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ORIGINAL REPORT

# Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study

*Arti Hurria, Kayo Togawa, Supriya G. Mohile, Cynthia Owusu, Heidi D. Klepin, Cary P. Gross, Stuart M. Lichtman, Ajeet Gajra, Smita Bhatia, Vani Katheria, Shira Klapper, Kurt Hansen, Rupal Ramani, Mark Lachs, F. Lennie Wong, and William P. Tew*

Arti Hurria, Kayo Togawa, Smita Bhatia, Rupal Ramani, and F. Lennie Wong, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte; Kurt Hansen, University of California Davis School of Medicine, Sacramento, CA; Supriya G. Mohile, University of Rochester Medical Center, Rochester; Stuart M. Lichtman, Shira Klapper, and William P. Tew, Memorial Sloan-Kettering Cancer Center; Mark Lachs, Weill Cornell Medical College, New York; Ajeet Gajra, State University of New York Upstate Medical University and Veterans Administration Medical Center, Syracuse, NY; Cynthia Owusu, Case Western Reserve University, Cleveland, OH; Heidi D. Klepin, Wake Forest University School of Medicine, Winston-Salem, NC; Cary P. Gross, Yale Comprehensive Cancer Center, New Haven, CT; and Vani Katheria, Georgetown University, Washington, DC.

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Corresponding author: Arti Hurria, MD, City of Hope, 1500 E. Duarte Rd, Duarte, CA 91010; e-mail: ahurria@coh.org.



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## ABSTRACT

### Purpose
Older adults are vulnerable to chemotherapy toxicity; however, there are limited data to identify those at risk. The goals of this study are to identify risk factors for chemotherapy toxicity in older adults and develop a risk stratification schema for chemotherapy toxicity.

### Patients and Methods
Patients age ≥ 65 years with cancer from seven institutions completed a prechemotherapy assessment that captured sociodemographics, tumor/treatment variables, laboratory test results, and geriatric assessment variables (function, comorbidity, cognition, psychological state, social activity/support, and nutritional status). Patients were followed through the chemotherapy course to capture grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (death) as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events.

### Results
In total, 500 patients with a mean age of 73 years (range, 65 to 91 years) with stage I to IV lung (29%), GI (27%), gynecologic (17%), breast (11%), genitourinary (10%), or other (6%) cancer joined this prospective study. Grade 3 to 5 toxicity occurred in 53% of the patients (39% grade 3, 12% grade 4, 2% grade 5). A predictive model for grade 3 to 5 toxicity was developed that consisted of geriatric assessment variables, laboratory test values, and patient, tumor, and treatment characteristics. A scoring system in which the median risk score was 7 (range, 0 to 19) and risk stratification schema (risk score: percent incidence of grade 3 to 5 toxicity) identified older adults at low (0 to 5 points; 30%), intermediate (6 to 9 points; 52%), or high risk (10 to 19 points; 83%) of chemotherapy toxicity ($P < .001$).

### Conclusion
A risk stratification schema can establish the risk of chemotherapy toxicity in older adults. Geriatric assessment variables independently predicted the risk of toxicity.

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## INTRODUCTION

Cancer is a disease associated with aging. Patients age 65 years and older have an 11-fold increase in cancer incidence and a 16-fold increase in cancer mortality when compared with those younger than 65 years of age.[1] This population of older adults is growing rapidly. By 2030, 20% of the population in the United States will be older than age 65 years. Oncologists are ill prepared for this demographic shift, because older adults have been underrepresented in oncology clinical trials that set the standard of care.[2,3] The available data suggest that older adults derive benefit from chemotherapy similar to that derived by younger adults,[4,5] older age is a risk factor for chemotherapy toxicity,[6] and older adults are less likely to be offered chemotherapy because of concerns regarding their ability to tolerate the treatment.[7,8] Although tools have been developed to quantify chemotherapy benefit by age,[9] there are no tools to characterize the risks of chemotherapy in older adults.

Currently, there is no consensus within the geriatric or oncology communities regarding a standard assessment that can identify those older adults at risk for chemotherapy toxicity. Existing oncology performance status measures (such as Karnofsky performance status [KPS][10] or Eastern Cooperative Oncology Group performance status[11]) are applied to all adult patients with cancer regardless of age to estimate functional status, assess eligibility for clinical trials, and predict treatment toxicity and survival.[12-14] However, these tools were validated in

younger patients and do not address the heterogeneity in the aging process. Geriatricians perform a geriatric assessment that measures independent clinical predictors of morbidity and mortality in older adults[15]; however, this assessment has not typically been used in daily oncology practice to assist in decision making.

A predictive model that incorporates geriatric and oncologic correlates of vulnerability to chemotherapy toxicity in older adults could help both the healthcare provider and the patient weigh the benefits and risks of chemotherapy treatment and could serve as a platform to test interventions to decrease the risk of chemotherapy toxicity. The primary objective of this prospective longitudinal study was to develop a predictive model for grade 3 to 5 toxicity in a cohort of older adults with cancer that uses age, sociodemographic factors, tumor and treatment characteristics, laboratory data, and geriatric assessment variables. Furthermore, we assessed the predictive capability of this model for chemotherapy toxicity in comparison to KPS, a commonly used oncology performance status measure.

