

## Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer

Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Andrew Chapman, Tao Feng, David Smith, Can-Lan Sun, Nienke De Glas, Harvey Jay Cohen, Vani Katheria, Caroline Doan, Laura Zavala, Abrahm Levi, Chie Akiba, and William P. Tew

Arti Hurria, Tao Feng, David Smith, Can-Lan Sun, Vani Katheria, Caroline Doan, Laura Zavala, Abrahm Levi, and Chie Akiba, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA; Supriya Mohile, University of Rochester Medical Center, Rochester; Ajeet Gajra, Upstate Medical University and Syracuse VA Medical Center, Syracuse; William P. Tew, Memorial Sloan Kettering Cancer Center, New York, NY; Heidi Klepin, Wake Forest University School of Medicine, Winston Salem; Hyman Muss, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill; Harvey Jay Cohen, Duke University, Durham, NC; Andrew Chapman, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; and Nienke De Glas, Leiden University Medical Centre, Leiden, the Netherlands.

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

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### A B S T R A C T

#### Purpose

Older adults are at increased risk for chemotherapy toxicity, and standard oncology assessment measures cannot identify those at risk. A predictive model for chemotherapy toxicity was developed (N = 500) that consisted of geriatric assessment questions and other clinical variables. This study aims to externally validate this model in an independent cohort (N = 250).

#### Patients and Methods

Patients age  $\geq 65$  years with a solid tumor, fluent in English, and who were scheduled to receive a new chemotherapy regimen were recruited from eight institutions. Risk of chemotherapy toxicity was calculated (low, medium, or high risk) on the basis of the prediction model before the start of chemotherapy. Chemotherapy-related toxicity was captured (grade 3 [hospitalization indicated], grade 4 [life threatening], and grade 5 [treatment-related death]). Validation of the prediction model was performed by calculating the area under the receiver-operating characteristic curve.

#### Results

The study sample (N = 250) had a mean age of 73 years (range, 65 to 94 [standard deviation, 5.8]). More than one half of patients (58%) experienced grade  $\geq 3$  toxicity. Risk of toxicity increased with increasing risk score (36.7% low, 62.4% medium, 70.2% high risk;  $P < .001$ ). The area under the curve of the receiver-operating characteristic curve was 0.65 (95% CI, 0.58 to 0.71), which was not statistically different from the development cohort (0.72; 95% CI, 0.68 to 0.77;  $P = .09$ ). There was no association between Karnofsky Performance Status and chemotherapy toxicity ( $P = .25$ ).

#### Conclusion

This study externally validated a chemotherapy toxicity predictive model for older adults with cancer. This predictive model should be considered when discussing the risks and benefits of chemotherapy with older adults.

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### INTRODUCTION

Approximately 60% of all cancers and 70% of cancer mortality occurs in individuals age  $\geq 65$  years, defining cancer as a disease of older adults.<sup>1</sup> Chemotherapy remains a standard component of cancer treatment. The literature is replete with studies that demonstrate that older adults experience similar chemotherapy efficacy; however, these patients are also at increased risk for chemotherapy toxicity compared with younger adults.<sup>2-4</sup> Furthermore, older adults are less likely to be offered chemotherapy because of concerns about their capacity to endure treatment.<sup>5,6</sup> To make personalized treatment decisions and to

anticipate serious adverse effects, it is important to identify those older adults who are at risk.

Conventional oncology performance status measures, such as the Karnofsky Performance Status (KPS)<sup>7</sup> or the Eastern Cooperative Oncology Group performance status,<sup>8</sup> are used in patients with cancer to predict treatment toxicity and survival, regardless of age<sup>9-11</sup>; however, it is not clear if they are valid predictors of toxicity, especially in older adults, as these tools were validated in younger adults and do not address the diversity in health status of the older cancer population. Instead, it has been widely recognized that incorporating geriatric assessment tools can identify areas of vulnerability beyond chronologic age by

providing an evaluation of functional status, cognition, nutrition, social support, psychological state, comorbidity, and medications.<sup>12,13</sup> A validated tool to assess chemotherapy toxicity risk in older adults with cancer is needed.<sup>14</sup>

To determine the utility of a geriatric assessment in anticipating chemotherapy toxicity in older adults with cancer, a prospective study of 500 older adults with cancer was previously conducted. A predictive model for chemotherapy toxicity was developed that consisted of 11 questions, including factors obtained in everyday oncology practice—patient age, number of chemotherapy drugs, dosing, and laboratory values—and factors not typically used in everyday oncology practice—geriatric assessment questions.<sup>2</sup> The model identified older adults at risk for chemotherapy toxicity, whereas the commonly used measure of performance status in oncology practice, KPS, did not. The model was internally validated using a 10-fold validation process. The aim of this study is to externally validate the predictive model in an independent cohort of older adults. This study fills a gap in the literature by providing evidence of external validation, which is needed to demonstrate generalizability of results and support translation of research into practice.

