Published in final edited form as:

Support Care Cancer. 2018 October ; 26(10): 3563–3570. doi:10.1007/s00520-018-4212-3.

Factors Associated with Falls in Older Adults with Cancer: A Validated Model from the Cancer and Aging Research Group

Tanya M. Wildes, MD, MSCI¹, Ronald J. Maggiore, MD², William P. Tew, MD³, David Smith, PhD⁴, Can-Lan Sun, PhD⁴, Harvey Cohen, MD⁵, Supriya G. Mohile, MD, MS², Ajeet Gajra, MD⁶, Heidi D. Klepin, MD, MS⁷, Cynthia Owusu, MD⁸, Cary P. Gross, MD, PhD⁹, Hyman Muss, MD¹⁰, Andrew Chapman, MD¹¹, Stuart M. Lichtman, MD³, Vani Katheria⁴, Arti Hurria, MD⁴, and On Behalf of the Cancer and Aging Research Group

¹Washington University School of Medicine, Division of Medical Oncology, St Louis MO USA

²University of Rochester Medical Center, Rochester NY USA

³Memorial Sloan Kettering Cancer Center, New York NY USA

⁴City of Hope, Duarte CA USA

⁵Duke University Raleigh-Durham NC USA

⁶Upstate University Hospital, Syracuse NY USA

⁷Wake Forest University, Wake Forest NC USA

⁸Case Western Reserve University School of Medicine, Cleveland OH USA

⁹Yale University, New Haven CT USA

¹⁰University of North Carolina, Lineberger Cancer Center, Chapel Hill NC USA

¹¹Thomas Jefferson University, Philadelphia PA USA

Abstract

BACKGROUND—Falls in older adults with cancer are common, yet factors associated with fall-risk are not well-defined and may differ from the general geriatric population. This study aims to develop and validate a model of factors associated with prior falls among older adults with cancer.

METHODS—In this cross-sectional secondary analysis, two cohorts of patients aged ≥65 with cancer were examined to develop and validate a model of factors associated with falls in the prior 6 months. Potential independent variables, including demographic and laboratory data and a geriatric assessment (encompassing comorbidities, functional status, physical performance, medications and psychosocial status), were identified. A multivariate model was developed in the derivation cohort using an exhaustive modeling approach. The model selected for validation

Corresponding author: Tanya Wildes, 660 South Euclid Ave, Campus Box 8056, St Louis MO 63110 USA, Phone 314-362-5817, Fax 314-362-3895, twildes@dom.wustl.edu.

ORCID ID: 0000-0002-1479-7626

Conflicts of Interest: The authors have no relevant conflicts of interest to disclose.

offered a low Akaike Information Criteria value and included dichotomized variables for ease of clinical use. This model was then applied in the validation cohort.

RESULTS—The development cohort (N=498) had a mean age of 73 (range 65-91). Nearly one-fifth (18.2%) reported a fall in the prior 6 months. The selected model comprised 9 variables involving functional status, objective physical performance, depression, medications and renal function. The AUC of the model was 0.72 (95% confidence intervals 0.65-0.78). In the validation cohort (N=250), the prevalence of prior falls was 23.6%. The AUC of the model in the validation cohort was 0.62 (95% confidence intervals 0.51-0.71).

CONCLUSION—In this study, we developed and validated a model of factors associated with prior falls in older adults with cancer. Future study is needed to examine the utility of such a model in prospectively predicting incident falls.

Keywords

Neoplasms; Geriatric Assessment; Accidental Falls; Polypharmacy; Activities of Daily Living

Introduction

Falls are a common, costly and serious event in the lives of older adults. In the general population, one-in-three older adults fall each year.[1] The CDC estimates that, in the United States, the direct annual healthcare cost of falls was \$30 billion in 2010 and is expected to reach \$54.9 billion by 2020.[2] The consequences of falls are manifold: falls may result in severe injuries, including fractures and intracranial hemorrhage, nursing home placement, functional decline and fear-of-falling.[3–5] Older adults with cancer are at greater risk of serious injuries related to falls than matched controls without cancer.[6] Further, falls are associated with increased risk of death and lower quality of life.[7, 8] In older adults with cancer, falls are associated with increased risk of toxicity of chemotherapy.[9] Functional decline subsequent to a fall may make an older patient less able to tolerate subsequent cancer therapy.