## PATIENTS AND METHODS

The Cancer and Aging Research Group Study "Determining the Utility of an Assessment Tool for Older Adults with Cancer" was open at seven participating institutions. Between November 2006 and November 2009, 500 patients were recruited from the outpatient oncology practices. Eligible patients were age ≥ 65 years, had a diagnosis of cancer, were scheduled to receive a new chemotherapy regimen, and were fluent in English (since all measures in the geriatric assessment tool were not validated in other languages). Assuming a prevalence rate of 30% for grade 3 to 5 toxicity, 500 patients would provide 80% power to detect a prevalence difference of 11% for a dichotomous predictor in logistic regression. The study was approved by the institutional review board at each participating institution. Participating patients completed the informed consent process.

### Study Schema

Before initiation of the chemotherapy regimen, a geriatric assessment tool was completed. The measures in the tool are outlined in a prior publication describing the development of the tool.[16] The geriatric assessment tool (Table 1) had a health care provider and a patient portion. The health care provider portion consisted of three items: the patient's KPS,[10] the Timed Up & Go measure (a performance-based measure of functional status),[22] and the Blessed Orientation-Memory-Concentration test[23] (a screening measure of cognitive function). The patient portion consisted of self-reported measures of functional status, comorbidity, medications, nutrition, psychological state, and social support/function. A member of the health care team assisted those who needed help with completing the questionnaires.

Tumor characteristics (tumor type and stage) and pretreatment laboratory data (WBC count, hemoglobin, blood urea nitrogen, creatinine, albumin, and liver function tests) were recorded. The following treatment characteristics were captured: chemotherapy regimen, line of chemotherapy (first line or greater), the use of WBC or RBC growth factors, and the timing of initiation of WBC growth factors (primary or secondary prophylaxis). The chemotherapy

**Table 1.** Domains and Measures in the Geriatric Assessment Questionnaire[16]

| Domain | Measure | No. of Items | Description | Range of Scores | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|---|
| Functional status | Activities of Daily Living (subscale of MOS Physical Health)[19] | 10 | Measures limitations in a wide range of physical functions (from bathing/dressing to vigorous activities such as running) | 0-100 (higher score: better physical function) | 68.5 | 26 | 75.0 | 0-100 |
| | Instrumental Activities of Daily Living (subscale of the OARS)[20] | 7 | Measures ability to complete activities required to maintain independence in the community (shopping, meal preparation, making telephone calls, money management) | 0-14 (higher score: less need for assistance) | 12.9 | 1.8 | 14 | 4-14 |
| | Karnofsky Self-Reported Performance Rating Scale[10] | 1 | Global indicator of patient function determined by patient self-report ranging from "normal" to "severely disabled" | 40-100 (higher score: better physical function) | 85.6 | 13.7 | 90 | 40-100 |
| | Karnofsky Physician-Rated Performance Rating Scale[21] | 1 | Global indicator of patient function determined by physician report ranging from "normal" to "dead" | 0-100 (higher score: better physical function) | 84.7 | 11.4 | 90 | 50-100 |
| | No. of falls in last 6 months | 1 | Indicates number of times fallen in the last 6 months | | 0.3 | 0.8 | 0 | 0-6 |
| Comorbidity | Physical Health Section (subscale of the OARS)[20] | | Presence/absence of 13 comorbid illnesses: Number of comorbid illnesses | | 2.5 | 1.7 | 2 | 0-9 |
| Psychological state | Hospital Anxiety and Depression Scale[20a] | 14 | Assesses the level of depression and anxiety experienced in the past week | 0-100 (higher score: poorer psychological state) | 8.3 | 6.0 | 7 | 0-35 |
| Social activity | MOS Social Activity Survey[19] | 4 | Measures the degree in which physical or emotional problems interfere with level of social activity | 0-100 (higher score: better social activity) | 56.2 | 22.8 | 58.3 | 0-100 |
| Social support | MOS Social Support Survey: Emotional/Information and Tangible Subscales[21a] | 12 | Measures the perceived availability of social support | 0-100 (higher score: better social support) | 84.9 | 21.3 | 95.8 | 0-100 |
| Nutrition | Body mass index | 1 | Weight in kg/(height in m)$^2$ | | 26.2 | 4.7 | 25.0 | 14.9-52.2 |
| | Percent unintentional weight loss in last 6 months | 1 | (Unintentional weight lost in last 6 months/baseline body weight) × 100 | | 4.7 | 6.2 | 2.0 | 0-32.3 |

Abbreviations: MOS, Medical Outcomes Study; OARS, Older American Resources and Services; SD, standard deviation.

  

dosing for the first cycle of treatment was categorized as standard or dose reduced per the National Comprehensive Cancer Network guidelines.[24]

The patient was followed from beginning until the end of the chemotherapy course. Toxicities were captured at each clinical encounter (scheduled or emergency visits). Two physicians (the national study principal investigator and site principal investigator) reviewed the patient's chemotherapy course to capture grade 3 to 5 chemotherapy-related toxicities (grade 3, severe; grade 4, life-threatening; and grade 5, fatal) by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.[25] Blood values were captured as grade 3 to 5 toxicity if they met the criteria on the date of scheduled chemotherapy or at the time the patient was seeking attention because of chemotherapy toxicities.

