Systematic Review and Meta-Analysis on the Associations of Polypharmacy and Potentially Inappropriate Medication with Adverse Outcomes in Older Cancer Patients

Running head: Polypharmacy and PIM in Cancer Patients

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Main Text Word Count: 4,422

Number of data elements (Tables and Figures): 5

References count: 80

Abstract

Background: Both polypharmacy and potentially inappropriate medication (PIM) intake are highly prevailing in older cancer patients. However, only studies on the association of polypharmacy and post-operative complications have been meta-analyzed previously.

Methods: A systematic review and a meta-analysis of prospective/retrospective observational studies reporting associations of polypharmacy or PIM with at least 1 out of 5 pre-defined adverse health outcomes in a population of older cancer patients (≥ 60 years) were carried out. PubMed and Web of Science were used to search for relevant studies published between January 1991 and March 2020. Data were pooled by adopting a random-effects model.

Results: Overall, 42 publications were included in the systematic review. Meta-analyses could be performed on 39 studies about polypharmacy and 13 studies about PIM. Polypharmacy was found to be statistically significantly associated with all-cause mortality (risk ratio [95% confidence interval]: 1.37 [1.25–1.50]), hospitalization (1.53 [1.37–1.71]), treatment-related toxicity (1.22 [1.01–1.47]), and postoperative complications (1.73 [1.36–2.20]). The association of polypharmacy with prolongation of hospitalization was not statistically significant at the $p<0.05$ significance level (1.62 [0.98–2.66]). With respect to PIM, a statistically significant association with all-cause mortality (1.43 [1.08–1.88]) was observed but not with other adverse outcomes.

Conclusion: Polypharmacy was found to be associated with several adverse outcomes and PIM use with all-cause mortality in older cancer patients. However, these results should be interpreted with caution because about three-quarters of the studies identified did not adjust for comorbidity and are prone to confounding by indication.

Keywords: Geriatric Oncology; Mortality; Hospitalizations; Adverse Drug Reaction; Postoperative Complications

Introduction

Polypharmacy is common in the general older population due to highly comorbid status of older adults: prevalence ranges from 22.8% to 44% when defined as concurrent use of 5 drugs or more.[1-3] Polypharmacy is at least as common in older cancer patients. Depending on the cancer site studied, the prevalence of polypharmacy in older cancer patients varied between 11% and 96% in previous studies.[4]

Cancer patients are particularly prone to unintended consequences of polypharmacy because chemotherapy may entail risk to drug-drug interactions and adverse drug events, which might include chemotherapy-related toxicity.[5] However, evidence on the safety of polypharmacy in older cancer patients is sparse. Also, clinical trials are seldom conducted in old, multi-morbid individuals and mostly cover too short follow-up for evaluating drug safety.[6] Thus, evidence from prospective cohort studies is additionally needed.

Potentially inappropriate medication (PIM) is defined as prescriptions in adults, which have a negative benefit-risk ratio and could be replaced by safer alternatives.[7] Today, several different lists are available to identify PIM.[8-11] Depending on the PIM lists used, PIM prevalence varies widely. In the general older German population, it was determined to lay between 14% and 37%,[12] and ranged from 15.5% to 51% in older cancer patients.[13,14] Previous studies observed an association of PIM use with drug-related problems in the general older population.[15,16] In older cancer populations, however, evidence on the safety of PIM use is still sparse.[4] There is a need for a review summarizing the results of currently available studies carried out on the safety of PIM use in cancer patients while taking the heterogeneity of the different applied PIM lists into account.

Therefore, the aim of this comprehensive systematic review about polypharmacy and PIM intake in older cancer patients is to systematically search, review, appraise, and meta-analyze the currently available evidence from observational studies about their associations with all-cause mortality,

hospitalization, prolongation of hospitalization, treatment-related toxicity, and postoperative complications, as polypharmacy or PIM use was previously conjectured to increase the risk of these outcomes.[4]

Methods

The protocol of this systematic review was registered at PROSPERO (no. CRD42019131810) and its results are being reported in line with the recommendations of the MOOSE Statement (**M**eta-analyses **O**f **O**bservational **S**tudies in **E**pidemiology; **Appendix, Table A1**).[17]

Searching Strategy and Data Extraction

Two medical databases, PubMed and Web of Science, were used to search for relevant studies in March 2020. PubMed focuses on life sciences, whereas Web of Science on more scientific fields. A specific advantage of PubMed is that it provides early online ahead of print publications. A specialty of Web of Science is that it also includes very old publications because its indexed and archived records go back to 1900.[18] In brief, we created the following search string using all possible synonymous terms for the named search terms:

("polypharmacy" OR "potentially inappropriate medication") AND "neoplasm". The full search strings for PubMed and Web of Science can be seen in **Appendix Table A2** and **Appendix Table A3**, respectively.

We did not place any restriction on the publication language. The publication period was fixed from the year 1991 on when the first PIM list was published.[19] Case reports, comments, editorials, letters, and reviews were filtered out in the next step.

Publications captured through our search string were imported into the EndNote™ reference management software (Clarivate Analytics, Philadelphia, USA). Duplicate articles and ineligible types of publications (case reports, comments, editorials, letters, and reviews) were automatically

removed by the software. Next, titles and abstracts were reviewed to exclude those not relevant to the topic. In full-text review, publications fulfilling the following exclusion criteria were eliminated:

1. No cohort study design or prospective/retrospective observational study design applied to a randomized controlled trial (RCT) population.
2. The study population was not limited to older cancer patients (defined as aged 60 years or older).
3. Polypharmacy or PIM was assessed but only reported combined with other evaluation tools.
4. Polypharmacy or PIM was not assessed.
5. Publication was retracted.
6. The study used the same cohort as other publication(s).
7. No data on any of the health outcomes of interest (i.e., all-cause mortality, hospitalization, prolongation of hospitalization, treatment-related toxicity defined by Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3, and postoperative complications).
8. No hazard ratio or odds ratio including 95% confidence intervals (CI) reported for dichotomous polypharmacy or PIM variable or provided by corresponding authors.

The corresponding authors of all publications initially meeting the last exclusion criterion were contacted and asked to provide the effect size data needed for a meta-analysis. Overall, n=3 corresponding authors replied and their studies could be included in the review.[20-22] Furthermore, cross-referencing was done in all included publications to identify further studies. The full-text selection and data extraction were conducted independently by two reviewers (L.-J. C. and K. T.). If no consensus was reached between the two aforementioned authors, a third researcher (B. S.) was consulted.

Risk of Bias and Confounding Assessment

With a modified Newcastle-Ottawa-Scale (NOS), we evaluated the risk of selection bias and confounding by indication as well as the adequacy of outcome assessment.[23] The study quality score

of the NOS ranges from 0 to 9 points, with more points indicating lower risk of bias (see legend of **Appendix Table A5** for details). Besides, we assessed the risk for bias forms which need special attention in pharmacoepidemiological studies,[24] in particular, healthy-user/ sick-stopper bias,[25,26] and immortal time bias[27,28].

Statistical Methods

The software Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ) was used to pool risk ratios (RR) and 95% CIs by random-effects meta-analysis, which allows heterogeneity between studies and produces larger 95% CIs with increasing heterogeneity.[29] We applied the I^2 statistic and Cochrane's Q test to examine the heterogeneity across included studies and Egger's test for publication bias. Furthermore, we addressed publication bias by an appraisal of the symmetry of funnel plots and imputed missing study results by the trim and fill method of Duval and Tweedie.[30]

Depending on the availability of data, meta-analyses were performed for the associations of polypharmacy and PIM with each outcome of interest (i.e., all-cause mortality, hospitalization, prolongation of hospitalization, treatment-related toxicity, and postoperative complications). Besides, stratified meta-analyses were conducted for the cut-off point used to define polypharmacy (≥3 or ≥4, ≥5, and ≥6), PIM criteria used, and adjustment for co-morbidity (yes or no). A planned analysis, stratifying by cancer sites, was retracted since appropriate studies were not sufficiently available.

If a study used a polypharmacy variable with 3 or more categories (e.g. < 5 (Reference), 5-9, and ≥ 10 drugs), results for all categories including at least ≥ 4 drugs were pooled by fixed-effects meta-analysis within these studies. The result was then used for the main meta-analysis with other studies. If a study reported results for more than one PIM definition or more than one postoperative complication, the effect estimate with the strongest positive association was chosen for the meta-analysis. A sensitivity analysis was conducted using the weakest positive association.

Results

Literature Search

The literature search is depicted in **Appendix, Figure A1**. Overall, 7,801 studies were screened, and 128 publications were included in the full-text selection, and none of them was written in languages other than English. In total, 87 publications were excluded during full-text selection. They are listed in **Appendix, Table A4** sorted by the exclusion criterion met. Cross-referencing disclosed one additional study to be included.[31] Overall, this systematic review comprises 42 publications.

Description of included studies

From the included 42 publications, results of n=39 individual studies about polypharmacy were extracted (three studies reported results for more than one population: Lu-Yao et al.[32], Karuturi et al.[33], and Kenis et al.[34]). Their study designs are depicted in **Table 1**. With only four exceptions with cut-offs ≥7, ≥8, or ≥10 drugs,[35-38] the studies defined polypharmacy by ≥3, ≥4, ≥5 or ≥6 drugs or polypharmacy categories could be merged so that they met this definition. Most of the studies (n=28) comprised only hospital inpatients and used collected primary data (n=32). Only the studies of Lu-Yao et al.[32], Karuturi et al.[33], Williams et al.[38], and Westley et al.[39] were conducted with claims data. Studies by Lu-Yao et al.[32] (n=7,309 and n=5,490) and Westley et al.[39] (n=24,463) were also outliers concerning sample size. The largest study of those using primary data was conducted by de Glas et al.[31] (n=3,179). Sample sizes of all other studies ranged from n=40 to n=1,595. Three of the four large studies were conducted with breast cancer patients. The fourth study recruited lung cancer patients. The smaller studies mostly combined different cancer types. The results of the individual studies are summarized in **Table 2.** The prevalence of polypharmacy varied between 13.5% and 73.7% among the studies.

