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ORIGINAL ARTICLE

Polypharmacy cut-points in older people with cancer: how many medications are too many?

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Abstract
Purpose Polypharmacy is often defined as use of 'five-or-more-medications'. However, the optimal polypharmacy cut-point for predicting clinically important adverse events in older people with cancer is unclear. The aim was to determine the sensitivities and specificities of a range of polypharmacy cut-points in relation to a variety of adverse events in older people with cancer.
Methods Data on medication use, falls and frailty criteria were collected from 385 patients aged ≥70 years presenting to a medical oncology outpatient clinic. Receiver operating characteristic (ROC) curves were produced to examine sensitivities and specificities for varying definitions of polypharmacy in relation to exhaustion, falls, physical function, Karnofsky Performance Scale (KPS) and frailty. Sub-analyses were performed when stratifying by age, sex, comorbidity status and analgesic use.
Results Patients had a mean age of 76.7 years. Using Youden's index, the optimal polypharmacy cut-point was 6.5 medications for predicting frailty (specificity 67.0 %, sensitivity 70.0 %), physical function (80.2 %, 49.3 %) and KPS (69.8 %, 52.1 %), 5.5 for falls (59.2 %, 73.0 %) and 3.5 for exhaustion (43.4 %, 74.5 %). For polypharmacy defined as five-or-more-medications, the specificities and sensitivities were frailty (44.9 %, 77.5 %), physical function (58.0 %, 69.7 %), KPS (47.7 %, 69.4 %), falls (44.5 %, 75.7 %) and exhaustion (52.6 %, 64.1 %). The optimal polypharmacy cut-points were similar when the sample was stratified by age, sex, comorbidity status and analgesic use.
Conclusions Our results suggest that no single polypharmacy cut-point is optimal for predicting multiple adverse events in older people with cancer. In this population, the common definition of five-or-more-medications is reasonable for identifying 'at-risk' patients for medication review.

Keywords Aged · Polypharmacy · Deprescribing · Cancer

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Background

Polypharmacy in older people has been associated with adverse events including falls [1], hospital admission [2], and mortality [3]. The limited research investigating polypharmacy in older people with cancer has shown polypharmacy is associated with increased falls [4], increased frailty [5], reduced efficacy of certain chemotherapies [6], drug interactions [7] and adverse drug events (ADEs) [6]. However, there is no single accepted definition for polypharmacy. Polypharmacy has been defined as taking more medications than are clinically indicated [8]. However, most studies use a cut-point to define polypharmacy. The most

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common cut-point is the concomitant use of 'five-or-more-medications' [8]. However, definitions vary and have included more than two [9], three [10], four [1], five [8], seven [11] or nine medications [12]. More recently, the term 'hyperpolypharmacy' has been used to describe the use of ten or more medications [13]. The suitability of a cut-point for identifying patients at risk of adverse events may depend on the clinical and medication use characteristics of the population. The optimal polypharmacy cut-point for predicting clinically important adverse events in older people with cancer is unclear.

There are important reasons to investigate if optimal polypharmacy cut-points are associated with important adverse events. Firstly, polypharmacy is increasingly being used to identify patients in need services such as medication review. The number of medications a patient takes is used as a referral trigger for medication review in the USA [12] and Australia [14] and has been recommended for older people with cancer [15]. Identifying an optimal polypharmacy cut-point may assist clinicians and policy makers to target services to patients most likely to benefit. Secondly, in pharmacoepidemiology, the number of medications taken by study participants is often categorized without strong evidence to inform this categorization. Finally, identifying an optimal polypharmacy cut-point would help develop consensus terminology. This would improve comparability of research conducted in different countries and settings.

Both multimorbidity and polypharmacy increase with age [16]. In clinical settings, it may be difficult to separate whether multimorbidity or polypharmacy is associated with adverse events. Our previous work demonstrated that polypharmacy (defined as ≥5 medications) was associated with a fourfold increased risk of frailty, even after adjusting for comorbidity [5]. We used the standard cut-point of five-or-more-medications to define polypharmacy. It is not clear whether other polypharmacy cut-points have better sensitivities or specificities for predicting clinically important adverse events. This is important to know because older people with cancer may be at increased risk of harm from polypharmacy. This is due to potential drug-drug interactions between medications (prescription, non-prescription, or complementary and alternative medications) and chemotherapy and supportive treatments [6, 7, 17]. Furthermore, older people with cancer may be more susceptible to adverse events due to the higher prevalence of geriatric syndromes [18].

Receiver operating characteristic (ROC) curves have been used to determine the optimal cut-point for polypharmacy in relation to falls among community-dwelling older people in Tokyo (≥4.5 medications) [19] and in relation to falls (≥4.5), mortality (≥4.5), disability (≥5.5) and frailty (≥6.5) among older Australian men [8]. However, it is not clear whether these findings are applicable to older people with cancer.

The objective of this study was to determine the sensitivities and specificities of a range polypharmacy cut-points in relation to a range of adverse events in older people with cancer.

Methods

Participants and setting

The Royal Adelaide Hospital (RAH) is a 650-bed tertiary referral hospital located in metropolitan Adelaide, South Australia. The medical oncology department at the RAH referred all patients aged ≥70 years to the geriatric oncology outpatient multidisciplinary clinic. This study includes all patients who presented between January 2009 and July 2010 [5].