### Statistical Analyses

Descriptive analyses were performed to summarize patient, tumor, and treatment characteristics and geriatric assessment results. The incidence of the specific categories (hematologic and nonhematologic) and types of NCI CTCAE grade 3, 4, or 5 toxicity were calculated.

*Model development.* A predictive model for chemotherapy toxicity was developed. The $\chi^2$ test was used to examine the association between grade 3 to 5 toxicity and the following variables: sociodemographic factors (age, sex, education, marital status, household composition, employment status, race/ethnicity), study site, cancer type (breast, GI, genitourinary [GU], gynecologic [GYN], lung, and other), cancer stage, chemotherapy dosing (standard or dose reduced), number of chemotherapy drugs (mono- or polychemotherapy), line of treatment (first line or greater), chemotherapy duration, receipt of primary prophylaxis with WBC growth factor, prechemotherapy laboratory values (WBC, hemoglobin, liver function tests, albumin, creatinine clearance [calculated by the Cockgroft and Gault,[26] Jeliffe,[27] Modification of Diet in Renal Disease,[28] and Wright[29] formulas]), and responses to the items in the Geriatric Assessment measures (Table 1).

For numerical variables, the Youden Index[30] was used to identify the cut point with the highest sensitivity and specificity in classifying the presence or absence of toxicity. The variables that reached a $P$ value of less than .1 and clinically relevant variables (chemotherapy dosing [standard or dose reduced], number of drugs [mono- or polychemotherapy], chemotherapy duration, and receipt of primary prophylaxis with WBC growth factor) were further examined in a multivariate logistic regression model by using the best subset method[31] to identify the best combined sets of risk factors that best predicted chemotherapy toxicity. We evaluated the discrimination of those models by calculating the area under the receiver operation characteristic (ROC) curve and goodness-of-fit by using the Hosmer-Lemeshow test.[32] Interactions among the selected risk factors were evaluated by introducing interaction terms to the model one at a time.

*Developing the scoring system.* A risk score for each risk factor was calculated by dividing the $\beta$ coefficient of the variable by the lowest $\beta$ coefficient in the model, rounded to the nearest whole number.[33,34] The sum of the scores for each patient was calculated. The sample was divided into three risk strata (low, medium, and high risk) on the basis of approximate quartiles of risk score with the middle two quartiles combined. The difference in toxicity incidence among the strata was evaluated by using the $\chi^2$ test. The discrimination and calibration of the predictive model were assessed by using the total score as a predictor of chemotherapy toxicity.

*Internal validation.* The model was internally validated by using the 10-fold cross-validation process.[35,36] The study sample was randomly partitioned into 10 groups, by using nine-tenths of the cohort to obtain the $\beta$ coefficient and then applying the $\beta$ coefficient to examine the area under the ROC curve in the tenth group. This process was repeated 10 times to obtain the average area under the ROC curve of the model. All statistical analyses were performed by using SAS 9.1 (SAS Institute, Cary, NC).

## RESULTS

### Patient, Tumor, and Treatment Characteristics

The study cohort consisted of 500 patients age ≥ 65 years with stage I to IV cancer (Table 2). The mean age of participants was 73 years (standard deviation [SD], 6.2; range, 65 to 91 years) with stage I (5%), II (12%), III (22%), and IV (61%) cancer. The most common tumor types were lung (29%), GI (27%), GYN (17%), and breast (11%). Seventy percent received polychemotherapy, 76% received standard doses of chemotherapy, 71% received first-line treatment, and 18% received primary prophylaxis with WBC growth factors.

**Table 2.** Patient Characteristics (N = 500)

| Characteristic | No. of Patients | % Patients |
|---|---|---|
| Age, years | | |
| 65-69 | 175 | 35 |
| 70-74 | 127 | 25 |
| 75-79 | 105 | 21 |
| 80-84 | 73 | 15 |
| 85-91 | 20 | 4 |
| Sex | | |
| Female | 281 | 56 |
| Male | 219 | 44 |
| Cancer type | | |
| Breast | 57 | 11 |
| Lung | 143 | 29 |
| GI | 135 | 27 |
| GYN | 87 | 17 |
| GU | 50 | 10 |
| Other | 28 | 6 |
| Cancer stage | | |
| I | 23 | 5 |
| II | 59 | 12 |
| III | 109 | 22 |
| Limited | 2 | 0 |
| IV/extensive | 307 | 61 |
| Educational level | | |
| Less than high school | 18 | 4 |
| High school graduate | 175 | 35 |
| Associate/bachelor's degree | 202 | 40 |
| Advanced degree | 104 | 21 |
| Missing | 1 | 0 |
| Marital status | | |
| Married | 306 | 61 |
| Widowed | 113 | 23 |
| Single | 16 | 3 |
| Separated, divorced | 65 | 13 |
| Employment status | | |
| Full or part-time | 83 | 17 |
| Retired, homemaker, unemployed | 395 | 79 |
| Disabled, medical leave | 21 | 4 |
| Missing | 1 | 0 |
| Household composition | | |
| Lives alone | 106 | 21 |
| Lives with spouse, partner, or child | 390 | 78 |
| Missing | 4 | 1 |
| Race/ethnicity | | |
| White | 426 | 85 |
| Black | 42 | 8 |
| Asian | 26 | 5 |
| Other | 6 | 1 |

Abbreviations: GU, genitourinary; GYN, gynecologic.