## PATIENTS AND METHODS

The chemotherapy toxicity prediction model was developed from data collected in a prospective longitudinal study of 500 patients age  $\geq 65$  years. Study methods and derivation of the toxicity model have been previously described.<sup>2</sup> A prediction model that consisted of 11 prechemotherapy variables—geriatric assessment questions, laboratory values, tumor characteristics, planned treatment, and age—was developed (Table 1). In the prediction model, risk scores were assigned to each variable. Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk). The cohort was divided into three categories on the basis of this risk score: low risk (0 to 5 points), medium risk (6 to 9 points), and high risk (10 to 19 points). The treating team was blind to the calculated risk score and category of the patient.

In this article, external validation of this predictive model is described. Between April 2008 and October 2012, 250 patients age  $\geq 65$  years were recruited at eight institutions—six participated in the development study; two new sites participated in the validation cohort—across the United States. Eligibility criteria were age  $\geq 65$  years, diagnosis of any type of solid tumor, scheduled to receive a new chemotherapy regimen, and fluent in English (because all geriatric assessment measures were not validated in other languages). Patients completed the informed consent process to participate. This study was approved by the institutional review board at each participating institution.

Study procedures for the validation cohort were identical to those used in the development cohort. Patients completed a prechemotherapy geriatric assessment that captured socio-demographics, tumor and treatment variables, laboratory test results, and geriatric assessment domains. Patients were observed through the chemotherapy course and grade 3 (hospitalization indicated), grade 4 (life-threatening), and grade 5 (treatment-related death) adverse events, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, were captured by chart review.<sup>15</sup> Two physicians reviewed toxicities and concurred that they were attributable to chemotherapy. Routine blood counts checked between chemotherapy cycles were not included as hematologic toxicity. Hematologic toxicity was only considered to be attributable to chemotherapy if blood counts were checked because the patient was symptomatic and sought medical attention or if low blood counts led to a delay or modification on the day of scheduled treatment.

**Table 1.** Prediction Model and Scoring Algorithm for Chemotherapy Toxicity

Variable	Value/Response	Score
Age of patient	$\geq 72$ years	2
	$< 72$ years	0
Cancer type	GI or GU cancer	2
	Other cancer types	0
Planned chemotherapy dose	Standard dose	2
	Dose reduced upfront	0
Planned No. of chemotherapy drugs	Polychemotherapy	2
	Monochemotherapy	0
Hemoglobin	$< 11$ g/dL (male), $< 10$ g/dL (female)	3
	$\geq 11$ g/dL (male), $\geq 10$ g/dL (female)	0
Creatinine clearance (Jelliffe, ideal weight)	$< 34$ mL/min	3
	$\geq 34$ mL/min	0
How is your hearing (with a hearing aid, if needed)?	Fair, poor, or totally deaf	2
	Excellent or good	0
No. of falls in the past 6 months	$\geq 1$	3
	None	0
Can you take your own medicine?	With some help/unable	1
	Without help	0
Does your health limit you in walking one block?	Somewhat limited/limited a lot	2
	Not limited at all	0
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

NOTE. See Hurria et al.<sup>2</sup>  
Abbreviation: GI, gastrointestinal; GU, genitourinary.

## Statistical Analyses

Baseline characteristics of patients in the development and validation cohorts were tabulated and compared by using  $\chi^2$  statistics for categorical variables and by two-sampled *t* tests for continuous variables. National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used to capture grade 3 to 5 hematologic and nonhematologic toxicity.<sup>15</sup>

A chemotherapy toxicity score was calculated for each individual patient in the validation cohort by using the 11 prechemotherapy variables that were included in the predictive model for chemotherapy toxicity derived from the development cohort. Patients were categorized as being at low, intermediate, or high risk of toxicity on the basis of specified cut points. Observed grade 3 to 5 toxicity rates between groups were compared by using a  $\chi^2$  test of proportions. This distribution of toxicity over the different risk groups was compared with the ability of KPS to predict toxicity. For this, KPS scores were divided into three groups (90 to 100, 80, and  $\leq 70$ ) and differences were likewise assessed by using a  $\chi^2$  test of proportions. We assessed the validity of the model by composing receiver-operating characteristic (ROC) curves and calculating the area under the curve (also known as C-statistic) for the prediction model and KPS scores.<sup>16</sup> Areas under the curve were compared by using the Delong nonparametric approach.<sup>17</sup>

For approximately 80% power to detect a substantial difference in model performance, the validation sample had to include a minimum of 100 patients with and 100 patients without the study endpoint.<sup>18</sup> This assumed that approximately 50% of patients had experienced at least one grade 3 to 5 toxicity, which is consistent with data from the development cohort. We thus increased the sample size of this validation cohort to 250 patients to exceed 80% power.