Falls are preventable.[10] Because of the great risk and cost of falls in older adults with cancer, it is imperative that we understand what factors are associated with falls and identify individuals at greater risk for incident falls. Results have been inconsistent across studies, with some studies identifying no factors predictive of falls and others finding no association with factors considered strongly predictive of falls in non-cancer populations. These inconsistencies are likely due to different populations studied, varying definitions of falls used, and differing methods of fall ascertainment.[11–15] Reliable identification of individuals at greater risk for falls will allow targeted intervention to ultimately prevent falls in this vulnerable population.

In this study, we sought to develop and validate a model of factors associated with a higher likelihood of prior falls in the last 6 months in a cohort of older adults with cancer who underwent geriatric assessment prior to initiation of chemotherapy.

Methods

This cross-sectional study is a secondary analysis of baseline data from a previously published, IRB approved, prospective cohort study which aimed to develop and validate a predictive model of chemotherapy toxicity in older adults.[16, 17] Eligible patients were age 65 or older, with a diagnosis of cancer, who were to begin, but had not yet begun, a new course of chemotherapy. Five hundred patients participated in the development cohort in the initial study (enrolled 2006-2009), and 250 participated in the validation cohort in the initial study (enrolled 2008-2012). The development cohort in the chemotherapy toxicity study was used as the development cohort in this analysis,[9] and the initial validation cohort was used as the validation cohort in this analysis.[17] Participants completed a baseline geriatric assessment,[9] including a self-report of prior falls in the past 6 months, before initiation of a new course of chemotherapy. Cases were excluded if they were missing data on falls.

Clinical data available included demographics, laboratory values, cancer type, stage, and receipt of prior chemotherapy. The geriatric assessment included an assessment of performance status (both self-reported and clinician-reported), functional status, comorbidities, medications, social support, psychological state, cognition, and hearing/visual impairment. Medication were categorized by the number of prescription and nonprescription medications as well as the specific classes of drugs. Participants were asked if they had fallen in the 6 months prior to assessment, and, if so, how many times. Data on fall-related injuries or healthcare utilization (e.g. emergency department visits) were not available.

The primary outcome was self-reported falls in the 6 months prior to assessment. It was dichotomized into a yes/no variable and logistic regression was used for analysis. Independent variables examined included demographics, cancer type and stage, prior chemotherapy, hemoglobin, creatinine clearance and all geriatric assessment parameters. For model selection, R glmulti package with exhaustive modeling approach was used to select the best set of independent variables with the best model fitting.[18] An exhaustive modeling approach fits models for every combination of all terms, from smallest (one term versus the outcome) to the largest (all terms included). The Akaike's information criterion (AIC) and residual were calculated for each potential model. The five best models with lowest AIC and residual were selected. All five models were similarly low in terms of AIC and residual; we chose the model with the fewest variables to move forward. Once the model variables were selected, cut-points for the continuous variables were selected using the Standardized Wilcoxon statistic to ease clinical comprehension and utility of the model. A point scale was developed based on the z statistic for each variable in the final model and rounded up to the nearest integer. The Cancer and Aging Research Group Fall Score was created by summing up all the points. The area under the curve (AUC) was calculated to determine the discrimination of the model. Calibration was examined by comparing between the observed rate of prior falls versus expected rate of prior falls as estimated by the model for each fall score. Youden index was used to select the best cutoff point for fall score with the highest sensitivity and specificity in classifying the presence or absence of prior falls.

The model derived from the development cohort was then applied to the validation cohort. The fall scores were calculated using the same scoring system. As in the development

cohort, the area under the curve (AUC) of the model was determined and calibration in the validation set was examined by comparing the observed versus expected rate of prior falls for each fall score. R and SAS 9.3 (SAS institute, Cary, NC) were used for data analysis.

Results

In the development cohort, two participants in the original 500 patient cohort were not evaluable due to missing data on falls, resulting in a cohort of 498 patients. Table 1 presents the baseline data of the patients in the development cohort. In the development cohort, the prevalence of falls in the 6 months prior to assessment was 18.2%. Among those with falls, there were 59 patients who reported 1 fall (11.8%), 13 patients who reported 2 falls (2.6%), and 19 patients who reported 3 falls (3.8%).

