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Authors	Walsh, Darren J.;O'Driscoll, Michelle;Horgan, Anne M.;Tabb, Eoin;Hannan, Michelle;Morris, Colette;Sahm, Laura J.
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UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Hospitalisation and Adverse Drug Events in a Geriatric Oncology Setting: A Systematic Review of the Literature

Key words:
Drug-Related Side Effects and Adverse Reactions, systematic review, polypharmacy, unplanned hospitalisation, geriatric oncology

Key Points

- Studies designed to assess the incidence of unplanned hospitalisation in older adults with cancer, due to adverse drug events, should assess the clinical significance of medication optimization in this patient cohort.
- The current literature appears to focus solely on patients who are actively receiving systemic anti-cancer therapy.
- There is a paucity of studies that assess unplanned hospitalisation due to adverse drug events in patients who are not receiving systemic anti-cancer therapy. Very few studies assess unplanned hospitalisation due to adverse drug events caused or contributed to by non-systemic anti-cancer therapy medications.

Abstract

Background

Geriatric Oncology is a specialty where a multidisciplinary approach can address the unmet needs of older adults with cancer. Older adults are at increased risk of adverse drug events (ADE) due to age-related changes in pharmacokinetics and pharmacodynamics, increasing treatment complexity, and medication burden.

Objectives

To review the literature to determine the incidence of unplanned hospitalisation due to ADE for all medications, both systemic anticancer therapy (SACT) and non-SACT medications.

Methods

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search included the following databases: PubMed, CINAHL, and Embase. A manual search of Scopus was then performed. Study quality was assessed using the Cochrane Handbook for Systematic Reviews of Interventions, Mixed Methods Appraisal Tool (MMAT) and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.

Results

Overall, three studies were included. One observational study reported 19% of unplanned hospital admissions due to ADE in patients aged ≥70 years with cancer. The first retrospective study reported 24% of unplanned hospital admissions are due to ADE in patients aged ≥70 years with cancer, and the second retrospective study reported 26% of patients with metastatic melanoma treated with immune checkpoint inhibitors had an unplanned hospital admission due to an ADE.

Conclusion

There is a paucity of studies assessing unplanned hospitalisation due to ADE in older adults with cancer. Future studies are needed and should account for the reporting of potential ADE relative to supportive care, ancillary medications, and indeed chronic medications used to treat long-standing comorbidities.

Introduction

Geriatric Oncology is a specialty where a multidisciplinary approach can address the unmet needs of older adults with cancer.[1-3] The International Society of Geriatric Oncology (SIOG) published recommendations in 2005 recommending the use of a Comprehensive Geriatric Assessment (CGA) in older adults with cancer.[4] These recommendations were updated in 2014[5] and in 2018 the American Society of Clinical Oncology (ASCO) introduced guidelines for patients receiving chemotherapy.[6] This was followed by the National Comprehensive Cancer Network (NCCN) in the United States of America (USA) introducing their guidelines for Older Adult Oncology in 2021.[7]

In 2018 the International Group for Reducing Inappropriate Medication Use and Polypharmacy (IGRIMUP) issued a position statement that said, "polypharmacy is an urgent issue that requires a coordinated global effort to provide medical care systems that better serve patients with multimorbidity". [8] This need has been recognised by practitioners for over a decade. Scott *et al* in 2009 called "for concerted action in accordance with the principles of evidence-based medicine and good gerontologic practice" [9] in relation to addressing polypharmacy (commonly defined as prescribing of five or more medications concomitantly).

Older adults are at increased risk of adverse drug events (ADE), defined as "noxious and unintended responses to drugs occurring at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [10]. This is commonly due to age-related changes in pharmacokinetics and pharmacodynamics, increasing treatment complexity, and medication burden [11]. Potentially inappropriate medications (PIM) in older adults, are medications in which the risks of harm and/or ADE potentially outweigh the benefits in the clinical context of an older adult [12], and that the avoidance of, or deprescribing of these medications may prevent ADE[13].

The prevalence of medication related hospitalisation in the general older adult population appears to be in the region of 7.2% - 12.8% of the population [14] with approximately half of ADE reported hypothesised as being preventable [15]. Older adults with cancer are particularly vulnerable to ADE, with the prevalence of systemic anticancer therapy (SACT) toxicity leading to a hospital visit of 51% in those receiving a CGA, and 71% in those receiving standard of care, in the GAP70+ trial [1]. Hence, we see higher rates of medication-related toxicity in older adults with cancer receiving systemic therapy, compared to the general older adult population.

There is a recognized need for medication optimization in older adults in general. [9, 13] The addition of a cancer diagnosis further complicates this. Treatment modalities for cancer, such as SACT, surgery, and radiotherapy all require supportive care medications for the treatment of cancer and cancer-related issues.[16] This may increase the prevalence of polypharmacy and PIM prescribing, in the absence of a structured medication review. Optimization of medication prior to, and during treatment, may offset some of this medication related risk. It is recognised in the literature that ageing-related changes in pharmacokinetics and pharmacodynamics can have a significant impact on SACT efficacy and toxicity, as well as pharmacological interventions to help prevent and manage SACT toxicities [17, 18]. In addition to ageing, tumour site, surgical resection of tumours, and radiotherapy can impact pharmacokinetics, thus predisposing older adults with cancer to a higher risk of developing ADE [19, 20].

