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Original Article

External Validity of Two Scores for Predicting the Risk of Chemotherapy Toxicity Among Older Patients With Solid Tumors: Results From the ELCAPA Prospective Cohort

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Abstract

Background: Severe chemotherapy-related toxicities are frequent among older patients. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) and the Cancer and Aging Research Group Study (CARG) score were both developed to predict these events.

Patients and Methods: The objective of this study was to evaluate the scores' predictive performance in a prospective cohort, which included patients aged 70 years and older referred for a geriatric assessment prior to chemotherapy for a solid tumor. The main endpoints were grades 3/4/5 toxicities for the CARG score and grades 4/5 hematologic toxicities and grades 3/4/5 non-hematologic toxicities for the CRASH score.

Results: A total of 248 patients were included, of which 150 (61%) and 126 (51%) experienced at least one severe adverse event as defined respectively in CARG and CRASH studies. The incidence of adverse events was not significantly greater in the intermediate and high-risk CARG groups than in the low-risk group (odds ratio (OR) [95% CI] = 0.3 [0.1-1.4] (P = .1) and 0.4 [0.1-1.7], respectively). The area under curve (AUC) was 0.55. Similarly, the incidence of severe toxicities was no greater in the intermediate-low, intermediate-high, and high-risk CRASH groups than in the low-risk CRASH group (OR [95%CI] = 1 [0.3-3.6], 1 [0.3-3.4], and 1.5 [0.3-8.1], respectively). The AUC was 0.52. The type of cancer, performance status, comorbidities, body mass index, and MAX2 index were independently associated with grades 3/4/5 toxicities.

Conclusion: In an external cohort of older patients referred for a pretherapeutic GA, the CARG and CRASH scores were poor predictors of the risk of chemotherapy severe toxicities.

Key words: antineoplastic agents; toxicity; neoplasms; aged; geriatric assessment.

Implications for Practice

Severe chemotherapy-related toxicities are frequent among older adults being treated for solid tumors. The CARG and CRASH scores did not predict chemotherapy toxicity for aged patients in the French Elderly Cancer Patients (ELCAPA) prospective cohort. Thus, these scores should be used with caution in clinical practice, especially for a no-treatment decision. In this cohort, performance status, cancer type, the MAX2 index, severe comorbidities, and body mass index were independently associated with the occurrence of severe adverse events. These parameters should be used to help choosing chemotherapy regimens and doses for elderly patients.

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Introduction

The incidence of cancer among older adults is increasing; in Europe, 60% of cancers are diagnosed after the age of 65 years.[1] The heterogeneity of this population means that oncologists have to adapt their practice.[2] To this end, it has been suggested that the results of a geriatric assessment (GA) can identify vulnerabilities among older adults patients and can guide the choice of an appropriate therapeutic strategy (especially chemotherapy) for individual patients.[3,4]

Several studies have reported that the incidence of severe chemotherapy toxicity is higher in older patients than in younger patients.[5,6] Moreover, the lack of predictors of severe chemotherapy-associated adverse events might prompt oncologists to be cautious and thus undertreat their patients.[7] Hence, it is essential to estimate the risk of chemotherapy toxicity and then adapt the treatment strategy accordingly.

Two specific scores have been developed to predict the risk of severe chemotherapy toxicity in older patients. In a US study of patients aged ≥65 (led by the Cancer and Aging Research Group (CARG)), Hurria et al developed a score that includes age, the type of cancer, the baseline chemotherapy dosing, the number of chemotherapy drugs (monochemotherapy vs. polychemotherapy), the hemoglobin level, the creatinine clearance rate, and several patient-reported variables (hearing impairment, at least one fall in the previous 6 months, inability to take medications unaided, difficulty in walking a block unaided, and a decrease in social activity due to health or emotional problems.[5] The score's internal predictive performance (measured as the area under the curve (AUC)) was 0.72.[5] On the same lines, Extermann et al developed the Chemotherapy Risk Assessment Scale for High-age patients (CRASH) in a cohort of patients aged ≥70; severe toxicity was defined as a grade 4 hematologic adverse event (graded according to the Common Terminology Criteria for Adverse Events (CTCAE)) or a grade 3 or 4 non-hematologic adverse event.[8] The hematologic, non-hematologic, and combined scores comprised the following variables: diastolic blood pressure, the instrumental activities of daily living (IADL) score, the serum lactate dehydrogenase level, Eastern Cooperative Oncology Group performance status (ECOG PS), the Mini Mental State Examination (MMSE) score, the Mini Nutritional Assessment (MNA) score, and the MAX2 index of severe toxicity (based on the nature of the chemotherapy and the adverse events reported in clinical trials).[9] The CRASH score's internal predictive performance (AUC) for hematologic and non-hematologic adverse events was 0.65.

