreviations: ADR, adverse drug reaction; AE, adverse event; DMARD, disease-modifying antirheumatic drug; DOAC, direct oral anticoagulants; SACT, systemic anti-cancer treatment.

**Figure 3.** Distribution and classification of ADRs.

Abbreviation: ADRs, adverse drug reactions.

deprescribing are required so that medication cessation or dose adjustment is not viewed as withdrawal of care but rather prescription optimization to minimize ADRs, drug-drug, and drug-disease interactions.

There were some limitations to this study. First, patients with cancer *not* under the care of an oncology service were excluded. Such patients may be ineligible for SACT or radiotherapy but may also have complex multimorbidity, polypharmacy,

and ADRs. Prescribing optimization and review of therapeutic goals in these patients is also warranted. Second, patients could only enroll once in this study. Therefore, prevalence rates of multimorbidity and polypharmacy are accurate; however, it is possible that ADRs on repeat admissions were missed because of this exclusion.

This study highlights the importance of an integrated care approach for patients with cancer, particularly older

Table 5. Univariate analysis of association

Variable	ADRs (n = 75)	No ADRs (n = 275)	Total (n = 350)	p value
Gender (female)	47 (57.3%)	140 (50.9%)	183 (52.3%)	.323
Age, years, median (IQR), range	65 (56–70), 16–89	66 (57–72), 18–90	65.5 (57–72), 16–90	.599
Conditions, median (IQR), range	6 (4–8), 1–15	6 (4–8), 1–18	6 (4–8), 1–18	.816
CIRS score, median (IQR), range	13 (10–17), 4–29	12 (9–16), 2–30	13 (9–16), 2–30	.292
Medications, median (IQR), range	5 (3–8), 0–24	5 (3–8), 0–22	5 (3–8), 0–24	.502
Length of stay, median (IQR)	5 (3–10)	6 (4–11)	6 (3–10)	.389
Death during index admission	6 (8%)	10 (3.6%)	16 (4.6%)	.109
Death within 6 months of enrollment	29 (38.7%)	99 (36%)	127 (39.1%)	.364
Currently prescribed SACT	55 (73.3%)	187 (68%)	242 (69.1%)	.375

Abbreviations: ADRs, adverse drug reactions; CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; SACT, systemic anticancer treatments.

adults. Older adults may benefit from CGA at the time of cancer diagnosis and during treatment when the risk of drug-drug and drug-disease interactions is likely to be at its peak. Such an approach may result in optimization of cognitive and functional abilities and appropriate optimization of medications to include dose adjustment and deprescribing where appropriate. The application of prescribing tools such as STOPP [38, 39] and OncPal [40] could assist in reducing medication burden in a structured fashion and thus prevent ADRs. Medication reviews are an important part of the treatment of cancer, and oncologists, GPs, and other treating physicians need to be educated regarding the potential for medication-related harm during this high-risk time.

CONCLUSION

This study shows that multimorbidity, polypharmacy, and ADRs are highly prevalent in patients with cancer and that ADRs caused by SACT and non-cancer medications are a significant cause of acute hospitalization in oncology patients, accounting for 35.8% of emergency admissions and affecting 21.5% of the study population. Such patients may benefit from Comprehensive Geriatric Assessment and specialist medication evaluation at this time.

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