### Geriatric Assessment Results

The mean score on the instrumental activities of daily living scale was 12.9 (SD, 1.8; range, 4 to 14), with 43% of patients requiring

assistance with those activities. The mean score on the Medical Outcomes Study (MOS) Physical Health Scale was 68.5 (SD, 26; range 0 to 100), with a score of 0 indicating completely dependent and a score of 100 indicating full physical capacity. The patients' KPS ranged from 40% to 100% with 79% of patients with a status greater than 70%. Eighteen percent reported at least one fall in the last 6 months, and 90% had at least one comorbid condition. The most common comorbid conditions were hypertension (52%), arthritis (46%), heart disease (20%), and stomach disorders (19%). Twelve percent had a low body mass index of less than 22, and 18% were obese (body mass index > 30). Thirty-eight percent reported unintentional weight loss of more than 5% of body weight over the past 6 months (Table 1).

### Chemotherapy Toxicity

At least one grade 3 to 5 toxicity occurred in 53% of patients (39% grade 3, 12% grade 4, and 2% grade 5 [percentages reflect the worst grade of toxicity experienced]; Table 3). Grade 3 to 5 hematologic and nonhematologic toxicity occurred in 26% and 43%, respectively. The most common grade 3 to 5 hematologic toxicities were neutropenia (11%), leucopenia (10%), and anemia (10%). The most common grade 3 to 5 nonhematologic toxicities were fatigue (16%), infection (10%), and dehydration (9%). Thirty-one percent of patients required a dose reduction during therapy, 31% had a dose delay, and 23% were hospitalized during treatment.

**Table 3.** Treatment-Related Adverse Events

| Toxicity Type | Grade 3 to 5 | | Grade 3 | | Grade 4 | | Grade 5* | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| Hematologic and nonhematologic† | 265 | 53 | 197 | 39 | 58 | 12 | 10 | 2 |
| Hematologic | 131 | 26 | 90 | 18 | 39 | 8 | 2 | 0 |
| ANC | 57 | 11 | 40 | 8 | 17 | 3 | 0 | 0 |
| WBC | 49 | 10 | 41 | 8 | 8 | 2 | 0 | 0 |
| Hemoglobin | 48 | 10 | 45 | 9 | 3 | 1 | 0 | 0 |
| Platelets | 25 | 5 | 14 | 3 | 11 | 2 | 0 | 0 |
| Infection with abnormal ANC | 10 | 2 | 7 | 1 | 1 | 0 | 2 | 0 |
| Nonhematologic | 217 | 43 | 184 | 37 | 25 | 5 | 8 | 2 |
| Fatigue | 81 | 16 | 79 | 16 | 2 | 0 | 0 | 0 |
| Infection with normal ANC | 48 | 10 | 40 | 8 | 5 | 1 | 3 | 1‡ |
| Dehydration | 43 | 9 | 41 | 8 | 2 | 0 | 0 | 0 |
| Thrombosis/embolism | 22 | 4 | 17 | 3 | 4 | 1 | 1 | 0‡ |
| Hyponatremia | 22 | 4 | 22 | 4 | 0 | 0 | 0 | 0 |
| Diarrhea | 22 | 4 | 19 | 4 | 3 | 1 | 0 | 0 |
| Hypokalemia | 15 | 3 | 15 | 3 | 0 | 0 | 0 | 0 |
| Dyspnea | 13 | 3 | 5 | 1 | 7 | 1 | 1 | 0 |
| Syncope | 13 | 3 | 13 | 3 | 0 | 0 | 0 | 0 |
| Neuropathy | 13 | 3 | 13 | 3 | 0 | 0 | 0 | 0 |
| Nausea | 12 | 2 | 12 | 2 | 0 | 0 | 0 | 0 |

Abbreviation: ANC, absolute neutrophil count.
*Additional causes of grade 5 toxicities include cardiac ischemia/infarction, liver dysfunction/failure, pneumonitis/pulmonary infiltrate, and sudden death.
†The percentages for grades 3 to 5 toxicity reflect the worst grade of toxicity experienced by the individual. Since patients could have both hematologic and nonhematologic toxicity, the sum of hematologic and nonhematologic toxicities is greater than the number of all types of toxicity.
‡One patient had grade 5 infection with normal ANC and grade 5 thrombosis/embolism. Another patient had grade 5 infection with normal ANC and grade 5 metabolic encephalopathy.

### Factors Associated With Increased Risk of Chemotherapy Toxicity

The risk factors (Table 4) associated with grade 3 to 5 toxicity in univariate analysis ($P < .1$) and variables deemed to be of clinical importance (chemotherapy dosing [standard or dose reduced], number of chemotherapy drugs [mono- or polychemotherapy], and primary prophylaxis with WBC growth factor) were used to derive the model for chemotherapy toxicity which includes the following risk factors: age ≥ 72 years, cancer type (GI or GU), standard dosing of chemotherapy, polychemotherapy, hemoglobin (males: < 11 g/dL; females: < 10 g/dL), creatinine clearance less than 34 mL/min (Jelliffe formula[27] using ideal weight), hearing impairment described as fair or worse, ≥ one fall in the last 6 months, limited in walking one block, need for assistance in taking medications, and decreased social activities because of physical or emotional health. No significant interaction among the selected variables was found. Both the model of 11 risk factors and the model of total risk score achieved good calibration (Hosmer-Lemeshow test, $P = .85$ and $P = .25$, respectively) and discrimination (both models: ROC = 0.72; Tables 5 and 6).