Several cohort studies have assessed the external validity of the CARG score,[10-16] and 2 of these studies also assessed the CRASH score.[17,18] Overall, the results were contradictory, and the AUC varied markedly (from 0.52[13] to 0.78[12]). Thus, it is still not clear whether the CARG and CRASH scores can reliably predict severe chemotherapy toxicity in older cancer patients.

The primary objective of the present study was to evaluate the CARG and CRASH scores' ability to predict the risk of severe chemotherapy toxicity in older patients with cancer, using data from a prospective cohort. The secondary objective was to identify independent factors associated with severe chemotherapy toxicity.

Patients and Methods

Design and Patients

The Elderly Cancer Patients (ELCAPA) study is a French, prospective, multicenter, open cohort study of patients aged ≥70 with a solid or hematological cancer and who are referred for a GA prior to treatment selection; the study has been described in detail elsewhere.[19] All participants gave their oral, informed non-opposition prior to inclusion. The protocol was approved by the appropriate institutional review board (*CPP Ile-de-France I*, Paris, France; approval code 12.00005.013216-MS06). The study was registered at ClinicalTrials.gov (NCT02884375).

For the purposes of the present analysis, we included all patients aged 70 or over and referred for a GA (from July 2010 to March 2017) before chemotherapy for a solid tumor (regardless of the stage) at Henri Mondor teaching hospital (Créteil, France). The non-inclusion criteria were hematologic cancers, absence of chemotherapy, chemotherapy administered in another center, chemoradiotherapy, loss to follow up or death from a cause other than chemotherapy prior to the second course of chemotherapy, and GA performed after chemotherapy initiation.

Data Collection

Baseline data for the following variables were collected prospectively: demographic characteristics (age and sex), clinical characteristics (ECOG PS, cancer site and stage, body mass index (BMI), and systolic and diastolic blood pressure values); standard blood test results (including serum hemoglobin, creatinine, and lactate dehydrogenase levels), geriatric parameters (including the IADL,[20] MMSE,[21] MNA,[22] Cumulative Illness Rating Scale-Geriatric (CIRS-G)[23] scores, and self-reported hearing impairments, numbers of falls in the previous 6 months, and the ability to walk outside unaided). For each chemotherapy regimen, the MAX2 index was determined retrospectively (as described by Extermann et al) as the average of the highest frequency of grade 4 hematologic adverse events and the highest frequency of grades 3/4 non-hematologic adverse events in published clinical trials.[9] MAX2 index values between 0 and 0.44, between 0.45 and 0.57, and over 0.57 add, respectively 0, 1, and 2 points to the CRASH score.[8] For univariate and multivariate analysis for prediction of severe toxicities, continuous variables as BMI, ECOG PS, or geriatric scores were converted to categorical variables based on clinical criteria or published thresholds.

Calculation of the Chemotherapy Toxicity Scores

The CRASH[8] and CARG[5] scores were calculated retrospectively for each patient. For the CARG score, we lacked data on the "difficulty in walking a block" and "decreased social activity" items and so replaced them as follows: 2 points were awarded if the patient stated that he/she was unable to walk outside unaided, and one point was awarded if the patient had answered "worse" to the question "In comparison with other people of the same age, how does the patient consider his/her health status?" from the MNA.[22] Patients with missing data were only included in the score validation analysis if the value of the data item did not change their risk group assignment.

Follow-up

Data on chemotherapy administration and safety were collected retrospectively from the patients' medical records; they included the chemotherapy regimen, the MAX2 index,[9] the baseline chemotherapy dose (standard or reduced), the dates of the first and last courses of chemotherapy, and adverse events. Adverse events were classified according to version 4.03 of the CTCAE,[24] and all grade ≥3 hematologic and non-hematologic adverse events were recorded. Any chemotherapy dose reductions, unplanned hospital admissions, or early discontinuation of chemotherapy were also retrospectively recorded. The follow-up period ran from the start of the first course of chemotherapy to 6 months after the end of the last course or the start of a new chemotherapy regimen initiation.

The study's primary endpoint was severe toxicity, defined as a grade ≥3 adverse event for CARG score, a grade ≥4 hematologic adverse event, and/or a grade ≥3 non-hematologic adverse event for the CRASH score.

Statistical Analysis

The oncologic, geriatric, and laboratory data (particularly the CARG and CRASH score items) were described as the frequency (percentage) for categorical variables and the median [interquartile range] for continuous variables. For the CARG score, patients with grade ≥3 adverse events were compared to patients without. Categorical variables were compared in a chi-squared test, and continuous variables were compared in Student's *t*-test. Each of the CRASH and CARG score items was tested separately. The strength of associations of the CARG score (as a continuous variable and in classes) with grade ≥3 adverse events was assessed by calculating the odds ratio (OR) [95% CI] in a logistic regression model. Calibration and discriminative performance were assessed using the Hosmer-Lemeshow test and the AUC. A similar method was used to evaluate the association between the CRASH score and hematologic, non-hematologic, and combined toxicities.