Data collection

Prior to attending the geriatric oncology outpatient multidisciplinary clinic, patients were mailed a five-page structured data collection instrument based on the principles of comprehensive geriatric assessment. The data collection instrument was completed by the patient with or without assistance from their carer/family member. At the initial appointment, any sections of the data collection instrument which were incomplete were completed in conjunction with a nurse. Patients were then assessed by the geriatric oncology multidisciplinary team consisting of a geriatrician, medical oncologist, geriatric oncology nurse, social worker, dietitian, pharmacist, occupational therapist and palliative care nurse.

The data collection instrument captured information on age, sex, diagnoses (used to calculate Charlson Comorbidity Index [CCI] [20]), medications, falls (patient self-reported in previous 6 months), weight loss (patient self-reported over previous 6 months), exhaustion (using two questions from the CES-D scale [21], as adapted by Fried [22]), physical function (SF-36 physical function domains) [23], instrumental activities of daily living (IADLs) [24] and Karnofsky Performance Scale (KPS) [25].

Medication use

The data collection instrument asked patients to list their prescription and non-prescription medications, and separately list their complementary and alternative medications (CAMs) to ensure a full medication history was obtained. Medication use was assessed as the point prevalence at each patient's initial appointment. At the initial appointment, a nurse with access to each patient's medical records confirmed the self-reported medication list. Any additional medication not self-reported using the structured data collection instrument was added to the list. As these data were collected during each patient's first visit to the medical oncology clinic, no patients were receiving chemotherapy.

All medications were coded as International Non-proprietary Names (INN) and Anatomical Therapeutic Chemical (ATC) codes recommended by the World Health Organization [26]. For each patient, the medication count included all medications taken by the patient, including prescription, over-the-counter and

CAMs. Medications used on a regular and as-needed basis were included in the medication count.

Measures and definitions

An adapted version of Fried's frailty phenotype was used to define frailty [5, 22, 27]. We assessed the same five criteria that comprise Fried's frailty phenotype using variables included in the structured data collection instrument. These five criteria were weight loss of >5 % during the preceding 6 months, an exhaustion score ≥3, dependence in at least one SF-36 physical function domain, dependence in at least one IADL and KPS <70 %. Patients were considered frail if they had four or five criteria of concern [5].

In addition to frailty, the exhaustion and KPS components of the frailty score (i.e. an exhaustion score of ≥3 and KPS< 70 %) were analysed as separate adverse events [5]. Additional adverse events included two or more falls in the past 6 months and a physical function score of ≥20.

Statistical analyses

For each adverse event, a ROC curve was derived to determine the sensitivities and specificities for the following polypharmacy cut-points: ≥2, ≥5, ≥7 and ≥10 concomitant medications. The optimal cut-point was calculated using Youden's index. Youden's index was calculated as the sum of the sensitivity and specificity minus one and was used to calculate the cut-point which provided the highest combination of sensitivity and specificity [28]. The area under the curve (AUC) was calculated for each ROC curve. The closer the AUC was to one, the higher the sensitivity and specificity of the ROC curve with an AUC of 0.5 indicating that the ROC curve was no better than chance at predicting the event of interest [29].

Sub-analyses were performed when stratifying the sample by age, sex, comorbidity status and analgesic use. For each adverse event, ROC curves were generated for each of the following sub-groups, age (70–79 or 80+) [30], sex (male, female), CCI (0-2, 3+) and analgesic use. This comorbidity stratification was performed because it has been associated with reduced survival and reduced tolerance to chemotherapy [18, 31]. Youden's index was calculated for each sub-group, and the AUCs were assessed for statistical differences (Table 3). The bootstrap 95 % confidence intervals (95%CI) were derived for each sub-group ROC curve before being overlaid on the same figure to facilitate comparison (Fig. 2). Analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) Version 21 and R [32, 33].

Ethical considerations

This study was approved by the Royal Adelaide Hospital Human Research Ethics Committee, University of South Australia Human Research Ethics Committee and Monash University Human Research Ethics Committee.

Results

Between January 2009 and July 2010, a total of 413 patients aged ≥70 years presented to the medical oncology outpatient clinic. Complete data collection instruments were available for 385 patients.

The average age of patients was 76.7 years (standard deviation [SD] 4.8 years, range 70–92) with 59 % being male. The most prevalent cancer diagnoses were gastrointestinal (26.2 %, *n*=101), lung (23.6 %, *n*=91), breast (10.6 %, *n*=41), prostate (6.0 %, *n*=23) and hematological malignancies (4.4 %, *n*=17). The most prevalent comorbidities were hypertension (58.4 %, *n*=225), hypercholesterolemia (32.5 %, *n*=125), arthritis (29.4 %, *n*=113), diabetes (25.5 %, *n*=98), airways diseases (24.6 %, *n*=95), gastrointestinal disorders (22.0 %, *n*=80) and coronary artery disease (16.9 %, *n*=65) (Table 1).