There is now data showing the benefit of a CGA in older adults with cancer. A CGA consists of a multidimensional process that identifies medical, social and functional needs of older adults. [5] These

randomized controlled trials (RCT) have demonstrated reductions in unplanned hospitalisation due to SACT[1], in patients who undergo a CGA compared to those who do not, however, they did not examine ADE related to non-SACT medications (all medications taken by the patient that are not direct anticancer agents, including ancillary medications to SACT protocols, medications for non-malignant chronic conditions, over-the-counter medications, and herbal remedies). Healthcare professionals encounter a cohort of patients who have unplanned hospitalisations due to non-oncological and non-SACT related issues, which may be exacerbated by non-SACT medications, including medications used in supportive cancer care.

One of these RCTs, the GAP70+ study, demonstrated reduced rates of unplanned hospitalisation due to SACT in patients who underwent a CGA prior to starting treatment, compared to patients who received standard of care. [1] A sub analysis of this trial identified polypharmacy, and drug-drug interactions as independent risk factors for adverse outcomes in older adults with cancer receiving SACT. [21] The prevalence of polypharmacy and PIM is increased in older adults.[22] The presence of ≥8 medications [23] and PIM in patients aged ≥70 years with cancer was associated with physical function impairments. It was found that 71% of patients received five or more medications at baseline, with 62% of patients having at least one PIM. [24] Polypharmacy and PIM are associated with increased adverse outcomes, including unplanned hospitalisation.

This literature review sought to identify and evaluate studies that assessed unplanned hospitalisation due to ADE in older adults with cancer, including supportive care medication, and long-term medication related admissions.

Methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. [25] A completed PRISMA checklist is provided in Appendix 1. The study protocol[26] was registered on PROSPERO (Ref: CRD42022307356).[27]

The search strategy was developed, and search terms identified in consultation with a medical librarian. The relevant databases identified were Embase, PubMed and CINAHL (Appendix 2). All publication types were included in the initial search strategy, without language, geographical region, or date restrictions. The inclusion criteria were identified by using a Patient population, Intervention, Comparator, Outcome, Setting, Timing (PICOST) table (supplementary data).

Inclusion criteria

Studies that included older adults with cancer (can be defined as either ≥65 years or ≥70 years dependent upon definition of study authors) were deemed eligible for inclusion. In order to be included studies had to report ADE for both SACT and non-SACT medications. Studies that assessed both preventable and unpreventable ADE were included.

The exclusion criteria comprised of case reports; randomised controlled trials (RCTs) examining investigational medicinal products; studies that only included haematological malignancies; studies that reported unplanned hospitalisations, but where the proportion due to ADE was unclear; and studies that did not have a full text or an English language version available. Studies that only reported SACT toxicity and did not report non-SACT toxicity were also excluded. Emergency department visits without hospitalisation were not included.

Study selection and data extraction

The results of the search were combined and uploaded into Rayyan. [28] Duplicates were detected and excluded, and the remaining studies underwent title and abstract review, followed by full text review of those papers deemed eligible. The primary author (DW) reviewed all papers, and the papers were then divided up between the other authors to complete an independent and blind review. In the case of conflicts, the two reviewers discussed, and where consensus was not possible, the decision of a third author was sought, at each stage of the process.

Authors who were involved in more than one of the papers that were accepted after title and abstract review then had their bibliography hand searched on SCOPUS.

Studies identified as meeting the inclusion criteria had their data extracted using the Cochrane data collection form for RCTs [29] adapted for our systematic review. Data were extracted by DW and verified by a second author.

Assessment of methodological quality

Chapter 8 and chapter 25 of the Cochrane Handbook for Systematic Reviews of Interventions[30] was used as a guide to identify bias in included studies, and the risk of bias was identified as low, high or unclear. DW assessed the bias of each included study, and a second reviewer for each included paper independently assessed the primary author's assessment.

When synthesizing the study data from each included study, attrition rate – defined as an attrition ≥5% of the study population at baseline [31] was identified as having a high risk of attrition bias, due to incomplete data on the entire study population being present. Study quality was assessed using the Mixed Methods Appraisal Tool (MMAT) for quantitative non-randomized studies (Table 2). [32]

Certainty assessment on each study was carried out using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. [33] As GRADE is a subjective ranking, the primary author performed a ranking, and this was independently assessed by a second author. A third author resolved any conflict (Table 3).

For the incidence of hospitalisation due to ADEs, whether statistical significance (p value) was attributed to the effect in the study was assessed. Reported odds ratio (OR) relative risk (RR) and the confidence intervals (CI) reported in the study were also noted. Information on the statistical methods used to calculate these effects in each included study are provided in the adapted Cochrane data collection and risk of bias form, available from the primary author upon request. `

Data synthesis

The adapted Cochrane data collection tool [29] was used to define outcomes sought. Study characteristics were then assessed. These included the type of study, the participants involved, the types of interventions, comparisons made in the study and the outcomes measured.

The following characteristics of included studies were collated:

Methods:

Aim of study, design, unit of allocation (study subjects), start date, end date, duration of participation, ethical approval.

Participants:

Population description, setting, inclusion criteria, exclusion criteria, method of recruitment, informed consent obtained, total population, clusters (if applicable), baseline laboratory results,

withdrawals and exclusions, age, sex, ethnicity, severity of illness, comorbidities, other relevant sociodemographic details, where available.

Outcomes:

Outcome name, time point measured, time points reported, outcome definition, person measuring/reporting outcomes, unit of measurement, upper and lower limits, validation of outcome tool, imputation of missing data, assume risk estimate, power, all where appropriate.

