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Hospitalization due to Adverse Drug Events in Older Adults with Cancer, a Retrospective Analysis

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Abstract

Introduction

Geriatric oncology is a rapidly evolving field of practice, where comprehensive geriatric assessments (CGA) and multidisciplinary team (MDT) input have the potential to improve patient outcomes. Polypharmacy and potential drug interactions (PDI) have been associated with an increased risk of adverse outcomes in older adults with cancer, receiving systemic anti-cancer therapy (SACT). Our aim was to assess the incidence of unplanned hospitalization in older adults with cancer attending medical oncology outpatient clinics and to determine whether an unplanned hospitalization was potentially due to an adverse drug event (ADE).

Materials and Methods

We identified patients who attended a medical oncology outpatient appointment from January 1st to March 31st, 2018. Medical records were examined to identify any unplanned hospital admissions between the clinic visit date and three and six months after initial clinic visit. Incidences of unplanned hospitalization were assessed to determine if an ADE potentially occurred.

Results

Data collected from 174 patients were analyzed. Over half (57%) were female, median age was 75 years and 53% had a favorable performance status. The most common malignancies were gastrointestinal (GI) at 31% (n=54), breast 29% (n=51), and genitourinary 22% (n=37). Seventy-two percent had advanced disease (Stage III/IV) and 61% had systemic therapy (SACT and hormonal therapy). Polypharmacy (≥5 medications) was observed in 77% of patients. The total number of admissions at six months was 99, with 55% of these potentially due to an ADE. On multivariate analysis breast cancer (p=<0.001), lung cancer (p=0.034) performance status (p=<0.001), monochemotherapy (p=0.012), polychemotherapy (p=<0.001) radiotherapy (p=0.048), and polypharmacy (p=0.06) were independent predictors of unplanned hospitalization. Breast cancer (p=0.008), GI cancer (p=0.019), monochemotherapy (p=0.039), and polychemotherapy (p=<0.001) were independent predictors of unplanned hospitalization due to ADE on multivariate analysis

Discussion

We observed that older adults with cancer have a high risk of unplanned hospitalization due to ADE. Medication review as part of a CGA in newly diagnosed older adults with cancer by a clinical pharmacist is recommended. This may identify opportunities to avoid medications that could potentially lead to unplanned hospitalization.

Background

Geriatric oncology is a rapidly evolving field of practice, where comprehensive geriatric assessments (CGA) and multidisciplinary team (MDT) input have the potential to improve patient outcomes [1]. The optimization of medicines in this patient cohort is an area where pharmacists may have the opportunity to reduce the incidence of hospitalization as a result of adverse drug events (ADE) [2]. The literature widely reports the incidence of hospitalization due to systemic anti-cancer therapy (SACT) toxicity in both retrospective and prospective studies [[3-6]]. However, there are few studies with a focus on hospitalization due to non-SACT medications in older adults with cancer. In an observational study conducted in Ireland, Lavan and colleagues reported that more than a quarter of hospitalizations in older adults with cancer were potentially due to ADE, which included both SACT toxicity and non-SACT ADE [7]. Nightingale et al. have also reported on the lack of data in this area, and highlighted it as a research priority for clinicians caring for older adults with cancer [8].

Polypharmacy and potential drug interactions (PDI) have been associated with an increased risk of adverse outcomes in older adults with cancer, receiving SACT [9].These patients have the added complexity of potentially being offered both radiotherapy and surgery as part of their cancer journey [10]. Each of these treatment options typically contain additional ancillary medications as part of the treatment protocol, which can add to pre-existing polypharmacy, potentially inappropriate medications (PIM), and PDI. This in turn can lead to ADEs, which may potentially result in unplanned hospitalization [9]. Pharmacist-led medication reviews have demonstrated a benefit in preventing ADE in older adults in an inpatient setting, [11] and in identifying PIM and medication related issues in older adults with cancer [[2, 12, 13]] and reducing the prevalence of PIM in this cohort [14].