Overall thirteen studies about PIM were included in this systematic review. The studies of Karuturi et al.[13,33] 2018 and 2019 used the same study population but different criteria to define PIM

use and were therefore combined. However, as Karuturi et al.[13,33] separately reported results of a colorectal cancer (CRC) and a breast cancer (BC) cohort, the publications are nevertheless listed with two studies. The designs of the thirteen studies about PIM are described in **Table 3.** Except for studies by Jeon et al.[40], Samuelsson et al.[41] and Chun et al.[20], all studies adopted an edition of the Beers criteria or combined them with other PIM criteria.[5,13,27,33,42-47] The majority of the studies (n=8) were conducted solely with hospitalized inpatients,[27,40,42-47] four were conducted with outpatients,[5,13,20,33] and one study combined in- and outpatients.[41] The four studies, which used claims data, were the largest.[13,20,33,41] The study of Samuelsson et al.[41] included n=7,279 CRC patients, the study of Chun et al.[20] included n=2,401 BC patients and the two cohort studies conducted by Karuturi et al.[13,33] included n=1,528 CRC and n=1,595 BC patients. All other studies with primary data had sample sizes between n=150 and n=677 and cancer sites varied largely. The prevalence of PIM ranged from 10.8% to 57.5% (**Table 4**). The results of all assessed outcomes in these studies are shown in **Table 4**.

Risk of Bias and Confounding Assessment

For NOS assessment, except for studies by Klepin et al.[48] and Kristjansson et al.[49], all included studies got scores between seven and nine points, which was regarded as low risk of bias (**Appendix Table A5**). However, about three-quarters of the studies (30 out of 39 reporting on polypharmacy, 10 out of 13 for PIM) did not adjust for comorbidity and were therefore vulnerable to confounding by indication (**Tables 2** and **4**). Moreover, except for the study by Chiang et al,[27] all included studies adopted a prevalent user design, which implies a high risk for the healthy-user/ sick-stopper bias.[5,13,20-22,31-66] The study by Chiang et al,[27] however, was the only study with apparent immortal time bias and was therefore not included in any meta-analysis.

Associations with All-Cause Mortality

Eighteen studies investigated the association of polypharmacy with all-cause mortality in older

cancer patients.[22,34,36,37,45,46,48,52-57,59-61,63] The study of Kenis et al.[34] 2018 included two independent cohorts. The pooled effect estimate indicated statistical significance, and mortality increased by 37% (RR [95%CI]: 1.37 [1.25–1.50]) among polypharmacy users. Heterogeneity between study results was low (Q=20.19, P=0.260, I^2=15.8%) (**Figure 1A**).

Six cohort studies assessed the associations of PIM intake with all-cause mortality.[13,41,42,45,47] The study by Karuturi et al.[13] reported results on two separate cohorts. The pooled effect estimate indicated a 43% increased mortality of PIM user and the association did reach statistical significance (RR [95%CI]: 1.43 [1.08–1.88]). In addition, heterogeneity was moderate (Q=9.99, P=0.076, I^2=49.9%) (**Figure 1B**).

Associations with Hospitalization

Thirteen studies examined the association of polypharmacy with hospitalization in older cancer patients.[5,22,32,33,38,39,43,44,46,65] The study by Lu-Yao et al.[32] reported results on three different cohorts. The study by Karuturi et al.[33] reported data for two independent cohorts. The pooled effect estimate indicated a 53% increased risk for hospitalization, and the association was statistically significant (RR [95%CI]: 1.53 [1.37–1.71]). However, heterogeneity was statistically significant (Q=42.2, P<0.001, I^2=71.6%) (**Figure 1C**). If the study of Westley et al.[39] and the CRC cohort of Karuturi et al.[33], which both assessed only emergency room admissions and had relatively weak but statistically significant effect estimates, were excluded, the heterogeneity was substantially lower (Q=9.96, P=0.354, I^2=9.6%) and the pooled RR remained statistically significant (RR [95%CI]: 1.62 [1.50–1.74]).

Eight studies were included in the meta-analysis on the association of PIM intake and hospitalization.[5,13,20,33,40,43,44,46] Karuturi et al.[13,33] reported data for two independent cohorts. The pooled effect estimate suggested a 14% increased risk for PIM users (RR [95%CI]: 1.14 [0.99–1.32]) but the association was not statistically significant. No important heterogeneity was detected (Q=9.34, P=0.229, I^2=25.1%) (**Figure 1D**).

Associations with Prolongation of Hospitalization

Four studies investigated the association of polypharmacy with prolongation of hospitalization.[44,45,51,64] The pooled effect estimate demonstrated an approximately 60% higher risk for prolongation of hospitalization for patients with polypharmacy, but the association did not reach statistical significance (RR [95%CI]: 1.62 [0.98–2.66]). We detected no signs of heterogeneity in the meta-analysis (Q=2.39, P=0.495, I^2=0%) (**Figure 1E**).

Three studies assessed the association of PIM intake with prolongation of hospitalization.[41,44,45] The pooled effect estimate suggested an approximately 20% increased risk but was not statistically significant (RR [95%CI]: 1.19 [0.88–1.59]). Heterogeneity was low in this meta-analysis (Q=2.37, P=0.306, I^2=15.5%) (**Figure 1F**).

Associations with Treatment-related Toxicity

There were seven studies pooled in the meta-analysis on the association of polypharmacy and treatment-related toxicity defined as CTCAE grade ≥ 3.[5,44,46,50,56,62,66] The pooled effect estimate suggested a 22% increased risk for polypharmacy user and was statistically significant (RR [95%CI]: 1.22 [1.01–1.47]). In addition, no important heterogeneity was observed (Q=8.42, P=0.210, I^2=28.7%) (**Figure 1G**).

Three studies examined the association of PIM intake with treatment-related toxicity defined as CTCAE grade ≥ 3.[5,42,44]. The pooled effect estimate suggested an approximately 50% increased risk in treatment-related toxicity for patients with PIM, but the association did not reach statistical significance (RR [95%CI]: 1.56 [0.79–3.08]). Moreover, heterogeneity was considerable (Q=5.06, P=0.080, I^2=60.5%) (**Figure 1H**).

Associations with Postoperative Complications

Six studies investigated the association of polypharmacy with postoperative

complications.[21,31,35,49,58,64] The pooled effect estimate indicated a statistically significant, about 70% increased risk for postoperative complications for patients with polypharmacy (RR [95%CI]: 1.73 [1.36–2.20]). Heterogeneity was low (Q=5.32, P=0.378, I^2=6.0%) (**Figure 1I**).

Publication Bias Assessment

The Egger test indicated statistically significant publication bias for only one of the conducted meta-analyses, which was the one on the association of polypharmacy with all-cause mortality. Visual examination of the funnel plot (not shown) suggested five missing studies on the left side (towards a weaker association). Imputing the missing studies with the trim and fill method resulted in a slightly weaker but still statistically significant pooled effect estimate for the association between polypharmacy and all-cause mortality (RR [95%CI]: 1.31 [1.18–1.45]).

Stratified Meta-Analyses and Sensitivity Analysis

Meta-analyses were additionally conducted stratified by 1) the cut-off point used to define polypharmacy, 2) the PIM criteria used, and 3) adjustment for co-morbidity. No relevant differences were detected compared to the main results (data not shown). Replacing the strongest associations reported for different PIM definitions or various postoperative complications with the weakest reported associations did not change the conclusions of any of the meta-analyses (**Appendix, Figure A2**).

Discussion

This systematic review and meta-analysis revealed that polypharmacy is statistically significantly associated with increased mortality, hospitalization, treatment-related toxicity and postoperative complications in older cancer patients. The effect estimate for prolongation of hospitalization was substantially increased but not statistically significant. Fewer studies have been published for PIM exposure and only the association of PIM intake and all-cause mortality reached

statistical significance.

Comparison with Other Reviews

To the best of our knowledge, this is the second and most extensive systematic review on the associations of polypharmacy and PIM with adverse outcomes in older cancer patients. A previous systematic review by Mohamed et al.[67] searched the literature until September 2018 and performed only one meta-analysis including four studies on the association between polypharmacy and postoperative complications. We updated this meta-analysis with six studies published until March 2020 and confirmed the statistically significant association. Moreover, we performed eight additional meta-analyses on associations of polypharmacy and PIM with further adverse outcomes, namely all-cause mortality, hospitalization, prolongation of hospitalization, and treatment-related toxicity, providing a comprehensive picture on the risks of polypharmacy and PIM in older cancer patients.

Narrative reviews on this issue have been published by Sharma et al. and Nightingale et al. and neither did contain a systematic literature search or meta-analysis.[4,68] Both reviews give an overview of the results of studies about polypharmacy and adverse outcomes in cancer patients. The outcomes addressed, however, were too heterogeneous to make any clear conclusions. The review of Sharma et al.[4] additionally addressed the importance of deprescribing PIM but did not review the results of the studies published on this topic.

Individual Study Results for Polypharmacy

Study results for polypharmacy were quite homogenous across all assessed outcomes despite the different cut-offs used to define polypharmacy by the studies. This may be explained by the low number of studies that used cut-offs of ≥7 drugs (n=4). The majority of studies used the cut-offs ≥3, ≥4, ≥5, or ≥6 and thus centered around the most commonly used cut-off of ≥ 5.

Several studies reported statistically significant findings for associations of polypharmacy and

adverse health outcomes. We, therefore, focus on the discussion on the largest studies using claims data and collected primary data, which were both conducted with BC patients.

The study of Westley et al.[39] was conducted with claims data and had the highest sample size of all studies (n=24,463). The results showed that having 6-10 prescriptions (1.23 [1.15–1.31]) and >10 prescriptions (1.53 [1.33–1.77]) were both statistically significant predictors for 45-day postoperative emergency department admission in BC patients aged ≥ 65 years. However, the study did not adjust for comorbidity and the results were therefore susceptible to confounding by indication (i.e., the association of polypharmacy with 45-day postoperative emergency department admission could be confounded by the patients' comorbidity).

The largest study using collected primary data was conducted by de Glas et al.[31] (n=3,179). Polypharmacy (defined as ≥ 5 drugs) was found to be statistically significantly associated with postoperative complications (RR [95%CI]:1.76 [1.39–2.23]) in BC patients aged 65 to 98 years. This result was also vulnerable to confounding by indication because comorbidity was not considered in the main model. Of note, the study showed that having ≥ 4 concomitant diseases was associated with postoperative complications as well (RR [95%CI]: 1.86 [1.20–2.09]). Therefore, it is uncertain to what extent the statistically significant association between polypharmacy and postoperative complications may be attributed to comorbidity.