Data and analysis:

Comparison, outcome, subgroup, time point, results, any other results reported, number of missing participants, reasons missing, reasons moved, unit of analysis, statistical methods used, if reanalysis required, if reanalysis possible, reanalysed results, all where available and appropriate.

Other information:

Key conclusions of study authors, reference to other relevant studies, correspondence required for further study information, reviewer notes.

The data from the included studies were tabulated, with relevant information to the primary research question populated (Tables 1 - 3).

Results

The search was conducted on 10.03.2022, updated on 09.02.2023, and updated on 27.10.23.

A total of 5,586 records were identified using the search strategy, of which 332 were identified as duplicates using Rayyan [28] duplication detection, and manual screening. The resulting 5254 records were screened to assess the title and abstract for possible inclusion. This process resulted in the exclusion of 5135 results. Of the 119 papers remaining, 2 were not available as full text. Assessment of the 117 available full texts was conducted, of which 3 were deemed to have met the inclusion criteria. Reasons for exclusion of other papers are outlined in Figure 1.

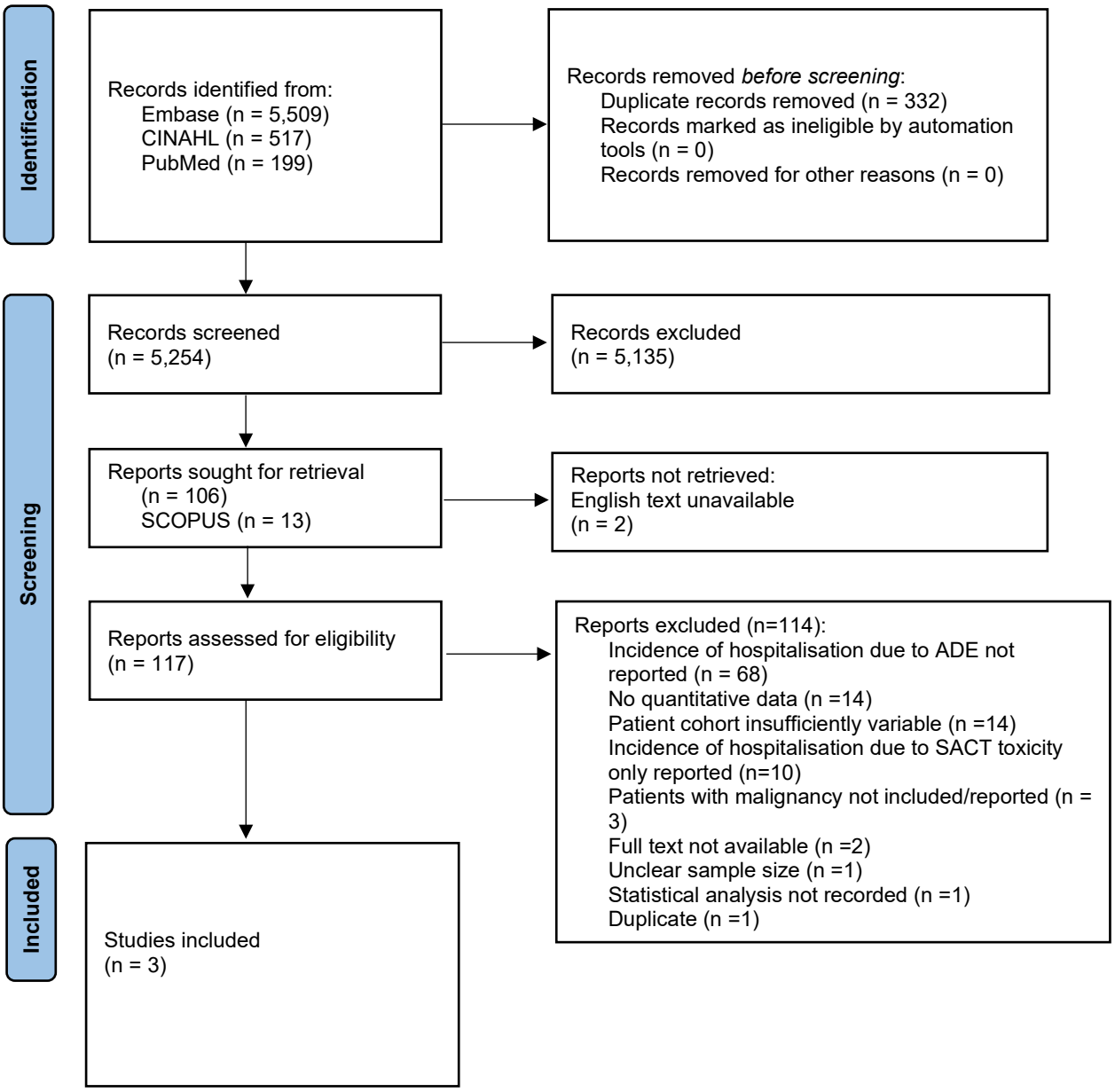


Figure 1: PRISMA flow chart outlining the identification, screening, and subsequent inclusion of relevant papers.

Study designs

Across the three studies, 2,511 older adults with cancer were included. Two studies were conducted in the Republic of Ireland (n=295),[34, 35] one study was conducted in the Netherlands (n= 2,216). [36]

Table 1 summarizes studies that reported all ADEs.

Table 1: Papers that reported all ADEs in older adults with cancer.