Many ADEs that result in unplanned hospitalization due to SACT toxicity, such as neutropenic sepsis due to cytotoxic chemotherapy, are unavoidable [15]. In contrast, ADEs in non-SACT medications, in older adults have been shown to be potentially avoidable in approximately 50% of cases [[16, 17]].

Our aim was to assess the incidence of unplanned hospitalization in older adults with cancer attending medical oncology outpatient clinics and to determine whether an unplanned hospitalization was potentially due to an ADE.

Materials and Methodology

Objectives

To conduct a retrospective analysis of older adults with cancer seen in a medical oncology outpatient setting and assess the incidence of hospitalization due to ADE at 3- and 6-month time points after the index clinic visit.

Secondary objectives included assessment of the incidence of hospitalization in older adults with cancer associated with non-SACT medication and investigate any association between polypharmacy and hospitalization.

Patient Identification

Our institution is a tertiary cancer center, with approximately 431 inpatient and 85 day care beds, catering for a population of approximately 500,000 people in the Southeast of Ireland.

A report was generated using the Integrated Patient Management System (iPMS) software to identify all patients who had attended a medical oncology outpatient department (OPD) (new or review appointment) from January 1st to March 31st, 2018. The following exclusion criteria were applied: <70 years at the clinic visit date; patients who did not attend their OPD appointment; older adults with cancer not attending a medical oncology appointment were also excluded.

Ethical approval was obtained from the Health Service Executive (HSE) Southeast Research Ethics Committee.

Data Collection and Extraction

The following patient data were collected from iPMS: age; gender; clinic visit date. A medical chart review was used to collect the cancer type, cancer stage and Eastern Cooperative Oncology Group performance status (ECOG PS) [18]. A G8 score [19], was calculated for the patient using medical notes in conjunction with clinic visit notes. Co-morbidities were identified using the patients' medical record, and the Charlson Comorbidity Index [20] was used to quantify the co-morbidity burden. Height and weight were obtained from the clinic visit notes and ideal body weight, and body surface area (BSA), using actual and ideal body weight, was calculated using the Dubois and Dubois method [21]. Biochemistry results from the clinic visit were also examined and levels of alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, and serum creatinine were obtained. Creatinine clearance

was calculated using the Cockcroft and Gault equation [22]. The patient's medication list was retrieved from the medical records. Non-polypharmacy was defined as <5 medications, polypharmacy was defined as ≥5 medications and hyperpolypharmacy was defined as ≥10 medications. The patient's treatment type was retrieved from either the medical notes, or the chemotherapy dispensing software from the pharmacy department. Patients were categorized into hormone/targeted therapy, monochemotherapy (one cytotoxic agent), polychemotherapy (>1 cytotoxic agent), radiotherapy (patients who received radiation alone as their treatment), surgery (patients who only received surgical intervention to treat their cancer), or supportive care/surveillance (patients who were not on active cancer therapy at the time of their clinic visit). iPMS and the medical records were examined to identify any unplanned hospital admissions between the clinic visit date and two time points, namely three and six months after initial clinic visit date. For patients who were admitted, two pharmacists examined whether an ADE was possibly associated with the admission by analyzing the patient's medication list on admission. If an ADE was suspected, the summary of product characteristics (SPC) of the medication was used to see if the ADE was listed. The likelihood of the ADE being avoidable was assessed using the method outlined by Hallas and colleagues, adapted for retrospective analysis [23]. We also examined, in the case of SACT toxicity, the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading of the toxicity [24], and whether, as a result of the ADE, SACT dosing was subsequently altered or discontinued. Two pharmacists undertook the review of each patient's medical record independently and validated their findings. In the case of any disagreement a third pharmacist was the final arbiter.

Data Analysis

The mean, standard deviation, and range for continuous variables and the frequencies for categorical variables were calculated as part of a descriptive analysis.

A univariate logistic regression analysis was used to assess the impact of cancer site, gender, stage, comorbidities performance status, treatment type, and polypharmacy status (non-polypharmacy, polypharmacy and hyperpolypharmacy) on unplanned hospitalization (dependent variable) and ADE (dependent variable) separately. Multivariate logistic regression analysis was then used to identify independent predictors of unplanned

hospitalization (dependent variable) and ADE (dependent variable) separately. A priori level of p <0.05 was deemed statistically significant.