Risk scores were assigned to each risk factor, as described in the Statistical Analyses section (Table 5). The median overall risk score was 7 (range, 0 to 19). The cohort was divided into three categories on the basis of the risk of grade 3 to 5 toxicity: low risk (0 to 5 points, 30%), intermediate risk (6 to 9 points, 52%), and high risk (10 to 19 points, 83%). There was a significant difference in toxicity among the risk groups ($P < .001$; Fig 1 and Table 6).

Exploratory analyses were performed to calculate the ROC of the model by using the total risk score for each tumor type: GI (0.72), GU (0.76), breast (0.66), lung (0.68), GYN (0.66), and other (0.81) cancers.

### Ability of the Model to Predict Toxicity in Comparison With KPS

The association between KPS and chemotherapy toxicity is described in Figure 1 and Table 6. There was no significant difference in the incidence of toxicity across the KPS-based risk groups ($P = .19$). The ROC of the model with KPS (as a continuous variable) was 0.53 which was lower than the ROC of the risk score model, 0.72. Furthermore, the addition of KPS to our final model did not improve the ROC.

### Internal Validation of the Predictive Model

A 10-fold cross validation yielded an area under the curve statistic of 0.72, indicating that the model retained a good discrimination.

## DISCUSSION

This prospective multicenter study demonstrated that chemotherapy toxicity is common in older adults, with 53% experiencing at least one grade 3 to 5 toxicity. Among these, 2% experienced a treatment-related mortality. A predictive model was developed to identify those patients at greatest risk, including factors obtained in everyday practice (patient age, number of chemotherapy drugs, dosing, and laboratory values) and factors not typically used in everyday oncology practice (geriatric assessment variables). This model had a greater

  

**Table 4.** Association Between Patient Characteristics and Toxicity

| Variable* | Patients | | No Grade 3 to 5 Toxicity | | Grade 3 to 5 Toxicity | | P† |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| Sociodemographics | | | | | | | |
| Age, years | | | | | | | |
| 65 to < 72 | 230 | 46 | 128 | 54 | 102 | 38 | |
| ≥ 72 | 270 | 54 | 107 | 46 | 163 | 62 | < .001 |
| Tumor/treatment variables | | | | | | | |
| Cancer type | | | | | | | |
| Other | 315 | 63 | 170 | 72 | 145 | 55 | |
| GI or GU | 185 | 37 | 65 | 28 | 120 | 45 | < .001 |
| Dose | | | | | | | |
| Reduced | 120 | 24 | 59 | 25 | 61 | 23 | |
| Standard | 380 | 76 | 176 | 75 | 204 | 77 | .5854 |
| No. of chemotherapy agents | | | | | | | |
| Monochemotherapy | 149 | 30 | 76 | 32 | 73 | 28 | |
| Polychemotherapy | 351 | 70 | 159 | 68 | 192 | 72 | .2422 |
| WBC growth factor (primary prophylaxis) | | | | | | | |
| No | 410 | 82 | 190 | 81 | 220 | 83 | |
| Yes | 89 | 18 | 45 | 19 | 44 | 17 | |
| Missing | 1 | 0 | 0 | 0 | 1 | 0 | .4697 |
| RBC growth factor | | | | | | | |
| No | 420 | 84 | 202 | 86 | 218 | 82 | |
| Yes | 80 | 16 | 33 | 14 | 47 | 18 | .2609 |
| Laboratory variables | | | | | | | |
| Hemoglobin, g/dL | | | | | | | |
| ≥ 10 (female), ≥ 11 (male) | 429 | 86 | 215 | 91 | 214 | 81 | |
| < 10 (female), < 11 (male) | 62 | 12 | 16 | 7 | 46 | 17 | |
| Missing | 9 | 2 | 4 | 2 | 5 | 2 | < .001 |
| Albumin, g/dL | | | | | | | |
| > 3.6 | 303 | 61 | 153 | 65 | 150 | 57 | |
| ≤ 3.6 | 179 | 36 | 76 | 32 | 103 | 39 | |
| Missing | 18 | 4 | 6 | 3 | 12 | 5 | .0878 |
| Geriatric assessment variables | | | | | | | |
| Physician-rated KPS (%) | | | | | | | |
| > 70 | 402 | 80 | 198 | 84 | 204 | 77 | |
| ≤ 70 | 86 | 17 | 33 | 14 | 53 | 20 | |
| Missing | 12 | 2 | 4 | 2 | 8 | 3 | .0666 |
| Timed Up & Go, seconds | | | | | | | |
| ≤ 10 | 156 | 31 | 83 | 35 | 73 | 28 | |
| > 10 | 249 | 50 | 107 | 46 | 142 | 54 | |
| Missing | 95 | 19 | 45 | 19 | 50 | 19 | .0446 |
| Falls in past 6 months | | | | | | | |
| 0 | 407 | 81 | 204 | 87 | 203 | 77 | |
| ≥ 1 | 91 | 18 | 30 | 13 | 61 | 23 | |
| Missing | 2 | 0 | 1 | 0 | 1 | 0 | .003 |
| BMI | | | | | | | |
| > 26.5 | 197 | 39 | 106 | 45 | 91 | 34 | |
| ≤ 26.5 | 301 | 60 | 128 | 54 | 173 | 65 | |
| Missing | 2 | 0 | 1 | 0 | 1 | 0 | .0136 |
| Unintentional weight loss, % | | | | | | | |
| ≤ 6 | 328 | 66 | 164 | 70 | 164 | 62 | |
| > 6 | 170 | 34 | 71 | 30 | 99 | 37 | |
| Missing | 2 | 0 | 0 | 0 | 2 | 0 | .0809 |
| Chronic liver or kidney disease | | | | | | | |
| No | 476 | 95 | 227 | 97 | 249 | 94 | |
| Yes | 22 | 4 | 6 | 3 | 16 | 6 | |
| Missing | 2 | 0 | 2 | 1 | 0 | 0 | .0606 |
| Hearing | | | | | | | |
| Excellent/good | 370 | 74 | 183 | 78 | 187 | 71 | |
| Fair/poor/deaf | 123 | 25 | 47 | 20 | 76 | 29 | |
| Missing | 7 | 1 | 5 | 2 | 2 | 1 | .0303 |

