1-1-2020

Associations of Polypharmacy and Inappropriate Medications with Adverse Outcomes in Older Adults with Cancer: A Systematic Review and Meta-Analysis

Mostafa R. Mohamed
University of Rochester Medical Center

Erika Ramsdale
University of Rochester Medical Center

Kah Poh Loh
University of Rochester Medical Center

Asad Arastu
University of Rochester Medical Center

Huiwen Xu
University of Rochester Medical Center

See next page for additional authors

Recommended Citation

Mohamed, M. R., Ramsdale, E., Loh, K. P., Arastu, A., Xu, H., Obrecht, S., Castillo, D., Sharma, M., Holmes, H. M., Nightingale, G., Juba, K. M., & Mohile, S. G. (2020). Associations of Polypharmacy and Inappropriate Medications with Adverse Outcomes in Older Adults with Cancer: A Systematic Review and Meta-Analysis. The Oncologist, 25(1). https://doi.org/10.1634/theoncologist.2019-0406

The Oncologist®

Geriatric Oncology

Associations of Polypharmacy and Inappropriate Medications with Adverse Outcomes in Older Adults with Cancer: A Systematic Review and Meta-Analysis

Mostafa R. Mohamed,[a,†] Erika Ramsdale,[a,†] Kah Poh Loh,[a] Asad Arastu,[a] Huiwen Xu,[a,c] Spencer Obrecht,[a] Daniel Castillo,[d] Manvi Sharma,[e] Holly M. Holmes,[f] Ginah Nightingale,[g] Katherine M. Juba,[h,b] Supriya G. Mohile[a]

[a]James P. Wilmot Cancer Center and [b]Department of Pharmacy, University of Rochester Medical Center, Rochester, New York, USA; [c]Department of Public Health and [d]MLIS-Miner Library, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA; [e]Department of Pharmacy Administration, University of Mississippi School of Pharmacy, University, Mississippi, USA; [f]The University of Texas Health Science Center at Houston, Houston, Texas, USA; [g]Department of Pharmacy Practice, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [h]Department of Pharmacy Practice, Wegmans School of Pharmacy, Rochester, New York, USA

[†]Contributed equally.

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

Key Words. Polypharmacy • Potentially inappropriate medications • Outcomes • Older adults with cancer • Geriatric oncology

Abstract

Background. Polypharmacy (PP) and potentially inappropriate medications (PIM) are highly prevalent in older adults with cancer. This study systematically reviews the associations of PP and/or PIM with outcomes and, through a meta-analysis, obtains estimates of postoperative outcomes associated with PP in this population.

Materials and Methods. We searched PubMed, Embase, Web of Science, and Cochrane Register of Clinical Trials using standardized terms for concepts of PP, PIM, and cancer. Eligible studies included cohort studies, cross-sectional studies, meta-analyses, and clinical trials which examined outcomes associated with PP and/or PIM and included older adults with cancer. A random effects model included studies in which definitions of PP were consistent to examine the association of PP with postoperative complications.

Results. Forty-seven articles met the inclusion criteria. PP was defined as five or more medications in 57% of the studies. Commonly examined outcomes included chemotherapy toxicities, postoperative complications, functional decline, hospitalization, and overall survival. PP was associated with chemotherapy toxicities (4/9 studies), falls (3/3 studies), functional decline (3/3 studies), and overall survival (2/11 studies). A meta-analysis of four studies indicated an association between PP (≥5 medications) and postoperative complications (overall odds ratio, 1.3; 95% confidence interval [1.3–2.8]). PIM was associated with adverse outcomes in 3 of 11 studies.

Conclusion. PP is associated with postoperative complications, chemotherapy toxicities, and physical and functional decline. Only three studies showed an association between PIM and outcomes. However, because of inconsistent definitions, heterogeneous populations, and variable study designs, these associations should be further investigated in prospective studies. ***The Oncologist*** 2020;25:e94–e108

Implications for Practice: Polypharmacy and potentially inappropriate medications (PIM) are prevalent in older adults with cancer. This systematic review summarizes the associations of polypharmacy and PIM with health outcomes in older patients with cancer. Polypharmacy and PIM have been associated with postoperative complications, frailty, falls, medication nonadherence, chemotherapy toxicity, and mortality. These findings emphasize the prognostic importance of careful medication review and identification of PIM by oncology teams. They also underscore the need to develop and test interventions to address polypharmacy and PIM in older patients with cancer, with the goal of improving outcomes in these patients.

Correspondence: Erika Ramsdale, M.D., James P. Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 704, Rochester, New York 14642, USA. Telephone: 585-275-2376; e-mail: erika_ramsdale@urmc.rochester.edu Received May 28, 2019; accepted for publication July 11, 2019; published Online First on September 30, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0406

Introduction

In the U.S., more than half of new cancer cases and about 70% of cancer deaths occur in adults aged 65 years or older [1]. Compared with younger cohorts, older adults are more likely to have comorbid conditions for which medications are prescribed [2]. Older adults with cancer also have a higher rate of frailty and geriatric syndromes compared with those without cancer [3]. For patients receiving cancer treatment, chemotherapy and supportive care regimens often involve the prescription of multiple medications. Because of these factors, older adults with cancer are at high risk of polypharmacy (PP), defined as the simultaneous use of multiple medications. In community-dwelling populations of older adults without cancer, PP has been associated with increased falls [4], hospitalization [5], and mortality [6].

There is a wide variability in the definition of PP in the existing literature [7]. In one study of community-dwelling older adults with cancer, 84% were on five or more medications and 43% were on 10 or more medications [8]. The use of five or more medications is the most commonly used definition of PP in the literature, whereas the use of 10 or more medications is commonly referred to as "extreme PP" or "hyperpolypharmacy." Multiple cutoffs are used in the literature, and studies vary as to how medications are counted (i.e., whether only scheduled prescription medications are included, or whether supplements, over-the-counter medications, and as-needed medications are counted as well [8]).

Definitions of PP typically do not account for the appropriateness of medications. PP increases the risk that one or more medications is "potentially inappropriate"; these potentially inappropriate medications (PIMs) have risks higher than anticipated benefits in older adults. PIMs may be assessed using multiple validated instruments including the Beers criteria [9], Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria [10], Zhan criteria [11], and medication appropriateness index (MAI) [12]. In older adults, PIMs are associated with increased risks of adverse drug events, hospitalizations, and mortality [13], as well as higher health care costs [14]. However, supportive care regimens may include medications (such as benzodiazepines for treatment of nausea) that would otherwise be deemed PIM but may be clinically appropriate based on oncology supportive care guidelines.

Although the literature on PP and PIM in older adults is increasing, data in older adults with cancer remain sparse. Extrapolation of data from the general population of older adults is problematic: older adults with cancer have more frailty and multimorbidity than patients without cancer, they take more medications on average, and the initiation of chemotherapy and supportive care regimens can significantly increase the risk of drug-drug interactions and adverse drug events [15]. It also remains unclear whether PP and PIM affect outcomes in older adults with cancer. This systematic review and meta-analysis evaluates the association of PP and PIM with outcomes in older adults with cancer.

Materials and Methods

Search Strategy

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16]. We searched for articles from the following databases between the database inception and September 2018: PubMed, Web of Science, Embase, and Cochrane Register of Controlled Trials. Standardized terms and keywords were combined in the search for the following concepts: oncology/cancer, polypharmacy, and inappropriate medications (supplemental online Appendix 1). Reference lists of relevant articles were screened to identify other relevant articles ("snowball" search). All results were exported to EndNote, and duplicates were identified and removed.

Selection Criteria

We included studies if they (a) examined any outcomes associated with PP and/or PIM; (b) included patients with cancer (as either the whole sample or a subgroup); (c) included adults aged ≥65 (a common cutoff to identify older adults in the literature); (d) were clinical trials, observational cohort studies, cross-sectional studies, or meta-analyses; and (e) were written in English. We excluded studies that did not specifically evaluate the associations of PP and/or PIM with outcomes (i.e., studies that described the prevalence of PP and/or PIM only) and those that were published in abstract form only. Two investigators (M.M. and A.A.) independently reviewed the titles and abstracts of retrieved articles to select potential articles. The full texts were further reviewed independently by M. M. and A.A. for final selection of articles. Disagreements were resolved by a third investigator (K.P.L.).