Individual Study Results for Potentially Inappropriate Medication

The PIM-related studies applied the Beers 2012 and 2015 criteria,[69,70] HEDIS-DAE,[11] Zhan's classification,[71] Beers 2012 criteria in combination with other PIM criteria (Beers 2012, Zhan, and HEDIS-DAE), the Screening tool of older people's prescriptions (STOPP) criteria,[9] the pre-operative discontinuation requiring medication list (PDRM),[40] and the Socialstyrelsen criteria.[72] Only five studies reported statistically significant findings, which we review in the following.

The study of Samuelsson et al.[41] was conducted with n=7,279 CRC patients aged 75 years and

older. It applied the “avoid” and the “avoid as long-term use” parts of the Socialstyrelsen criteria to identify PIM, which mainly include antidepressants, antipsychotics, and benzodiazepines. These drug groups are associated with an increased risk of falls in the older population.[73] A serious fall in turn might cause hospitalization, prolonged hospital stay, and even mortality.[74] The focus on these drug groups and the high statistical power of this by far largest PIM-related study may explain the detection of statistically significant findings.

Lin et al. 2018 reported a statistically significant association of PIM use determined by the Beers 2015 criteria with all-cause mortality and treatment-related toxicity in patients with aggressive non-Hodgkin lymphoma (NHL).[42] Lin et al. 2019 reported a statistically significant association of Beers 2015 PIM use with all-cause mortality in older patients undergoing hematologic stem cell transplantation.[47] As all other studies applying the Beers criteria reported non-significant results, these notable findings may be explained by the characteristics of patients with aggressive NHL and patients who undergo hematologic stem cell transplantation.

Karuturi et al.[13,33] used the HEDIS-DAE and STOPP PIM criteria and observed a statistically significantly increased all-cause mortality and risk for hospitalization of PIM users with BC but not with CRC. However, these results should be considered with caution due to the lack of correction for multiple testing. Overall, Karuturi al.[13,33] applied 24 tests for associations of different PIM criteria with various adverse health outcomes in two distinct cohorts with either BC or CRC patients (**Table 4**). Only 2 out of 24 tests were statistically significant (2/24=8.33%), which is close to the proportion of tests that can be expected to be statistically significant just by chance when multiple testing is being performed (5%). Therefore, further studies are needed to validate this single significant finding form the study of Karuturi et al.[13,33]

The study of Jeon et al.[40] was performed with n=473 cancer patients aged 65 years and older who required surgical removal of the cancer. The PDRM list was designed by the authors themselves and was tailored to surgical risks.[40] Thus, it includes only anticoagulants, antiplatelet agents, other

hemorrheologic agents (Ibudilast, Mesoglycan), non-steroidal anti-inflammatory drugs, Raloxifene, Tibolone, Artemisia asiatica extract, Ginkgo biloba leaf extract, and Metformin.[40,75] The focus on these drugs and the specific population undergoing surgery may explain the statistically significant association of this PIM definition with hospitalization.

Limitations of Included Studies

The most important limitations of most of the included studies are the lack of control for confounding by indication and a high risk for the healthy-user/ sick-stopper bias. Confounding occurs when variables are associated with both exposure and outcome of interest but are not on the causal pathway in between. In studies on polypharmacy and PIM, the indications for drug use (i.e., diseases) are potential confounders. Therefore, models should be adjusted for comorbidity to give unbiased results.[76] However, this was only done by a minority of the included studies and several studies did not adjust their models for any potential confounder. Although meta-analyses stratified by adjustment for comorbidity did not produce different results, this limitation should not be disregarded when interpreting the results of the meta-analyses. We cannot rule out that all associations of polypharmacy and adverse health outcomes in older cancer patients observed in this review are just a result of confounding by indication.

Another limitation, which was present in all studies that could be included in the meta-analyses, was the susceptibility to the healthy-user/ sick-stopper bias. This bias can occur when rather healthy patients tend to put up well with and adhere to a treatment, while rather sick patients, have a higher propensity not to get a treatment or not to adhere to a treatment.[26,77] Results might then be biased towards a null or even inverse association with adverse health outcomes leading to underestimation of harmful effects of a treatment.[77,78] The only way to avoid the healthy-user/ sick-stopper bias is to use a new user design, which defines exposure only via new use of polypharmacy or PIM.[26]

Strengths and Limitations of the Systematic Review and Meta-Analysis

This systematic review presents an in-depth review of the literature regarding the topic of polypharmacy and PIM use in older cancer patients and thoroughly appraised the risk of bias in the included studies. We also performed random-effects meta-analyses for five major adverse health outcomes of cancer therapy. Besides, we further carried out meta-analyses stratified by suspected major sources of heterogeneity between studies: the definition of polypharmacy adopted, the PIM criteria used, and whether studies were adjusted for comorbidity. However, it was not possible to stratify by cancer site because there was too much variation between the studies. If more individual studies on specific cancer sites are available in the future, future reviews should focus on specific cancers (e.g. BC or CRC). Finally, it should be noted that despite all efforts made to provide highly accurate meta-analyses, their value is determined by the quality of the included studies.

Clinical Relevance of the Findings and Needs for Future Research

In this meta-analysis of observational studies, polypharmacy was found to be statistically significantly associated with all-cause mortality, hospitalization, treatment-related toxicity, and postoperative complications in older cancer patients, but it remains unclear whether these associations truly exist because most studies did not adjust for comorbidity. The main reason for this high number of studies with insufficient adjustment is that these studies had the aim to assess polypharmacy as a prognostic factor and not as a risk factor. Polypharmacy is often incorporated in comprehensive geriatric assessments that have the aim to predict adverse treatment outcomes in frail cancer patients. For these prognostic studies, adjustment for potential confounders is not needed. Therefore, based on the current study data, polypharmacy assessment can be considered to be clinically relevant for the prognosis of cancer therapy in older cancer patients concerning the adverse outcomes all-cause mortality, hospitalization, treatment-related toxicity, and postoperative complications. Whether polypharmacy is a risk factor for these outcomes independent from co-morbidity status has to be determined by future studies.

For PIM among older cancer patients, a significant association was only found for all-cause mortality. However, this result should be interpreted with caution because of the substantial heterogeneity of the studies regarding the PIM definitions and cancer populations. Given the low number of the studies conducted so far, PIM use may nevertheless be a risk factor for other adverse outcomes. Further well-designed studies are required to elucidate whether avoiding PIM use in cancer patients has positive effects on health outcomes. In addition to the outcomes addressed by this review, frailty, falls and measures of functional status should be taken into account by future studies because of their high relevance for older cancer patients and the sparse evidence so far.[67] Future studies should also adopt a new user design when possible and adjust for comorbidity and further potential confounders. Moreover, future studies on polypharmacy should use the common polypharmacy definition of ≥ 5 drugs for better comparability of findings with other studies.

Conclusions

In this comprehensive systematic review and meta-analysis of prospective observational studies, polypharmacy was statistically significantly associated with all-cause mortality, hospitalization, treatment-related toxicity, and postoperative complications in the older cancer population. The association of polypharmacy with prolongation of hospitalization was not statistically significant at the $p<0.05$ level but the effect estimate was substantially higher than 1 (RR, 95%CI: 1.62 [0.98–2.66]). For PIM use, a statistically significant association was only observed in the meta-analysis on all-cause mortality. These results should be interpreted with caution because of the presence of confounding by indication and healthy-user/ sick-stopper bias in most of the included studies. Further studies, avoiding these sources of bias, are unquestionably needed.

Funding

No funding was obtained for this research project.

Acknowledgments

L.-J.C. and B.S. contributed to the concept, design, and search strategy development of this systematic review and meta-analysis. L.-J.C. did the study selection up to the full-text selection. The full-text selection and data extraction from included studies was independently done by L.-J.C. and K.T., L.-J.C. performed the meta-analyses. L.-J.C. drafted the manuscript and B.S. revised and edited it. K.T., D.C.L., N.T.N.M., and H.B. commented critically on an advanced manuscript version regarding the interpretation of the results and the discussion. All authors read and approved the final version of the manuscript. L.-J.C., K.T., D.C.L., N.T.N.M., H.B., and B.S. take responsibility for the integrity and accuracy of the data and the statistical analysis.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

References

1. Rawle MJ, Richards M, Davis D, Kuh D. The prevalence and determinants of polypharmacy at age 69: a British birth cohort study. *BMC geriatrics.* 2018;18(1):118. doi:10.1186/s12877-018-0795-2
2. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clinical epidemiology.* 2018;10:289-298. doi:10.2147/clep.S153458
3. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *Jama.* 2015;314(17):1818-1831. doi:10.1001/jama.2015.13766
4. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *Journal of geriatric oncology.* 2016;7(5):346-353. doi:10.1016/j.jgo.2016.07.010
5. 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. *Journal of the American Geriatrics Society.* 2014;62(8):1505-1512. doi:10.1111/jgs.12942
6. Broekhuizen K, Pothof A, de Craen AJ, Mooijaart SP. Characteristics of randomized controlled trials designed for elderly: a systematic review. *PloS one.* 2015;10(5):e0126709. doi:10.1371/journal.pone.0126709
7. Beer C, Hyde Z, Almeida OP, et al. Quality use of medicines and health outcomes among a cohort of community dwelling older men: an observational study. *British journal of clinical pharmacology.* 2011;71(4):592-599. doi:10.1111/j.1365-2125.2010.03875.x
8. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society.* 2019;67(4):674-694. doi:10.1111/jgs.15767
9. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213-218. doi:10.1093/ageing/afu145
10. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol.* 1992;45(10):1045-1051. https://ac.els-cdn.com/089543569290144C/1-s2.0-089543569290144C-main.pdf?_tid=dc425602-fd31-4803-a83a-a5a72a538d08&acdnat=1551797451_71993de06704c4c0810c1ad5cab42acd.
11. The National Committee for Quality Assurance. HEDIS 2017 Final NDC Lists - Use of High-Risk Medications in the Elderly (DAE). https://www.ncqa.org/hedis/measures/hedis-2017-national-drug-code-ndc-license/hedis-2017-final-ndc-lists/. Accessed March 5, 2019.
12. Muhlack DC, Hoppe LK, Stock C, Haefeli WE, Brenner H, Schottker B. The associations of geriatric syndromes and other patient characteristics with the current and future use of

potentially inappropriate medications in a large cohort study. *European journal of clinical pharmacology.* 2018;74(12):1633-1644. doi:10.1007/s00228-018-2534-1

13. Karuturi MS, Holmes HM, Lei X, et al. Potentially inappropriate medication use in older patients with breast and colorectal cancer. *Cancer.* 2018;124(14):3000-3007. doi:10.1002/cncr.31403

14. Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. 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(13):1453-1459. doi:10.1200/JCO.2014.58.7550

15. Heider D, Matschinger H, Meid AD, et al. Health Service Use, Costs, and Adverse Events Associated with Potentially Inappropriate Medication in Old Age in Germany: Retrospective Matched Cohort Study. *Drugs Aging* 2017;34(4):289-301. doi:10.1007/s40266-017-0441-2

16. Fick DM, Mion LC, Beers MH, Waller JL. Health Outcomes Associated With Potentially Inappropriate Medication Use in Older Adults. *Res Nurs Health* 2008;31(1):42-51. doi:10.1002/nur.20232

17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama.* 2000;283(15):2008-2012. https://jamanetwork.com/journals/jama/articlepdf/192614/jst00003.pdf. Published 2000/05/02.

18. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. *Faseb j.* 2008;22(2):338-342. doi:10.1096/fj.07-9492LSF

19. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Archives of internal medicine.* 1991;151(9):1825-1832. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/615518. Published 1991/09/01.

20. Chun DS, Peacock-Hinton S, Lund JL. Potentially inappropriate medication use and emergency department visits in older women diagnosed with breast cancer initiating chemotherapy. *Pharmacoepidemiol Drug Saf.* 2018;27:295-295.

21. 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. *Journal of geriatric oncology.* 2017;8(5):320-327. doi:10.1016/j.jgo.2017.07.008

22. Hakozaki T, Hosomi Y, Shimizu A, et al. Polypharmacy as a prognostic factor in elderly patients with advanced non-small cell lung cancer treated with anti-PD-1/PD-L1 antibody based immunotherapy. J Canc Res Clin Oncol. 2020, in press.

23. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the

quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Published 2019. Accessed April 15, 2019.
24. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Published 2019. Accessed April 30, 2019.
25. Muhlack DC, Hoppe LK, Weberpals J, Brenner H, Schottker B. The Association of Potentially Inappropriate Medication at Older Age With Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies. *Journal of the American Medical Directors Association.* 2017;18(3):211-220. doi:10.1016/j.jamda.2016.11.025
26. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *Journal of general internal medicine.* 2011;26(5):546-550. doi:10.1007/s11606-010-1609-1
27. Chiang LY, Liu J, Flood KL, et al. Geriatric assessment as predictors of hospital readmission in older adults with cancer. *Journal of geriatric oncology.* 2015;6(4):254-261. doi:10.1016/j.jgo.2015.04.003
28. Suissa S. Immortal time bias in pharmaco-epidemiology. *American journal of epidemiology.* 2008;167(4):492-499. doi:10.1093/aje/kwm324
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials.* 1986;7(3):177-188. https://www.sciencedirect.com/science/article/pii/0197245686900462?via%3Dihub. Published 1986/09/01.
30. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56(2):455-463. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.0006-341X.2000.00455.x?sid=nlm%3Apubmed. Published 2000/07/06.
31. de Glas NA, Kiderlen M, Bastiaannet E, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast cancer research and treatment.* 2013;138(2):561-569. doi:10.1007/s10549-013-2462-9
32. Lu-Yao G, Nightingale G, Nikita N, et al. Relationship between polypharmacy and inpatient hospitalization among older adults with cancer treated with intravenous chemotherapy. *Journal of geriatric oncology.* 2020. doi:10.1016/j.jgo.2020.03.001
33. Karuturi MS, Holmes HM, Lei X, et al. Potentially inappropriate medications defined by STOPP criteria in older patients with breast and colorectal cancer. *Journal of geriatric oncology.* 2019;10(5):705-708. doi:10.1016/j.jgo.2019.01.024
34. Kenis C, Baitar A, Decoster L, et al. The added value of geriatric screening and assessment for predicting overall survival in older patients with cancer. *Cancer.* 2018;124(18):3753-3763. doi:10.1002/cncr.31581
35. Lee YH, Oh HK, Kim DW, et al. Use of a Comprehensive Geriatric Assessment to Predict

Short-Term Postoperative Outcome in Elderly Patients With Colorectal Cancer. *Annals of coloproctology.* 2016;32(5):161-169. doi:10.3393/ac.2016.32.5.161

36. Jonna S, Chiang L, Liu J, Carroll MB, Flood K, Wildes TM. Geriatric assessment factors are associated with mortality after hospitalization in older adults with cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2016;24(11):4807-4813. doi:10.1007/s00520-016-3334-8
37. Ommundsen N, Wyller TB, Nesbakken A, et al. Frailty is an independent predictor of survival in older patients with colorectal cancer. *The oncologist.* 2014;19(12):1268-1275. doi:10.1634/theoncologist.2014-0237
38. Williams GR, Dunham L, Chang Y, et al. Geriatric Assessment Predicts Hospitalization Frequency and Long-Term Care Use in Older Adult Cancer Survivors. *J Oncol Pract.* 2019;15(5):e399-e409. doi:10.1200/jop.18.00368
39. 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. *Journal of geriatric oncology.* 2018;9(3):204-213. doi:10.1016/j.jgo.2017.10.003
40. Jeon MS, Jeong YM, Yee J, et al. Association of pre-operative medication use with unplanned 30-day hospital readmission after surgery in oncology patients receiving comprehensive geriatric assessment. *Am J Surg.* 2019. doi:10.1016/j.amjsurg.2019.06.020
41. Samuelsson KS, Egenvall M, Klarin I, Lokk J, Gunnarsson U. Inappropriate drug use in elderly patients is associated with prolonged hospital stay and increased postoperative mortality after colorectal cancer surgery: a population-based study. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland.* 2016;18(2):155-162. doi:10.1111/codi.13077
42. Lin RJ, Ma H, Guo R, Troxel AB, Diefenbach CS. Potentially inappropriate medication use in elderly non-Hodgkin lymphoma patients is associated with reduced survival and increased toxicities. *British journal of haematology.* 2018;180(2):267-270. doi:10.1111/bjh.15027
43. 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 clinical and experimental research.* 2018;30(10):1177-1185. doi:10.1007/s40520-018-0904-2
44. 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. *Journal of cancer research and clinical oncology.* 2016;142(5):1031-1040. doi:10.1007/s00432-015-2108-x
45. Elliot K, Tooze JA, Geller R, et al. The prognostic importance of polypharmacy in older adults treated for acute myelogenous leukemia (AML). *Leukemia research.* 2014;38(10):1184-1190. doi:10.1016/j.leukres.2014.06.018
46. Hong S, Lee JH, Chun EK, et al. Polypharmacy, Inappropriate Medication Use, and Drug Interactions in Older Korean Patients with Cancer Receiving First-Line Palliative

Chemotherapy. *The oncologist.* 2020;25(3):e502-e511. doi:10.1634/theoncologist.2019-0085
47. Lin RJ, Hilden PD, Elko TA, et al. Burden and impact of multifactorial geriatric syndromes in allogeneic hematopoietic cell transplantation for older adults. *Blood Adv.* 2019;3(1):12-20. doi:10.1182/bloodadvances.2018028241
48. Klepin HD, Ritchie E, Major-Elechi B, et al. Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: Report of CALGB 361006 (Alliance). *Journal of geriatric oncology.* 2020;11(1):107-113. doi:10.1016/j.jgo.2019.10.002
49. Kristjansson SR, Jordhoy MS, Nesbakken A, et al. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *Journal of geriatric oncology.* 2010;1(2):57-65. doi:10.1016/j.jgo.2010.06.001
50. Antonio M, Carmona-Bayonas A, Saldana 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. *Clinical colorectal cancer.* 2018;17(1):e59-e68. doi:10.1016/j.clcc.2017.09.003
51. 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. *Journal of surgical oncology.* 2013;108(3):182-186. doi:10.1002/jso.23369
52. Bourdel-Marchasson I, Diallo A, Bellera C, et al. One-Year Mortality in Older Patients with Cancer: Development and External Validation of an MNA-Based Prognostic Score. *PloS one.* 2016;11(2):e0148523. doi:10.1371/journal.pone.0148523
53. Dhakal P, Lyden E, Muir KE, et al. Prevalence and effects of polypharmacy on overall survival in acute myeloid leukemia. *Leuk Lymphoma.* 2020:1-7. doi:10.1080/10428194.2020.1737687
54. Hamaker ME, Buurman BM, van Munster BC, Kuper IM, Smorenburg CH, de Rooij SE. The value of a comprehensive geriatric assessment for patient care in acutely hospitalized older patients with cancer. *The oncologist.* 2011;16(10):1403-1412. doi:10.1634/theoncologist.2010-0433
55. Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. *Annals of hematology.* 2014;93(6):1031-1040. doi:10.1007/s00277-013-2001-0
56. 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 (Edinburgh, Scotland).* 2014;23(1):81-87. doi:10.1016/j.breast.2013.11.004
57. Kanesvaran R, Li H, Koo KN, Poon D. Analysis of prognostic factors of comprehensive

geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(27):3620-3627. doi:10.1200/jco.2010.32.0796

58. Kenig J, Olszewska U, Zychiewicz B, Barczynski M, Mitus-Kenig M. Cumulative deficit model of geriatric assessment to predict the postoperative outcomes of older patients with solid abdominal cancer. *Journal of geriatric oncology.* 2015;6(5):370-379. doi:10.1016/j.jgo.2015.03.004

59. Ku JY, Roh JL, Kim SB, Choi SH, Nam SY, Kim SY. Prognostic value of neutrophil-to-lymphocyte ratio in older patients with head and neck cancer. *Journal of geriatric oncology.* 2019. doi:10.1016/j.jgo.2019.06.013

60. Nishijima TF, Deal AM, Lund JL, Nyrop KA, Muss HB, Sanoff HK. The incremental value of a geriatric assessment-derived three-item scale on estimating overall survival in older adults with cancer. *Journal of geriatric oncology.* 2018;9(4):329-336. doi:10.1016/j.jgo.2018.01.007