R studio was used to conduct data analysis [25]

Results

Data collected from 174 patients who attended the medical oncology OPD were analyzed. Patient demographics are summarized in Table 1. Over half (57%; n= 100) were female, median age was 75 years and 53% (n=92) had a favorable performance status (ECOG of 0-1). The most common malignancies were gastrointestinal (GI) at 31% (n=54), breast 29% (n=51) and genitourinary 22% (n=37). Seventy-two percent (n=126) had advanced disease (Stage III/IV) and 61% (n=107) had systemic therapy (SACT and hormonal therapy), with 18% (n=31) receiving polychemotherapy (≥2 SACT agents). Polypharmacy was observed in 77% (n=134) of patients with 37% (n=49) of these receiving hyperpolypharmacy.

Hospitalization

The incidence of unplanned hospitalization at 3 and 6 months, as well as the prevalence of unplanned hospitalization potentially due to ADE, as well as potentially avoidable ADE is outlined in Table 2. Within three months of clinic attendance, 30% (n=52) of patients were hospitalized, of whom 60% (n=31) were hospitalized potentially due to an ADE (Table 2). At the six months' time point, the total number of hospitalized patients rose to 43% (n=75), with 56% (n=42) of all those hospitalizations potentially due to an ADE. Multiple unplanned hospitalizations were observed in 9% of patients (n=16).

The total number of admissions at six months was 99 admissions in 75 patients, with 55% (n=54) of these potentially due to an ADE (figure 2). Thirty-three percent (n=18) of these admissions were deemed to be potentially avoidable. The relationship between unplanned hospitalization and the total number of medications a patient was taking is represented in figure 1. Unplanned hospitalization potentially due to ADE is shown in figure 2. SACT and non-SACT Toxicity in Hospitalized Patients

Data for SACT and non-SACT toxicity are summarized in Table 3. SACT toxicity was deemed potentially responsible for 72% (n=39) of patient admissions due to ADE. SACT dosing was subsequently dose reduced in 28% of these patients (n=11) and discontinued in 41% (n=16)

of these patients. Non-SACT toxicity was potentially responsible for 28% (n=15) of unplanned hospitalizations due to ADE.

The most frequent non-SACT medications suspected of causing or contributing to an unplanned hospitalization were proton pump inhibitors (PPIs) (n=3), non-steroidal anti-inflammatory drugs (NSAIDs) (n=2), and antipsychotics (n=2).

Medications implicated in potential non-SACT related admissions met either the Screening Tool of Older Person's Prescriptions (STOPP) [26] or Beers criteria [27] in 7/15 (47%) of admissions.

Predictors of Unplanned Hospitalization and Adverse Drug Events

Breast and lung cancer diagnoses, performance status, monochemotherapy, polychemotherapy, radiotherapy, polypharmacy, and hyperpolypharmacy were all found to be statistically significantly associated with unplanned hospitalization on univariate analysis (Table 4). On multivariate analysis breast cancer (p=<0.001), lung cancer (p=0.034) performance status (p=<0.001), monochemotherapy (p=0.012), polychemotherapy (p=<0.001) radiotherapy (p=0.048), and polypharmacy (p=0.06) were independent predictors of unplanned hospitalization.

Breast and GI cancer diagnoses, stage, monochemotherapy, polychemotherapy, and hyperpolypharmacy were statistically significantly associated with unplanned hospitalization due to ADE on univariate analysis (Table 5). Breast cancer (p=0.008), GI cancer (p=0.019), monochemotherapy (p=0.039), and polychemotherapy (p=<0.001) were independent predictors of unplanned hospitalization due to ADE on multivariate analysis.

Discussion

To our knowledge, this is the first report of the incidence of unplanned hospitalization due to any ADE in older adults with cancer, including those on active surveillance, receiving supportive care, surgery, radiotherapy alone and/or SACT. The prevalence of ADE in hospitalized older adults with cancer in an Irish setting has been previously reported [7], however, that study did not include an ambulatory patient cohort.