The average number of medications was 5.7 (SD 3.7, range zero to 20). The most prevalent medication classes were agents acting on the renin-angiotensin system (40.7 %, *n*=181), antithrombotic agents (37.9 %, *n*=146), lipid modifying agents (37.4 %, *n*=144), medications for acid-related disorders (35.6 %, *n*=137) and analgesics (32.2 %, *n*=124). Overall, 95.6 % (*n*=368) of patients reported taking medications (range 1–20, median 5), with 94.6 % (*n*=364) taking prescription or

Table 1 Characteristics of patients referred to the geriatric oncology outpatient multidisciplinary clinic

	All patients (*n*=385), % (*n*)
Age[a]	76.7 (4.8, 70–92)
Sex (male)	59.0 (227)
Number of medications[a]	5.7 (3.7, 0–20)
Comorbidities	
Hypertension	58.4 (225)
Hypercholesterolemia	32.5 (125)
Arthritis	29.4 (113)
Diabetes mellitus	25.5 (98)
Airways disease	24.6 (95)
Gastrointestinal disorders	22.0 (80)
Coronary artery disease	16.9 (65)
Clinical parameters	
Exhaustion (≥3) (*n*=383)	60.3 (231)
Falls (≥2) (*n*=383)	9.7 (37)
Physical function (≥20) (*n*=376)	56.6 (211)
KPS (<70) (*n*=379) (*n*=379)	31.4 (121)
Frail (*n*=385)	10.4 (40)

KPS Karnofsky Performance Scale

[a] Mean (SD, range)

non-prescription medications (range 1–17, median 5) and 31.4 % (n=121) taking CAMs (range 1–6, median 1).

The ROC curves for individual adverse events are shown in Fig. 1. Each curve displays the AUC and the sensitivities and specificities for the pre-specified and optimal cut-points. The sensitivities and specificities are also shown in Table 2. The optimal cut-points for exhaustion and falls were 3.5 (specificity 43.4 %, sensitivity 74.5 %, AUC 61.7 %) and 5.5 (59.2 %, 73 %, 66.2 %), respectively. Use of ≥6.5 medications gave the highest Youden's index for frailty (67.0 %, 70.0 %, 71.1 %), impaired physical function (80.2 %, 50.2 %, 70.0 %) and reduced KPS (69.8 %, 52.1 %, 64.8 %). For polypharmacy defined as five-or-more-medications, the specificity and sensitivity were frailty (44.9 %, 77.5 %), physical function (58.0 %, 69.7 %), KPS (47.7 %, 69.4 %), falls (44.5 %, 75.7 %) and exhaustion (52.6 %, 64.1 %).

For all adverse events, low specificities and high sensitivities were observed for ≥2 medications, and high specificities and low sensitivities were observed for ≥10 medications (Table 2; Fig. 1). For physical function, KPS and frailty, the cut-point of ≥7 medications yielded identical sensitivities and specificities to the optimal cut-point for these events (6.5 medications).

Stratification of ROC curves by age, sex, comorbidities or analgesic use did not significantly modify the association between number of medications and adverse events. Sub-group analysis produced varying optimal cut-points for each adverse event, with the exception of the age and gender sub-groups for frailty (Table 3). However, there were no cases where the AUCs were statistically different, indicating that neither sub-group analysis had a better sensitivity and specificity profile. This was further demonstrated by the overlapping of the 95%CIs for each sub-group analysis (Fig. 2).

Discussion

The main finding of this study was that no single polypharmacy cut-point was optimal for predicting multiple adverse events. Furthermore, the optimal cut-point for each adverse event was not significantly different when stratifying by age, sex, comorbidities or analgesic use. In this cohort, the optimal polypharmacy cut-points ranged from 3.5 for exhaustion to 6.5 for impaired physical function, KPS and frailty.

Our main finding is supported by Gnjidic et al., who identified a range of polypharmacy cut-points (from 4.5 to 6.5 medications) for falls (4.5), mortality (4.5), disability (5.5) and frailty (6.5) in a cohort of community-dwelling older Australian men [8]. The optimal cut-point for frailty in the present study (6.5 medications) was the same as in Gnjidic et al. (sensitivity and specificity from Gnjidic et al.: 47.4 %, 83.6 %). Both Gnjidic et al. and Kojima et al. [19] identified 4.5 as the optimal cut-point for falls, while our study showed that 5.5 medications had the highest sensitivity and specificity. This may be because patients in our study were recently diagnosed with cancer. A population-based cohort study identified that people newly diagnosed with cancer take increased numbers of medications in the 6 months prior to diagnosis, potentially reflecting an increase in medications used to treat early signs and symptoms of cancer [34].

Both medication count and specific classes of medications have been implicated with adverse events in older people, making it difficult to determine if adverse events are due to polypharmacy or specific medications. Frailty has been associated with use of sedative and anticholinergic medications [13], Beers Criteria medications [35] and analgesics [36]. In this study, analgesics were among the most prevalent medications. A sub-group analysis comparing patients who did and did not use analgesics found no significant difference between the optimal polypharmacy cut-points. This is important because unlike sedatives, anticholinergics and Beers Criteria medications which may be inappropriate in older people, analgesic use is generally considered appropriate in older people with cancer.

The suitability of a cut-point for identifying patients at risk of adverse events may potentially be influenced by clinical factors including age, sex, specific medications or comorbidities. People with multiple comorbidities are likely to be taking multiple medications [37]. Furthermore, people with multiple comorbidities are more likely to be frail and have functional impairment (e.g. reduced physical function, increase in falls or exhaustion). This can make it difficult to determine if the functional impairments are attributable to patients' comorbidities or polypharmacy [2]. This study demonstrated that the optimal polypharmacy cut-points for each adverse event were similar when the sample was stratified by age, sex, analgesic use or comorbidities. This is supported by a recent study that investigated the relationship between numbers of comorbidities and various definitions of polypharmacy [38]. Hospital admissions were associated with most polypharmacy definitions regardless of the number of comorbidities.