(continued on following page)

**Table 4.** Association Between Patient Characteristics and Toxicity (continued)

| Variable* | Patients | | No Grade 3 to 5 Toxicity | | Grade 3 to 5 Toxicity | | *P*† |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| Mobility | | | | | | | |
| No assistance | 411 | 82 | 204 | 87 | 207 | 78 | |
| Requires assistance | 89 | 18 | 31 | 13 | 58 | 22 | .0112 |
| Housework | | | | | | | |
| No assistance | 320 | 64 | 162 | 69 | 158 | 60 | |
| Requires assistance | 178 | 36 | 72 | 31 | 106 | 40 | |
| Missing | 2 | 0 | 1 | 0 | 1 | 0 | .0292 |
| Medication intake | | | | | | | |
| No assistance | 461 | 92 | 224 | 95 | 237 | 89 | |
| Requires assistance | 39 | 8 | 11 | 5 | 28 | 11 | .0143 |
| Vigorous activities | | | | | | | |
| Not limited at all | 64 | 13 | 39 | 17 | 25 | 9 | |
| Limited | 433 | 87 | 195 | 83 | 238 | 90 | |
| Missing | 3 | 1 | 1 | 0 | 2 | 1 | .0174 |
| Moderate activities | | | | | | | |
| Not limited at all | 253 | 51 | 135 | 57 | 118 | 45 | |
| Limited | 244 | 49 | 100 | 43 | 144 | 54 | |
| Missing | 3 | 1 | 0 | 0 | 3 | 1 | .0057 |
| Limited in walking several blocks | | | | | | | |
| Not limited at all | 286 | 57 | 146 | 62 | 140 | 53 | |
| Limited | 208 | 42 | 85 | 36 | 123 | 46 | |
| Missing | 6 | 1 | 4 | 2 | 2 | 1 | .0251 |
| Limited in walking one block | | | | | | | |
| Not limited at all | 386 | 77 | 192 | 82 | 194 | 73 | |
| Limited | 109 | 22 | 40 | 17 | 69 | 26 | |
| Missing | 5 | 1 | 3 | 1 | 2 | 1 | .016 |
| Limited in bathing and dressing | | | | | | | |
| Not limited at all | 449 | 90 | 219 | 93 | 230 | 87 | |
| Limited | 49 | 10 | 15 | 6 | 34 | 13 | |
| Missing | 2 | 0 | 1 | 0 | 1 | 0 | .0156 |
| Decreased social activity because of health/emotional problems | | | | | | | |
| A little, or none of the time | 278 | 56 | 142 | 60 | 136 | 51 | |
| Some, most, all of the time | 218 | 44 | 92 | 39 | 126 | 48 | |
| Missing | 4 | 1 | 1 | 0 | 3 | 1 | .0493 |
| Limited social activity compared with others your age | | | | | | | |
| About the same, somewhat, or much less limited than others | 334 | 67 | 167 | 71 | 167 | 63 | |
| Somewhat, or much more limited than others | 160 | 32 | 66 | 28 | 94 | 35 | |
| Missing | 6 | 1 | 2 | 1 | 4 | 2 | .0683 |

Abbreviations: BMI, body mass index; GU, genitourinary; KPS, Karnofsky performance status.

*For numerical variables, the Youden Index[30] was examined to determine the cut point in the responses that had the highest sensitivity and specificity in classifying the presence or absence of toxicity. The variables that reached a *P* value of $< .1$ as well as clinically relevant variables (chemotherapy dosing [standard or dose reduced], number of chemotherapy drugs in the regimen [mono- or polychemotherapy], and receipt of primary prophylaxis with WBC growth factor) were further examined in a multivariate logistic regression model.