Title	Author	Study type	Tumour Type	Total Number in Group (n)	Incidence of Hospitalisation due to ADE (%)	Findings	Conclusions
Adverse Drug Reactions in an Oncological Population: Prevalence, Predictability, and Preventability [34]	Lavan *et al.* 2019	• Prospective observational study • Older adults were defined as ≥70 years	All carcinoma	121/350	19	• Many ADR*s in patients with cancer in this study were not caused by SACT • ADRs occurred in similar frequencies in older and younger patients secondary to SACT (8.3% vs. 13.1%, p =0 .295), non-SACT (10.7% vs. 8.3%, p = .107), and a combination of both (0% vs. 1.3%, p = .240). • Twenty-two ADRs (29.3%) were definitely avoidable, 25 (33.3%) possibly avoidable, and 28 (37.4%) unavoidable	• This study shows that multimorbidity, polypharmacy, and ADE are highly prevalent in patients with cancer • ADE caused by SACT and non-cancer medications are a significant cause of acute hospitalisation in oncology patients. • Patients may benefit from Comprehensive Geriatric Assessment and specialist medication evaluation at this time
Hospitalization due to adverse drug events in older adults with cancer: A retrospective analysis [35]	Walsh *et al.* 2023	• Retrospective single-centre study • Older adults were defined as ≥70 years	All carcinoma	174	24	• Unplanned hospitalisation rate was 43% (n = 75), with 56% (n = 42associated with an ADE. • Thirty-three percent of admissions were deemed to be potentially avoidable.	• Medication review as part of a CGA by a clinical pharmacist is recommended. • This may identify opportunities to avoid medications that could potentially lead to

							unplanned hospitalisation.
Toxicity, Response and Survival in Older Patients with Metastatic Melanoma Treated with Checkpoint Inhibitors [36]	De Glas *et al.* 2021	• Retrospective registry analysis • Older adults were defined as ≥65 years	Melanoma	2216	26	• Unplanned hospitalisation occurred in 24.2% of patients due to toxicity from immune checkpoint inhibitors and 1.8% of patients due to toxicity from other treatment.	• Future studies should investigate aging-related predictors and quality of life in older patients treated with checkpoint inhibitors. • The authors did not have a conclusion in relation to unplanned hospitalisation due to ADE.

**Note: Lavan et al use the phrase Adverse Drug Reaction (ADR) in a manner interchangeable with our use of Adverse Drug Event (ADE)*

Key:

ADE – Adverse Drug Event; ADR – Adverse Drug Reaction; CGA – Comprehensive Geriatric Assessment; NSAIDs – Non-Steroidal Inflammatory Drugs; SACT – Systemic Anti-Cancer Therapy

Our search strategy revealed three papers that report the incidence of unplanned hospitalisation due to ADEs in their respective study populations. Lavan *et al* [34] report 19% of unplanned hospital admissions are due to ADE in patients aged ≥70 years with cancer. Walsh *et al* [35] report 24% of unplanned hospital admissions are due to ADE in patients aged ≥70 years with cancer. De Glas *et al* [34, 36] report 26% of patients with metastatic melanoma treated with immune checkpoint inhibitors had an unplanned hospitalisation due to an ADE.

Quality Appraisal

Risk of bias was assessed using the Mixed Methods Appraisal Tool (MMAT) [32] for quantitative non-randomized studies. As all studies were quantitative non-randomized studies, one being prospective observational, one being a single centre retrospective analysis, and one being a retrospective registry database analysis this was deemed an appropriate assessment. The risk of bias assessment in both studies can be found in Table 2. Bias was found to be low in all studies, with sound methodological approaches for the study type, with some uncertainty about outcomes, due to no discernible comparator in Lavan *et al* [34] and Walsh *et al* [35], and a lack of clarity surrounding the assessment of confounders for non-treatment toxicity in De Glas *et al* [36]

Table 2: MMAT assessment for included studies using the Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers [32]

Lavan *et al* [34]					
Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comment
Screening questions	S1. Are there clear research questions?	X			
	2. Do the collected data allow to address the research questions?	X			
Quantitative non-randomized	3.1. Are the participants representative of the target population?	X			
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	X			
	3.3. Are there complete outcome data?	X			
	3.4. Are the confounders accounted for in the design and analysis?	X			
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?			X	
Walsh *et al* [35]					
Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comment
Screening questions	S1. Are there clear research questions?	X			
	2. Do the collected data allow to address the research questions?	X			
Quantitative non-randomized	3.1. Are the participants representative of the target population?	X			
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	X			
	3.3. Are there complete outcome data?	X			
	3.4. Are the confounders accounted for in the design and analysis?	X			
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?			X	
De Glas *et al* [36]					
Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comment
Screening questions	S1. Are there clear research questions?	X			
	2. Do the collected data allow to address the research questions?	X			
Quantitative non-randomized	3.1. Are the participants representative of the target population?	X			
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	X			
	3.3. Are there complete outcome data?	X			
	3.4. Are the confounders accounted for in the design and analysis?			X	

	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?			X	

The GRADE tool [37] was used to assess each paper for certainty of evidence and to establish the quality of evidence in the literature. In total it was found that one paper ranked low certainty one paper ranked very low certainty, when grading them for certainty of evidence relative to the research question, and one paper ranked moderate certainty. The baseline certainty for two studies was low, as they were either observational studies or retrospective studies. One study [34] was upgraded because the sample size was deemed significant, and the reported outcome matched the research question. A summary of the GRADE assessment can be found in table 3.

Table 3: Reporting biases and certainty of evidence for included studies.