All analyses were performed in SAS (Version 9.2; SAS Institute, Cary, NC). All tests were two-sided, and a *P* value of  $< .05$  was considered statistically significant.

**Table 2.** Patient and Treatment Characteristics: Development and Validation Cohorts

Characteristic	Development Cohort	Validation Cohort	P
<b>Patient</b>			
Age, years			.78
65-69	175 (35)	86 (34)	
70-74	127 (25)	67 (27)	
75-79	105 (21)	60 (24)	
80-84	73 (15)	30 (12)	
≥ 85	20 (4)	7 (3)	
Mean (SD)	73 (6)	73 (6)	
Sex			.79
Female	281 (56)	138 (55)	
Male	219 (44)	112 (45)	
Cancer type			< .01
Breast	57 (11)	59 (24)	
Lung	143 (29)	64 (26)	
GI	135 (27)	68 (27)	
GYN	87 (17)	18 (7)	
GU	50 (10)	30 (12)	
Other	28 (6)	11 (4)	
Cancer stage			.02
I	23 (5)	10 (4)	
II	59 (12)	40 (16)	
III	111 (22)	68 (27)	
IV	307 (61)	129 (52)	
Other	0 (0)	3 (1)	
Education			.41
Less than high school	18 (4)	14 (6)	
High school graduate	175 (35)	82 (33)	
Associate/bachelor's degree	202 (40)	109 (44)	
Advanced degree	104 (21)	45 (18)	
Missing	1 (0)	0 (0)	
Race			.01
White	426 (85)	206 (82)	
Black	42 (8)	20 (8)	
Asian	26 (5)	10 (5)	
Other	6 (1)	14 (6)	
<b>Treatment</b>			
Standard dose			.90
No	120 (24)	61 (24)	
Yes	380 (76)	189 (76)	
No. of chemo drugs			.96
Monochemotherapy	149 (30)	74 (30)	
Polychemotherapy	351 (70)	176 (70)	
Line of chemotherapy			.86
First line	355 (71)	176 (70)	
> First line	145 (29)	74 (30)	
Growth factor use			.75
No	294 (59)	144 (58)	
Yes	206 (41)	106 (42)	

NOTE. Data are given as No. (%) unless otherwise noted.  
Abbreviations: SD, standard deviation; GI, gastrointestinal; GYN, gynecologic; GU, genitourinary.

**RESULTS**

**Patient, Tumor, and Treatment Characteristics**

Table 2 includes patient characteristics for the development and validation cohorts. Mean age for participants in the development cohort was 73.1 years (standard deviation [SD], 6.2) and 73.0 years (SD, 5.8) in the validation cohort ( $P = .78$ ); 56% of patients in the development cohort were female compared with 55% in the validation

cohort ( $P = .79$ ). Significant differences between the two cohorts were observed for cancer type and stage. In the development cohort, more patients had gynecologic cancers (17% in the development cohort  $\nu$  7% in the validation cohort), whereas in the validation cohort, breast cancer was more prevalent (11% in the development cohort  $\nu$  24% in the validation cohort;  $P < .001$ ). In addition, the development cohort included more patients with metastatic disease compared with the validation cohort ( $P = .02$ ). There were no significant differences between the two cohorts regarding the following treatment characteristics: receiving the standard dose of chemotherapy (per National Comprehensive Cancer Network guidelines), receiving polychemotherapy (a multidrug regimen), line of therapy (first line or greater than first line), and use of growth factors.

Geriatric assessment variables and laboratory values are presented in Table 3. The development cohort reported a slightly higher level of social activity (development cohort: mean, 56.2 [SD, 22.8]; validation cohort: mean, 60.3 [SD, 21.8];  $P = .02$ ). All other geriatric assessment characteristics showed no significant differences between the two cohorts (Table 3). Mean physician-rated KPS was 84.7 (SD, 11.4) and 85.8 (SD, 13.0) for the development and validation cohorts, respectively ( $P = .50$ ). Of patients in the development cohort, 56% had abnormal liver function tests compared with 26% in the validation cohort ( $P < .001$ ). There were no statistically significant differences in other laboratory variables between the two cohorts.