Factors associated with grade 3 or 4 adverse events with $pP < .20$ were fed into a multivariate analysis. Step-by-step manual analysis was performed to identify confounding factors. We tested for interactions between the type cancer, metastatic status, the MAX2 index, polychemotherapy, and ECOG-PS. The final logistic regression model was the most parsimonious model that included all the variables with $P < .05$.

The threshold for statistical significance was set to $P < .05$. All tests were 2-tailed, and all statistical analyses were performed with Stata software (version 15, StataCorp, College Station, TX, USA).

Results

Characteristics of the Study Population

Between July 2010 and March 2017, 492 patients aged ≥70 were referred for a GA before chemotherapy initiation, and 248 were included in the present analysis (Fig. 1 and Table 1). The median (range) age was 79 (70-91). Almost half of the patients had been treated for a gastrointestinal tract cancer (49%), with 68 (27%) treated for a genitourinary tract cancer, and 36 (15%) treated for breast cancer. One hundred and fifty-five patients (63%) had metastatic cancer on inclusion. The results of the GA are summarized in Table 2.

Chemotherapy Toxicity

One hundred and fifty patients (61%) presented at least one grade 3 adverse event (Table 3). Ninety-one patients (37%) had a chemotherapy dose reduction during their treatment. Ninety-eight patients (40%) were hospitalized at least once, and 69 (28%) of these hospital admissions were due to chemotherapy toxicity. Chemotherapy was discontinued early because of toxicity in 37 (15%) patients. In total, 9 patients (4%) died as a result of chemotherapy toxicity.

The Predictive Value of the CRASH and CARG Scores

Risk groups were determined according to the CARG score for 231 patients. There were 11 patients in the low-risk group (5%), 104 in the intermediate-risk group (45%), and 116 (50%) in the high-risk group; in these groups, respectively 9 (82%), 58 (56%), and 71 (61%) patients experienced at least one grade ≥3 adverse event. The incidence of severe adverse events was no greater in the intermediate-risk group or the high-risk group than in the low-risk group (OR [95%CI]: 0.3 [0.1-1.4] ($P = .12$) and 0.4 [0.1-1.7] ($P = .19$), respectively). The AUC was 0.55.

Risk groups according to the combined CRASH score classification were determined for 165 patients. There were 11 patients in the low-risk group (7%), 64 in the medium-low-risk group (39%), 79 in the medium-high risk group (48%), and 11 in the high-risk group (7%), and there were respectively 6 (55%), 35 (55%), 42 (53%), and 7 (64%) patients with grade ≥4 hematologic adverse events and/or grade ≥3 non-hematologic adverse events in each group. The incidence of severe adverse events was similar in medium-low-risk group vs. the low-risk group (OR [95%CI]: 1 [0.3-3.6] ($P = .99$)), the medium-high-risk group vs. the low-risk group (1 [0.3-3.4] ($P = .93$)), and the high-risk vs. the low-risk group (1.5 [0.3-8.1] ($P = .67$)). The AUC was 0.52. Separate analyses of the CRASH scores for hematologic adverse events and non-hematological adverse events gave similar results.

Risk Factors Associated with Severe Adverse Events

In a univariate analysis, the factors associated with grade ≥3 adverse events were age, type of cancer, metastatic status, ECOG-PS, MAX2 index, BMI, serum albumin, the MNA score, the total Cumulative Illness Rating Scale-Geriatric (CIRS-G) score, the number of CIRS-G grade 3 comorbidities, and the presence of a physician-diagnosed depressive syndrome (Tables 1 and 2).

In a multivariate analysis with colorectal cancer as the reference (Table 4), non-colorectal gastrointestinal cancer, genitourinary cancer, breast cancer, and other types of cancer were independently associated with chemotherapy toxicity. Patients with an ECOG-PS of 1 or 2 were at a greater risk of severe adverse events than patients with ECOG-PS 0. The presence of at least one severe (grade 3 or 4) CIRS-G comorbidity was associated with a greater risk of severe adverse events. Patients who were overweight (BMI = 25-30 kg/m²) or obese (BMI > 30 kg/m²) had a lower risk of severe adverse events. A MAX2 index of 1 (but not 2) was associated with severe adverse events. The multivariate model's AUC was 0.78.