The relationship between prior falls and baseline demographic, geriatric assessment, and laboratory characteristics were examined on univariate analysis (Table 2). Factors significantly associated with prior falls comprised a number of variables in different domains, including functional status, comorbidities, medications and laboratory data. Exhaustive modeling of candidate independent variables resulted in 8 potential models (Supplementary Table). The best model selected to move forward contained 9 variables: 1) any dependence in instrumental activities of daily living (IADLs), 2) slower objective physical performance (Timed Up and Go test >13.5 seconds) 3) polypharmacy (4 medications), 4) creatinine clearance <30 milliliters/minute) 5) depressed mood (Hospital Anxiety and Depression scale) 6) selective serotonin reuptake inhibitor (SSRI) use 7) benzodiazepine use 8) proton pump inhibitor (PPI) use and 9) self-report of "I feel like I am slowed down." The discrimination of the model was fair, with an AUC of 0.72 (95% confidence intervals 0.65-0.78). Scores were assigned to each variable as described in the statistical section and presented in Table 3. The fall score was then calculated as the sum of each individual score. The median fall score was 4, ranged from 0 to 15 in the development cohort. Comparing to patients with a fall score of 6 or under, those with fall scores 7 or above were 4 times more likely to report falls in the past 6 months (OR 3.86, 95%CI 2.21-6.74, $p<0.001$).

The model was then applied to the validation cohort. In the validation cohort, all 250 patients were evaluable. Baseline characteristics of the validation cohort are provided in Table 1. The prevalence of prior falls in the validation cohort was 23.6%, with 15.6% reporting one fall, 4.8% reporting 2 falls and 3.2% reporting 3 or more falls. The fall score was calculated using the same scoring system as the development cohort. The median fall score was 5 (range 0 - 16). For the validation cohort, the AUC of the model was 0.62 (95% confidence intervals 0.51-0.71). Figure 1 demonstrates the calibration plots of the observed prevalence of prior falls versus the expected rate of prior falls associated with the fall score in the development and validation cohorts. Comparing to patients with a fall score of 6 or under, those with fall scores 7 or above were 2 times more likely to report falls in the past 6 months (OR=2.34, 95%CI 1.21-4.59, $p=0.01$).

Discussion

In this study, we developed and validated a model of factors associated with prior falls within the last 6 months in older adults with cancer. Because prior falls are strongly predictive of future falls,[19, 20] with prospective validation, this model may inform approaches to assessing fall risk that can be employed clinically to determine which older adults with cancer are at greater risk for incident falls, rather than waiting for them to have their first fall and then reacting. Identification of patients at higher risk is essential, as falls are potentially preventable through fall-prevention interventions, particularly when targeted to those at higher risk.[10]

The factors associated with prior falls in our model have face validity, based on associations seen in other studies of older adults with cancer or in general geriatric populations. For example, the need for assistance with IADLs is strongly associated with falls both in community-dwelling older adults and in older adults with cancer.[12, 21] The report of feeling “slowed down” was also associated with prior falls in our model. Interestingly, this association was independent of both depression, antidepressant use and slow performance on the Timed Up and Go test. Hence, the feeling of being “slowed down” is possibly more reflective of fatigue, which has been associated with falls.[13] Self-reported slowing is also reported as a component of phenotypic frailty,[22] which is associated with a greater than two-fold increased risk of falls in community dwelling older adults without cancer.[23]

Symptoms of depression are associated with prior falls in our model, as seen in other studies of community dwelling older adults.[24] Of note, use of antidepressants was also significant in our model, independent of symptoms of depression. Others have found SSRI use to be associated with falls,[25, 26] even after controlling for residual symptoms of depression.[25] The mechanism for this association is not well-understood; however, one study suggested an association between paroxetine use and impaired balance which, hence, increased the risk of falls.[27]