**Chemotherapy Toxicity**

More than one half of patients in the validation cohort (58%) experienced grade 3 to 5 toxicity compared with 53% of patients in the development cohort (Table 4). Of patients in the validation cohort, 34% experienced hematologic toxicity and 55% experienced nonhematologic toxicity. The most frequent hematologic toxicities were grade 3 absolute neutrophil count (12%) and grade 3 anemia (7%). The most frequent nonhematologic toxicities were grade 3 fatigue (20%) and grade 3 infections (10%). Of patients in both the development and validation cohorts, 2% died as a result of chemotherapy toxicity.

**Model Validation**

Risk score ranges from 0 to 19 points and was divided into three groups (low, 0 to 5 points; medium, 6 to 9 points; high, 10 to 19 points). Most patients (53%) were classified as intermediate risk, 24% of patients were classified as low risk, and 23% were classified as high risk. In the development cohort, risk of toxicity increased with increasing risk score (Fig 1). In the validation cohort, the increase in toxicity risk with increasing risk score was slightly attenuated but statistically significant (36.7% in the low-risk group, 62.4% in the medium-risk group, and 70.2% in the high-risk group;  $P < .001$ ; Fig 1). Area under the ROC curve for the predictive model in the validation cohort (0.65 [95% CI, 0.58 to 0.71]) was not statistically different from the development cohort (0.72 [95% CI, 0.68 to 0.77];  $P = .09$ ; Appendix Fig A1, online only).<sup>2</sup>

Physician-rated KPS was not predictive of chemotherapy toxicity in either the development cohort ( $P = .19$ ) or the validation cohort ( $P = .25$ ). Area under the ROC curve for KPS was 0.54 (95% CI,

**Table 3.** Geriatric Assessment and Laboratory Values: Development and Validation Cohorts

Variable	Development Cohort	Validation Cohort	P
<b>Functional status</b>			
MOS-ADL, mean (SD)	68.5 (26)	64.9 (27)	.10
IADL, mean (SD)	12.9 (2)	13 (2)	.67
PKPS, mean (SD)	85.6 (14)	84.7 (14)	.50
MDKPS, mean (SD)	84.7 (11)	85.8 (13)	.50
<b>Falls, No. (%)</b>			
0	407 (82)	196 (78)	.32
≥ 1	91 (18)	54 (22)	
Mean (SD)	0.3 (0.8)	0.4 (2.3)	
<b>Nutritional status</b>			
Body mass index, mean (SD)	26.2 (5)	26.7 (5)	.14
<b>Percent unintentional weight loss in last 6 months, No. (%)</b>			
≤ 6%	328 (66)	178 (72)	
> 6%	170 (34)	70 (28)	
Mean (SD)	4.7 (6)	4.0 (6)	.13
<b>No. of comorbid conditions, No. (%)</b>			
0	48 (10)	16 (6)	.08
1	110 (22)	40 (16)	
2	121 (24)	67 (27)	
≥ 3	221 (44)	126 (51)	
<b>Cognition, No. (%)</b>			
Blessed Orientation–Memory Concentration test score ≥ 11	29 (5.8)	16 (6.5)	.74
<b>Psychological state, mean (SD)</b>			
Hospital anxiety and depression scale	8.3 (6)	8.2 (6)	.84
<b>Social support, mean (SD)</b>			
MOS-social activity survey	56.2 (23)	60.3 (22)	.02
MOS-social support survey	84.9 (21)	84.2 (21)	.79
<b>Laboratory value</b>			
WBC (k/μL), mean (SD)	7.9 (4)	7.5 (3)	.08
Albumin (g/dL), mean (SD)	3.8 (0.5)	3.9 (0.5)	.87
Hemoglobin (<11 g/dL [male], < 10 g/dL [female]), No. (%)	62 (12)	33 (13)	.83
Creatinine clearance (Jelliffe, ideal weight) < 34 mL/min, No. (%)	44 (9)	15 (6)	.14
Abnormal liver function tests, No. (%)	267 (56)	66 (26)	< .01

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; MDKPS, Karnofsky physician-rated performance status; MOS, Medical Outcomes Study; PKPS, Karnofsky self-reported performance status; SD, standard deviation; WBC, white blood cell count.