†$\chi^2$ test was conducted for observations without missing values.

ability to discriminate risk of chemotherapy toxicity than the KPS, which is commonly used in oncology practice.

Older adults are at increased risk for chemotherapy toxicity; however, oncologists are left with little guidance when it comes to identifying risk factors other than chronologic age. It is generally recognized that chronologic age does not equate to physiologic age. Geriatricians perform a geriatric assessment to identify clinical predictors of morbidity and mortality[15]; however, this assessment has not been routinely incorporated into oncology care because of the time and resource requirements. Furthermore, there is a lack of guidelines regarding how to interpret the findings in the context of oncology care.

The predictive model identified patient age, tumor, treatment, laboratory values, and geriatric assessment variables as risk factors for chemotherapy toxicity. There is a rational explanation for why each of these factors may predict chemotherapy toxicity. Although older age is associated with an accumulation of physiologic deficit, there is controversy about which chronologic age defines an individual as "older." Age $\geq$ 72 years as a risk factor for chemotherapy toxicity provides

**Table 5.** Predictive Model

| Risk Factor | Prevalence No. | Prevalence % | Grades 3 to 5 Toxicity No. | Grades 3 to 5 Toxicity % | OR | 95% CI | Score |
|---|---|---|---|---|---|---|---|
| Age ≥ 72 years | 270 | 54 | 163 | 60 | 1.85 | 1.22 to 2.82 | 2 |
| Cancer type GI or GU | 185 | 37 | 120 | 65 | 2.13 | 1.39 to 3.24 | 2 |
| Chemotherapy dosing, standard dose | 380 | 76 | 204 | 54 | 2.13 | 1.29 to 3.52 | 2 |
| No. of chemotherapy drugs, polychemotherapy | 351 | 70 | 192 | 55 | 1.69 | 1.08 to 2.65 | 2 |
| Hemoglobin < 11 g/dL (male), < 10 g/dL (female) | 62 | 12 | 46 | 74 | 2.31 | 1.15 to 4.64 | 3 |
| Creatinine clearance (Jelliffe, ideal weight) < 34 mL/min | 44 | 9 | 34 | 77 | 2.46 | 1.11 to 5.44 | 3 |
| Hearing, fair or worse | 123 | 25 | 76 | 62 | 1.67 | 1.04 to 2.69 | 2 |
| No. of falls in last 6 months, 1 or more | 91 | 18 | 61 | 67 | 2.47 | 1.43 to 4.27 | 3 |
| IADL: Taking medications, with some help/unable | 39 | 8 | 28 | 72 | 1.50 | 0.66 to 3.38 | 1 |
| MOS: Walking 1 block, somewhat limited/limited a lot | 109 | 22 | 69 | 63 | 1.71 | 1.02 to 2.86 | 2 |
| MOS: Decreased social activity because of physical/emotional health, limited at least sometimes | 218 | 44 | 126 | 58 | 1.36 | 0.90 to 2.06 | 1 |

Abbreviations: GU, genitourinary; IADL, instrumental activities of daily living; MOS, Medical Outcomes Study; OR, odds ratio.

**Table 6.** Ability of Risk Score Versus Physician-Rated KPS to Predict Chemotherapy Toxicity

| Risk Strata | No Toxicity No. | No Toxicity % | Toxicity No. | Toxicity % | Total | *P* | ROC |
|---|---|---|---|---|---|---|---|
| By total score | | | | | | < .001 | 0.72* |
| 0-5 (low) | 89 | 70 | 39 | 30 | 128 | | |
| 6-9 (mid) | 110 | 48 | 117 | 52 | 227 | | |
| 10-19 (high) | 19 | 17 | 90 | 83 | 109 | | |
| By physician-rated KPS (%) | | | | | | .19 | 0.53* |
| 90-100 | 125 | 49 | 128 | 51 | 253 | | |
| 80 | 73 | 49 | 76 | 51 | 149 | | |
| ≤ 70 | 33 | 38 | 53 | 62 | 86 | | |

Abbreviations: KPS, Karnofsky performance status; ROC, receiver operating characteristic.
*Risk score and physician-rated KPS were treated as continuous to calculate the ROC.

evidence for the seventh decade of life as a time when the cumulative effects of aging are associated with increased vulnerability.

Tumor and treatment variables were identified as risk factors for chemotherapy toxicity. Patients with GI and GU cancers were at increased risk for toxicity, possibly reflective of the type of chemotherapy delivered or alterations in physiology (diarrhea/impaired fluid balance) associated with the cancer or the treatment. Receipt of polychemotherapy and/or standard dosing of chemotherapy were associated with an increased risk of toxicity. Aging is associated with decreased bone marrow reserve and an increased risk of myelosuppressive-associated complications from chemotherapy.[37,38] The receipt of polychemotherapy further increases the risk of myelosuppressive effects from chemotherapy and can potentially amplify the physiologic stress of a regimen secondary to overlapping toxicities.