Polypharmacy is currently used as a basis for referral for a medication review service in oncology clinics [15]. While a single optimal definition for polypharmacy was not identified, the range of cut-points suggests that older people with cancer taking five-or-more-medications may be at increased risk of exhaustion, falls, reduced physical function, lower KPS or frailty. This suggests that older people with cancer who take multiple medications should have their medications reviewed. This is supported by Yeoh et al., who investigated a medication therapy management service in older people with cancer [39]. They identified >90 % of patients who took at least one chronic medication experienced medication-related problems. Furthermore, 52 % of older patients with metastatic cancer experienced ADEs from their preventative medications [40].

Medication reviews can identify people at risk from potentially inappropriate medications (PIMs). Polypharmacy in older people with cancer has been associated with PIMs [35]. There are a number of explicit and implicit approaches that can be

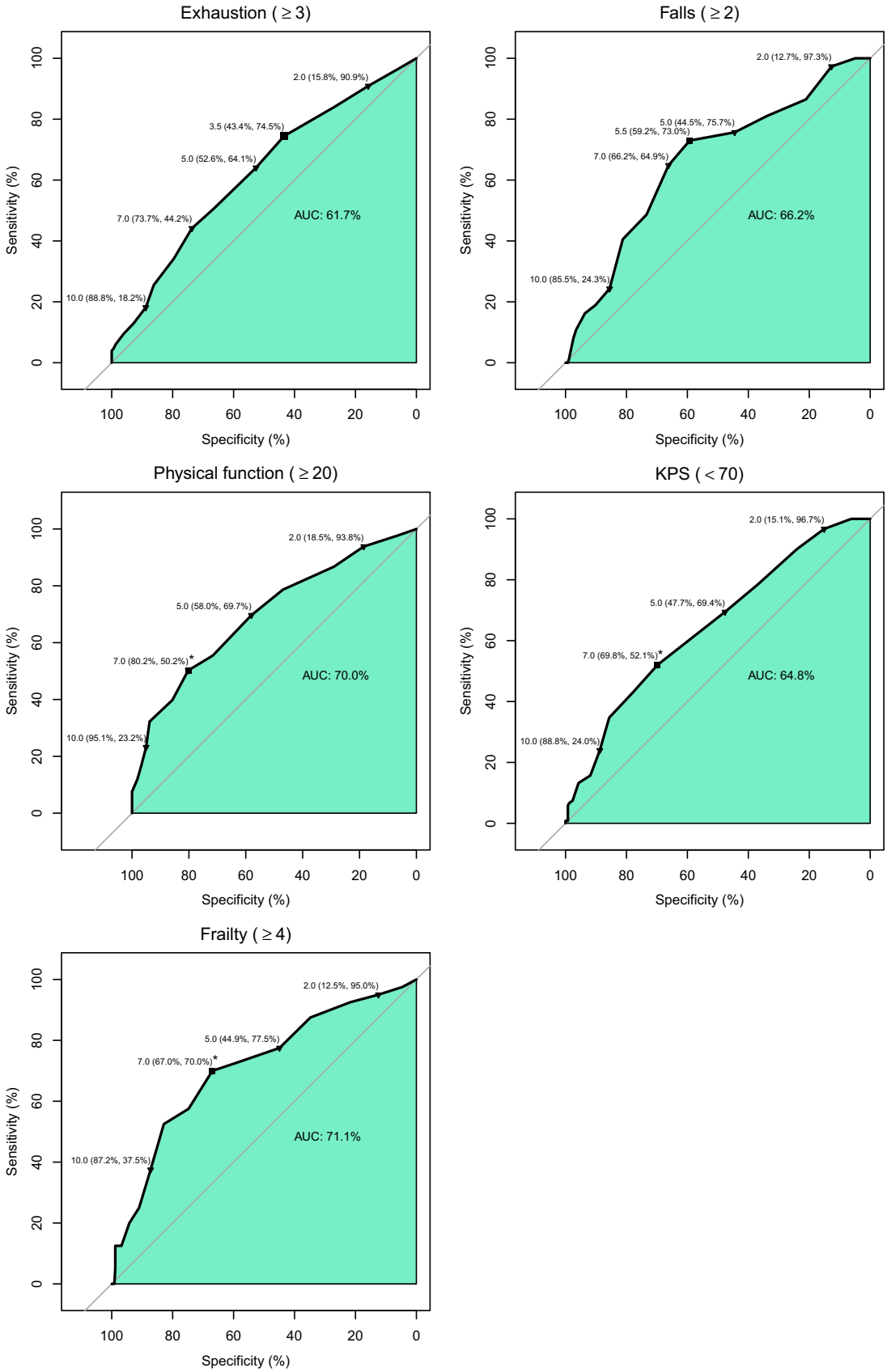

Fig. 1 Receiver operating characteristic (ROC) curves

Table 2 Sensitivity and specificity for various polypharmacy cut-points and Youden's index