Data Extraction and Analysis

A predefined data extraction template was developed and included name of the first author, year of publication, country, study design, sample size, age, definition of PP and PIM, prevalence of PP and PIM, cancer type, treatment planned or received, outcome variables, and findings on the association between PP and PIM and outcome measures. Two independent authors (M.M. and A.A., K.P.L., or S.O.) reviewed full texts of each identified article and extracted the data.

After data extraction, outcomes were categorized into the following domains: postoperative outcomes, chemotherapy outcomes, physical function, survival, and miscellaneous/other outcomes. Odds ratios (OR), p values, and 95% confidence intervals (CI) were reported for significant results (defined as $p < .05$ or 95% CI did not cross 1) if available. Nonsignificant results are reported as NS, but p values and OR are not reported as most studies did not report these for nonsignificant results.

Meta-Analysis

Studies evaluating the association of PP with postoperative complications used a consistent definition of PP (≥5 medications) and postoperative complications (using the Clavien-Dindo classification; $n = 4$ studies) [17]. We performed a random-effects model to combine the OR and 95% CI in these four studies. Heterogeneity of included studies was measured using chi-square test and the I^2 statistic, with a significant heterogeneity defined as $I^2 > 50\%$. Forest plots present individual and pooled risk estimates. All statistical analyses were conducted using Stata 13.0 (Stata Corp, College Station, TX). Meta-analyses for other outcomes were not

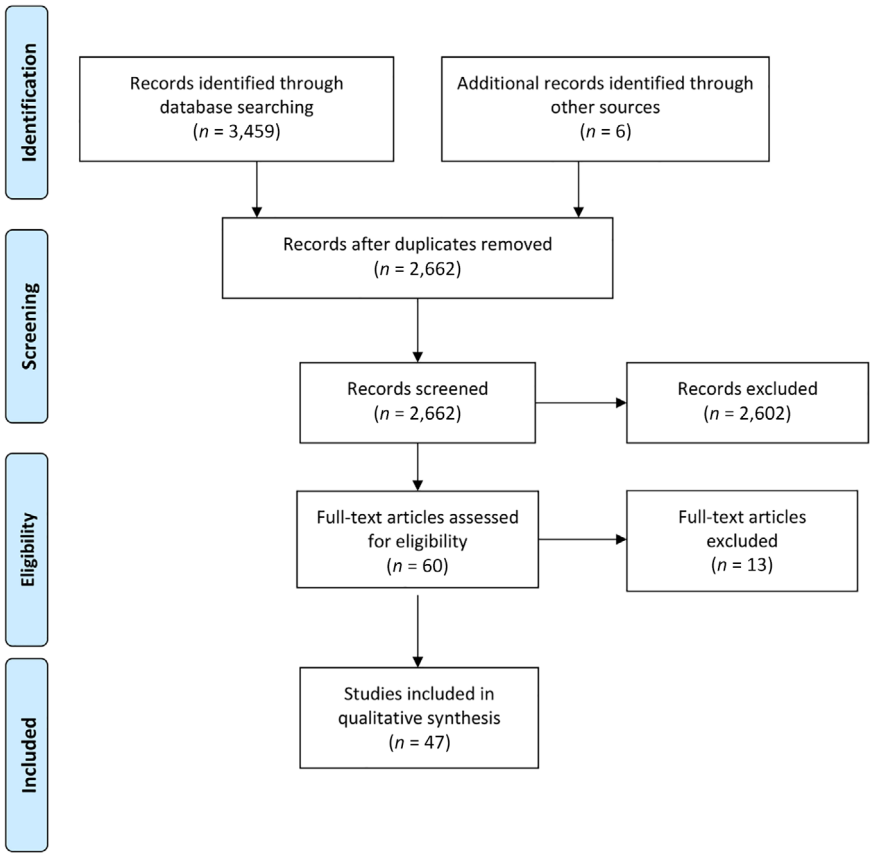

Figure 1. PRISMA flow diagram. This diagram details our search and study selection process applied during the study according to PRISMA checklist.

undertaken because of heterogeneity of definitions of PP and PIM.

Quality Appraisal

Two independent authors (M.M. and A.A., K.P.L., E.R., or S.O.) assessed the quality of each selected study. We used the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [18] as a guide. We rated the data quality related to PP and PIM and outcomes as good, fair, or poor. Disagreements among the reviewers were discussed and resolved during consensus meetings.

Results

Study Characteristics

The initial search strategy identified 3,459 titles and abstracts. An additional six articles were identified from the reference lists of selected articles (Fig. 1). In total, 47 studies were included (number of patients ranged from 16 to 40,009). These studies were published between 2005 and 2018 from 19 countries. Study designs included retrospective cohort (23 studies), prospective cohort (14 studies), cross-sectional (9 studies), and meta-analysis (1 study). Of these studies, 46.8% (22/47) included patients with only one cancer type. Common cancer types were gastrointestinal (GI; 24/47, 51.1%), breast (20/47, 42.5%), and lung (8/47, 17%).

Quality Appraisal

The articles were judged to be good (n = 2, 4.2%), fair (n = 32, 68.1%), or poor quality (n = 13, 27.6%) based on the NIH Quality Assessment Tool (supplemental online Tables 1 and 2). All studies clearly stated their research objectives and study population. Sample sizes were clearly stated in all studies; however, only two studies provided a justification for the sample size. Only five studies assessed the exposure more than once. Based on the authors' judgment, 19 of the 47 articles did not adequately adjust for potential confounding variables.

Definition and Prevalence of PP and PIM

When defining PP, only 19 studies clearly stated which types of medications were included in their analyses (i.e., prescription, supplemental, and/or over-the-counter medications; supplemental online Table 1). Overall, the prevalence of PP ranged from 2.0% to 80.0%. PP was defined as the use of five or more medications in 57.4% (27/47) of the studies; in these studies, the prevalence ranged from 14.0% to 80.0%. Other definitions included (a) 10 or more medications (7/47, with prevalence ranging from 5.6% to 43.0%), (b) 9 or more medications (1/47, with no prevalence reported), (c) 6 or more medications (3/47, 8.0% to 38.0%), (d) 4 or more medications (4/47, 49.0% to 86.0%), (e) 3 or more medications (2/47, 43.0% to 52.0%), (f) any concomitant (≥1) medications in addition to cancer treatment (2/47, 2.0%, and 69.0%), and (g) other definitions (2/47).

Overall, the prevalence of PIM ranged from 19.0% to 52.0% (assessed in 11/47 studies). Ten of 11 studies used the