We have demonstrated that older adults with cancer have a high prevalence of polypharmacy, which is important given the association between polypharmacy and ADE in this patient cohort [[28-32]]. Drug-drug interactions have also been identified as being highly prevalent and implicated in poorer outcomes in older adults with cancer [[9, 33]].

The independent predictors for unplanned hospitalization we identified are unsurprising. Patients with poorer performance status, and patients receiving either monochemotherapy, polychemotherapy or radiation therapy, and polypharmacy were all independently associated with an increased risk of hospitalization, as well as patients with a diagnosis of breast or lung cancer as their primary malignancy.

The analysis in unplanned hospitalization due to ADE, however, is interesting. Monochemotherapy and polychemotherapy were strong, independent predictors of ADE as opposed to polypharmacy status, as well as patients with a diagnosis of breast or lung cancer as their primary malignancy. Hyperpolypharmacy was significantly associated with unplanned hospitalization due to ADE on univariate analysis, but not on multivariate analysis. This could possibly be driven by patients on SACT, who require ancillary and supportive care medications, creating an overlap between the subgroups. This would suggest that the chemotherapeutic components of the medication list for patients with hyperpolypharmacy was ultimately responsible for ADE. A larger, prospective study would help reaffirm this hypothesis.

Cancer stage was also significantly associated with unplanned hospitalization due to ADE on univariate analysis, but not on multivariate analysis. Our hypothesis for this finding is that patients with advanced cancer are typically offered chemotherapy, often polychemotherapy, whereas patients with lower grade cancers may require surgical intervention alone. Finally, monochemotherapy was significantly associated with unplanned hospitalization due to ADE, but to a lesser degree than polychemotherapy. This may be in part, due to the less toxic nature of monochemotherapy relevant to polychemotherapy [34]. This suggests that the level of risk associated with the medication being administered is as important for ADE as the actual total number of medications, and in some instances may be more important, clinically [9].

Our data analysis evaluates data prior to patients routinely receiving a CGA at our institution. The effective introduction of a medication review and optimization of medication use, as part

of a CGA, could prevent potentially avoidable ADEs, hospitalization due to ADE and drug-drug interactions. Potentially inappropriate medications would be identified and deprescribed where appropriate [35], using tools such as Screening Tool of Older Person's Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) [26] and Beers Criteria [27]. A clinical pharmacist with specialist knowledge of oncology is ideally placed to conduct these medication reviews. The International Society of Geriatric Oncology (SIOG) Nursing and Allied Healthcare (NAH) working group have recently published guidance on how to conduct these reviews [36].

It is recognized that the feasibility of offering a medication review, as part of a CGA, to all older adults with cancer may be challenging from a resource viewpoint [36]. However, given that patients experiencing polypharmacy and drug-drug interactions are at an increased risk of adverse outcomes [28], and there is no single cut-off for polypharmacy in terms of predicting adverse outcomes with the definition of five or more medications being deemed as "reasonable" [37] it may be tempting to propose a prioritization strategy.

Where medication review as part of a CGA is being implemented and pharmacist resources are scarce, prioritizing patients with hyperpolypharmacy, followed by polypharmacy and then non-polypharmacy is reasonable. However, based on our data, an alternative approach, that considers patients eligible for either monochemotherapy or polychemotherapy may be more clinically relevant, due to the increased risk for unplanned hospitalization and unplanned hospitalization due to ADE. The aim should unequivocally be to reach a level where all patients aged ≥70 years are offered a medication review. Our data show that a prioritization strategy based on number of medications may in fact miss the higher-risk medications that may result in hospital-requiring-ADEs even in the context of a low number of medications, as patients still may experience an unplanned hospitalization due to ADE in the absence of polypharmacy (Figure 2).

Our study has some limitations. It is a retrospective analysis with a relatively small sample size. A further limitation is the challenge, in a retrospective study, to accurately calculate the likelihood of an admission being caused by a suspected ADE, especially in relation to non-SACT medications. Ideally, this should be done prospectively [7]. A limitation of retrospective studies is the inability to address confounding in the study design.