0.48 to 0.61) for the validation cohort compared with 0.53 (95% CI, 0.48 to 0.57) for the development cohort.<sup>2</sup> The C-statistic for KPS was 0.54 (95% CI, 0.48 to 0.61), which is statistically significantly smaller than the C-statistic for the predictive model ( $P = .02$ ).

## DISCUSSION

This study confirms that the risk of chemotherapy toxicity is high in older adults with cancer, with more than one half of all patients experiencing grade 3 to 5 toxicity. In both the development and validation cohorts, this model had a greater ability to discriminate toxicity risk in older adults than did the present standard oncologic assessment of performance status, the KPS score. Weighing the risks and benefits of chemotherapy in older adults is challenging as there are few older adults included in randomized clinical trials to inform this risk. Furthermore, those older adults

who are included in clinical trials are physically fit and not representative of the general older population.<sup>19,20</sup> Hence, this study fills a gap in knowledge by developing a validated tool to assess chemotherapy toxicity risk among older adults who receive chemotherapy in everyday practice to aid in clinical decision making.

The high risk of chemotherapy toxicity demonstrated in this study is consistent with previous studies<sup>2-4</sup> and can be explained by several factors. First, physiologic reserves in all organ systems decrease with age, which may influence the capacity to endure treatment. Aging is associated with decreased bone marrow reserve and an increased risk of chemotherapy-related myelosuppression.<sup>21,22</sup> In addition, clearance of chemotherapy can be influenced by impaired renal function, which is highly prevalent in older adults.<sup>23</sup> Furthermore, practical issues may influence adherence to supportive care. For example, patients with a poor support system may be less able to seek medical attention when they experience adverse effects. Patients with impaired hearing or cognitive impairment may not have understood how to take their supportive care medications or when to seek attention if they develop a treatment-related adverse effect.

Therefore, identifying areas of vulnerability before the start of treatment is essential. A geriatric assessment can be used for this purpose<sup>13,24</sup> and has been shown to be feasible in oncologic practices and clinical trials.<sup>25</sup> In addition, several studies have suggested that findings from the geriatric assessment influence treatment decisions in 20% to 50% of patients.<sup>26</sup> The International Society for Geriatric Oncology and the National Comprehensive Cancer Network therefore advises performing at least a screening geriatric assessment in all older adults with cancer.<sup>13,24</sup>

Other chemotherapy risk scores have been developed for older adults with cancer. For example, the Chemotherapy Risk Assessment Scale for High-Age Patients was also developed in a population of older adults with cancer and predicts grade 4 hematologic or grade 3 to 4 nonhematologic toxicity on the basis of clinical and geriatric assessment variables.<sup>3</sup> This model was developed ( $N = 331$ ; ROC, 0.65) and validated ( $N = 187$ ; ROC, 0.64) in older adults with cancer. Variables predicting grade 4 hematologic toxicity were diastolic blood pressure, instrumental activity of daily living score, lactate dehydrogenase, and estimated toxicity of the chemotherapy regimen on the basis of the MAX2 score. Variables predicting grade 3 and 4 nonhematologic toxicity were Eastern Cooperative Oncology Group performance status, mini-mental health status, mini-nutritional assessment, and the MAX2 score. A main difference between these two predictive models is that we sought to identify specific questions that were predictive of chemotherapy toxicity risk, rather than full measures, to increase the ease of calculation and scoring.

This study has some important limitations. Although the model was able to discriminate toxicity risk better than KPS, it was less able to discriminate between moderate and high-risk toxicity than we expected on the basis of the development study. Therefore, the tool may be best used in distinguishing patients at a lower than average risk versus those who are at a higher than average risk for chemotherapy toxicity (Appendix Figs A2 and A3, online only, Appendix Tables A1 and A2, online only). In addition, the area under the ROC was slightly attenuated in the current study;