Table 1. Studies examined the association between PP and postoperative outcomes

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results[b]
McAlpine, 2008, Canada [24]	Single center, retrospective cohort	103	Median: 72 (range, 60–91)	≥5 medications	Mean no. of medications preoperatively = 6.28, mean no. of medications postoperatively = 8.47	Gynecologic cancers	Surgery	Postoperative delirium	OR, 1.9; 95% CI, NR; p = .008
Kristjansson, 2010, Norway [22]	Multicenter, prospective cohort	182	Median: 80 (range, 70–94)	≥5 medications	26.0%	Colorectal	Surgery	30-d major postoperative complications (CD) and survival	NS
Badgwell, 2013, U.S. [20]	Single center, prospective cohort	111	Median: 72 (range, 65–89)	≥5 medications	48.0%	GI	Intra-abdominal surgery	Prolonged hospital stay, readmission within 30 days of surgery, and discharge to an SNF	Prolonged hospital stay: OR, 2.5; 95% CI, 1.1–5.5; p = .003 Other outcomes: NS
de Glas, 2013, The Netherlands [28]	Multicenter, retrospective cohort	3,179	Median: 74 (range, 65–98)	≥5 medications	13.5%	Breast cancer	Breast cancer surgery	30-d postoperative complications	OR, 1.8; 95% CI, 1.4–2.2; p < .001
Pujara, 2015, U.S. [23]	Single center, retrospective cohort	279	Median: 64 (range, 25–88), 46% were ≥65 yrs	≥5 medications	20.1% (not specific to older adults)	Gastric	Intra-abdominal surgery	Major postoperative complications (CD), prolonged hospital stay >14 d, and readmission within 30 d of surgery	OR, 2.4; 95% CI, 1.1–5.2; p = .03 Other outcomes: NS
Kenig, 2015, Poland [21]	Single center, prospective cohort	75	Mean: 73 (SD 5.8; range, 65–93)	2 cutoff values were used: ≥4 or ≥ 5 medications	44.0%	GI	Intra-abdominal surgery	30-d major postoperative complications (CD)	≥4 medications: OR, 4.2; 95% CI, 1.4–12.1, p = NR ≥5 medications: OR, 2.8; 95% CI, 1.1–8.2, p = NR
Jeong, 2016, South Korea [27]	Single center, retrospective cohort	475	Median: 76 (range, 65–96)	≥5 medications	50.5%	Any	Surgery	Postoperative delirium	NS
Westley, 2017, Canada [26]	Population-based retrospective cohort	24,463	Median: 74	PP: ≥5 medications EPP: ≥10 medications	31.8% and 5.6%	Breast cancer	Curative cancer surgery	Initial emergency department visit within 45 d of definitive breast cancer surgery	>5 medications: HR, 1.3; 95% CI, 1.2–1.3; p < .0001 ≥10 medications: HR, 1.5; 95% CI, 1.3–1.8; p < .0001
Fagard, 2017, Belgium [19]	Single center, retrospective cohort	190	Median: 77 (61% 70–79, 39% >80)	≥5 medications	47.4%	Colorectal	Intra-abdominal surgery	30-d postoperative complications (CD)	NS
Choi, 2018, South Korea [25]	Single center, retrospective cohort of prospective data	475	Median: 76 (range 65–96)	≥5 medications ≥10 medications	50.5% and 27.9%	Any	Cancer surgery	30-d mortality and postdischarge institutionalization	Postdischarge institutionalization: OR, 3.8; 95% CI, 1.04–13.8; p < .05 Other outcome: NS

[a]Median or mean, SD (range if available).
[b]Multivariate unless otherwise specified.
Abbreviations: CD, Clavien Dindo; CI, confidence interval; d, day; EPP, excessive polypharmacy; GI, gastrointestinal; HR, hazard ratio; NR, not reported; NS, nonsignificant; OR, odds ratio; PP, polypharmacy; SNF, skilled nursing facility.

Beers criteria to screen for PIM. Several tools were used in addition to the Beers criteria including Drugs to Avoid in Elderly (DAE) list (2/47), STOPP criteria (1/47), HEDIS (1/47), National Board of Health and Welfare Criteria (1/47), and Zhan (1/47).

Outcomes

Among all studies, 77.0% (36/47), 6.0% (3/47), and 17.0% (8/47) investigated outcomes associated with PP, PIM, or both PP and PIM, respectively. Postoperative outcomes (e.g., postoperative complications, delirium, extended hospital stay, and emergency department visit after cancer surgery) were evaluated in 11/47 studies (23%; Table 1) [19–29]. Chemotherapy-related outcomes, such as chemotherapy-related toxicities, chemotherapy completion, hospitalization after chemotherapy, complete remission (CR), chemotherapy dose reductions or delay, and blood transfusion, were evaluated in 12/47 studies (26%; Table 2) [30–41]. Frailty, falls, and physical and functional outcomes were evaluated in 7/47 studies (15%; Table 3) [42–48]. Survival outcomes were assessed in 12/47 studies (26%; Table 4) [22, 29, 30, 34, 36, 37, 49–54]. Other outcomes (e.g., medication adherence, caregiver burden and alternative medications use; supplemental online Table 3) [32, 39, 49, 53, 55–63].

Postoperative Outcomes

See Table 1. A meta-analysis of four studies (n = 726 patients with GI cancers) [19, 21–23] indicated a significant association between PP and postoperative complications (overall OR, 1.9; 95% CI, 1.3–2.8; p = .001; Fig. 2). A study assessing the relationship between PP and postoperative delirium found that patients with gynecologic malignancies who received five or more medications before cancer surgery were at a higher risk of postoperative delirium (OR, 1.9; 95% CI, not reported [NR]; p = .008) [24].

Chemotherapy-Related Outcomes

See Table 2. Of the 12 studies that examined the association between PP and chemotherapy-related outcomes, 9 evaluated chemotherapy toxicity [31–34, 36, 37, 39–41]. The cancer types and treatments in these studies were heterogeneous. Four studies demonstrated that PP was significantly associated with severe chemotherapy toxicity [33, 36, 37, 39]. In a meta-analysis of three phase II/III trials by Woopen et al. that included 1,213 patients with advanced ovarian cancer, PP (≥5 medications) was associated with grade 3–4 hematological and nonhematological toxicities (OR, 1.1; 95% CI, NR; $p < .001$) [37]. In a single-center prospective study of 78 patients with breast cancer receiving first-line chemotherapy, PP (≥5 medications) was associated with grade 3–4 toxicities (OR, 6.38; 95% CI, 2.0–23.5; p = .001) [36]. In a single center retrospective study of 172 patients with solid tumors receiving irinotecan-based therapy, the presence of any concomitant drug used to manage comorbid conditions besides cancer was associated with grade 4 neutropenia and/or grade 3–4 diarrhea (OR, 4.7; 95% CI, 1.04–21.3; p = .04) [33]. PP (≥6 medications) was also associated with hospitalization (OR, 2.3; 95% CI, 1.3–3.9; p = .002) in a single center retrospective study of 318 patients with solid tumors receiving chemotherapy [40]. Two additional studies did not demonstrate any association between PP and hospitalization [30, 31]. PP was not associated with chemotherapy completion, dose reduction, or delay in four studies [37, 38, 40, 41].

Frailty, Falls, and Physical and Functional Outcomes

See Table 3. Seven studies examined the association between PP and frailty, falls, or physical and functional outcomes. Three studies demonstrated a positive association between PP and falls [44, 47, 48]. PP was associated with impairment in either Activity of Daily Living or Instrumental Activity of Daily Living in three studies [43, 45, 46]. In a single center cross-sectional study of 385 older patients with various types of cancers (both solid and hematological), PP (≥5 medications) was associated with frailty (OR, 4.5; 95% CI, 1.9–10.5; p = NR) and prefrailty (OR, 2.4; 95% CI, 1.4–3.9; p = NR) [42].

Survival Outcomes

See Table 4. Only two studies demonstrated a positive association between PP and mortality [30, 52]. In a single-center prospective study of 83 patients with advanced ovarian cancer, PP (≥6 medications) was associated with lower overall survival (OS; OR, NR; 95% CI, NR; p = .04) [52]. In another single center retrospective study of 150 patients with acute myeloid leukemia, PP (≥5 medications) was associated with increased 30-day mortality (OR, 9.98; 955 CI, 1.18–84.13; p = NR) and overall mortality (hazard ratio [HR], 2.13; 95% CI, 1.15–3.92; p = NR) [30].

Other Outcomes

See supplemental online Table 3. Of the four studies evaluating medication adherence, three demonstrated an association of PP with adherence [39, 55, 57]. In a single center prospective study of 47 patients with breast cancer, PP (≥4 medications) was associated with patients receiving nonoperative radiotherapy despite being a candidate for surgery on univariate analysis (no multivariate analysis was done; OR, NR; 95% CI, NR; p = .002) [59]. In another multicenter cross-sectional study, PP was associated with clinical depression (OR, 1.6; 95% CI, 1.1–2.3; p = .008) [60]. PP was also associated with use of complementary and alternative medications (OR, NR; 95% CI, NR; p = .04) and caregiver burden (OR, 2.2; 95% CI, 1.1–4.3; p = .02) [58, 62]. PP was not associated with impaired geriatric assessment domains using the Geriatric 8 screening tool, nor with radiation treatment completion or change in cancer treatment plan [49, 53, 63].