Conclusions

The data from this retrospective analysis shows that older adults with cancer receiving either monochemotherapy or polychemotherapy have a high risk of unplanned hospitalization due to ADE, as well as patients with a diagnosis of breast or GI cancer as their primary malignancy. Medication review as part of a CGA in an outpatient setting for all older adults with cancer, or as part of an inpatient service for newly diagnosed older adults with cancer by a clinical pharmacist is recommended. This may identify opportunities to avoid medications that could potentially lead to unplanned hospitalization.

Figures and Tables

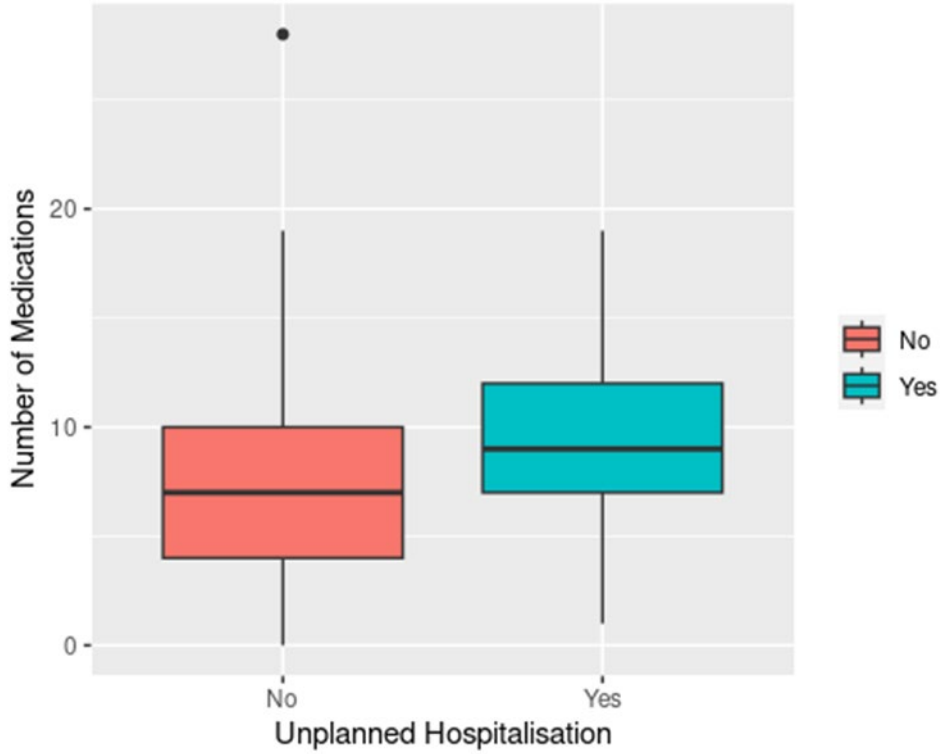


Figure 1: Boxplot distribution of patients according to hospitalization status and number of medications