61. Ommundsen N, Nesbakken A, Wyller TB, et al. Post-discharge complications in frail older patients after surgery for colorectal cancer. *Eur J Surg Oncol.* 2018;44(10):1542-1547. doi:10.1016/j.ejso.2018.06.024

62. Reed M, Patrick C, Quevillon T, Walde N, Voutsadakis IA. Prediction of hospital admissions and grade 3-4 toxicities in cancer patients 70 years old and older receiving chemotherapy. *Eur J Cancer Care.* 2019;28(6):9. doi:10.1111/ecc.13144

63. Sales J, Azevedo C, Santos C, et al. RISK FACTORS COMPREHENSIVE GERIATRIC ASSESSMENT FOR EARLY DEATH IN ELDERLY PATIENTS WITH GYNECOLOGICAL CANCER. A PROSPECTIVE COHORT STUDY. *Int J Gynecol Cancer.* 2019;29:A159-A159. doi:10.1136/ijgc-2019-IGCS.386

64. Samuelsson KS, Egenvall M, Klarin I, Lokk J, Gunnarsson U. Preoperative geriatric assessment and follow-up of patients older than 75years undergoing elective surgery for suspected colorectal cancer. *Journal of geriatric oncology.* 2019. doi:10.1016/j.jgo.2019.01.020

65. Sud S, Lai P, Zhang T, Clemons M, Wheatley-Price P. Chemotherapy in the oldest old: The feasibility of delivering cytotoxic therapy to patients 80 years old and older. *Journal of geriatric oncology.* 2015;6(5):395-400. doi:10.1016/j.jgo.2015.07.002

66. Woopen H, Richter R, Ismaeel F, et al. The influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and overall survival in ovarian cancer. *Gynecol Oncol.* 2016;140(3):554-558. doi:10.1016/j.ygyno.2016.01.012

67. Mohamed MR, Ramsdale E, Loh KP, et al. Associations of Polypharmacy and Inappropriate Medications with Adverse Outcomes in Older Adults with Cancer: A Systematic Review and Meta-Analysis. *The oncologist.* 2020;25(1):e94-e108. doi:10.1634/theoncologist.2019-0406

68. Nightingale G, Skonecki E, Boparai MK. The Impact of Polypharmacy on Patient Outcomes in Older Adults With Cancer. *Cancer journal (Sudbury, Mass).* 2017;23(4):211-218. doi:10.1097/ppo.0000000000000277

69. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society.* 2015;63(11):2227-2246. doi:10.1111/jgs.13702
70. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society.* 2012;60(4):616-631. doi:10.1111/j.1532-5415.2012.03923.x
71. 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(22):2823-2829. doi:10.1001/jama.286.22.2823
72. Swedish National Board of Health and Welfare (Socialstyrelsen): Indikatorer för god läkemedelsterapi hos äldre. https://www.socialstyrelsen.se/publikationer/. Published 2010. Accessed March 6, 2019.
73. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of internal medicine.* 2009;169(21):1952-1960. doi:10.1001/archinternmed.2009.357
74. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age and ageing.* 2006;35 Suppl 2:ii37-ii41. doi:10.1093/ageing/afl084
75. 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 geriatrics.* 2016;16:134. doi:10.1186/s12877-016-0311-5
76. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *American journal of epidemiology.* 2007;166(6):646-655. doi:10.1093/aje/kwm165
77. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. *Epidemiology (Cambridge, Mass).* 2013;24(3):375-378. doi:10.1097/EDE.0b013e31828ac9cb
78. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology (Cambridge, Mass).* 2001;12(6):682-689. Published 2001/10/27.
79. Orsini N. From floated to conventional confidence intervals for the relative risks based on published dose-response data. *Computer methods and programs in biomedicine.* 2010;98(1):90-93. doi:10.1016/j.cmpb.2009.11.005
80. Altman DG, Bland JM. How to obtain the confidence interval from a P value. *Bmj.* 2011;343:d2090. doi:10.1136/bmj.d2090

Figure legend

Figure 1. Forest plots of studies assessing the association of polypharmacy or potentially

inappropriate medication (PIM) use with adverse health outcomes in older cancer patients.

[a] Results for all categories including at least ≥ 4 drugs were pooled by fixed-effects meta-analysis first within these studies.

[b] The adverse health outcome with the strongest positive association was chosen for the meta-analysis. A sensitivity analysis using the weakest positive association is presented in Figure A2 (Appendix).

Table 1. Designs of Studies Investigating the Association of **Polypharmacy** with Adverse Health Outcomes in Older Adults with Cancer

First Author, Year	Polypharmacy Definition	Study Design	Country	Claims Data	Data Collection	Study Population				
						Cancer Type	Population	Total (N)	Female (%)	Age (Years)
Dhakal et al, 2020[53]	≥ 5 drugs	RCS, PU	U.S.	No	2000-2016	AML	Inpatients	235	N.R.	≥ 60[a]
Hong et al, 2020[46]	≥ 5 drugs[b]	PCS, PU	South Korea	No	2014-2015	Solid cancer	Inpatients	301	30.9	70 - 93
Klepin et al, 2020[48]	≥ 5 drugs	RCT, PU	U.S.	No	2011-2014	AML	In- and outpatients	40	40	61-83
Lu-Yao et al, 2020_BC[32]	≥ 5 drugs[c]	PCS, PU	U.S.	Yes	1991-2014	BC	Inpatients	5,490	100	≥ 65
Lu-Yao et al, 2020_LC[32]	≥ 5 drugs[c]	PCS, PU	U.S.	Yes	1991-2014	LC	Inpatients	7,309	N.R.	≥ 65
Lu-Yao et al, 2020_PC[32]	≥ 5 drugs[c]	PCS, PU	U.S.	Yes	1991-2014	PC	Inpatients	1,430	0	≥ 65
Hakozaki et al, 2019[22]	≥ 5 drugs	RCS, PU	Japan	No	2016-2019	NSCLC	In- and outpatients	157	36.3	≥ 65
Karuturi et al, 2019_BC[33]	≥ 5 drugs	RCS, PU	U.S.	Yes	2007-2009	BC	Outpatients	1,595	100	≥ 66
Karuturi et al, 2019_CRC[33]	≥ 5 drugs	RCS, PU	U.S.	Yes	2007-2009	CRC	Outpatients	1,528	50.4	≥ 66
Ku et al, 2019[59]	≥ 3 drugs	PCS, PU	South Korea	No	2010-2014	HNSCC	Outpatients	233	15.5	65-84
Reed et al, 2019[62]	≥ 6 drugs	RCS, PU	Canada	No	N.R.	Any	Inpatients	275	57.5	≥ 70
Sales et al, 2019[63]	N.R.	PCS, PU	Brazil	No	2015-2017	Gynecologic cancer	Outpatients	84	100	60-96
Samuelsson et al, 2019[64]	≥ 5 drugs	PCS, PU	Sweden	No	2010-2016	CRC	Inpatients	49	53.1	≥ 75
Williams et al, 2019[38]	≥ 10 drugs	RCS, PU	U.S.	Yes	2009-2013	Any	In- and outpatients	125	80	65-93
Nishijima et al, 2018[60]	≥ 5 drugs	PCS, PU	U.S.	No	2009-2014	Any	Inpatients	546	72	65-100
Ommundsen et al, 2018[61]	≥ 6 drugs	PCS, PU	Norway	No	2011-2014	CRC	Inpatients	114	49	65-95
Westley et al, 2018[39]	≥ 6 drugs[d]	RCS, PU	Canada	Yes	1998-2012	BC	Inpatients	24,463	100	≥ 65
Kenis et al, 2018_1[34]	≥ 5 drugs	PCS, PU	Belgium	No	2009-2011	BC, CRC, LC, PC, OC	Inpatients	763	67.8	70 - 95
Kenis et al, 2018_2[34]	≥ 5 drugs	PCS, PU	Belgium	No	2011-2012	BC, CRC, LC, PC, OC	Inpatients	402	66.7	70 - 95
Choi et al, 2018[43]	≥ 5 drugs	RCS, PU	South Korea	No	2014-2015	All surgical	Inpatients	475	54.7	65 - 96
Antonio et al, 2018[50]	≥ 6 drugs	PCS, PU	Spain	No	2008-2016	CRC (stage II and III)	Inpatients	193	37.3	75 - 89
Fagard et al, 2017[21]	≥ 5 drugs	PCS, PU	Belgium	No	2009-2015	CRC	Inpatients	190	44.7	70 - 97
Woopen et al, 2016[66]	≥ 5 drugs	RCT, PU	Germany	No	2000-2009	OC	Inpatients	134	100	≥ 70[e]
Park et al, 2016[44]	≥ 5 drugs	RCS, PU	South Korea	No	2008-2013	HNC	Inpatients	229	16.2	65 - 87
Lee et al, 2016[35]	≥ 8 drugs	RCS, PU	South Korea	No	2009-2014	CRC	Inpatients	240	42.5	70 - 96
Jonna et al, 2016[36]	≥ 7 drugs	RCS, PU	U.S.	No	2000-2008	Any	Inpatients	803	48.2	≥ 65
Bourdel-Marchasson et al, 2016[52]	≥ 4 drugs	RCT, PU	France	No	2007-2012	Any except lymphoma	Inpatients	606	47.4	≥ 70
Sud et al, 2015[65]	≥ 6 drugs	RCS, PU	Canada	No	2005-2010	Solid cancer	In- and outpatients	318	44	80 - 92
Kenig et al, 2015[58]	≥ 5 drugs	PCS, PU	Poland	No	2013-2014	Solid abdominal tumors	Inpatients	75	44.0	65 - 93
Ommundsen et al, 2014[37]	≥ 8 drugs	PCS, PU	Norway	No	2006-2008	CRC	Inpatients	178	57.3	70 - 94
Maggiore et al, 2014[5]	≥ 4 drugs[f]	PCS, PU	U.S.	No	2006-2009	Solid tumor	Outpatients	500	56.2	≥ 65
Hamaker et al, 2014[56]	≥ 5 drugs	RCT, PU	Netherlands	No	2007-2011	BC	Inpatients	73	100	66 - 87
Hamaker et al, 2014[55]	≥ 5 drugs	PCS, PU	Austria	No	2009-2013	Hematologic malignancy	Inpatients	108	47	67.1 - 98.9

First Author, Year	Polypharmacy Definition	Study Design	Country	Claims Data	Data Collection	Study Population				
						Cancer Type	Population	Total (N)	Female (%)	Age (Years)
Elliot et al, 2014[45]	≥ 4 drugs[g]	RCS, PU	U.S.	No	2004-2009	AML	Inpatients	150	39	61 - 87
de Glas et al, 2013[31]	≥ 5 drugs	RCS, PU	Netherlands	No	1997-2011	BC	Outpatients	3,179	100	65 - 98
Badgwell et al, 2013[51]	≥ 6 drugs	PCS, PU	U.S.	No	2010-2012	Abdominal cancer	Inpatients	111	45.0	65 - 89
Kanesvaran et al, 2011[57]	≥ 5 drugs	RCS, PU	Singapore	No	2007-2010	Any	Outpatients	249	38.6	70 - 94
Hamaker et al, 2011[54]	≥ 5 drugs	PCS, PU	Netherlands	No	2002-2008	Any	Inpatients	292	48.8	65 - 96
Kristjansson et al, 2010[49]	≥ 5 drugs	PCS, PU	Norway	No	2006-2008	CRC	Inpatients	182	57.1	70 - 94

Abbreviations: AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; HNC, head and neck cancer; LC, lung cancer; N.R., not reported; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, prostate cancer; PCS, prospective cohort study; PU, prevalent user design; RCS, retrospective cohort study; RCT, randomized controlled trial

[a] Only patients aged 60 years or above were included in this systematic review and meta-analysis.