Association of PIM with Outcomes

See Table 5. Among 11 studies [25, 27, 29–32, 45, 54, 58, 64, 65], three demonstrated an association between PIM and clinical outcomes. In a single center retrospective study of 171 patients with aggressive non-Hodgkin lymphoma, PIM use by Beers criteria was associated with grade ≥ 3 toxicity (HR, 1.02; 95% CI, 1.00–1.04; p = .01), worse progression-free survival (HR, 2.81; 95% CI, 1.4–5.8; p = .005), and higher mortality (HR, 3.12; 95% CI, 1.5–6.5; p = .003) [64]. In another single center retrospective study of 475 patients (Beers criteria), PIM was associated with postoperative delirium (OR, 5.53; 95% CI, 2.02–15.10; $p < .001$) [27]. A retrospective study that included 7,279 patients with colorectal cancer who underwent cancer surgery identified an association between PIM (using the

Table 2. Studies examined the association between PP and chemotherapy-related outcomes

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results[b]
Sasaki, 2013, Japan [33]	Single center, retrospective cohort	172 (71% ≥65)	Median: 64 (range, 31–78)	Any concomitant drug used to manage comorbid conditions besides cancer	69.0%	Solid tumors	Irinotecan-based therapy	Severe toxicity (grade 4 neutropenia and/or grade 3/4 diarrhea)	OR, 4.7; 95% CI, 1.04–21.3; p = .04
Hamaker, 2013, The Netherlands [36]	Single center, prospective study	78	Median: 76 (range, 66–87)	≥5 medications	51.0%	Breast cancer	First-line chemotherapy	Grade 3–4 toxicity	OR, 6.4; 95% CI, 2.0–23.5; p = .001
Maggiore, 2014, U.S. [31]	Multicenter, retrospective cohort	500	Median not reported: 54% ≥72	≥4 medications ≥10 medications	49.0% and 11.0%	Solid tumors	Outpatient chemotherapy	Chemotherapy-related toxicity and hospitalization	NS
Elliot, 2014, U.S. [30]	Single center, retrospective cohort	150	Median: 69 (range, 61–87)	≥5 medications ≥4 medications	≥5: 38.0%	Acute myeloid leukemia	Induction chemotherapy	CR status, prolonged hospital stay, and ICU admission	CR status: OR, 0.2; 95% CI, 0.1–0.6; p = NR Other outcomes: NS
Iurlo, 2014, Italy [35]	Single center, retrospective cohort	16	Median: 72 (range, 65–88)	≥3 medications	43.7%	Chronic myeloid leukemia	Imatinib	CCR and change of chemotherapy regimen	CCR: 4/7 patients with PP vs. 5/9 patients without PP[c] Change of chemotherapy regimen: 2/7 patients with PP vs. 3/9 patients without PP[c]
Kim, 2014, South Korea [38]	Single center, retrospective cohort	98	87.8% >70	≥6 medications	39.8%	Any cancer	Palliative chemotherapy	Early discontinuation of chemotherapy	NS
Ting, 2015, Singapore [39]	Single center, cross-sectional study	294	Mean: 71.8	≥5 medications	62.9%	Any cancer	Outpatient chemotherapy	Drug-related problems (potential drug interactions, adverse events, and nonadherence)	OR, 3.2; 95% CI, 1.4–7.3; p = .006
Sud, 2015, Canada [40]	Single center, retrospective cohort	318	Median: 82 (range, 80–92)	≥6 medications	38%	Solid tumors	Chemotherapy	Rate of discontinuation due to toxicity, rate of dose reduction/ omission/delay, hospitalization, and blood transfusion	Hospitalization: OR, 2.3; 95% CI, 1.3–3.9; p = .002 Other outcomes: NS
Park, 2016, Korea [32]	Single center, retrospective cohort	229	Median: 73 (range, 65– 87)	≥5 medications	29.3%	Head and neck cancers	Surgery, radiotherapy, or chemo-radiation	Grade 3–4 toxicity and hospitalization	NS
Iurlo, 2016, Italy [34]	Multicenter, retrospective cohort	296	Mean: 79.4	≥5 medications	36.1%	Chronic myeloid leukemia	Imatinib	CCR, event-free survival, and toxicities	NS

(continued)

Table 2. (continued)

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results[b]
Woopen, 2016, Germany [37]	Meta-analysis (the original patient data of three phase II/III trials)	1,213 (% older adults not reported)	Median: 59 (range, 21–83)	≥5 medications	56.3%	Advanced ovarian cancer	Various chemotherapy regimens	Overall grade 3–4 toxicities, grade 3–4 hematological and nonhematological toxicity, and early discontinuation of chemotherapy	Overall grade 3–4 toxicities: OR, 1.1; 95% CI, NR; $p < .001$ Grade 3–4 hematological toxicities: OR, 1.056; 95% CI, NR; $p < .001$ Severe nonhematological toxicity: OR, 1.1; 95% CI, NR; $p < .001$ Other outcomes: NS
Antonio, 2018, Spain [41]	Single center, prospective cohort	193	Mean: 79.6 (range, 75–89)	≥6 medications	64%	Colorectal cancer	Adjuvant chemotherapy with or without radiotherapy	Treatment refusal, grade 3 toxicity, and completion of at least 80% of the planned chemotherapy dose	Treatment refusal: OR, 5.3; 95% CI, 1.6–18.4; $p = .01$ Other outcomes: NS

[a]Median or mean, SD (range if available).
[b]Multivariate unless otherwise specified.
[c]No analysis, only absolute numbers were reported.
Abbreviations: CI, confidence interval; CCR, complete cytogenic response; CR, completer response; HR, hazards ratio; ICU, intensive care unit; NR, not reported; NS, nonsignificant; OR, odds ratio; PP, polypharmacy.

National Board of Health and Welfare criteria) [66] and length of hospital stay (OR, 1.1; 95% CI, 1.0–1.3; $p = .046$) and 30-day postoperative mortality (OR, 1.4; 95% CI, 1.1–1.9; $p = .006$) [29].

Discussion

To the authors' knowledge, this is the first systematic review that summarizes the associations of PP/PIM with outcomes in older adults with cancer. Included studies were heterogeneous in terms of study design, study population, sample size, PP definitions, and outcomes examined. The wide range of definitions used contributes to the wide range of PP prevalence reported, from 2% [56] to 80% [45]. PIMs were assessed using the Beers criteria in the vast majority of the studies, which is the most commonly used tool for evaluation of PIMs in both clinical and research settings; other tools supplemented the use of the Beers criteria in some studies.

The meta-analysis shows that PP is associated with postoperative complications using the Clavien-Dindo classification. In addition, several studies suggest that PP is associated with chemotherapy toxicity, frailty, falls, and medication nonadherence. Most studies did not show an association between PP and survival, and no studies showed an association between PP and chemotherapy completion. PIM is associated with postoperative complications (delirium and readmission), and two studies indicate that PIM may be associated with higher mortality and lower progression-free survival [29, 64].

Most studies did not show an association between PP and survival, and no studies showed an association between PP and chemotherapy completion. PIM is associated with postoperative complications (delirium and readmission), and two studies indicate that PIM may be associated with higher mortality and lower progression-free survival.

Other reviews in the general geriatric population have found a positive association of PP with functional decline [67, 68]. However, this is the first systematic review to summarize the association between PP and postoperative outcomes and chemotherapy toxicity in older adults with cancer. Because of increased frailty and geriatric syndrome burden in older adults with cancer, as well as the contribution of chemotherapy and supportive care regimens to the overall number of medications, data from general older adult populations are unlikely to be generalizable.