Several other medications, in addition to antidepressants, were associated with prior falls in our study, including benzodiazepines and proton pump inhibitors. Benzodiazepines are well-established to be considered potentially inappropriate in older adults.[28] They are strongly associated with falls[29, 30] in a dose-dependent manner.[31] We also found an association between proton pump inhibitor (PPI) use and prior falls. Literature is emerging regarding an association between PPI use and falls, with proposed potential mechanisms related to altered calcium homeostasis or impaired B12 absorption with long-term PPI use.[32] Lastly, we found that the use of 4 or more medications was associated with prior falls, as has been seen in other populations.[33] Polypharmacy is extremely common in older adults with cancer, with 85% of patients in one cohort taking 5 or more medications.[34] Turner *et al* found a statistical cut point of 5.5 medications to be associated with repeated falls.[35] Others have found the impact of polypharmacy on fall-risk to be greatest in the presence of benzodiazepines or antidepressants.[36]

Impaired renal function was associated with prior falls in our study, an association noted in populations without cancer.[37] Potential explanations for a mechanism of the association

could be related to altered Vitamin D metabolism, with impaired conversion of 25-hydroxy Vitamin D to 1,25 dihydroxy Vitamin D.[37] Alternate potential explanations for the association between falls and impaired renal function include muscle weakness associated with chronic kidney disease,[38] increased risk of adverse drug reactions,[39] or supratherapeutic drug levels,[40] which are areas to explore in future research.

Finally, slowed performance on the Timed Up and Go (TUG) was associated with prior falls in our study; measures of physical performance have been associated with falls in other studies of populations with cancer.[41] Some studies of community dwelling older adults suggest that alternate tests, such as gait speed, may have greater utility, and that the TUG should not be used in isolation for predicting fall-risk.[42] Indeed, in our study, the TUG was only one of 9 factors comprising the fall score, supporting the multifactorial nature of falls that physical function alone does not entirely encompass.

Strengths of our study include a large, diverse cohort of older adults with multiple types of malignancy, allowing application to a broad population of older adults with cancer. In addition, the model was developed and validated in separate populations, supporting its generalizability. We used advanced statistical techniques to create a robust, generalizable, clinically useful model of the likelihood of prior falls. While the AUC of the model was lower in the validation cohort than in the development cohort, the decrement in the AUC related to the optimism of the model in the development cohort is on par with that seen in simulation models using bootstrapping in development and validation cohorts.[43]

Nonetheless, this study has several limitations. First, the cross-sectional design does not allow for prospective assessment of incident falls and their relationship with baseline factors. Retrospective recall of falls has been shown to be unreliable, resulting in misclassification bias. Consensus groups have recommended that, optimally, a primary outcome of falls should be ascertained prospectively, grounded with a validated definition of falls to limit subjectivity in participants' appraisal of what events constitute a fall.[44] Recall bias may result in differential reporting of prior falls and spurious associations.

Second, the cross-sectional design only allows us to identify factors associated with prior falls, rather than factors prospectively predictive of incident falls; it is possible that some of the associations actually *resulted* from the prior fall, such as slowed gait speed or increased symptoms of depression. It is unknown how this model, prospectively applied, will compare with other approaches to fall-risk prediction. Finally, the available data did not allow us to explore some candidate factors associated with falls in other studies of older adults with cancer, such as pain, brain metastases or prior falls.[31] We are also unable to explore consequences of falls, such as whether falls resulted in injury. Finally, the AUC of the model in the validation set was only fair, at 0.62, with 95% confidence intervals of 0.51-0.71, the lower bound approaching chance. Unfortunately, this highlights global limitations in our ability to predict falls in older adults, as model of falls in community dwelling older adults using commonly used predictors, including prior falls, gait speed, and the Short Physical Performance Battery, have AUCs of 0.57-0.59.[45] A prospective study to validate the CARG fall score and explore time-varying predictors is underway [NCT02912273].

Another limitation is that factors that may be associated with falls in older adults with cancer, particularly peripheral neuropathy, sarcopenia or brain metastases, are not available in our dataset. For example, data on the presence of pre-existing neuropathy or chemotherapy-induced peripheral neuropathy for those receiving 2nd or subsequent lines of therapy are not available. Peripheral neuropathy is a well-established risk factor for falls in older adults with cancer.[46–49] Similarly, we have data on neither the presence of sarcopenia, which is associated with falls in community-dwelling older adults[50], nor the presence of brain metastases, which was associated with falls in older adults with advanced cancer.[31]