Sensitivity and specificity for various polypharmacy cut-points					
	≥2 Meds	≥5 Meds	≥7 Meds	≥10 Meds	Youden's index
Exhaustion (≥3)					3.5 Meds
Sensitivity	90.9 %	64.1 %	44.2 %	18.2 %	74.5 %
Specificity	15.8 %	52.6 %	73.7 %	88.8 %	43.4 %
Falls (≥2)					5.5 Meds
Sensitivity	97.3 %	75.7 %	64.9 %	24.3 %	73.0 %
Specificity	12.7 %	44.5 %	66.2 %	85.5 %	59.2 %
Physical function (≥20)					6.5 Meds
Sensitivity	93.8 %	69.7 %	50.2 %	23.2 %	50.2 %
Specificity	18.5 %	58.0 %	80.2 %	95.1 %	80.2 %
KPS (<70)					6.5 Meds
Sensitivity	96.7 %	69.4 %	52.1 %	24.0 %	52.1 %
Specificity	15.1 %	47.7 %	69.8 %	88.8 %	69.8 %
Frailty					6.5 Meds
Sensitivity	95.0 %	77.5 %	70.0 %	37.5 %	70.0 %
Specificity	12.5 %	44.9 %	67.0 %	87.2 %	67.0 %

Number of medications (specificity, sensitivity). For each ROC curve (adverse event), the square indicates the optimal cut-point, while the triangles represents the cut-points for 2, 5, 7, 10 medications. For physical function, KPS and frailty, the sensitivities and specificities for ≥7 medication were the same as Youden's index

KPS Karnofsky Performance Scale

used to identify PIMs, including Beers Criteria [41], Sedative Load Model [42], STOPP/START [43] and the Medication Appropriateness Index [44]. Identifying medications that are potentially inappropriate is the first step in reducing or 'deprescribing' medications. Patients with polypharmacy may be willing to reduce their medications in conjunction with their physician [45]. However, in end-of-life situations, medication discontinuation is best undertaken cautiously to alleviate potential fears that health care providers have given up hope [46].

ROC curves generate a population average model, producing a simple screening tool applicable at a population level. The benefit of a simple screening tool is its ability to facilitate efficient and timely identification of patients who may be at risk of adverse events. The utility of any screening tool is reliant on its ability to have high sensitivity (ability to correctly identify a true positive) and high specificity (ability to correctly identify a true negative). Table 2 shows that the sensitivity for identifying patients with a clinically important adverse event is high when polypharmacy is defined as ≥2 medications; however, the corresponding specificity is low. As the definition of polypharmacy changes to include more medications, sensitivity decreases while specificity increases. Youden's index was used to find the point on the ROC curve with the highest combination of sensitivity and specificity [28]. This is important because it allows for limited resources to be used judiciously. Considering the range of adverse events analysed, the choice of cut-point needs to reflect the desired sensitivity or specificity. The sensitivities and specificities of the common definition five-or-more-medications ranged from 50.2 to 74.5 and 43.4 to 80.2 %, respectively.

Strengths and limitations

The study participants were a consecutive group of well-characterized older people newly diagnosed with cancer. Multiple polypharmacy definitions were assessed against a range of clinically important adverse events. The analysis included all patients regardless of their comorbid conditions. The results, therefore, are potentially applicable to a wide range of patients.

Stratification of the ROC curves was undertaken to assess whether age, sex, specific medications or comorbidity modified the association between number of medications and adverse events. We believe that stratifying the ROC curve analysis was superior to using an adjusted ROC curve. This was because it allowed for easy clinical application of the results for each sub-population without the need for statistical software.

Self-reported medication and clinical data were verified at each patient's initial consultation. There was a 79 % concordance between patient self-reported medications and a clinical pharmacist's medication history for prescription medications [47]. This level of concordance is comparable to medication histories routinely used in hospital wards [48]. Medication use was clearly defined with the data collection instrument requiring respondents to report prescription and non-prescription medication, and CAMs separately. This was important because the contribution of CAMs to polypharmacy is widely

Table 3 Sensitivity, specificity and AUC for Youden's index optimal cut-points stratified by age, sex, CCI and analgesic use

Optimal cut-points for adverse events once stratified					
	Youden's index	Sensitivity	Specificity	AUC	*P* value
Exhaustion (≥3)					
Age 70–79	4.5	67.9 %	52.2 %	62.6 %	0.681
Age 80+	5.5	47.0 %	69.2 %	59.8 %	
Male	3.5	75.2 %	46.2 %	62.8 %	0.638
Female	5.5	55.1 %	59.3 %	59.9 %	
CCI 0–2	3.5	67.4 %	50.5 %	61.5 %	0.670
CCI 3+	6.5	60.9 %	53.7 %	57.4 %	
Analgesic use: no	6.5	32.1 %	82.2 %	55.7 %	0.423
Analgesic use: yes	3.5	92.0 %	17.4 %	49.6 %	
Falls (≥2)					
Age 70–79	5.5	79.2 %	58.4 %	70.2 %	0.299
Age 80+	6.5	61.5 %	69.2 %	59.0 %	
Male	5.5	78.9 %	63.3 %	71.1 %	0.227
Female	8.5	50.0 %	77.7 %	59.7 %	
CCI 0–2	6.5	52.4 %	74.9 %	62.9 %	0.536
CCI 3+	5.5	93.8 %	41.4 %	65.1 %	
Analgesic use: no	6.5	58.8 %	77.7 %	62.3 %	0.832
Analgesic use: yes	8.5	65.0 %	60.6 %	60.1 %	
Physical function (≥20)					
Age 70–79	4.5	73.3 %	57.4 %	70.0 %	0.994
Age 80+	6.5	49.2 %	85.0 %	70.0 %	
Male	6.5	50.4 %	83.2 %	71.6 %	0.364
Female	8.5	34.7 %	90.9 %	66.6 %	
CCI 0–2	3.5	72.7 %	53.3 %	67.5 %	0.725
CCI 3+	8.5	41.0 %	92.5 %	71.4 %	
Analgesic use: no	6.5	37.2 %	87.2 %	64.2 %	0.460
Analgesic use: yes	8.5	53.3 %	82.8 %	68.8 %	
KPS (<70)					
Age 70–79	6.5	57.0 %	69.4 %	67.9 %	0.198
Age 80+	7.5	40.5 %	79.0 %	59.3 %	
Male	6.5	50.0 %	71.4 %	67.2 %	0.319
Female	7.5	44.1 %	77.3 %	61.1 %	
CCI 0–2	5.5	48.5 %	70.6 %	63.7 %	0.912
CCI 3+	8.5	43.6 %	80.3 %	61.2 %	
Analgesic use: no	6.5	38.3 %	78.7 %	60.2 %	0.656
Analgesic use: yes	8.5	49.2 %	62.3 %	57.2 %	
Frailty					
Age 70–79	6.5	70.4 %	65.5 %	69.8 %	0.544
Age 80+	6.5	69.2 %	71.0 %	75.2 %	
Male	6.5	71.4 %	69.4 %	74.3 %	.0478
Female	6.5	68.4 %	63.3 %	67.7 %	
CCI 0–2	6.5	59.1 %	75.6 %	71.6 %	0.829
CCI 3+	8.5	61.1 %	75.7 %	68.7 %	
Analgesic use: no	6.5	56.3 %	77.1 %	62.69 %	0.709
Analgesic use: yes	8.5	70.8 %	63.0 %	66.7 %	