Four studies assessing the impact of PP on postoperative outcomes used a similar population (patients with gastrointestinal cancers), the same definition of PP (≥5 medications), and the same outcome (postoperative complications using the Clavien-Dindo classification). A pooled analysis of these studies demonstrated that PP was associated with postoperative complications, with an overall OR

Table 3. Studies examined the association between PP and frailty, falls, and physical and functional outcomes

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results[b]
Prithviraj, 2012, U.S. [45]	Single center, cross- sectional study	117	Mean: 74.6 (range, 65–85)	≥5 medications	80.0%	Solid tumors	Chemotherapy	IADL and VES score	IADL: OR, NR; 95% CI, NR; p = .007 (univariate only) VES score: OR, NR; 95% CI, NR; p = .03 (univariate only) PP was associated with IADL and VES score impairment
Vande Walle, 2014, Belgium [48]	Multicenter, prospective cohort	937	Median: 76 (range, 70–95)	≥5 medications	53.1%	Any cancer	Not specified	Falls	NS
Turner, 2014, Australia [42]	Single center, cross-sectional study	385	Median: 76.7 (range, 70–92)	≥5 medications	57.0%	Any cancer	Not specified	Physical impairment, frailty, and prefrailty	Physical impairment: OR, 1.1; 95% CI, 1.1–1.2; p = NR Frail: OR, 4.5; 95% CI, 1.9–10.5; p = NR Prefrail: OR, 2.4; 95% CI, 1.4–3.8; p = NR
Williams, 2015, U.S. [47]	Multicenter, cross-sectional study	1,172	Mean: 73 (range, 65–99)	≥9 medications	Not reported	Any cancer	Not specified	Falls	OR, 1.6; 95% CI, 1.2–2.3; p < .001
Turner 2016, Australia [44]	Single center, cross- sectional study	385	Median: 76.7 (range, 70–92)	≥5 medications	57.0%	Any cancer	Not specified	Falls, physical impairment, and frailty	≥5.5 medications was associated with increased falls[c] ≥6.5 medications was associated with physical impairment and frailty[c]
Pamoukdjian 2017, France [46]	Multicenter, cross-sectional study	290	Mean: 80.6	≥5 medications	67.4%	Any cancer except HCC	Not specified	Disability (impairment in ADL and/or IADL)	OR, 2.3; 95% CI, 1.01–4.4; p = .04
van Abbema, 2017, The Netherlands [43]	Multicenter, retrospective cohort	837 (21.4% ≥70)	Median: 60 (range, 50–69 y) Median in patients aged ≥70: 75 (range, 70–93)	≥5 medications	26.8% in patients aged ≥70	Breast and colorectal cancers	Surgery	Functional status (ADL, IADL, and combined)	ADL: OR, 2.1; 95% CI, 1.1–3.8; p = NR IADL: OR, 1.9; 95% CI, 1.1–3.4; p = NR Combined ADL and IADL: OR, 2.1; 95% CI, 1.3–3.5; p = NR

[a]Median or mean, SD (range if available).
[b]Multivariate unless otherwise specified.
[c]Odds ratio and p value were not reported (sensitivity and specificity values).
Abbreviations: CI, confidence interval; ADL, activity of daily living; IADL, instrumental activity of daily living; HCC, hepatocellular carcinoma; NR, not reported; NS, nonsignificant; OR, odds ratio; PP, polypharmacy; VES, Vulnerable Elders-13 Survey.

Table 4. Studies examined the association between PP and survival outcomes

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results
Freyer, 2005, France [52]	Single center, prospective cohort	83	Median: 76	≥6 medications	8.0%	Ovarian cancer	First-line palliative chemotherapy	40-mo OS	PP was associated with lower OS (p = .04)[b]
Kristjansson, 2010, Norway [22]	Multicenter, prospective cohort	182	Median: 80 (range, 70–94)	≥5 medications	26.0%	Colorectal	Surgery	30-d major postoperative complication (CD) and survival	NS
Hamaker, 2013, The Netherlands [36]	Single center, prospective study	78	Median: 76 (range, 66–87)	≥5 medications	51.0%	Breast cancer	First-line chemotherapy	OS	NS
Falandry, 2013, France [51]	Multicenter phase II clinical trial	111	Median: 79 (range, 71–93)	≥4 medications	68.0%	Ovarian cancer	First-line carboplatin	OS	NS
Hamaker, 2014, The Netherlands [49]	Single center, retrospective cohort	108	Median: 78.2 (range, 67.1–98.9)	≥5 medications	65.0%	Hematologic cancer	Standard treatment, adjusted treatment, or no treatment	1-y mortality	NS
Elliot, 2014, U.S. [30]	Single center retrospective cohort	150	Median: 69 (range, 61–87)	≥5 medications ≥4 medications	≥5: 38.0%	Acute myeloid leukemia	Induction chemotherapy	30-d mortality and overall mortality	30-day mortality: OR, 9.9; 95% CI, 1.2–84.1, p = NR Overall mortality: HR, 2.1; 95% CI, 1.2–3.9; p = NR
Woopen, 2016, Germany [37]	Meta-analysis the original patient data of three phase II/III trials	1,213	Median: 62	≥6 medications	56.0%	Ovarian cancer	Chemotherapy	Progression-free survival and 5-year OS	NS
Caparrotti, 2016, Canada [50]	Single center, retrospective cohort	287	Median: 74–75	Comorbidity-PP score (sum of comorbidity and medications), 6 or more	47.0%	Oropharyng-eal cancer	Definitive radiation (chemotherapy is allowed)	5-year OS	NS
Iurlo, 2016, Italy [34]	Multicenter, retrospective cohort	296	Mean: 79.4	≥5 medications	36.0%	Chronic myeloid leukemia	Imatinib	OS (from date of imatinib initiation)	NS

(continued)

Table 4. (continued)

Study	Study design	Sample size	Age[a]	Definition of PP	PP rate	Cancer type	Treatment	Outcome measures	Results
Nieder, 2017, Norway [53]	Single center, retrospective cohort	280	Median: 77 (range, 70–95)	≥5 medications	7.03%	Any cancer	Palliative radiation	30-d mortality and OS	NS
Karuturi, 2018, U.S. [54]	Population-based retrospective cohort	3,123 (1848 > 70 years)	Breast: 55.4% >70 years Colorectal: 63% >70 years	≥5 medications ≥11 medications	41.4% and 31.0%	Breast and colorectal cancers	Adjuvant chemotherapy	mortality	NS

[a]Median or mean, SD (range if available).
[b]Odds ratio was not reported.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; NS, nonsignificant; PP, polypharmacy; OS, overall survival.

Figure 2. Meta-analysis. Forest plot for a meta-analysis of studies evaluated the association of polypharmacy (≥5 medications) and postoperative complications (using the Clavien-Dindo classification).
Abbreviation: CI, confidence interval.

of 1.9 (95% CI, 1.3–2.8). This may be due to an increased risk of adverse drug events and drug-drug interactions in the presence of anesthetic and other perioperative medications such as analgesics and antibiotics. In addition, hospitalization itself is associated with an increased risk of postdischarge medication-related adverse events [69]. We are unable to determine which medications or class of medications were most associated with postoperative complications; medications assessed as being potentially inappropriate by Beers criteria or other PIM measures have shown associations with postoperative length of stay, mortality, and postoperative delirium across several studies [27, 29], but the effect of PIM on postoperative complications in older patients with cancer is unknown.

Similarly, the association between PP and chemotherapy outcomes remains unclear. Several studies demonstrate that PP is associated with grade ≥ 3 chemotherapy toxicity, but other studies failed to show an association with chemotherapy dose intensity or early discontinuation of therapy. It remains unclear whether PP affects receipt of chemotherapy and, in turn, cancer-related survival. This question may be most critical in older patients being treated with curative intent, for whom chemotherapy dose delays or reductions may substantially affect survival outcomes. PP increases the risk of clinically relevant drug-drug interactions which may potentiate chemotherapy toxicity and/or adverse drug events [70].

PP was found to be significantly associated with reduced OS in only 2 out of 11 studies [30, 52]. The lack of association in other studies may be due to the advanced stage of cancer and poor overall prognosis of the included patients. In very sick patients, PP may be appropriate and may serve to prolong survival [71]. Competing risk of cancer mortality is also possible: patients with advanced cancer may die from their cancer before the adverse effects of PP accrue.