Study	GRADE Assessment							
	Baseline Certainty	Risk of Bias	Imprecision	Inconsistency	Indirectness	Publication Bias	Reason for Ranking Up	GRADE Rating
Lavan *et al* [34]	Low – Observational Study	N/A	N/A	N/A	N/A	N/A	A sample of 333 patients was required to detect an ADR rate of 7% with a margin of error of 2% at 95% confidence. Incidence of ADR was 19% in older adults, total population sample size was 350.	Moderate quality
Walsh *et al* [35]	Low – retrospective study	N/A	N/A	N/A	N/A	N/A	N/A	Low
De Glas *et al* [36]	Low – retrospective study not representative of entire oncology patient cohort	Selective reporting bias relative to our research question	N/A	N/A	N/A	N/A	N/A	Very low

Discussion

Summary of evidence

This article is the first, to our knowledge, to systematically review and analyse the literature regarding the incidence of hospitalisation due to ADE in the geriatric oncology setting, encompassing SACT and non-SACT medication. We have identified that there is a paucity of studies relating to this outcome. Our systematic review only found two papers that reported the prevalence in patients once hospitalized [34, 35] and one paper that reported the incidence, confined to patients with metastatic melanoma receiving immune checkpoint inhibitors. [36] Two papers reported the preventability of ADE, ranging from 33% [35] to 62.7% [34].

These findings, however, show that hospitalisation due to ADE in older adults with cancer is prevalent, largely predictable and in many cases potentially avoidable, thus supporting the integration of a comprehensive geriatric assessment, complete with medicines review in line with SIOG guidelines.[38] Studies that have identified SACT toxicity as a primary outcome [1-3, 39] have been designed to demonstrate that a CGA is beneficial in reducing SACT toxicity. These papers also excluded older adults who are either unfit for SACT or elect not to receive SACT. These trials have contributed significantly to the literature but were not designed to answer our research question. GAP70+ [1]and GAIN [2] demonstrated a reduction in Grade 3-5 SACT toxicity and INTEGERATE [3] demonstrated reduced rates of functional decline in patients who receive a CGA, however non-SACT related hospitalisations were not examined in these papers. Lavan *et al*, Walsh *et al*, and De Glas *et al* [34-36] have demonstrated that older adults with cancer experienced unplanned hospitalisations, in addition to that caused by SACT toxicity. Prospective interventional studies may help to support these findings.

De Glas *et al* [36] does differ from the other studies, in respect to patient cohort. As this study included patients with metastatic melanoma, being treated with immune checkpoint inhibitors, it is difficult to compare the findings of this study to the other papers discussed in this review. A recent meta-analysis found that performance status and organ function was a predictor of immune checkpoint toxicity, independently of increasing age [40]. The higher rates of Grade 1 and Grade 2 toxicities in older adults in this study, may not have resulted in hospitalisation, however, the impact of these toxicities on quality of life needs to be further understood, and the clinical significance of non-hospitalisation toxicities is beyond the scope of this review.

Nightingale *et al* [41] demonstrated that a pharmacist led comprehensive medication assessment is effective in identifying high rates of patients with polypharmacy (5-9 medications), hyperpolypharmacy (≥10 medications) and PIM using a combination of tools [42-44]. Turner *et al* supports this approach [45] showing multimorbidity in patients with cancer can lead to ADE, polypharmacy, prescribing of PIM and potential drug-drug interactions. Of note, the protocol of a single-blinded, randomized, controlled trial assessing the optimization of polypharmacy in geriatric oncology (the OPTIMAL study) has been published and is underway. [46]

Medication optimization should be considered for all older adults with cancer, where feasible. The role of the clinical pharmacist, with oncological and gerontological expertise could potentially ameliorate some risk in this patient population. Guidance on conducting medication reviews in older adults with cancer have been published [38] and current clinical pharmacist practices have been reported. [47]

Opportunities to optimize medications used to treat chronic conditions in older adults with cancer, and cancer survivors, in primary healthcare settings may further reduce hospitalisation in older

adults with cancer and cancer survivors. Medication optimization in primary care settings have shown efficacy in improving deprescribing of PIM, in older adults [48] in a general practice setting. High rates of PIM and polypharmacy have also been observed in long-term care facilities [49] and these can be addressed by the multidisciplinary primary care team.

Education and research opportunities for clinical pharmacists in the field of geriatric oncology are scarce at present. Expanding teams and creating educational resources so that pharmacists in oncology roles can expand their geriatric knowledge, and pharmacists involved in the care of the older adults can expand their oncology knowledge, should be a consideration for teaching institutes, cancer centres and national cancer control programmes to ensure appropriate measures are taken to optimize medications in older adults with cancer. [50] [51]

In conclusion, multidisciplinary efforts to prevent ADE is an unmet need of older adults with cancer. The CGA process has been shown to reduce the incidence of SACT toxicity [1, 2], however, the impact of this on non-SACT related ADE is at present unknown. Our review supports these findings, where drug related issues are under-represented in the literature. The relevance and clinical significance of non-SACT toxicity is yet to be determined, despite well devised studies evaluating SACT toxicity. In addition, there is an absence of studies evaluating ADE in patients on best supportive care strategies. Data is also lacking in patients under active surveillance who have undergone curative treatment, despite the increasingly growing number of patients who fall under the umbrella of cancer survivorship.