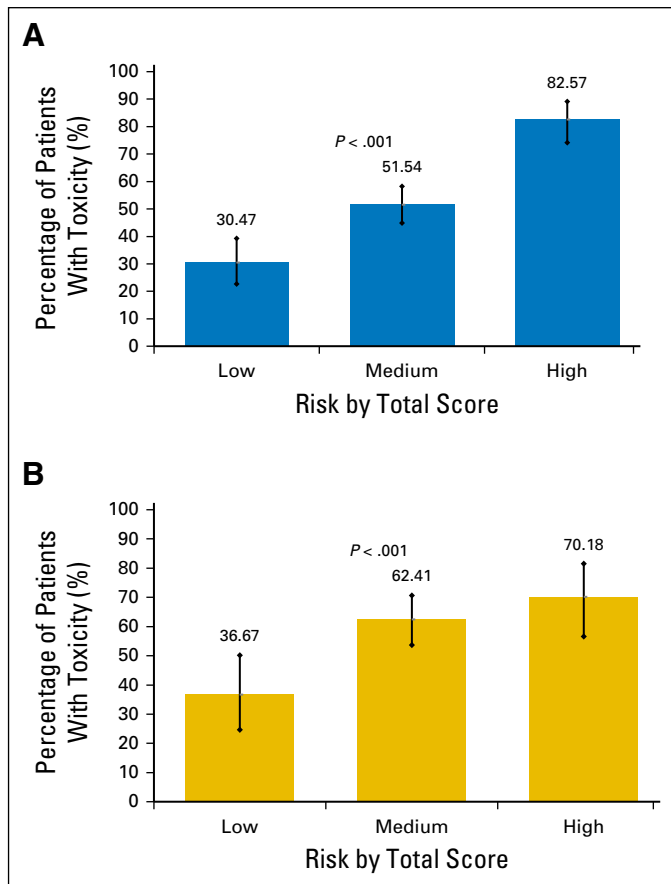


**Table 4.** Toxicity in Development Cohort and Validation Cohorts

Toxicity Type	Development Cohort				Validation Cohort			
	Grade 3 to 5	Grade 3	Grade 4	Grade 5	Grade 3 to 5	Grade 3	Grade 4	Grade 5
Hematologic and Nonhematologic	265 (53)	197 (39)	58 (12)	10 (2)	145 (58)	132 (53)	38 (15)	6 (2)
Hematologic	131 (26)	90 (18)	39 (8)	2 (0)	86 (34)	58 (23)	26 (10)	2 (1)
ANC	57 (11)	40 (8)	17 (3)	0 (0)	51 (20)	31 (12)	20 (8)	0 (0)
WBC	49 (10)	41 (8)	8 (2)	0 (0)	4 (2)	4 (2)	0 (0)	0 (0)
Hemoglobin	48 (10)	45 (9)	3 (1)	0 (0)	20 (8)	18 (7)	2 (1)	0 (0)
Platelets	25 (5)	14 (3)	11 (2)	0 (0)	6 (2)	4 (2)	2 (1)	0 (0)
Infection with abnormal ANC	10 (2)	7 (1)	1 (0)	2 (0)	7 (3)	6 (2)	1 (0)	1 (0)
Nonhematologic	217 (43)	184 (37)	25 (5)	8 (2)	132 (55)	110 (44)	17 (7)	5 (2)
Fatigue	81 (16)	79 (16)	2 (0)	0 (0)	53 (21)	49 (20)	2 (1)	0 (0)
Infection with normal ANC	48 (10)	40 (8)	5 (1)	3 (1)	27 (11)	24 (10)	2 (1)	1 (0)
Dehydration	43 (9)	41 (8)	2 (0)	0 (0)	12 (5)	11 (4)	1 (0)	0 (0)
Thrombosis/embolism	22 (4)	17 (3)	4 (1)	1 (0)	6 (2)	2 (1)	3 (2)	0 (0)
Hyponatremia	22 (4)	22 (4)	0 (0)	0 (0)	5 (2)	5 (2)	0 (0)	0 (0)
Diarrhea	22 (4)	19 (4)	3 (1)	0 (0)	9 (4)	7 (3)	2 (1)	0 (0)
Hypokalemia	15 (3)	15 (3)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Dyspnea	13 (3)	5 (1)	7 (0)	1 (0)	4 (2)	3 (1)	1 (0)	0 (0)
Syncope	13 (3)	13 (3)	0 (0)	0 (0)	4 (2)	4 (2)	0 (0)	0 (0)
Neuropathy	13 (3)	13 (3)	0 (0)	0 (0)	9 (4)	9 (4)	0 (0)	0 (0)
Nausea	12 (2)	12 (2)	0 (0)	0 (0)	11 (4)	10 (4)	1 (0)	0 (0)

NOTE. Data are given as No. (%).  
Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell count.

however, this was not statistically different. A decrease of 0.07 points in the area under the ROC from development to validation



**Fig 1.** Risk strata versus toxicity percentage for the (A) development and (B) validation cohorts.

has been described in the statistical literature as within an expected range.<sup>27</sup> There were some differences in patient characteristics between the two cohorts that may explain part of the decrease in the area under the ROC. Furthermore, we only predicted grade 3 to 5 toxicity, but grade 2 toxicity may be equally important in this older population. Patients included in this cohort had solid tumors and did not receive biologics or high-dose chemotherapy; therefore, these results primarily apply to patients with solid tumors who receive chemotherapy. Finally, to use the model in other populations, such as in countries outside of the United States or in patients with different cancer types, additional external validation studies must be performed.