AUC area under the curve, *CCI* Charlson Comorbidity Index, *KPS* Karnofsky Performance Scale

under-appreciated [49]. Clinicians may not have attributed the adverse events we investigated to polypharmacy, and therefore, assessing causality using the Naranjo scale at the time of data collection may not have been possible. It was beyond the scope of our research to investigate the clinical appropriateness of polypharmacy for specific patients. The research was conducted at one medical oncology multidisciplinary outpatient clinic. It is not clear to what extent the findings are generalizable to other patients and settings. Data for this study were collected at baseline, prior to starting

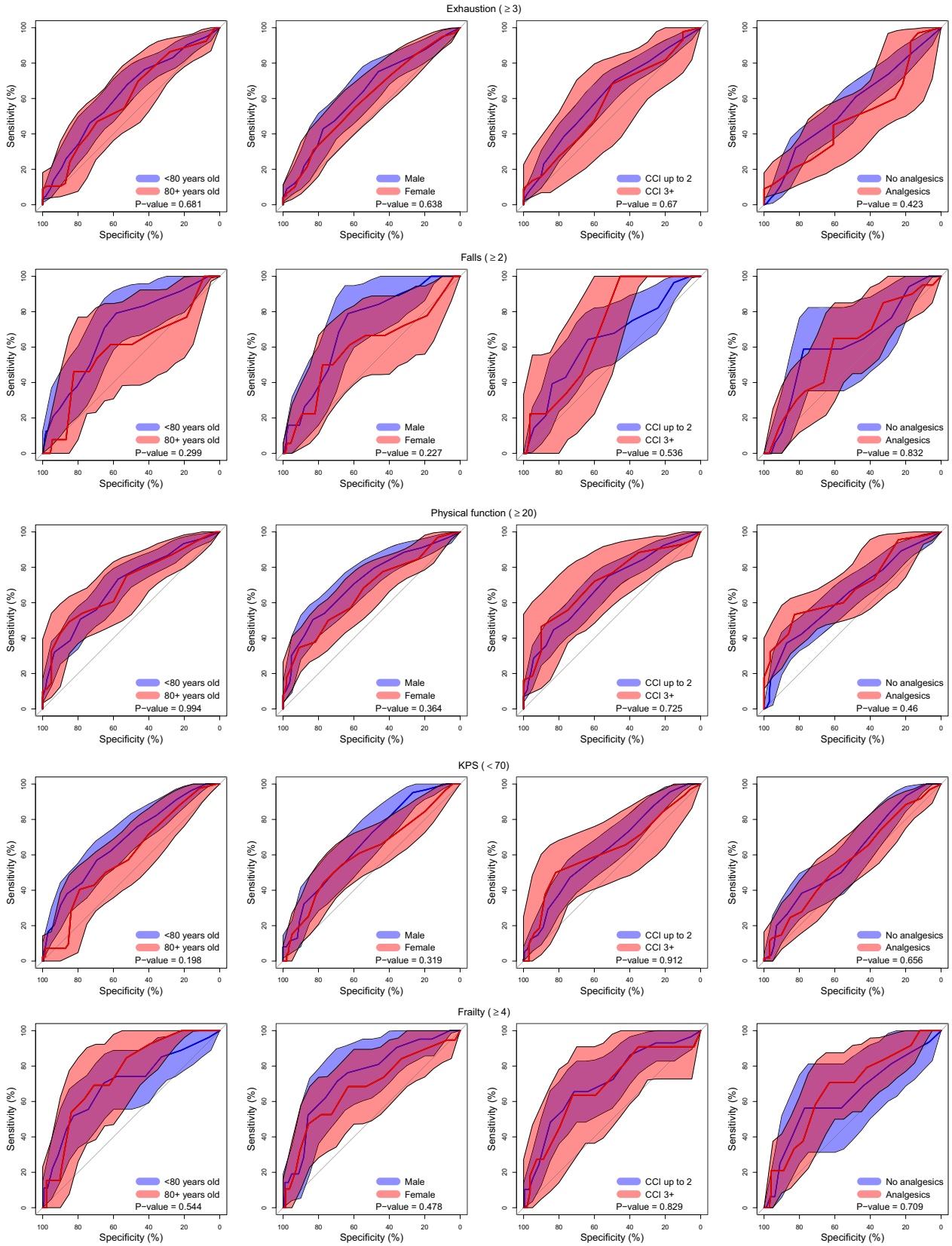

Fig. 2 Sub-group analysis showing receiver operating characteristic (ROC) curves for exhaustion

systemic therapy. We did not investigate the effects of polypharmacy for patients receiving active treatment.