Limitations and Strengths

This review was limited by the consideration of English language papers only, and the small number of studies included, which had methodological limitations. Not all full texts were readily available. A meta-analysis was deemed unfeasible due to the limited and heterogenous nature of the data available in the literature.

A strength of this review is that the review process was guided by a medical librarian in building a comprehensive search strategy. The data collection, extraction and analysis were conducted by a research group with a diverse background in clinical pharmacy, academic pharmacy, medical oncology, and oncology nursing, enable a broad knowledge base to be applied to the narrative discussion.

Implications for practice and future research

Future research is needed to identify the incidence of hospitalisation due to adverse drug events in the wider geriatric oncology population. Randomised controlled trials to date have utilized SACT toxicity as a primary objective, however, we have identified a lack of prospective studies that analyses all hospitalisations due to ADE. We have also identified a lack of studies that include patients on supportive care, or active surveillance who are still under the care of medical oncology specialties.

Research investigating methods to optimize medications in older adults with cancer, both those who are receiving SACT and those who do not, are needed to assess the impact of effective medication management [47] in this high-risk patient population. Studies should account for the reporting of potential ADE relative to supportive care, ancillary medications, and indeed chronic medications used to treat long-standing comorbidities.

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Supplementary data

PICOST TABLE						
Patient/Population		Intervention/Indicator	Control/Compare	Outcome	Study	Time/Type of Study
Geriatric	Oncology	Adverse drug effect	N/A	Hospitalisation	Quantitative data	N/A
Elderly	Cancer	Adverse drug event		Admission		
Aged	Carcinoma	Side effect		Readmission		
Older adult	Neoplasm	Polypharmacy				
Senior	Malignancy	Toxicity				
		Inappropriate prescribing				

Appendix 1: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods – Inclusion criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods – search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – Study selection and data extraction

Section and Topic	Item #	Checklist item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods – Study selection and data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods – data synthesis
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods – data synthesis
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – assessment of methodological quality
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods – data synthesis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods – data synthesis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods – data synthesis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods – data synthesis

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods – assessment of methodological quality
	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods – assessment of methodological quality
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results
Study characteristics	17	Cite each included study and present its characteristics.	Results – study designs
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results – Quality Appraisal

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results – quality appraisal
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A – not conducting meta-analysis
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results – quality appraisal
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results – quality appraisal
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion – summary of evidence
	23b	Discuss any limitations of the evidence included in the review.	Discussion – summary of evidence

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Discussion – limitations and strengths
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion – Implications for practice and future research
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Can be found in PROSPERO record
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Declaration of sources of funding
Competing interests	26	Declare any competing interests of review authors.	Declarations of conflict of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Availability of data, code and other materials

Appendix 2: Search Strategy

Embase Search Strategy:

Session Results

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No.	Query	Results	Date
#26.	#6 AND #13 AND #19 AND #25	4,965	27 Oct 2023
#25.	#23 OR #24	1,343,272	27 Oct 2023
#24.	#20 OR #21 OR #22	1,257,364	27 Oct 2023
#23.	((adverse AND ('drug'/exp OR drug) AND event*:ab,ti OR side) AND effect*:ab,ti OR adverse) AND ('drug'/exp OR drug) AND reaction*:ab,ti	178,439	27 Oct 2023
#22.	'adverse drug reaction'/exp	655,138	27 Oct 2023
#21.	'side effect'/exp	698,086	27 Oct 2023
#20.	'adverse event'/exp	1,042,464	27 Oct 2023
#19.	#17 OR #18	1,102,763	27 Oct 2023
#18.	#14 OR #15 OR #16	845,443	27 Oct 2023
#17.	(hospitali?ation:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR 'hospital'/exp OR hospital) AND admission:ab,ti	432,730	27 Oct 2023
#16.	'hospitalization'/exp	541,116	27 Oct 2023
#15.	'hospital readmission'/exp	100,602	27 Oct 2023
#14.	'hospital admission'/exp	282,556	27 Oct 2023
#13.	#11 OR #12	7,208,930	27 Oct 2023
#12.	#7 OR #8 OR #9 OR #10	6,141,129	27 Oct 2023
#11.	cancer:ab,ti OR oncolog*:ab,ti OR malignan*:ab,ti OR neoplas*:ab,ti OR tumo*:ab,ti OR carcinoma:ab,ti	5,504,000	27 Oct 2023
#10.	'oncology'/exp	182,409	27 Oct 2023
#9.	'neoplasm'/exp	6,102,703	27 Oct 2023

#8. 'carcinoma'/exp	1,549,592	27 Oct 2023
#7. 'malignant neoplasm'/exp	4,566,383	27 Oct 2023
#6. #4 OR #5	3,970,286	27 Oct 2023
#5. #1 OR #2 OR #3	3,829,994	27 Oct 2023
#4. (geriatr*:ab,ti OR elderly:ab,ti OR aged:ab,ti OR geront*:ab,ti OR older) AND adult:ab,ti OR senior*:ab,ti	209,689	27 Oct 2023
#3. 'aged'/exp	3,793,029	27 Oct 2023
#2. 'geriatric assessment'/exp	21,059	27 Oct 2023
#1. 'geriatrics'/exp	58,337	27 Oct 2023

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PubMed Search Strategy:

Search number	Query	Sort By	Filters	Search Details	Results	Time

23	(((((((((geriatr*[Title/Abstract]) OR (elderly[Title/Abstract])) OR (aged[Title/Abstract])) OR (geront*[Title/Abstract])) OR (older adult*[Title/Abstract])) OR (senior*[Title/Abstract])) OR ((((("Geriatrics"[Mesh]) OR ("Geriatric Assessment"[Mesh])) OR ("Aged"[Mesh])) OR ("Aged, 80 and over"[Mesh]))) AND (((((((cancer[Title/Abstract]) OR (oncolog*[Title/Abstract])) OR (malignan*[Title/Abstract])) OR (neoplas*[Title/Abstract])) OR (tumo*[Title/Abstract])) OR (carcinoma*[Title/Abstract])) OR ((("Neoplasms"[Mesh]) OR ("Carcinoma"[Mesh])) OR ("Medical Oncology"[Mesh])))) AND (((((hospitali?ation[Title/Abstract]) OR (admission[Title/Abstract])) OR (readmission[Title/Abstract])) OR (hospital admission[Title/Abstract])) OR ((("Hospitalization"[Mesh]) OR ("Patient Admission"[Mesh])) OR ("Patient Readmission"[Mesh])))) AND (("Drug-Related Side Effects and Adverse Reactions"[Mesh]) OR (((adverse drug event*[Title/Abstract]) OR (adverse drug reaction*[Title/Abstract])) OR (side effect*[Title/Abstract]))))			("geriatr*"[Title/Abstract] OR "elderly"[Title/Abstract] OR "Aged"[Title/Abstract] OR "geront*"[Title/Abstract] OR "older adult*"[Title/Abstract] OR "senior*"[Title/Abstract] OR ("Geriatrics"[MeSH Terms] OR "Geriatric Assessment"[MeSH Terms] OR "Aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms])) AND ("cancer"[Title/Abstract] OR "oncolog*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumo*"[Title/Abstract] OR "carcinoma*"[Title/Abstract] OR ("Neoplasms"[MeSH Terms] OR "Carcinoma"[MeSH Terms] OR "Medical Oncology"[MeSH Terms])) AND (("hospitali"[All Fields] AND "ation"[Title/Abstract]) OR "admission"[Title/Abstract] OR "readmission"[Title/Abstract] OR "hospital admission"[Title/Abstract] OR ("Hospitalization"[MeSH Terms] OR "Patient Admission"[MeSH	420	08:46:39

				Terms] OR "Patient Readmission"[MeSH Terms])) AND ("Drug-Related Side Effects and Adverse Reactions"[MeSH Terms] OR ("adverse drug event*"[Title/Abstract] OR "adverse drug reaction*"[Title/Abstract] OR "side effect*"[Title/Abstract]))		
22	("Drug-Related Side Effects and Adverse Reactions"[Mesh]) OR (((adverse drug event*[Title/Abstract]) OR (adverse drug reaction*[Title/Abstract])) OR (side effect*[Title/Abstract]))			"Drug-Related Side Effects and Adverse Reactions"[MeSH Terms] OR "adverse drug event*"[Title/Abstract] OR "adverse drug reaction*"[Title/Abstract] OR "side effect*"[Title/Abstract]	448,891	08:46:04
21	((adverse drug event*[Title/Abstract]) OR (adverse drug reaction*[Title/Abstract])) OR (side effect*[Title/Abstract])			"adverse drug event*"[Title/Abstract] OR "adverse drug reaction*"[Title/Abstract] OR "side effect*"[Title/Abstract]	333,413	08:45:54
20	"Drug-Related Side Effects and Adverse Reactions"[Mesh]	Most Recent		"Drug-Related Side Effects and Adverse Reactions"[MeSH Terms]	133,337	08:45:08

19	((((hospitali?ation[Title/Abstract]) OR (admission[Title/Abstract])) OR (readmission[Title/Abstract])) OR (hospital admission[Title/Abstract])) OR ((("Hospitalization"[Mesh]) OR ("Patient Admission"[Mesh])) OR ("Patient Readmission"[Mesh]))			("hospitali"[All Fields] AND "ation"[Title/Abstract]) OR "admission"[Title/Abstract] OR "readmission"[Title/Abstract] OR "hospital admission"[Title/Abstract] OR ("Hospitalization"[MeSH Terms] OR "Patient Admission"[MeSH Terms] OR "Patient Readmission"[MeSH Terms])	491,338	08:44:25
18	(("Hospitalization"[Mesh]) OR ("Patient Admission"[Mesh])) OR ("Patient Readmission"[Mesh])			"Hospitalization"[MeSH Terms] OR "Patient Admission"[MeSH Terms] OR "Patient Readmission"[MeSH Terms]	294,618	08:43:16
17	(((hospitali?ation[Title/Abstract]) OR (admission[Title/Abstract])) OR (readmission[Title/Abstract])) OR (hospital admission[Title/Abstract])			("hospitali"[All Fields] AND "ation"[Title/Abstract]) OR "admission"[Title/Abstract] OR "readmission"[Title/Abstract] OR "hospital admission"[Title/Abstract]	269,970	08:42:45
16	"Patient Readmission"[Mesh]	Most Recent		"Patient Readmission"[MeSH Terms]	23,011	08:24:10
15	"Patient Admission"[Mesh]	Most Recent		"Patient Admission"[MeSH Terms]	26,174	08:23:46
14	"Hospitalization"[Mesh]	Most Recent		"Hospitalization"[MeSH Terms]	294,618	08:23:19
13	((((((cancer[Title/Abstract]) OR (oncolog*[Title/Abstract])) OR (malignan*[Title/Abstract])) OR (neoplas*[Title/Abstract])) OR (tumo*[Title/Abstract])) OR (carcinoma*[Title/Abstract]			"cancer"[Title/Abstract] OR "oncolog*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumo*"[Title/Abstract] OR	5,143,761	08:22:50