Laboratory values (anemia and renal dysfunction) were identified as risk factors for chemotherapy toxicity. The presence of anemia can further increase susceptibility to myelosuppression with certain antineoplastic drugs that are heavily bound to RBCs (epipodophyllotoxins, anthracyclines, camptothecins) by increasing the volume of distribution of these drugs.[39] In the geriatric population, anemia is an independent predictor of hospitalization and mortality, perhaps representing a global measure of decreased reserve.[40] There is an age-related decrease in renal function which could impact the pharmacokinetics of renally metabolized drugs.[17]

Geriatric assessment variables were a critical part of the predictive model. Among geriatric patients, functional status is a strong predictor of morbidity and mortality.[18] Four questions that reflected the patient's functional status were included in the model (ability to walk one block, decreased social activities because of physical or emotional problems, falls in the last 6 months, and the need for assistance with taking medications). The need for assistance with taking medications could also be a surrogate measure of cognitive function, grip strength (unable to open the bottle), or vision (unable to see the instructions). A decrease in social activities because of physicalor emotional problems may represent both a functional measure and a measure of psychological state. Finally, poor hearing was identified

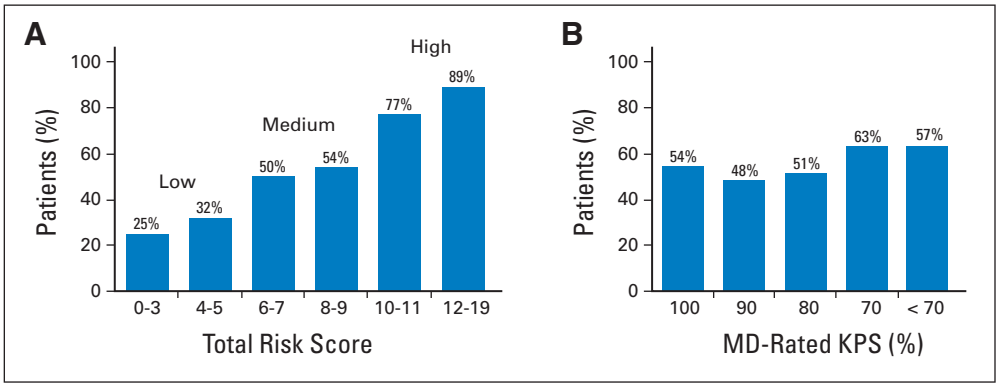


**Fig 1.** Ability of (A) risk score versus (B) physician-rated Karnofsky performance status (KPS) to predict chemotherapy toxicity. Graphs show grade 3 to 5 toxicity.

as a risk factor for chemotherapy toxicity, potentially reflecting whether the patient could hear the instructions regarding potentialadverse effects, supportive care medications, and indications of when to seek medical attention.

These findings contribute to an ongoing paradigm shift in oncology assessment. The commonly used oncology performance status measure (KPS) did not identify older adults at increased risk for chemotherapy toxicity, reflecting the limitations of trying to use one global assessment measure of functional status to describe the heterogeneity in the geriatric population. Furthermore, the KPS might be misleading. In older adults it is difficult to discriminate between a KPS of 80% ("normal activity with effort; some signs or symptoms of disease") and a KPS of 60% ("requires occasional assistance, but is able to care for most of his/her needs").

There are limitations to this study. This study reported on grade 3 to 5 toxicity; however, some grade 2 toxicities (diarrhea, neuropathy) may also be relevant to the geriatric population. Our study population was heterogeneous, consisting of patients with different tumor types and treatment regimens. Our rationale behind studying a heterogeneous population was to determine whether there are common factors that are predictive of vulnerability in the geriatric oncology population; however, there may be additional or different risk factors that are predictive of toxicity based on tumor type or treatment regimen. Exploratory analyses revealed that the ROC of the model was similar when applied to the different tumor types; however, our future research will focus on refining the model among patients with specific tumor types who are receiving specific treatment regimens. Finally, although the model was internally validated, these findings need to be validated externally in an independent cohort.

This study fills critical gaps in the knowledge of predictors for chemotherapy toxicity in older adults, something that does not currently exist and for which there is an enormous and growing need. It unites the fields of geriatrics and oncology by incorporating geriatric correlates of vulnerability, studying their impact in a diverse population of older adults with cancer, and identifying common risk factors for chemotherapy toxicity. Ultimately, these data will provide the basis for future intervention studies aimed at decreasing the risk of chemotherapy toxicity and maintaining the function and health of older adults with cancer.

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## AUTHOR CONTRIBUTIONS

**Conception and design:** Arti Hurria, Mark Lachs
**Financial support:** Arti Hurria
**Administrative support:** Arti Hurria
**Provision of study materials or patients:** Arti Hurria, Supriya G. Mohile, Cynthia Owusu, Heidi D. Klepin, Cary P. Gross, Stuart M. Lichtman, Ajeet Gajra, William P. Tew
**Collection and assembly of data:** Arti Hurria, Kayo Togawa, Supriya G. Mohile, Cynthia Owusu, Heidi D. Klepin, Cary P. Gross, Stuart M. Lichtman, Ajeet Gajra, Vani Katheria, Shira Klapper, Kurt Hansen, Rupal Ramani, William P. Tew
**Data analysis and interpretation:** Arti Hurria, Kayo Togawa, Supriya G. Mohile, Cynthia Owusu, Heidi D. Klepin, Cary P. Gross, Stuart M. Lichtman, Ajeet Gajra, Smita Bhatia, F. Lennie Wong, William P. Tew
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

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