[b] Categories "5-9 drugs" and "≥ 10 drugs" have been pooled for the meta-analysis.

[c] Categories "5-9 drugs", "10-14 drugs", and "≥ 15 drugs" have been pooled for the meta-analysis.

[d] Categories "6-10 drugs" and "> 10 drugs" have been pooled for the meta-analysis.

[e] Only patients aged 70 years or above were included in this systematic review and meta-analysis.

[f] Categories "4-9 drugs" and "≥ 10 drugs" have been pooled for the meta-analysis.

[g] Category "2-3 drugs" was not used for the meta-analysis.

Table 2. Follow-Up and Effect Size Data of Studies Investigating the Impact of **Polypharmacy** on Health Outcomes in Older Adults with Cancer

First Author, Year	Polypharmacy Definition	Prevalence of Polypharmacy (%)	Outcome	$N_{outcome}$	FUP	HR or OR (95% CI)	Adjusted Covariates		
							Age+ sex[a]	Comor-bidity	Other
Dhakal et al, 2020[53]	≥ 5 drugs	64.3	Overall survival	≈235[b]	12 years	1.12 (0.81-1.57)	-	x	Multiple[c]
Hong et al, 2020[46]	≥ 5 drugs	45.2	Hospitalization	123	30 days	**1.73 (1.18-2.55)**	x	x	ECOG PS
	5-9 drugs	36.5	Grade ≥ 3 CTCAE toxicity	162	28 days	1.13 (0.70-1.83)	-	-	-
	≥ 10 drugs	8.6	Grade ≥ 3 CTCAE toxicity	162	28 days	1.78 (0.75-4.22)	-	-	-
	5-9 drugs	36.5	Overall survival	≈230[b]	2.5 years	**1.51 (1.09-2.08)**	-	-	-
	≥ 10 drugs	8.6	Overall survival	≈230[b]	2.5 years	**2.04 (1.25-3.32)**	-	-	-
Klepin et al, 2020[48]	≥ 5 drugs	30	Overall survival	≈4	14.9 months[d]	1.25 (0.51-3.06)[e]	-	-	-
Lu-Yao et al, 2020_BC[32]	5-9 drugs	39.3	Hospitalization	N.R.	6 months	**1.17 (1.01–1.37)**[f]	-	-	-
	10-14 drugs	28.6	Hospitalization	N.R.	6 months	**1.61 (1.37–1.89)**[f]	-	-	-
	≥ 15 drugs	16.7	Hospitalization	N.R.	6 months	**2.01 (1.68–2.39)**[f]	-	-	-
Lu-Yao et al, 2020_LC[32]	5-9 drugs	31.9	Hospitalization	N.R.	6 months	**1.36 (1.19–1.72)**[f]	-	-	-
	10-14 drugs	33.7	Hospitalization	N.R.	6 months	**1.49 (1.30–1.72)**[f]	-	-	-
	≥ 15 drugs	25.7	Hospitalization	N.R.	6 months	**1.82 (1.57–2.11)**[f]	-	-	-
Lu-Yao et al, 2020_PC[32]	5-9 drugs	37.2	Hospitalization	N.R.	6 months	**1.42 (1.02-1.97)**[f]	-	-	-
	10-14 drugs	30.7	Hospitalization	N.R.	6 months	**1.75 (1.25–2.45)**[f]	-	-	-
	≥ 15 drugs	21.6	Hospitalization	N.R.	6 months	**2.14 (1.49–3.05)**[f]	-	-	-
Hakozaki et al, 2019[22]	≥ 5 drugs	59.9	Overall survival	74	7.1 months[d]	1.97 (1.14-3.42)	-	-	Multiple[g]
			Progression-free survival	111	7.1 months[d]	1.44 (0.95-2.18)	-	-	Multiple[h]
			Grade ≥2 irAE	27	7.1 months[d]	1.74 (0.67-4.93)	-	-	-
			Hospitalization	76	7.1 months[d]	3.14 (1.54-6.58)	-	-	-
Karuturi et al, 2019_BC[33]	≥ 5 drugs	73.7	Emergency room visit	552	9 months	**1.73 (1.31-2.29)**	-	-	-
			Hospitalization	369	9 months	**1.83 (1.29-2.59)**	-	-	-
			Overall survival	34	9 months	N.S.	-	-	-
			Emergency room visit/ Hospitalization/ Overall survival	598	9 months	N.R.	-	-	-
Karuturi et al, 2019_CRC[33]	≥ 5 drugs	71.2	Emergency room visit	552	9 months	**1.23 (1.04-1.47)**	-	-	-
			Hospitalization	369	9 months	N.S.	-	-	-
			Overall survival	34	9 months	N.S.	-	-	-
			Emergency room visit/ Hospitalization/ Overall survival	598	9 months	N.R.	-	-	-

First Author, Year	Polypharmacy Definition	Prevalence of Polypharmacy (%)	Outcome	$N_{outcome}$	FUP	HR or OR (95% CI)	Adjusted Covariates		
							Age+ sex[a]	Comor-bidity	Other
Ku et al, 2019[59]	≥ 3 drugs	N.R.	Overall survival	81	5.83 years	1.13 (0.73–1.74)	-	-	-
			Cancer-specific survival	57		1.26 (0.75–2.12)	-	-	-
			Non-cancer-specific survival	24		1.09 (0.42–2.82)	-	-	-
Reed et al, 2019[62]	≥ 6 drugs	52.7	Grade ≥ 3 CTCAE toxicity	199	1 month	1.16 (0.62–2.18)	-	-	Multiple[i]
Sales et al, 2019[63]	N.R.	N.R.	Overall survival	9	1 year	2.65 (0.71-9.81)	x	x	Multiple[j]
Samuelsson et al, 2019[64]	≥ 5 drugs	67.3	POCs	16	1 year	2.82 (0.67-11.85)	-	-	-
			Length of stay > 8 days	N.R.	8 days[d]	1.01 (0.29-3.45)	-	-	-
Williams et al, 2019[38]	≥ 10 drugs	41.2	Hospitalization	41	47 months	1.03[f] (0.64-1.65)[k]	x	x	-
			Long-term care stay	20		**0.33[f] (0.17-0.64)**[k]	x	x	-
Nishijima et al, 2018[60]	≥ 5 drugs	N.R.	Overall survival	191	5.7 years	**1.46 (1.08–1.98)**	-	-	-
Ommundsen et al, 2018[61]	≥ 6 drugs	51	Overall survival	46	51 months[d]	1.5 (0.8-2.7)	-	-	-
Westley et al, 2018[39]	6-10 drugs	26.2	Emergency department visit	3,129	45 days	**1.23 (1.15-1.31)**	x	-	Multiple[l]
	≥ 11 drugs	5.6	Emergency department visit	3,129	45 days	**1.53 (1.33-1.77)**	x	-	Multiple[l]
Kenis et al, 2018_1[34]	≥ 5 drugs	51.6	Overall survival	471	6.3 years	**1.43 (1.18-1.73)**[e]	-	-	Stage, tumor type
Kenis et al, 2018_2[34]	≥ 5 drugs	54.2	Overall survival	214	4.5 years	1.27 (0.96-1.68)[e]	-	-	Stage, tumor type
Choi et al, 2018[43]	≥ 5 drugs	50.7	Post-discharge institutionalization	14	30 days	**3.96 (1.05-14.86)**[m]	-	-	Transfusion, infection
Antonio et al, 2018[50]	≥ 6 drugs	64.8	Treatment refusal	141	36 weeks[n]	**5.34 (1.55-18.40)**	-	-	Cancer site, VES-13 ≥ 3, oncogeriatric group
			Grade ≥ 3 CTCAE toxicity	105	36 weeks[n]	1.26 (0.43-3.65)	-	-	-
			Completion ≥ 80% of planned dose	105	36 weeks[n]	0.50 (0.20-12.6)	x	-	Social support, toxicity
Fagard et al, 2017[21]	≥ 5 drugs	47.4	CD ≥ 2 30-day POCs	78	30 days	1.11 (0.49-2.54)[o]	x	x	-
Woopen et al, 2016[66]	≥ 5 drugs	N.R.	Grade ≥ 3 CTCAE toxicity	N.R.	19.7 months[d]	1.12 (1.02-1.24)[k]	x	-	Multiple[p]
Park et al, 2016[44]	≥ 5 drugs	29.3	Grade ≥ 3 CTCAE toxicity	21	N.R.	1.55 (0.61-3.94)	-	-	-
			Hospitalization > 1 month	20	1 month[q]	1.70 (0.66-4.36)	-	-	-
			Non-cancer health event[r]	66	2 years	1.81 (0.99-3.31)	-	-	-
Lee et al, 2016[35]	≥ 8 drugs	13.8	Major 30-day POCs[s]	99	30 days	1.02 (0.39-2.67)	-	x	Multiple[t]
Jonna et al, 2016[36]	≥ 7 drugs	N.R.	Overall survival	≈800[b]	6 years	**1.18 (1.02-1.38)**	-	-	-
Bourdel-Marchasson et al, 2016[52]	≥ 4 drugs	62.5	Overall survival	266	1 year	**1.62 (1.07-2.44)**[u]	-	-	Multiple[v]
Sud et al, 2015[65]	≥ 6 drugs	38	Toxicity-related therapy discontinuation	102	30 days	1.31 (0.77-2.22)	-	x	Mulitple[w]
			Hospitalization	102	30 days	**2.28 (1.34-3.88)**	-	x	Mulitple[w]