	)) OR (((("Neoplasms"[Mesh]) OR ("Carcinoma"[Mesh])) OR ("Medical Oncology"[Mesh]))			"carcinoma*"[Title/Abstract] OR "Neoplasms"[MeSH Terms] OR "Carcinoma"[MeSH Terms] OR "Medical Oncology"[MeSH Terms]		
12	(("Neoplasms"[Mesh]) OR ("Carcinoma"[Mesh])) OR ("Medical Oncology"[Mesh])			"Neoplasms"[MeSH Terms] OR "Carcinoma"[MeSH Terms] OR "Medical Oncology"[MeSH Terms]	3,895,235	08:22:40
11	(((((cancer[Title/Abstract]) OR (oncolog*[Title/Abstract])) OR (malignan*[Title/Abstract])) OR (neoplas*[Title/Abstract])) OR (tumo*[Title/Abstract])) OR (carcinoma*[Title/Abstract])			"cancer"[Title/Abstract] OR "oncolog*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumo*"[Title/Abstract] OR "carcinoma*"[Title/Abstract]	4,078,453	08:22:29
10	"Medical Oncology"[Mesh]	Most Recent		"Medical Oncology"[MeSH Terms]	30,391	08:21:08
9	"Carcinoma"[Mesh]	Most Recent		"Carcinoma"[MeSH Terms]	732,964	08:19:35
8	"Neoplasms"[Mesh]	Most Recent		"Neoplasms"[MeSH Terms]	3,885,329	08:19:17
7	((((((geriatr*[Title/Abstract]) OR (elderly[Title/Abstract])) OR (aged[Title/Abstract])) OR (geront*[Title/Abstract])) OR (older adult*[Title/Abstract])) OR (senior*[Title/Abstract])) OR ((((("Geriatrics"[Mesh]) OR ("Geriatric Assessment"[Mesh])) OR ("Aged"[Mesh])) OR ("Aged, 80 and over"[Mesh]))			"geriatr*"[Title/Abstract] OR "elderly"[Title/Abstract] OR "Aged"[Title/Abstract] OR "geront*"[Title/Abstract] OR "older adult*"[Title/Abstract] OR "senior*"[Title/Abstract] OR "Geriatrics"[MeSH Terms] OR "Geriatric	4,118,253	08:18:55

				Assessment"[MeSH Terms] OR "Aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms]		
6	((("Geriatrics"[Mesh]) OR ("Geriatric Assessment"[Mesh])) OR ("Aged"[Mesh])) OR ("Aged, 80 and over"[Mesh])			"Geriatrics"[MeSH Terms] OR "Geriatric Assessment"[MeSH Terms] OR "Aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms]	3,484,915	08:18:43
5	(((((geriatr*[Title/Abstract]) OR (elderly[Title/Abstract])) OR (aged[Title/Abstract])) OR (geront*[Title/Abstract])) OR (older adult*[Title/Abstract])) OR (senior*[Title/Abstract])			"geriatr*"[Title/Abstract] OR "elderly"[Title/Abstract] OR "aged"[Title/Abstract] OR "geront*"[Title/Abstract] OR "older adult*"[Title/Abstract] OR "senior*"[Title/Abstract]	1,152,033	08:18:20
4	"Aged, 80 and over"[Mesh]	Most Recent		"aged, 80 and over"[MeSH Terms]	1,016,673	08:17:01
3	"Aged"[Mesh]	Most Recent		"Aged"[MeSH Terms]	3,466,022	08:16:45
2	"Geriatric Assessment"[Mesh]	Most Recent		"Geriatric Assessment"[MeSH Terms]	32,440	08:16:19
1	"Geriatrics"[Mesh]	Most Recent		"Geriatrics"[MeSH Terms]	31,567	08:15:56

CINAHL Search Strategy:

#	Query	Limiters/Expanders	Last Run Via	Results
S23	S5 AND S11 AND S17 AND S22	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	575
S22	S20 OR S21	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	161,630
S21	S18 OR S19	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	34,645
S20	AB adverse event OR AB adverse reaction OR AB side effect	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	135,462
S19	(MH "Medication Side Effects (Saba CCC)")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1

S18	(MH "Adverse Drug Event+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	34,644
S17	S15 OR S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	256,307
S16	S12 OR S13 OR S14	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	151,977
S15	AB hospitali#ation OR AB admission OR AB readmission OR AB hospital admission	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	150,149
S14	(MH "Readmission")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	16,850

			Database - CINAHL Plus with Full Text	
S13	(MH "Patient Admission")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	21,625
S12	(MH "Hospitalization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	119,431
S11	S9 OR S10	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	575,263
S10	S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	164,363

S9	AB cancer OR AB oncolog* OR AB malignan* OR AB neoplas* OR AB tumo* OR AB carcinoma*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	515,968
S8	(MH "Oncology+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	12,932
S7	(MH "Carcinoma+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	106,036
S6	(MH "Cancer Patients")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	50,551
S5	S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	1,018,556

			Database - CINAHL Plus with Full Text	
S4	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	957,455
S3	AB geriatr* OR AB elder* OR AB geront* OR AB older adult* OR AB senior	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	182,056
S2	(MH "Aged+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	956,378
S1	(MH "Geriatric Assessment+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	18,694