Among the other outcomes evaluated, PP was associated with improved adherence to adjuvant endocrine therapy [55], except among patients frequently using opioid-containing analgesics, anxiolytics or antipsychotics, and antidepressants who had lower adherence to their cancer therapy. This suggests that certain drug classes may have a disproportionate effect on outcomes and that a simple count of medications to assess PP may incorrectly assess risk. Adherence is an important predictor

Table 5. Studies examined the outcomes associated with PIM

Study	Study design	Sample size	Age[a]	Definition of PIM	PIM rate	Cancer type	Treatment	Outcome measures	Results[b]
Prithviraj, 2012, U.S. [45]	Single center, cross-sectional study	117	Mean: 74.6 (range, 65–85)	Beers 2013	41%	Solid tumors	Chemotherapy	IADL and VES-13 score	NS
Elliot, 2014, U.S. [30]	Single center, retrospective cohort	150	Median: 69 (range, 61–87)	Beers 2012	19%	Acute myeloid leukemia	Induction chemotherapy	30-d mortality, CR status, prolonged hospital stay, and ICU admission	NS
Maggiore, 2014, U.S. [31]	Multicenter, retrospective cohort	500	54% ≥72	Beers, Zhan, and 2011 DAE list	Beers (29%), Zhan (11%), DAE (13%)	Solid tumors	Outpatient chemotherapy	Chemotherapy-related toxicity and hospitalization	NS
Chiang, 2015, U.S. [65]	Single center, retrospective cohort	677	Median: 72.7 (SD, 6.4)	Beers 2012	28.3%	Any	Not specified	Unplanned admission to any hospital for any reason within 30 d of discharge from the index hospital stay	NS
Nightingale, 2015, U.S. [58]	Single center, cross-sectional study	234	Mean: 79.9 (range, 61–98)	Beers 2012, STOPP, and HEDIS	51.7% (combined)	Any cancer	Any	CAM use	NS
Jeong, 2016, South Korea [27]	Single center, retrospective cohort	475	Median: 76 (range, 65–96)	Beers 2012	26.7%	Any	Surgery	Postoperative delirium	OR, 5.5; 95% CI, 2.0–15.1, $p < .001$
Park, 2016, Korea [32]	Single center, retrospective cohort	229	Median: 73 (range, 65–87)	Beers 2012	24%	Head and neck cancers	Surgery, radiotherapy, or chemo-radiation	Grade 3–4 toxicity and hospitalization	NS
Samuelsson, 2016, Sweden [29]	Population-based, retrospective cohort	7,279	Median: 81 (range, 75–98)	National Board of Health and Welfare criteria	22.5%	Colorectal cancer	Cancer surgery	Length of hospital stay and 30-d postoperative mortality	Length of hospital stay: OR, 1.1; 95% CI, 1–1.3; $p = .046$ 30-d postoperative mortality: OR, 1.4; 95% CI, 1.1–1.9; $p = .006$
Choi, 2018, South Korea [25]	Single center, retrospective cohort of prospective data	475	Median: 76 (range, 65–96)	Beers 2015	36%	Any	Cancer surgery	30-d mortality and postdischarge institutionalization	NS
Karuturi, 2018, U.S. [54]	Population-based retrospective cohort	3,123 (59% >70)	Breast: 55.4% >70 Colorectal: 63% >70	Beers 2015 and DAE list	Breast: 27.6% (Beers 2015) and 22% (DAE list) Colorectal: 24.8% (Beers 2015) and 15.5% (DAE list)	Breast and colorectal cancers	Adjuvant chemotherapy	Emergency room visit, hospitalization, and death	NS

(continued)

Table 5. (continued)

Study	Study design	Sample size	Age[a]	Definition of PIM	PIM rate	Cancer type	Treatment	Outcome measures	Results[b]
Lin, 2018, U.S. [64]	Single center, retrospective cohort	171	Median: 70 (range, 65–77)	Beers 2015	47%	Aggressive non-Hodgkin lymphoma	Chemo-immunotherapy	Treatment delay, dose reductions, grade 3–4 toxicity, PFS, OS	Grade 3–4 toxicity: HR, 1.02; 95% CI, 1–1.04; $p = .014$ PFS: HR, 2.8; 95% CI, 1.4–5.8; $p = .005$ OS: HR, 3.1; 95% CI, 1.5–6.5; $p = .003$ Other outcomes: NS

[a]Median or mean, SD (range if available).
[b]Multivariate unless otherwise specified.
Abbreviations: CAM, complementary alternative medicine; CI, confidence interval; CR, complete response; DAE, drugs to avoid in the elderly; HR, hazard ratio; IADL, instrumental activity of daily living; ICU, intensive care unit; NS, nonsignificant; OR, odds ratio; OS: overall survival; PFS, progression-free survival; PIM, potentially inappropriate medications; VES, Vulnerable Elders-13.

of clinical outcomes [72], and more data are needed to assess the effects of PP, PIM, and medication burden on adherence, particularly for the increasing number of oral chemotherapy agents [73]. It is also possible that medication burden could impair patients' ability to adhere to supportive care regimens, thereby adversely affecting outcomes, but no data specifically evaluates this hypothesis.

There are limited studies evaluating the association of PIM with clinical outcomes, and most did not show significant associations. Existing criteria and tools to determine PIM are primarily derived from the general geriatric population [74, 75], and the applicability of these tools in the setting of cancer is unclear. The time frame for identification of PIM in patients with cancer may be problematic: many are prescribed supportive care medications considered potentially inappropriate in older adults, although these are usually administered transiently and may be specifically appropriate to treat symptoms related to cancer or cancer treatment. One study has noted a transient elevation in PIM prevalence after a lung or colon cancer diagnosis, which was mostly due to the use of supportive care medications [76]. Most current PIM assessment tools consist of explicit criteria which account for little patient context; assessment of the appropriateness of medications could be improved with tools using implicit criteria, such as the MAI, but such tools require time and expertise for application. The MAI assesses the appropriateness of all medications on a patient's list: any medication may be inappropriate within a certain context (such as lack of an ongoing indication for the medication or lack of time to benefit based on life expectancy).

Two population-based studies were published after our search and were not included in our systematic review. The first found an association of PIM (using Beers criteria) with greater health care utilization and higher health care costs in a cohort of 17,630 older patients with breast, colorectal, and prostate cancers [77]. Another study of 3,123 older patients with breast and colorectal cancers did not find an association between PIM (using STOPP criteria) and emergency department visits, hospitalization, or death [78].

Despite some limited data suggesting that PP/PIM can affect outcomes in older adults with cancer, it is unknown whether intervening on PP or PIM can improve outcomes. There is growing interest in "deprescribing" interventions, involving planned withdrawal of medications. Deprescribing has been shown in preliminary studies to reduce the number of PIMs, falls, and mortality in certain populations. Although deprescribing has been shown to be feasible in older adults with cancer, data are lacking about its efficacy [79, 80].

Deprescribing has been shown in preliminary studies to reduce the number of PIMs, falls, and mortality in certain populations. Although deprescribing has been shown to be feasible in older adults with cancer, data are lacking about its efficacy.

More studies are needed to determine the prospective outcomes of targeted deprescribing interventions (whether decreasing PP will improve outcomes of interest) as well as

determine how these interventions can be implemented for older adults with cancer, including who should deliver them (oncologist, pharmacist, or other health care provider).

This review underscores the limited data available to assess the impact of PP and PIM on outcomes for older adults with cancer. Prospective data are limited; most studies are retrospective cohort or cross-sectional studies. Many studies were not designed with the specific objective to evaluate the effects of PP and PIM on outcomes. Many studies included PP and/or PIM as one of many covariates assessed (in the setting of geriatric assessment, for example), rather than as the primary variable of interest; this approach may be suboptimal for confounding controls and may lead to misinterpretation and lack of reproducibility [81]. The studies are not consistent in their definitions of PP, and most of the included studies did not specify how they counted the number of medications. Many medications contributing to the risk of adverse outcomes are over-the-counter (e.g., diphenhydramine) or are typically prescribed on an as needed basis (e.g., benzodiazepines). Omission of these groups of medications from the assessment could limit the validity and applicability of the data. In addition, patients who are on more medications are more likely to have more comorbidities and/or functional decline, which are important confounders to consider as they may lead to adverse outcomes; although some papers adjusted for these factors, it was not always possible to determine the independent contribution of PP and PIM. Finally, included studies were not limited to those enrolling only older adults, most did not assess the potential for interaction between age and PP and PIM, and studies included subjects with variable cancer types and other characteristics, which may carry different risks of adverse outcomes.

Our study has several additional limitations. We did not include non-English publications, and six studies were not identified in the initial search, so it is possible that other studies were missed. Most of the studies were perceived to have poor to fair quality in relation to the specific objective of this review. The majority were retrospective or cross-sectional in design, and the causal relationships between PP and the various outcomes cannot be determined. Most studies (27/47) evaluated PP in the context of a geriatric assessment (GA) and included limited information on the medications (e.g., classes, doses). We were unable to determine if the results of the GA were available to treating physicians; GA is known to influence discussion about medications and may drive medication changes, which in turn may affect outcomes of interest [82]. Although the majority of the included studies provided quantitative definition of PP, only about one-third clearly specified whether prescription, supplemental, and over-the-counter medications were included.