*note – intended for color reproduction

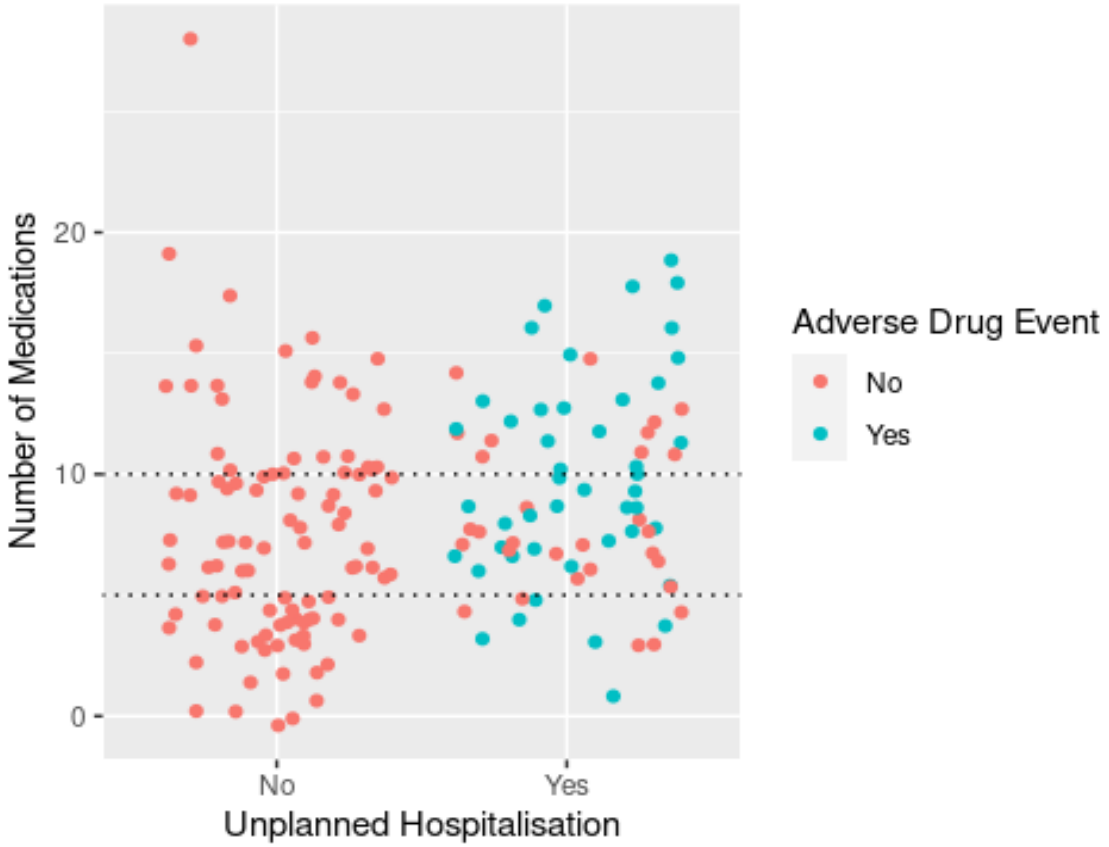


Figure 2: Jitter plot of patients who were hospitalized with an ADE. The dashed lines represent polypharmacy and hyperpolypharmacy on the y-axis.

*note – intended for color reproduction

Table 1: Patient Characteristics

n=174	n	%
Age (years)		
Mean	75.73	
Median (range)	75(70-94)	
Gender		
Male	74	43
Female	100	57
ECOG PS		
0	18	10
1	74	43
2	57	33

3	21	12
4	0	0
Unknown	4	2
Cancer Type		
GI	54	31
Breast	51	29
GU	37	22
Lung	23	13
Melanoma	4	2
CUP	4	2
Head and Neck	1	1
Cancer Stage		
I	6	4
II	42	24
III	37	21
IV	89	51
Treatment Regimen		
Hormone/Targeted therapy	46	26
Monochemotherapy	30	17
Polychemotherapy	31	18
XRT alone	10	6
Surgery alone	7	4
Surveillance	50	29
Medication Burden		
Mean number of medications (range)	12.16 (0 - 28)	
Non-polypharmacy	40	23
Polypharmacy	70	40
Hyperpolypharmacy	64	37

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; GI: gastrointestinal; GU: genitourinary; CUP: cancer of unknown primary; NET: neuroendocrine tumor; XRT: radiotherapy

Table 2: Hospitalization, and hospitalization potentially due to ADE incidence at three- and six-months post clinic visit.

n=174	3 months n(%)	6 months n(%)
Unplanned hospitalization	52 (30)	75 (43)
Unplanned hospitalization potentially due to ADE	31 (60)	42 (56)
Total admissions (n=99)	**n(%)**	
Total number of admissions potentially due to ADE	54 (55)	
Potentially avoidable admissions	18(33)	

Table 3: SACT and non-SACT Toxicity leading to unplanned hospitalization at six months

Potential ADE n=54	n	%
SACT Toxicity	**39**	**72**
CTCAE Grade 3 4 5	 28 9 2	 72 23 5
Subsequent dose reduction	11	28
Treatment discontinued	16	41
Non-SACT toxicity	**15**	**28**