This study has some major strengths as well. This study fills a gap in knowledge by providing evidence of external validation of a prediction model that is needed to demonstrate generalizability of results and support translation of research into practice. Furthermore, this model was validated in a prospective cohort of patients seen in daily practice at eight institutions across the United States, which increases the generalizability of the data. The prediction model is easy to use, thus increasing the feasibility of incorporation in daily practice, and the model can provide patients and oncologists with additional information to be included in the decision making process. Discussing the risks of treatment is essential to enable patients to make a well-informed decision regarding treatment. Moreover, it may enable oncologists to anticipate toxicity in patients with a high risk and to take preventive measures to try to decrease this risk.

There are a number of future directions for this research. First, toxicity may depend on the specific treatment. Hence, there are several new ongoing, multicenter studies evaluating the efficacy of this tool in predicting toxicity among patients with specific tumor types and treatment regimens. To decrease the impact of chemotherapy toxicity in older adults with cancer, future studies should assess how the trajectory of toxicity can be changed. In

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

## AUTHOR CONTRIBUTIONS

**Conception and design:** Arti Hurria

**Financial support:** Arti Hurria

**Administrative support:** Arti Hurria

**Provision of study materials or patients:** Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Andrew Chapman, William P. Tew

**Collection and assembly of data:** Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Andrew Chapman, Vani Katheria, Caroline Doan, Laura Zavala, Abraham Levi, Chie Akiba, William P. Tew

**Data analysis and interpretation:** Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Tao Feng, David Smith, Can-Lan Sun, Nienke De Glas, Harvey Jay Cohen, Vani Katheria, William P. Tew

**Manuscript writing:** All authors

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particular, studies are underway to determine whether geriatric assessment targeted interventions can decrease chemotherapy toxicity and improve functional outcomes and quality of life in older adults with cancer ([ClinicalTrials.gov: #NCT02054741](https://clinicaltrials.gov/ct2/show/study/NCT02054741)). Furthermore, studies are needed to understand how geriatric assessment and toxicity prediction results should impact treatment regimen, dosing, and supportive care. Impact of treatment toxicity risk on doctor and patient treatment preferences and decisions must be evaluated. Finally, the role of this tool in non-chemotherapy regimens, that is, targeted therapy, and among patients with hematologic malignancies is an area of needed investigation.

In conclusion, this external validation study confirms that it is possible to predict chemotherapy toxicity in older adults with cancer by using a prediction model that consists of 11 questions, including five geriatric assessment questions and six items captured in routine daily practice—tumor type, treatment, and laboratory values. These data should be considered when the risks and benefits of chemotherapy are discussed in older adults. Future studies should assess possible interventions that can decrease the risk of toxicity in older adults with cancer.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer**