In conclusion, the Cancer and Aging Research Group fall score provides insight into factors associated with prior falls in older adults with cancer. The factors associated with prior falls in our study include functional dependence, self-reported slowing, depression, use of SSRIs, benzodiazepines or PPIs, polypharmacy (i.e., use of ≥ 4 medications), impaired physical performance on the TUG and impaired renal function. In the future, we anticipate that more robust models will be developed and validated, incorporating the factors we have identified, along with other potentially relevant factors such as chemotherapy-induced peripheral neuropathy, brain metastases and other cancer-specific variables, to improve our ability to identify older adults with cancer at increased risk for falls in order to intervene and prevent falls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This publication was made possible by Grant Number 1K12CA167540 through the National Cancer Institute (NCI) at the National Institutes of Health (NIH) and Grant Number UL1 TR000448 through the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCI, NCATS or NIH. (T.W.) This work was also supported by the National Institutes of Health, National Institute on Aging Grant No. K23-AG026749-01 (A.H.), Paul Beeson Career Development Award in Aging Research, and American Society of Clinical Oncology, Association of Specialty Professors, Junior Development Award in Geriatric Oncology (A.H.).

Research reported in this publication included work performed in the Survey Research Core supported by the National Cancer Institute of the National Institutes of Health under award number P30CA33572. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funded in part through the Memorial Sloan Kettering Cancer Center Support Grant P30 CA008748 (S.L.)

References

1. WHO Global report on falls Prevention in older Age. 2008:1–53.
2. Englander F, Hodson TJ, Terregrossa RA. Economic dimensions of slip and fall injuries. J Forensic Sci. 1996; 41:733–746. [PubMed: 8789837]
3. Owens PL, Russo CA, Spector W, Mutter R. Emergency Department Visits for Injurious Falls among the Elderly, 2006: Statistical Brief #80. Agency for Health Care Policy and Research (US); Rockville (MD): 2006.

4. Collerton J, Kingston A, Bond J, et al. The personal and health service impact of falls in 85 year olds: cross-sectional findings from the Newcastle 85+ cohort study. *PLoS ONE*. 2012; 7:e33078.doi: 10.1371/journal.pone.0033078 [PubMed: 22427954]
5. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med*. 1997; 337:1279–1284. DOI: 10.1056/NEJM199710303371806 [PubMed: 9345078]
6. Toomey A, Friedman L. Mortality in cancer patients after a fall-related injury: The impact of cancer spread and type. *Injury*. 2014; 45:1710–1716. DOI: 10.1016/j.injury.2014.03.008 [PubMed: 24745652]
7. Huang MH, Lytle T, Miller KA, et al. History of falls, balance performance, and quality of life in older cancer survivors. *Gait & Posture*. 2014; 40:451–456. DOI: 10.1016/j.gaitpost.2014.05.015 [PubMed: 24931110]
8. Sylliaas H, Idland G, Sandvik L, et al. Does mortality of the aged increase with the number of falls? Results from a nine-year follow-up study. *Eur J Epidemiol*. 2009; 24:351–355. DOI: 10.1007/s10654-009-9348-5 [PubMed: 19452127]
9. Hurria A, Togawa K, Mohile SG, et al. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *Journal of Clinical Oncology*. 2011; 29:3457–3465. DOI: 10.1200/JCO.2011.34.7625 [PubMed: 21810685]
10. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2012; 9:CD007146.doi: 10.1002/14651858.CD007146.pub3
11. Wildes TM, Dua P, Fowler SA, et al. Systematic review of falls in older adults with cancer. *Journal of Geriatric oncology*. 2015; 6:70–83. DOI: 10.1016/j.jgo.2014.10.003 [PubMed: 25454770]
12. Williams GR, Deal AM, Nyrop KA, et al. Geriatric assessment as an aide to understanding falls in older adults with cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2015; 23:2273–2280. DOI: 10.1007/s00520-014-2598-0 [PubMed: 25576434]
13. Vande Walle N, Kenis C, Heeren P, et al. Fall predictors in older cancer patients: a multicenter prospective study. *BMC Geriatr*. 2014; 14:135.doi: 10.1186/1471-2318-14-135 [PubMed: 25511244]
14. Sattar S, Alibhai SMH, Spoelstra SL, et al. Falls in older adults with cancer: a systematic review of prevalence, injurious falls, and impact on cancer treatment. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2016; 24:4459–4469. DOI: 10.1007/s00520-016-3342-8 [PubMed: 27450557]
15. Puts MTE, Monette J, Girre V, et al. The fall rate of older community-dwelling cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2013; 21:775–783. DOI: 10.1007/s00520-012-1579-4 [PubMed: 22941117]
16. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *Journal of Clinical Oncology*. 2011; 29:1290–1296. DOI: 10.1200/JCO.2010.30.6985 [PubMed: 21357782]
17. Hurria A, Mohile S, Gajra A, et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *Journal of Clinical Oncology*. 2016; 34:2366–2371. DOI: 10.1200/JCO.2015.65.4327 [PubMed: 27185838]
18. Calcagno Vincentde M C. glmulti: An R Package for Easy Automated Model Selection with (Generalized) Linear Models. *Journal of Statistical Software*. 2010; 34:1–29.
19. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ. Will my patient fall? *JAMA: The Journal of the American Medical Association*. 2007; 297:77–86. DOI: 10.1001/jama.297.1.77 [PubMed: 17200478]
20. Stone C, Lawlor PG, Nolan B, Kenny RA. A prospective study of the incidence of falls in patients with advanced cancer. *J Pain Symptom Manage*. 2011; 42:535–540. DOI: 10.1016/j.jpainsymman.2011.01.006 [PubMed: 21444189]
21. Chen T-Y, Janke MC. Predictors of falls among community-dwelling older adults with cancer: results from the health and retirement study. *Support Care Cancer*. 2013; 22:479–485. DOI: 10.1007/s00520-013-2000-7

22. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56:M146–56. [PubMed: 11253156]
23. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med*. 2008; 168:382–389. DOI: 10.1001/archinternmed.2007.113 [PubMed: 18299493]
24. Menant JC, Wong AKW, Trollor JN, et al. Depressive Symptoms and Orthostatic Hypotension Are Risk Factors for Unexplained Falls in Community-Living Older People. *Journal of the American Geriatrics Society*. 2016; 64:1073–1078. DOI: 10.1111/jgs.14104 [PubMed: 27225359]
25. Carrière I, Farré A, Norton J, et al. Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people: the Three-City cohort. *Osteoporos Int*. 2016; 27:3187–3195. DOI: 10.1007/s00198-016-3667-7 [PubMed: 27311722]
26. Gebara MA, Lipsey KL, Karp JF, et al. Cause or Effect? Selective Serotonin Reuptake Inhibitors and Falls in Older Adults: A Systematic Review. *Am J Geriatr Psychiatry*. 2015; 23:1016–1028. DOI: 10.1016/j.jagp.2014.11.004 [PubMed: 25586602]
27. Hegeman J, van den Bemt B, Weerdesteyn V, et al. Unraveling the association between SSRI use and falls: an experimental study of risk factors for accidental falls in long-term paroxetine users. *Clin Neuropharmacol*. 2011; 34:210–215. DOI: 10.1097/WNF.0b013e31823337d1 [PubMed: 21996643]
28. The American Geriatrics Society. Beers Criteria Update Expert Panel (2015). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*. 2015; 63:2227–2246. DOI: 10.1111/jgs.13702 [PubMed: 26446832]
29. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009; 169:1952–1960. [PubMed: 19933955]
30. Leipzig RM, Cumming RG. Drugs and Falls in Older People: A Systematic Review and Meta-analysis: I. Psychotropic Drugs. *Journal of the American Geriatrics Society*. 1999; 47:30–39. DOI: 10.1111/j.1532-5415.1999.tb01898.x [PubMed: 9920227]
31. Stone CA, Lawlor PG, Savva GM, et al. Prospective study of falls and risk factors for falls in adults with advanced cancer. *Journal of Clinical Oncology*. 2012; 30:2128–2133. DOI: 10.1200/JCO.2011.40.7791 [PubMed: 22585687]
32. Lewis JR, Barre D, Zhu K, et al. Long-term proton pump inhibitor therapy and falls and fractures in elderly women: a prospective cohort study. *J Bone Miner Res*. 2014; 29:2489–2497. DOI: 10.1002/jbmr.2279 [PubMed: 24825180]
33. Huang ES, Karter AJ, Danielson KK, et al. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. *Journal of General Internal Medicine*. 2010; 25:141–146. DOI: 10.1007/s11606-009-1179-2 [PubMed: 19967465]
34. Nightingale G, Hajjar E, Swartz K, et al. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *Journal of Clinical Oncology*. 2015; 33:1453–1459. DOI: 10.1200/JCO.2014.58.7550 [PubMed: 25800766]
35. Turner JP, Jansen KM, Shakib S, et al. Polypharmacy cut-points in older people with cancer: how many medications are too many? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2016; 24:1831–1840. DOI: 10.1007/s00520-015-2970-8 [PubMed: 26449548]
36. Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults. *Age and Ageing*. 2014; 44:90–96. DOI: 10.1093/ageing/afu141 [PubMed: 25313240]
37. Gallagher JC, Rapuri P, Smith L. Falls are associated with decreased renal function and insufficient calcitriol production by the kidney. *J Steroid Biochem Mol Biol*. 2007; 103:610–613. DOI: 10.1016/j.jsbmb.2006.12.082 [PubMed: 17236758]
38. Boudville N, Inderjeeth C, Elder GJ, Glendenning P. Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure. *Clin Endocrinol*. 2010; 73:299–304. DOI: 10.1111/j.1365-2265.2010.03821.x