Inappropriate prescribing defined as under-prescribing of beneficial medications may not be identified by limiting reviews to patients with multiple medications [50]. However, polypharmacy is associated with under-prescribing, and therefore, medication reviews triggered by polypharmacy may identify people who would benefit from additional therapy [51].

Conclusion

Our results suggest that no single polypharmacy cut-point is optimal for predicting multiple adverse events in older people with cancer. Furthermore, the associations between number of medications and adverse events were not significantly different when stratifying by age, sex, comorbidities or analgesic use. It is reasonable to use the common polypharmacy definition of five-or-more-medications as a prompt for referral for comprehensive medication reviews in older people with cancer.

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Contributions of authors JT, KJ and SB contributed to the conception and design of the study.

NS and RP contributed to the acquisition of the data.

JT, KJ, SS and SB contributed to the analysis and interpretation of the data.

JT drafted the manuscript.

All authors critically revised the manuscript for important intellectual content.

All authors gave final approval for the manuscript to be published.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

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Conflict of interest The authors have declared no conflicts of interest.

References

1. Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P (2001) Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. J Clin Epidemiol 54:837–844
2. Marcum ZA, Amuan ME, Hanlon JT, Aspinall SL, Handler SM, Ruby CM, Pugh MJ (2012) Prevalence of unplanned hospitalizations caused by adverse drug reactions in older veterans. J Am Geriatr Soc 60:34–41. doi:10.1111/j.1532-5415.2011.03772.x
3. Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S (2009) Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging 26:1039–1048. doi:10.2165/11319530
4. Williams GR, Deal AM, Nyrop KA, Pergolotti M, Guerard EJ, Jolly TA, Muss HB (2015) Geriatric assessment as an aide to understanding falls in older adults with cancer. Support Care Cancer 23:2273–2280. doi:10.1007/s00520-014-2598-0
5. Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, Bell JS (2014) Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer 22:1727–1734. doi:10.1007/s00520-014-2171-x
6. Balducci L, Goetz-Parten D, Steinman MA (2013) Polypharmacy and the management of the older cancer patient. Ann Oncol 24(Suppl 7):vii36–vii40. doi:10.1093/annonc/mdt266
7. Tam-McDevitt J (2008) Polypharmacy, aging, and cancer. Oncology 22:1052–1055
8. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, McLachlan AJ, Cumming RG, Handelsman DJ, Le Couteur DG (2012) Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 65:989–995. doi:10.1016/j.jclinepi.2012.02.018
9. Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM (2000) The development of polypharmacy. A longitudinal study. Fam Pract 17:261–267
10. Iliffe S, Haines A, Gallivan S, Booroff A, Goldenberg E, Morgan P (1991) Assessment of elderly people in general practice. 2. Functional abilities and medical problems. Br J Gen Pract 41:13–15
11. Beloosesky Y, Nenaydenko O, Gross Nevo RF, Adunsky A, Weiss A (2013) Rates, variability, and associated factors of polypharmacy in nursing home patients. Clin Interv Aging 8:1585–1590. doi:10.2147/CIA.S52698
12. Morris J, Hawes C, Murphy K, Nonemaker S, Philips C, Fries B, Mor V (1991) Minimum data set resident assessment instrument training manual and resource guide. Elliot Press, Natick
13. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, McLachlan AJ, Abernethy DR, Banks E, Le Couteur DG (2012) High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther 91:521–528. doi:10.1038/clpt.2011.258
14. Gilbert AL, Roughead EE, Beilby J, Mott K, Barratt JD (2002) Collaborative medication management services: improving patient care. Med J Aust 177:189–192
15. Lakhanpal R, Yoong J, Joshi S, Yip D, Mileshkin L, Marx GM, Dunlop T, Hovey EJ, Della Fiorentina SA, Venkateswaran L, Tattersall MHN, Liew S, Field K, Singhal N, Steer CB (2015) Geriatric assessment of older patients with cancer in Australia—A multicentre audit. J Geriatr Oncol. doi:10.1016/j.jgo.2015.03.001
16. Hovstadius B, Astrand B, Petersson G (2009) Dispensed drugs and multiple medications in the Swedish population: an individual-based register study. BMC Clin Pharmacol 9:11. doi:10.1186/1472-6904-9-11
17. Corcoran ME (1997) Polypharmacy in the older patient with cancer. Cancer Control 4:419–428
18. Hurria A, Browner IS, Cohen HJ, Denlinger CS, deShazo M, Extermann M, Ganti AK, Holland JC, Holmes HM, Karlekar MB, Keating NL, McKoy J, Medeiros BC, Mrozek E, O'Connor T, Petersdorf SH, Rugo HS, Silliman RA, Tew WP, Walter LC, Weir AB 3rd, Wildes T (2012) Senior adult oncology. J Natl Compr Cancer Netw 10:162–209