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**Arti Hurria**

**Consulting or Advisory Role:** GTx, Seattle Genetics, Boehringer Ingelheim, On Q Health, Sanofi

**Research Funding:** GlaxoSmithKline (Inst), Celgene (Inst), Novartis (Inst)

**Supriya Mohile**

**Consulting or Advisory Role:** Seattle Genetics

**Ajeet Gajra**

**Consulting or Advisory Role:** Celgene, Bayer AG

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**Heidi Klepin**

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**Hyman Muss**

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No relationship to disclose

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No relationship to disclose

**Harvey Jay Cohen**

No relationship to disclose

**Vani Katheria**

No relationship to disclose

**Caroline Doan**

No relationship to disclose

**Laura Zavala**

No relationship to disclose

**Abrahm Levi**

No relationship to disclose

**Chie Akiba**

No relationship to disclose

**William P. Tew**

No relationship to disclose

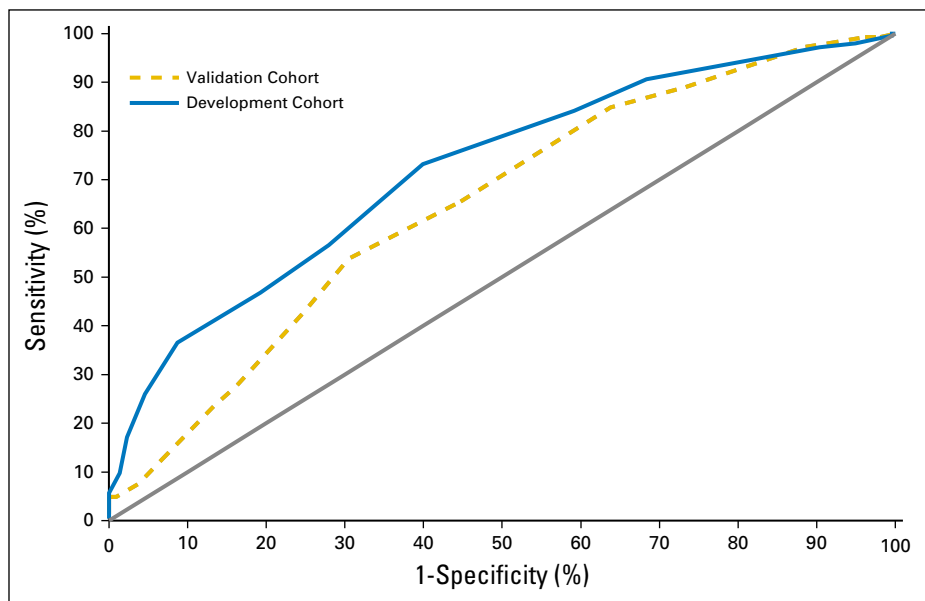
**Appendix**

*The following institutions participated in the development cohort:*

- City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA
- University of Rochester Medical Center, Rochester, NY
- Upstate Medical University and Syracuse VA Medical Center, Syracuse, NY
- Wake Forest University, Winston Salem, NC
- Yale University, New Haven, CT
- Case Western Reserve University, Cleveland, OH
- Memorial Sloan Kettering Cancer Center, New York, NY

*The following institutions participated in the validation cohort:*

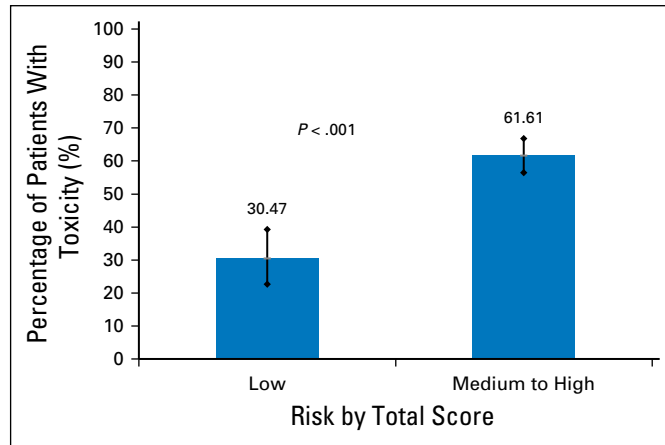
- City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA
- University of Rochester Medical Center, Rochester, NY
- Upstate Medical University and Syracuse VA Medical Center, Syracuse, NY
- Wake Forest University, Winston Salem, NC
- University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
- Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
- Memorial Sloan Kettering Cancer Center, New York, NY
- Case Western Reserve University, Cleveland, OH



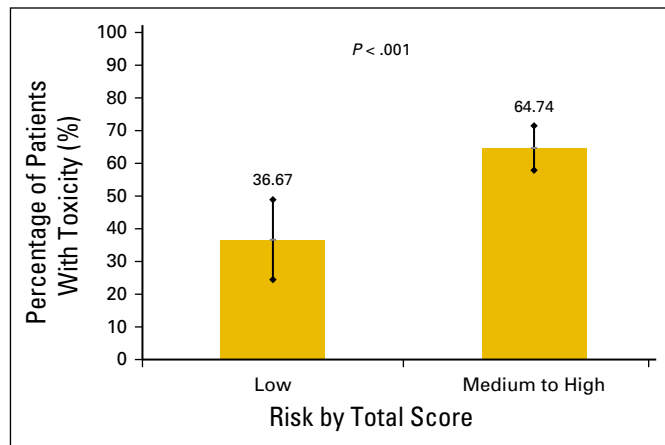
**Fig A1.** Receiver-operating characteristic curves for development and validation cohorts.



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**Fig A2.** Low risk versus combining medium and high-risk scores for the development cohort.



**Fig A3.** Low risk versus combining medium and high-risk scores for the validation cohort.

**Table A1.** Summary Statistics for Development Cohort

Risk Strata	Mean	Median	SD	Range
Low	3.9	4	1.0	0-5
High	8.7	8	2.5	6-19

Abbreviation: SD, standard deviation.

**Table A2.** Summary Statistics for Validation Cohort

Risk Strata	Mean	Median	SD	Range
Low	3.7	4	1.3	0-5
High	8.7	8	2.6	6-18

Abbreviation: SD, standard deviation.