39. Corsonello A, Pedone C, Corica F, et al. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med*. 2005; 165:790–795. DOI: 10.1001/archinte.165.7.790 [PubMed: 15824299]
40. Hartholt KA, Becker ML, van der Cammen TJM. Drug-induced falls in older persons: is there a role for therapeutic drug monitoring? *Ther Adv Drug Saf*. 2016; 7:39–42. DOI: 10.1177/2042098615627806 [PubMed: 27034772]
41. Overcash JA, Rivera HR. Physical performance evaluation of older cancer patients: a preliminary study. *Critical Reviews in Oncology/Hematology*. 2008; 68:233–241. DOI: 10.1016/j.critrevonc.2008.07.001 [PubMed: 18789714]
42. Barry E, Galvin R, Keogh C, et al. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. *BMC Geriatr*. 2014; 14:14.doi: 10.1186/1471-2318-14-14 [PubMed: 24484314]
43. Steyerberg EW, Bleeker SE, Moll HA. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. *Journal of Clinical Epidemiology*. 2003; 56:441–447. DOI: 10.1016/S0895-4356(03)00047-7 [PubMed: 12812818]
44. Lamb SE, Jørstad-Stein EC, Hauer K, et al. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *Journal of the American Geriatrics Society*. 2005; 53:1618–1622. DOI: 10.1111/j.1532-5415.2005.53455.x [PubMed: 16137297]
45. Palumbo P, Palmerini L, Bandinelli S, Chiari L. Fall Risk Assessment Tools for Elderly Living in the Community: Can We Do Better? *PLoS ONE*. 2015; 10:e0146247.doi: 10.1371/journal.pone.0146247 [PubMed: 26716861]
46. Ward PR, Wong MD, Moore R, Naeim A. Fall-related injuries in elderly cancer patients treated with neurotoxic chemotherapy: a retrospective cohort study. *Journal of Geriatric oncology*. 2014; 5:57–64. DOI: 10.1016/j.jgo.2013.10.002 [PubMed: 24484719]
47. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2012; 20:583–589. DOI: 10.1007/s00520-011-1127-7 [PubMed: 21380613]
48. Gewandter JS, Fan L, Magnuson A, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2013; 21:2059–2066. DOI: 10.1007/s00520-013-1766-y [PubMed: 23446880]
49. Winters-Stone KM, Horak F, Jacobs PG. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *Journal of Clinical Epidemiology*. 2017; doi: 10.1200/JCO.2017.73.6207
50. Scott D, Hayes A, Sanders KM, et al. Operational definitions of sarcopenia and their associations with 5-year changes in falls risk in community-dwelling middle-aged and older adults. *Osteoporos Int*. 2014; 25:187–193. DOI: 10.1007/s00198-013-2431-5 [PubMed: 23800748]

Figure 1.
Calibration plots of the observed fall rate versus the expected fall rate in the development and validation cohorts.