19. Kojima T, Akishita M, Nakamura T, Nomura K, Ogawa S, Iijima K, Eto M, Ouchi Y (2012) Polypharmacy as a risk for fall occurrence in geriatric outpatients. Geriatr Gerontol Int 12:425–430. doi:10.1111/j.1447-0594.2011.00783.x
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
21. Orme JG, Reis J, Herz EJ (1986) Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. J Clin Psychol 42:28–33
22. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146–M156. doi:10.1093/gerona/56.3.M146
23. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 30(6):473–483
24. Fillenbaum GG, Smyer MA (1981) The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 36:428–434
25. Karnofsky DA, Burchenal JH (1949) The clinical evaluation of chemotherapeutic agents in cancer. In: C.M. M (ed) Evaluation of chemotherapeutic agents. Columbia University Press, pp. 196.
26. WHO Collaborating Centre for Drug Statistics Methodology (2011) Guidelines for ATC classification and DDD assignment, 2012., Oslo
27. Hurria A, Gupta S, Zauderer M, Zuckerman EL, Cohen HJ, Muss H, Rodin M, Panageas KS, Holland JC, Saltz L, Kris MG, Noy A, Gomez J, Jakubowski A, Hudis C, Kornblith AB (2005) Developing a cancer-specific geriatric assessment: a feasibility study. Cancer 104:1998–2005. doi:10.1002/cncr.21422
28. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF (2008) Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. Biom J 50:419–430. doi:10.1002/bimj.200710415
29. Cook NR (2007) Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 115:928–935. doi:10.1161/CIRCULATIONAHA.106.672402
30. Santoni G, Angleman S, Welmer AK, Mangialasche F, Marengoni A, Fratiglioni L (2015) Age-related variation in health status after age 60. PLoS One 10:e0120077. doi:10.1371/journal.pone.0120077
31. Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, De Cataldis G, Iannelli A, Bilancia D, Belli M, Massidda B, Piantedosi F, Comella G, De Lena M (2000) Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18:2529–2536
32. R Core Team (2013) R: a language and environment for statistical computing. R Development Core Team, Vienna, Austria, URL http://www.R-project.org/
33. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Muller M (2011) pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf 12:77. doi:10.1186/1471-2105-12-77
34. Jorgensen T, Herrstedt J, Friis S, Hallas J (2012) Polypharmacy and drug use in elderly Danish cancer patients during 1996 to 2006. J Geriatr Oncol 3:33–40
35. Saarelainen LK, Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, Lees J, Bell JS (2014) Potentially inappropriate medication use in older people with cancer: prevalence and correlates. J Geriatr Oncol 5:439–446. doi:10.1016/j.jgo.2014.07.001
36. Koponen MP, Bell JS, Karttunen NM, Nykänen IA, Desplenter FA, Hartikainen SA (2013) Analgesic use and frailty among community-dwelling older people: a population-based study. Drugs Aging 30:129–136. doi:10.1007/s40266-012-0046-8
37. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW (2005) Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 294:716–724. doi:10.1001/jama.294.6.716
38. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO (2014) Is polypharmacy always hazardous?A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. doi:10.1111/bcp.12292
39. Yeoh TT, Si P, Chew L (2013) The impact of medication therapy management in older oncology patients. Support Care Cancer 21:1287–1293. doi:10.1007/s00520-012-1661-y
40. Cashman J, Wright J, Ring A (2010) The treatment of comorbidities in older patients with metastatic cancer. Support Care Cancer 18:651–655
41. American Geriatrics Society Beers Criteria Update Expert P (2012) American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 60:616–631. doi:10.1111/j.1532-5415.2012.03923.x
42. Taipale HT, Bell JS, Gnjidic D, Sulkava R, Hartikainen S (2012) Sedative load among community-dwelling people aged 75 years or older: association with balance and mobility. J Clin Psychopharmacol 32:218
43. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P (2015) STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44:213–218. doi:10.1093/ageing/afu145
44. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, Cohen HJ, Feussner JR (1992) A method for assessing drug therapy appropriateness. J Clin Epidemiol 45:1045–1051
45. Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S (2013) People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. J Am Geriatr Soc 61:1508–1514
46. Maddison AR, Fisher J, Johnston G (2011) Preventive medication use among persons with limited life expectancy. Prog Palliat Care 19:15
47. Lees J, Toh B (2009) Does a pharmacist derived medication history (MH) provide more information than a geriatric cancer patient-completed medication list, and does it matter? Asia Pac J Clin Oncol 5(Suppl 2):A176
48. Lau HS, Florax C, Porsius AJ, De Boer A (2001) The completeness of medication histories in hospital medical records of patients admitted to general internal medicine wards. Br J Clin Pharmacol 49:597–603. doi:10.1046/j.1365-2125.2000.00204.x
49. Lees J (2013) Management of polypharmacy in older cancer patients. Cancer Forum 37:230–233
50. Belfrage B, Koldestam A, Sjoberg C, Wallerstedt SM (2015) Number of drugs in the medication list as an indicator of prescribing quality: a validation study of polypharmacy indicators in older hip fracture patients. Eur J Clin Pharmacol 71:363–368. doi:10.1007/s00228-014-1792-9
51. Kuijpers MAJ, Van Marum RJ, Egberts ACG, Jansen PAF (2007) Relationship between polypharmacy and underprescribing. Br J Clin Pharmacol 65:130–133