Conclusion

This is the most comprehensive review to date assessing associations between PP and/or PIM and health outcomes in older patients with cancer. PP and PIM are prevalent in older adults with cancer, but definitions are very heterogeneous, complicating interpretability of associations with outcomes of interest. PP is associated with postoperative complications, functional impairment and possibly chemotherapy-related toxicity, although prospective studies with detailed medication reviews are needed to further investigate these associations. Data are very limited for associations with PIM and outcomes in older patients with cancer, and widely-used PIM measures may not be as useful in this population. Clear and validated definitions and instruments are needed to investigate PP and PIM in older adults with cancer and to develop interventions, such as deprescribing interventions, to improve outcomes for these vulnerable patients.

Acknowledgments

The work was funded through R01 CA177592 (S.G.M.), K24 AG056589 from the National Institute of Aging (S.G.M.), and a Wilmot Fellowship Award (E.R.). All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the official views of the funding agencies. The study was presented as a poster presentation at the 2018 International Society of Geriatric Oncology Annual Meeting.

Author Contributions

Conception/design: Mostafa R. Mohamed, Erika Ramsdale, Kah Poh Loh, Supriya G. Mohile

Collection and/or assembly of data: Mostafa R. Mohamed, Kah Poh Loh, Asad Arastu, Spencer Obrecht

Data analysis and interpretation: Mostafa R. Mohamed, Erika Ramsdale, Kah Poh Loh, Huiwen Xu, Daniel Castillo

Manuscript writing: Mostafa R. Mohamed, Erika Ramsdale, Kah Poh Loh, Manvi Sharma

Final approval of manuscript: Mostafa R. Mohamed, Erika Ramsdale, Kah Poh Loh, Asad Arastu, Huiwen Xu, Spencer Obrecht, Daniel Castillo, Manvi Sharma, Holly M. Holmes, Ginah Nightingale, Katherine M. Juba, Supriya G. Mohile

Disclosures

The authors indicated no financial relationships.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

2. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85:86–88.

3. Mohile SG, Fan L, Reeve E et al. Association of cancer with geriatric syndromes in older Medicare beneficiaries. J Clin Oncol 2011;29:1458–1464.

4. Dhalwani NN, Fahami R, Sathanapally H et al. Association between polypharmacy and falls in older adults: a longitudinal study from England. BMJ Open. 2017;7:e016358.

5. Jensen GL, Friedmann JM, Coleman CD et al. Screening for hospitalization and nutritional risks among community-dwelling older persons. Am J Clin Nutr 2001;74:201–205.

6. Leelakanok N, Holcombe AL, Lund BC et al. Association between polypharmacy and death: A systematic review and meta-analysis. J Am Pharm Assoc (2003) 2017;57:729–738.e10.

7. Masnoon N, Shakib S, Kalisch-Ellett L et al. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.

8. Nightingale G, Hajjar E, Swartz K et al. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. J Clin Oncol 2015;33:1453–1459.

9. American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate

Medication Use in Older Adults. J Am Geriatr Soc 2019;67:674–694.

10. O'Mahony D, O'Sullivan D, Byrne S et al. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age Ageing. 2015;44:213–218.

11. Zhan C, Sangl J, Bierman AS et al. Potentially inappropriate medication use in the community-dwelling elderly: Findings from the 1996 Medical Expenditure Panel Survey. JAMA 2001;286:2823–2829.

12. Hanlon JT, Schmader KE. The medication appropriateness index at 20: Where it started, where it has been, and where it may be going. Drugs Aging 2013;30:893–900.

13. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: A population-based study of the very old. Drugs Aging 2005;22:69–82.

14. Stockl KM, Le L, Zhang S et al. Clinical and economic outcomes associated with potentially inappropriate prescribing in the elderly. Am J Manag Care 2010;16:e1–e10.

15. Popa MA, Wallace KJ, Brunello A et al. Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol 2014;5:307–314.

16. Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.

18. National Institutes of Health. Quality assessment tool for observational cohort and cross-sectional studies. Available at https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort. Accessed February 1, 2018.

19. Fagard K, Casaer J, Wolthuis A et al. Value of geriatric screening and assessment in predicting postoperative complications in patients older than 70 years undergoing surgery for colorectal cancer. J Geriatr Oncol 2017;8:320–327.

20. Badgwell B, Stanley J, Chang GJ et al. Comprehensive geriatric assessment of risk factors associated with adverse outcomes and resource utilization in cancer patients undergoing abdominal surgery. J Surg Oncol 2013;108:182–186.

21. Kenig J, Olszewska U, Zychiewicz B et al. Cumulative deficit model of geriatric assessment to predict the postoperative outcomes of older patients with solid abdominal cancer. J Geriatr Oncol 2015;6:370–379.

22. Kristjansson SR, Jordhøy MS, Nesbakken A et al. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? J Geriatr Oncol 2010;1:57–65.

23. Pujara D, Mansfield P, Ajani J et al. Comprehensive geriatric assessment in patients with gastric and gastroesophageal adenocarcinoma undergoing gastrectomy. J Surg Oncol 2015;112:883–887.

24. McAlpine J, Hodgson E, Abramowitz S et al. The incidence and risk factors associated with postoperative delirium in geriatric patients undergoing surgery for suspected gynecologic malignancies. Gynecol Oncol 2008;109:296–302.

25. Choi KS, Jeong YM, Lee E et al. Association of pre-operative medication use with post-surgery mortality and morbidity in oncology patients receiving comprehensive geriatric assessment. Aging Clin Exp Res 2018;30:1177–1185.

26. Westley T, Syrowatka A, Henault D et al. Patterns and predictors of emergency department visits among older patients after breast cancer surgery: A population-based cohort study. J Geriatr Oncol 2018;9:204–213.

27. Jeong YM, Lee E, Kim KI et al. Association of pre-operative medication use with post-operative delirium in surgical oncology patients receiving comprehensive geriatric assessment. BMC Geriatr 2016;16:134.

28. de Glas NA, Kiderlen M, Bastiaannet E et al. Postoperative complications and survival of elderly breast cancer patients: A FOCUS study analysis. Breast Cancer Res Treat 2013;138:561–569.

29. Samuelsson K, Egenvall M, Klarin I et al. Inappropriate drug use in elderly patients is associated with prolonged hospital stay and increased postoperative mortality after colorectal cancer surgery: A population-based study. Colorectoral Dis 2016;18:155–162.

30. Elliot K, Tooze JA, Geller R et al. The prognostic importance of polypharmacy in older adults treated for acute myelogenous leukemia (AML). Leuk Res 2014;38:1184–1190.

31. Maggiore RJ, Dale W, Gross CP et al. Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: Effect on chemotherapy-related toxicity and hospitalization during treatment. J Am Geriatr Soc 2014;62:1505–1512.

32. Park JW, Roh JL, Lee SW et al. Effect of polypharmacy and potentially inappropriate medications on treatment and posttreatment courses in elderly patients with head and neck cancer. J Cancer Res Clin Oncol 2016;142:1031–1040.

33. Sasaki T, Fujita K, Sunakawa Y et al. Concomitant polypharmacy is associated with irinotecan-related adverse drug reactions in patients with cancer. Int J Clin Oncol 2013;18:735–742.

34. Iurlo A, Nobili A, Latagliata R et al. Imatinib and polypharmacy in very old patients with chronic myeloid leukemia: Effects on response rate, toxicity and outcome. Oncotarget 2016;7:80083–80090.

35. Iurlo A, Ubertis A, Artuso S et al. Comorbidities and polypharmacy impact on complete cytogenetic response in chronic myeloid leukaemia elderly patients. Eur J Intern Med 2014;25:63–66.

36. Hamaker ME, Seynaeve C, Wymenga AN et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: Results from the OMEGA study of the Dutch Breast Cancer Trialists' Group. Breast 2014;23:81–87.

37. Woopen H, Richter R, Chekerov R et al. The influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and survival in recurrent ovarian cancer patients: An individual participant data meta-analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO) of 1,213 patients. J Clin Oncol 2015;33(suppl)5533a.