Table 1

Baseline characteristics

Characteristic	Development cohort (N=498)	Validation cohort (N=250)
Age (Median, range)	72 (65–91)	72 (65–94)
Sex		
Female	280 (56.2%)	135 (54.0%)
Male	218 (43.8%)	115 (46.0%)
Race		
White	425 (85.3%)	208 (83.2%)
Black	41 (8.2%)	19 (7.6%)
Asian	26 (5.2%)	10 (4.0%)
Other	6 (1.2%)	13 (5.2%)
Cancer type		
Lung	143 (28.7%)	64 (25.6%)
Gastrointestinal	135 (27.1%)	68 (27.2%)
Gynecologic	86 (17.3%)	18 (7.2%)
Breast	57 (11.4%)	58 (23.6%)
Genitourinary	50 (10.0%)	30 (12.0%)
Other	27 (5.4%)	11 (4.4%)
Cancer Stage		
I	23 (4.6%)	9 (3.6%)
II	58 (11.6%)	40 (16.0%)
III	111 (22.3%)	62 (24.8%)
IV	306 (61.4%)	133 (53.2%)
Other		6 (2.4%)
Chemotherapy setting		
First-line therapy	353 (70.9%)	175 (70%)
Second or greater line of therapy	145 (29.12%)	75 (30%)

Table 2

Factors associated with falls on univariate analysis in development cohort

Parameter	Fallers (N=91)	Nonfallers (N=407)	P
Age	74.69 ± 0.64	72.79 ± 0.30	0.0077
Function			
Instrumental Activities of Daily Living total score	12.32 ± 0.19	13.03 ± 0.09	0.0024
MOS physical score	62.36 ± 2.71	69.74 ± 1.28	0.019
MD-reported Karnofsky Performance Status	82.16 ± 1.21	85.26 ± 0.57	0.034
Timed Up and Go	14.02 ± 0.68	11.70 ± 0.32	0.039
Comorbidities			
Number of comorbidities	3.09 ± 0.17	2.31 ± 0.08	0.0066
Arthritis	52/91 (57.1%)	177/407 (43.5%)	0.020
Medications			
Number of daily meds	6.07 ± 0.38	4.95 ± 0.18	0.019
Proton Pump Inhibitor	36/91 (39.6%)	93/407 (22.8%)	0.0015
Anti-emetics	22/91 (24.2%)	56/407 (13.8%)	0.017
Anti-diarrheal	5/91 (5.5%)	6/407 (1.5%)	0.034
Bowel aid (fiber supplement, stool softener, laxative)	22/91 (24.2%)	58/407 (14.3%)	0.026
Selective Serotonin Reuptake Inhibitor	16/91 (17.6%)	26/407 (6.4%)	0.0014
Benzodiazepine	20/91 (22.0%)	40/407 (9.8%)	0.0024
Sleep aid (e.g. zolpidem)	11/91 (12.1%)	20/407 (4.9%)	0.016
Prescription mineral supplement	40/91 (44.0%)	125/407 (30.7%)	0.029
Other medication	32/91 (35.2%)	93/407 (22.9%)	0.016
Laboratory values			
Creatinine clearance	66.57 ± 26.29	73.00 ± 26.58	0.039
Hemoglobin	11.93 ± 0.16	12.31 ± 0.078	0.037

Table 3

Cancer and Aging Research Group Fall Score *

Variable	Adjusted Odds Ratio (95% Confidence Interval) *	Z	Score **
Dependence in any Instrumental Activity of Daily Living	0.53 (0.29, 0.96)	2.09	3
“I feel as if I am slowed down”: Yes	0.95 (0.40, 2.11)	0.13	1
Depression: Hospital Anxiety and Depression Scale score 8	2.09 (0.93, 4.55)	1.83	2
Selective Serotonin Reuptake Inhibitor use	2.57 (1.14, 5.60)	2.34	3
Benzodiazepine use	2.58 (1.17, 5.56)	2.40	3
Proton pump inhibitor use	1.90 (1.03, 3.49)	2.06	3
Polypharmacy: 4 or more daily medications	0.91 (0.49, 1.70)	0.30	1
Creatinine clearance < 30 ml/minute	0.78 (0.21, 3.81)	0.35	1
Timed Up and Go >13.5 seconds	1.67 (0.88, 3.11)	1.59	2

* Note model includes variables that are not independently significant because the modeling approach used selects the best overall model, even if individual variables are not significant

** Total score is the sum of individual factor scores