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; SACT: systemic anti-cancer therapy

Table 4. Univariate and multivariate analysis for unplanned hospitalization

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Cancer Site				
Breast	0.34 (-1.74 - -0.47)	**<0.001***	2.61 (-5.31 - -2.24)	**<0.001***
Cancer of Unknown Primary	1.00 (-2.12 – 2.12)	1.00		
Gastrointestinal	0.74 (-0.84 – 0.24)	0.28		
Genitourinary	1.18 (-0.48 – 0.82)	0.62		
Head and Neck	0.00 (NA – 165.35)	0.99		
Lung	2.8 (0.16 – 2.06)	**0.03***	1.15 (-4.22 - -0.21)	**0.034***

Melanoma	3.33 (-4.12 – 0.96)	0.34		
Stage	0.97 (-0.12 – 0.06)	0.48		
ECOG PS	2.07 (0.34 – 1.14)	**<0.001***	2.41 (0.38 – 1.42)	**<0.001***
CCI	1.10 (-0.01 – 0.22)	0.07		
Treatment				
Monochemotherapy	3.97 (0.42 – 2.38)	**0.006***	4.77 (0.38 – 2.81)	**0.012***
Polychemotherapy	9.27 (1.22 – 3.33)	**<0.001***	1.29 (1.21 – 4.02)	**<0.001***
Radiotherapy	7.2 (0.53 – 3.64)	**0.01***	7.55 (0.08 – 4.14)	**0.048***
Surgery	0.52 (-3.66 – 1.25)	0.56		
Surveillance/Supportive Care	1.41 (-0.57 – 1.27)	0.47		
Polypharmacy Status				
Polypharmacy	3.24 (0.33 – 2.10)	**<0.001***	2.83 (-0.04– 2.19)	**0.06***
Hyperpolypharmacy	3.33 (0.34 – 2.13)	**<0.001***	1.29 (-0.89 – 1.42)	0.64

Abbreviations: ECOG PS: Eastern Co-operative Oncology Group Performance Status; CCI: Charlson Co-morbidity Index

*Statistically significant

Table 5: Univariate and multivariate analysis for ADE resulting in hospitalization

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Cancer Site				
Breast	2.14 (-2.32 - -0.89)	**<0.001***	0.06 (-5.14 - -0.88)	**0.008***
Cancer of Unknown Primary	1.00 (-2.12 – 2.12)	1.00		
Gastrointestinal	3.17 (-1.81 - -0.55)	**<0.001***	0.39 (-6.13 - -0.61)	**0.019***
Genitourinary	6.82 (-1.06 – 0.26)	0.25		
Head and Neck	0.00 (NA – 165.35)	0.99		
Lung	3.53 (-2.06 - -0.16)	0.03		
Melanoma	3.33 (-4.12 – 0.96)	0.34		
Stage	0.76 (-0.37 - -0.17)	**<0.001***	1.08 (-0.51 – 0.67)	0.79
ECOG PS	1.11 (-0.18 - 0.39)	0.47		
CCI	1.18 (-0.77 – 1.1)	0.73		
Treatment				

Monochemotherapy	2.42 (-0.16 – 1.97)	**0.006***	3.67 (0.78 – 2.57)	**0.039***
Polychemotherapy	11.02 (1.29 – 3.44)	**<0.001***	2.02 (1.64 – 4.51)	**<0.001***
Radiotherapy	1.16 (-1.86 – 1.75)	0.87		
Surgery	<0.001 (na – 64.97)	0.98		
Surveillance/Supportive Care	0.31 (-2.74 – 0.14)	0.1		
Polypharmacy Status				
Polypharmacy	2.48 (-0.10 – 2.09)	0.097		
Hyperpolypharmacy	3.56 (0.26 – 2.44)	**0.02***	1.38 (-0.93 - 1.67)	0.62

*Statistically significant

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Data Sharing Plan

Data sharing is restricted as part of the ethical approval obtained for the study. Any enquiries can be sent to the corresponding author for anonymized data for scientific purposes.

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Disclaimers

The authors have no conflicts to declare.

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