First Author, Year	Polypharmacy Definition	Prevalence of Polypharmacy (%)	Outcome	$N_{outcome}$	FUP	HR or OR (95% CI)	Adjusted Covariates		
							Age+ sex[a]	Comor-bidity	Other
Kenig et al, 2015[58]	≥ 5 drugs[x]	44.0	All POCs	38	30 days	1.6 (0.7-4.1)	x	-	Type of cancer, severity of surgery
			Major POCs[y]	20	30 days	**4.2 (1.4-12.1)**	x	-	Same as above
Ommundsen et al, 2014[37]	≥ 8 drugs	N.R.	Overall survival	93	5 years	**2.2 (1.1-4.3)**	-	-	-
Maggiore et al, 2014[5]	4-9 drugs	50.8	Grade ≥ 3 CTCAE toxicity	257	598 days	1.34 (0.92-1.97)	-	-	-
	≥ 10 drugs	11.5	Grade ≥ 3 CTCAE toxicity	257	598 days	0.82 (0.45-1.49)	-	-	-
	≥ 4 drugs	62.3	Hospitalization	112	598 days	1.34 (0.82-2.18)	-	x	Creatinine clearance
Hamaker et al, 2014[56]	≥ 5 drugs	50.7	Grade ≥ 3 CTCAE toxicity	27	N.R.	**6.38 (1.99-23.47)**	-	-	-
			Overall survival	54	2.67 years[d]	1.41 (0.82-2.44)	-	-	-
Hamaker et al, 2014[55]	≥ 5 drugs	65	Overall survival	≈70[b]	1 year	1.20 (0.64-2.24)	-	-	-
Elliot et al, 2014[45]	≥ 4 drugs	52	Overall survival	29	30 days	**9.98 (1.18-84.13)**	-	x	-
			Complete remission	71	132 days	**0.20 (0.06-0.65)**	-	x	-
			Intensive care unit stay	30	132 days	6.57 (0.80-53.72)	-	x	-
			Length of stay > 35 days	N.R.	132 days	0.94 (0.29-3.08)	-	x	-
de Glas et al, 2013[31]	≥ 5 drugs	13.5	POCs	618	30 days	**1.76 (1.39-2.23)**	x	-	Multiple[z]
Badgwell et al, 2013[51]	≥ 6 drugs	47.7	Length of stay > 7 days	55	35 days	**2.45 (1.09-5.48)**	-	-	Stage, weight loss ≥ 10%
Kanesvaran et al, 2011[57]	≥ 5 drugs	60.5	Overall survival	172	3 years	**1.62 (1.18-2.23)**	-	-	-
Hamaker et al, 2011[54]	≥ 5 drugs	47.8	Overall survival	187	1 year	1.10 (0.81-1.48)	-	-	-
Kristjansson et al, 2010[49]	≥ 5 drugs	25.8	Severe POCs[s]	N.R.	30 days	1.73 (0.87-3.44)	-	-	Tumor location
			All POCs	N.R.	30 days	1.67 (0.82-3.42)	-	-	Tumor location

Values in bold are statistically significant (p<0.05)

Abbreviations: BC, breast cancer; CD, Clavien-Dindo; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Effects; ECOG PS, Eastern Cooperative Oncology Group performance status; FUP, follow-up period; HR, hazard ratio; irAE, immune-related adverse events; LC, lung cancer; N.R., not reported; N.S., not significant; OR, odds ratio; PC, prostate cancer; POC, postoperative complication; VES-13, Vulnerable Elders Survey

[a] If the study population consisted only of males or females, no adjustment for sex is necessary and therefore a cross was made even if the study adjusted for age only.

[b] Number of deaths were not reported but estimated from Kaplan-Meier plots.

[c] Karnofsky Performance Status, cytogenetics, intensity of chemotherapy.

[d] Median follow up.

[e] OR was reversed so that no polypharmacy was the reference group.[79]

[f] Incidence rate ratio.

[g] ECOG PS, presence of liver metastasis, presence of bone metastasis, programmed death-ligand 1 (PD-L1) expression, epidermal growth factor receptor (EGFR) mutation, and the Gustave Roussy Immune Score (GRIm-Score).

[h] Smoking status, ECOG PS, presence of liver metastasis, PD-L1 expression, EGFR mutation, initially chosen immune checkpoint inhibitors (ICIs), and GRIm-Score.
[i] Weight loss, ECOG PS, cancer stage, hemoglobin, platelet count, neutrophils, and creatinine clearance.
[j] Site of cancer, cancer stage, malnutrition, and Katz index.
[k] 95 % CIs was estimated from reported point estimate and p-value.[80]
[l] Receipt of income supplement, access to primary care, type of surgery, number of surgeries before definitive surgery, benzodiazepine use, anticoagulants use, steroids use, diabetes, active cardiac disease, past hospitalization, institutional volume, postoperative radiotherapy and chemotherapy, clustering by surgical institution.
[m] Model with largest area under the curve (AUC).
[n] Patients were followed at least until 3 months after finishing the chemotherapy, which could last for 24 weeks for fit patients.
[o] Analysis was done in 115 patients with geriatric assessment data available. ORs and 95% CIs were estimated with the original study data, which have been provided by the corresponding author.
[p] International Federation of Gynecology and Obstetrics (FIGO) stage, histology, BMI, number of recurrence, number of administered chemotherapy cycles and study entered.
[q] The follow-up period lasted for at least 1 month.
[r] Defined as readmission to the hospital within 2 years after the initial treatment for any cause that was not directly related to the index cancer or newly developed second primary cancer.
[s] Defined as CD class equal to or greater than II.
[t] Activities of daily living, instrumental activities of daily living, mini mental state examination, Korean Older Depression Scale, delirium, mini nutritional assessment.
[u] The result was obtained from the model with higher AUC done in 565 patients.
[v] Food intake over the last 3 months, protein-rich food intake, calf circumference, cancer origin, metastasis, lymphocytes.
[w] Anemia, leukocytosis, estimated glomerular filtration rate (eGFR) < 60 mL/min, palliative intent, line of therapy ≥ 2, initial dose adjustment.
[x] Only results for ≥ 5 drugs were extracted and no results for ≥ 6 drugs.
[y] Defined as CD class III to V.
[z] Stage, type of surgery, most extensive axillary surgery, neoadjuvant treatment.

Table 3. Designs of Studies Investigating the Association of **Potentially Inappropriate Medication** with Adverse Health Outcomes in Older Adults with Cancer

First Author, Year	PIM Criterion Applied	Study Design	Country	Claims Data	Data Collection	Study Population				
						Cancer Type	Population	Total (N)	Female (%)	Age (Years)
Hong et al, 2020[46]	Beers 2015 (avoid)	PCS, PU	South Korea	No	2014-2015	Solid cancer	Inpatients	301	30.9	70-93
Jeon et al, 2019[40]	PDRM[a]	RCS, PU	South Korea	No	2014-2015	All surgical	Inpatients	473	54.8	65-96
Lin et al, 2019[47]	Beers 2015 (all)	RCS, PU	U.S.	No	2001-2016	Hematologic malignancy	Inpatients	527	39	60-78.7
Lin et al, 2018[42]	Beers 2015 (all)	RCS, PU	U.S.	No	2009-2014	Aggressive NHL	Inpatients	171	49	≥ 60
Karuturi et al, 2018 and 2019_BC[b] [13,33]	HEDIS-DAE (avoid); Beers 2012 (all); STOPP criteria	RCS, PU	U.S.	Yes	2007-2009	BC	Outpatients	1,595	100	≥ 66
Karuturi et al, 2018 and 2019_CRC[b] [13,33]	HEDIS-DAE (avoid); Beers 2012 (all); STOPP criteria	RCS, PU	U.S.	Yes	2007-2009	CRC	Outpatients	1,528	50.4	≥ 66
Chun et al, 2018[20]	N.R.	RCS, PU	U.S.	Yes	2007-2011	BC	Outpatients	2,401	100	≥ 66
Choi et al, 2018[43]	Beers 2015 (avoid)	RCS, PU	South Korea	No	2014-2015	All surgical	Inpatients	475	54.7	65 - 96
Samuelsson et al, 2016[41]	Socialstyrelsen criteria (avoid, long-term use)	RCS, PU	Sweden	Yes	2007-2010	CRC	In- and outpatients	7,279	52.4	75 - 98
Park et al, 2016[44]	Beers 2012 (all)	RCS, PU	South Korea	No	2008-2013	HNC	Inpatients	229	16.2	65 - 87
Chiang et al, 2015[27]	Beers 2012 (all)	RCS, NU	U.S.	No	2000-2008	Any	Inpatients	677	47.4	≥ 65
Maggiore et al, 2014[5]	Beers 2012 (avoid[c]) Zhan's classification (all) HEDIS-DAE 2011 (avoid) Combination of all 3 criteria above	PCS, PU	U.S.	No	2006-2009	Solid tumor	Outpatients	500	56.2	≥ 65
Elliot et al, 2014[45]	Beers 2012 (all)	RCS, PU	U.S.	No	2004-2009	AML	Inpatients	150	39	61 - 87

Abbreviations: AML; acute myeloid leukemia; avoid, drugs to avoid; BC, breast cancer; CRC, colorectal cancer; HEDIS-DAE, Healthcare Effectiveness Data and Information Set Drugs to Avoid in the Elderly; HNC, head and neck cancer; long-term use, drugs to avoid long-term use; NHL, non-Hodgkin lymphoma; NU, new user design; PCS, prospective cohort study; PDRM, pre-operative discontinuation requiring medications; PIM, potentially inappropriate medication; PU, prevalent user design; RCS, retrospective cohort study; STOPP, Screening Tool of Older Person's Prescriptions

[a] PDRM were defined as medications that should be discontinued before surgery due to surgical risks.