38. Kim JW, Kim YJ, Lee KW et al. The early discontinuation of palliative chemotherapy in older patients with cancer. Support Care Cancer 2014;22:773–781.

39. Ting YT, Yin TX, Si P et al. Drug-related problems in elderly patients with cancer receiving outpatient chemotherapy. J Geriatr Oncol 2015;6:280–287.

40. Sud S, Lai P, Zhang T et al. Chemotherapy in the oldest old: The feasibility of delivering cytotoxic therapy to patients 80 years old and older. J Geriatr Oncol 2015;6:395–400.

41. Antonio M, Carmona-Bayonas A, Saldaña J et al. Factors predicting adherence to a tailored-dose adjuvant treatment on the basis of geriatric assessment in elderly people with colorectal cancer: A prospective study. Clin Colorectal Cancer 2017;17:e59–e68.

42. Turner JP, Shakib S, Singhal N et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer 2014;22:1727–1734.

43. van Abbema D, van Vuuren A, van den Berkmortel F et al. Functional status decline in older patients with breast and colorectal cancer after cancer treatment: A prospective cohort study. J Geriatr Oncol 2017;8:176–184.

44. Turner JP, Jamsen KM, Shakib S et al. Polypharmacy cut-points in older people with cancer: How many medications are too many? Support Care Cancer 2016;24:1831–1840.

45. Prithviraj GK, Koroukian S, Margevicius S et al Patient Characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. J Geriatr Oncol 2012;3:228–237.

46. Pamoukdjian F, Aparicio T, Zelek L et al. Impaired mobility, depressed mood, cognitive impairment and polypharmacy are independently associated with disability in older cancer outpatients: The prospective Physical Frailty in Elderly Cancer patients (PF-EC) cohort study. J Geriatr Oncol 2017;8:190–195.

47. Williams GR, Deal AM, Nyrop KA et al. Geriatric assessment as an aide to understanding falls in older adults with cancer. Support Care Cancer 2015;23:2273–2280.

48. Vande Walle N, Kenis C, Heeren P et al. Fall predictors in older cancer patients: A multicenter prospective study. BMC Geriatr 2014;14:135.

49. Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. Ann Hematol 2014;93:1031–1040.

50. Caparrotti F, O'Sullivan B, Bratman SV et al. Exploring the impact of human papillomavirus status, comorbidity, polypharmacy, and treatment intensity on outcome of elderly oropharyngeal cancer patients treated with radiation therapy with or without chemotherapy. Int J Radiat Oncol Biol Phys 2017;98:858–867.

51. Falandry C, Weber B, Savoye AM et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: A GINECO prospective trial. Ann Oncol 2013;24:2808–2813.

52. Freyer G, Geay JF, Touzet S et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: A GINECO study. Ann Oncol 2005;16:1795–1800.

53. Nieder C, Mannsåker B, Pawinski A et al. Polypharmacy in older patients ≥70 years receiving palliative radiotherapy. Anticancer Res 2017; 37:795–799.

54. Karuturi MS, Holmes HM, Lei X et al. Potentially inappropriate medication use in older patients with breast and colorectal cancer. Cancer 2018;124:3000–3007.

55. Jun D, Lee W, Xing S, Calip G. Polypharmacy and adherence to adjuvant endocrine therapy for breast cancer. J Am Pharm Assoc 2016;56 (3):e13.

56. Kapoor J, Agrawal N, Ahmed R et al. Factors influencing adherence to imatinib in Indian chronic myeloid leukemia patients: A cross-sectional study. Mediterr J Hematol Infect Dis 2015;7: e2015013.

57. Kuo SZ, Haftek M, Lai JC. Factors associated with medication non-adherence in patients with end-stage liver disease. Dig Dis Sci 2017;62: 543–549.

58. Nightingale G, Hajjar E, Guo K et al. A pharmacist-led medication assessment used to determine a more precise estimation of the prevalence of complementary and alternative medication (CAM) use among ambulatory senior adults with cancer. J Geriatr Oncol 2015;6:411–417.

59. Parks RM, Hall L, Tang SW et al. The potential value of comprehensive geriatric assessment in evaluating older women with primary operable breast cancer undergoing surgery or non-operative treatment—A pilot study. J Geriatr Oncol 2015;6:46–51.

60. Canoui-Poitrine F, Reinald N, Laurent M et al. Geriatric assessment findings independently associated with clinical depression in 1092 older patients with cancer: The ELCAPA Cohort Study. Psychooncology 2016;25:104–111.

61. Şenel G, Uysal N, Oguz G et al. Delirium frequency and risk factors among patients with cancer in palliative care unit. Am J Hosp Pallat Care 2017;34:282–286.

62. Rajasekaran T, Tan T, Ong WS et al. Comprehensive Geriatric Assessment (CGA) based risk factors for increased caregiver burden among elderly Asian patients with cancer. J Geriatr Oncol 2016;7: 211–218.

63. Caillet P, Canoui-Poitrine F, Vouriot J et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol 2011;29:3636–3642.

64. Lin RJ, Ma H, Guo R et al. Potentially inappropriate medication use in elderly non-Hodgkin lymphoma patients is associated with reduced survival and increased toxicities. Br J Haematol 2018;180:267–270.

65. Chiang LY, Liu J, Flood KL et al. Geriatric assessment as predictors of hospital readmission in older adults with cancer. J Geriatr Oncol 2015; 6:254–261.

66. Fastbom J, Johnell K. National indicators for quality of drug therapy in older persons: The Swedish experience from the first 10 years. Drugs Aging 2015;32:189–199.

67. Hammond T, Wilson A. Polypharmacy and falls in the elderly: A literature review. Nurs Midwifery Stud 2013;2:171–175.

68. Todd A, Holmes HM. Recommendations to support deprescribing medications late in life. Ing J Clin Pharm 2015;37:678–681.

69. Forster AJ, Murff HJ, Peterson JF et al. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 2003;138:161–167.

70. Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer 2006;6:546–558.

71. McIsaac DI, Wong CA, Bryson GL et al. Association of polypharmacy with survival, complications, and healthcare resource use after elective noncardiac surgery: A population-based cohort study. Anesthesiology 2018;128:1140–1150.

72. Shingler SL, Bennett BM, Cramer JA et al. Treatment preference, adherence and outcomes in patients with cancer: Literature review and development of a theoretical model. Curr Med Res Opin 2014;30:2329–2341.

73. Krikorian S, Pories S, Tataronis G et al. Adherence to oral chemotherapy: Challenges and opportunities. J Oncol Pharm Pract 2018:1078155218800384.

74. Fick DM, Cooper JW, Wade WE et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–2724.

75. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): Application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673–679.

76. Lund JL, Sanoff HK, Peacock Hinton S et al. Potential medication-related problems in older breast, colon, and lung cancer patients in the United States. Cancer Epidemiol Biomarkers Prev 2018;27:41–49.

77. Feng X, Higa GM, Safarudin F et al. Potentially inappropriate medication use and associated healthcare utilization and costs among older adults with colorectal, breast, and prostate cancers. J Geriatr Oncol 2019 [Epub ahead of print].

78. Karuturi MS, Holmes HM, Lei X et al. Potentially inappropriate medications defined by STOPP criteria in older patients with breast and colorectal cancer. J Geriatr Oncol 2019 [Epub ahead of print].

79. Kua CH, Mak VSL, Huey Lee SW. Health outcomes of deprescribing interventions among older residents in nursing homes: A systematic review and meta-analysis. J Am Med Dir Assoc 2018;20:362–372.e11.

80. Whitman AM, DeGregory KA, Morris AL et al. A comprehensive look at polypharmacy and medication screening tools for the older cancer patient. ***The Oncologist*** 2016;21: 723–730.

81. Westreich D, Greenland S. The table 2 fallacy: Presenting and interpreting confounder and modifier coefficients. Am J Epidemiol 2013;177: 292–298.

82. Ramsdale E, Lemelman T, Loh KP et al. Geriatric assessment-driven polypharmacy discussions between oncologists, older patients, and their caregivers. J Geriatr Oncol 2018;9:534–539.

See http://www.TheOncologist.com for supplemental material available online.