[b] Studies by Karuturi et al.[13,33] published in 2018 and 2019 were combined because they both used the same study population but different criteria to define PIM use.

[c] Beers criteria's drugs to avoid except for lorazepam, prochlorperazine, metoclopramide, and atropine–diphenoxylate.

Table 4. Follow-Up and Effect Size Data of Studies Investigating the Impact of **Potentially Inappropriate Medication** on Health Outcomes in Older Adults with Cancer

First Author, Year	PIM Criterion	PIM Prevalence (%)	Outcome	$N_{outcome}$	FUP	HR or OR (95% CI)	Adjusted Covariates		
							Age + sex[a]	Comor-bidity	Other
Hong et al, 2020[46]	Beers 2015 (avoid)	45.5	Hospitalization	123	30 days	1.40 (0.98-1.99)	-	-	-
Jeon et al, 2019[40]	PDRM[b]	57.5	Readmission after surgery	37	30 days	**2.18 (1.01-4.70)**	x	x	Multiple[c]
Lin et al, 2019[47]	Beers 2015 (all)	46	Delirium	112	100 days	**1.79 (1.22-2.65)**	-	-	Multiple[d]
			Fall	34	100 days	1.36 (0.69-2.66)	-	-	-
			Non-relapse survival	167	11.9 years	**1.54 (1.14-2.09)**	-	-	-
			Overall survival	298	11.9 years	**1.28 (1.02-1.6)**	-	-	-
Lin et al, 2018[42]	Beers 2015 (all)	47	Treatment delay and/or dose reduction	101	N.R.	1.95 (0.99-3.84)	-	-	Albumin at diagnosis, IPI
			Grade ≥ 3 CTCAE toxicity	112	N.R.	**2.91 (1.42-5.97)**[e]	-	-	Albumin at diagnosis
			Progression-free survival	N.R.	28 months[f]	**2.81 (1.36-5.81)**	-	-	WBC, IPI
			Overall survival	41	28 months[f]	**3.12 (1.49-6.52)**	x	-	WBC, IPI
Karuturi et al, 2018 and 2019_BC[g13,33]	HEDIS-DAE (avoid)	22.2	Emergency department visit	552	9 months	0.96 (0.78-1.18)	x	x	Multiple[i]
			Hospitalization	369	9 months	0.96 (0.75-1.23)	x	x	Multiple[i]
			Overall survival	34	9 months	**2.31 (1.07-4.96)**	x	x	Multiple[i]
			Composite outcome[h]	598	9 months	0.96 (0.79-1.17)	x	x	Multiple[i]
	Beers 2012 (all)	27.6	Emergency department visit	552	9 months	1.02 (0.85-1.24)	x	x	Multiple[i]
			Hospitalization	369	9 months	1.00 (0.79-1.26)	x	x	Multiple[i]
			Overall survival	34	9 months	1.86 (0.88-3.96)	x	x	Multiple[i]
			Composite outcome[h]	598	9 months	0.99 (0.82-1.19)	x	x	Multiple[i]
	STOPP criteria	39	Emergency department visit	552	9 months	N.S.	-	-	-
			Hospitalization	369	9 months	**1.28 (1.02-1.61)**	-	-	-
			Overall survival	34	9 months	N.S.	-	-	-
			Composite outcome[h]	598	9 months	1.07 (0.89-1.29)	-	x	Multiple[j]
Karuturi et al, 2018 and 2019_CRC[g13,33]	HEDIS-DAE (avoid)	15.5	Emergency department visit	621	9 months	0.99 (0.8-1.23)	x	x	Multiple[i]
			Hospitalization	450	9 months	1.02 (0.79-1.32)	x	x	Multiple[i]
			Overall survival	76	9 months	0.80 (0.40-1.59)	x	x	Multiple[i]
			Composite outcome[h]	687	9 months	0.96 (0.78-1.19)	x	x	Multiple[i]
	Beers 2012 (all)	24.8	Emergency department visit	621	9 months	0.96 (0.79-1.16)	x	x	Multiple[i]
			Hospitalization	450	9 months	1.01 (0.81-1.27)	x	x	Multiple[i]
			Overall survival	76	9 months	0.80 (0.40-1.59)	x	x	Multiple[i]
			Composite outcome[h]	687	9 months	0.96 (0.78-1.19)	x	x	Multiple[i]
	STOPP criteria	30.9	Emergency department visit	621	9 months	N.S.	-	-	-
			Hospitalization	450	9 months	N.S.	-	-	-
			Overall survival	76	9 months	N.S.	-	-	-
			Composite outcome[h]	687	9 months	1.11 (0.94-1.33)	x	x	Multiple[k]

First Author, Year	PIM Criterion	PIM Prevalence (%)	Outcome	$N_{outcome}$	FUP	HR or OR (95% CI)	Adjusted Covariates		
							Age + sex[a]	Comor-bidity	Other
Chun et al, 2018[20]	N.R.	30.2	Emergency department visit	504	6 months	0.95 (0.76-1.18)[l]	x	x	Multiple[m]
Choi et al, 2018[43]	Beers 2015 (avoid)	26.7	Post-discharge institutionalization	14	30 days	0.76 (0.21–2.78)	-	-	-
Samuelsson et al, 2016[41]	Socialstyrelsen criteria (drugs to avoid as long-term use)	22.5	Length of stay ≥ 10 days	N.R.[n]	30 days	**1.14 (1.00 -1.29)**	x	-	Multiple[o]
			Overall survival	368	30 days	**1.43 (1.11-1.85)**	x	-	Multiple[o]
Park et al, 2016[44]	Beers 2012 (all)	24.0	Grade ≥3 CTCAE toxicity	21	N.R.	1.30 (0.48-3.53)	-	-	-
			Length of stay > 1 month	20	1 month[p]	2.30 (0.89-5.95)	-	-	-
			Non-cancer health event[q]	68	2 years	1.35 (0.71-2.57)	-	-	-
Chiang et al, 2015[27]	Beers 2012 (all)	28.3 (in N=675)	30-day unplanned readmission	238	30 days	1.36 (0.94-1.99)	x	-	Multiple[r]
Maggiore et al, 2014[5]	Beers 2012 (avoid[s])	30.1 (in N=488)	Grade ≥3 CTCAE toxicity	258	598 days	0.97 (0.66-1.43)	-	-	-
			Hospitalization	109	598 days	1.01 (0.64-1.61)	-	-	-
	Zhan's classification (all)	10.8 (in N=498)	Grade ≥3 CTCAE toxicity	264	598 days	1.03 (0.59-1.82)	-	-	-
			Hospitalization	114	598 days	0.64 (0.31-1.37)	-	-	-
	HEDIS-DAE 2011 (avoid)	13.8 (in N=499)	Grade ≥3 CTCAE toxicity	265	598 days	0.90 (0.54-1.49)	-	-	-
			Hospitalization	115	598 days	0.67 (0.35-1.29)	-	-	-
	Combination of all 3 PIM criteria above	29.7 (in N=498)	Grade ≥3 CTCAE toxicity	264	598 days	0.98 (0.67-1.44)	-	-	-
			Hospitalization	114	598 days	1.01 (0.64-1.59)	-	-	-
Elliot et al, 2014[45]	Beers 2012 (all)	19	Overall survival	29	30 days	0.89 (0.31-2.58)	-	-	-
			Complete remission	71	132 days	0.96 (0.42-2.19)	-	-	-
			Intensive care unit stay	30	132 days	0.42 (0.12-1.51)	-	-	-
			Length of stay > 35 days	N.R.	132 days	0.87 (0.32-2.34)	-	-	-

Values in bold are statistically significant (p<0.05)

Abbreviations: avoid, drugs to avoid; BC, breast cancer; CI, confidence interval; CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Effects; FUP, follow-up period; HEDIS-DAE, Healthcare Effectiveness Data and Information Set Drugs to Avoid in the Elderly; HR, hazard ratio; IPI, international prognostic index; long-term use; N.R., not reported; N.S., not significant; OR, odds ratio; PDRM, pre-operative discontinuation requiring medications; PIM, potentially inappropriate medication; STOPP, Screening Tool of Older Person's Prescriptions; WBC, white blood cell count at diagnosis.

[a] If the study population consisted only of males or females, no adjustment for sex is necessary and therefore a cross was made even if the study adjusted for age only.

[b] PDRM were defined as medications that should be discontinued before surgery due to surgical risks.

[c] Transfusion, gastrointestinal cancer, if the cancer stage is stage 4.

[d] Prior falls, platelet count on admission, creatinine clearance.

[e] OR was obtained from the meeting abstract being published before the main publication.

[f] Median follow up.

[g] Studies by Karuturi et al.[13,33] published in 2018 and 2019 were combined because they both used the same study population but different criteria to define PIM use.

[h] Composite outcome includes emergency department visit, hospitalization, and overall survival.
[i] Year of diagnosis, race, stage, poverty, education, number of baseline care providers, chemotherapy regimen, baseline emergency room visit/hospitalization.
[j] Year of diagnosis, poverty, education, number of care providers, chemotherapy regimen, baseline medications, cancer stage, and baseline emergency room visit/hospitalization.
[k] Year of diagnosis, poverty, education, number of care providers, chemotherapy regimen, race, and baseline emergency room visit/hospitalization.
[l] The original poster abstract reported an adjusted risk difference. The authors provided the OR and 95% CI shown in the table in reply to an inquiry from the review authors.
[m] Race, marital status, stage at diagnosis, claims-data based predicted frailty, medication burden.
[n] The number of cases with LOS ≥ 10 days was not reported but it can be estimated that almost half of the study population, which was n=7,279, had an LOS ≥ 10 days because the median LOS was 9 days in subjects without PIM and 10 days in subjects with PIM.
[o] American Society of Anesthesiologists classification of physical status class, type of surgical procedure, T stage, clinical stage, postoperative surgical complications, urgency of surgery
[p] The follow-up period lasted for at least 1 month.
[q] Defined as readmission to the hospital within 2 years after the initial treatment for any cause that was not directly related to the index cancer or newly developed second primary cancer.
[r] Race, Katz index feeding item, Lawton-housework questionnaire, reason for index admission.
[s] Beers criteria's drugs to avoid except for lorazepam, prochlorperazine, metoclopramide, and atropine–diphenoxylate.