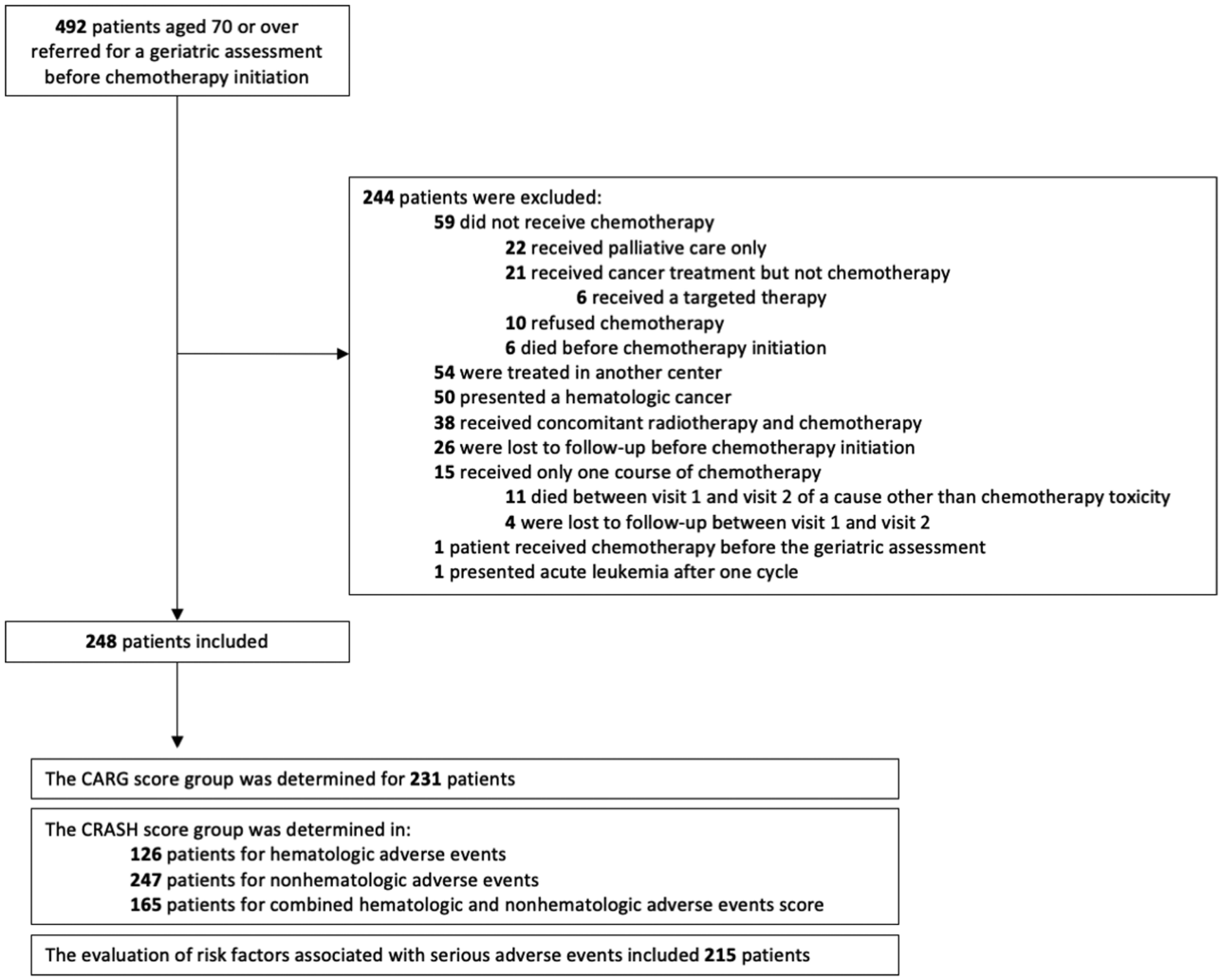

Figure 1. Study flow chart. Abbreviations: CGA, comprehensive geriatric assessment; CARG, Cancer and Aging Research Group Study; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients.

Discussion

In the ELCAPA cohort, 61% of the patients undergoing chemotherapy for solid tumors experienced at least one grade ≥3 adverse event. The CARG and CRASH scores were not predictive of severe adverse events in this cohort and had low AUC values (0.55 and 0.52, respectively). The independent predictors of severe adverse events in our study population were primary gastrointestinal, genitourinary and breast cancers, an intermediate ECOG-PS, the presence of severe comorbidities (according to the CIRS-G), and the MAX2 index, while a high BMI was a protective factor.

Several external evaluations of the CARG score have been published, and the populations and the findings differed markedly from one study to another.[10-16] Most of the patients were younger than in the ELCAPA cohort, and the median age was below 75.[10-13,15] Two of the studies looked at a single type of cancer only (lung cancer and prostate cancer, respectively),[11,14] and only 3 studies included more than 200 patients.[10,15,16] When considering the 4 studies in which predictive performance was estimated, 2 reported an AUC above 0.7 (0.72 and 0.78, respectively),[10,12] and 2 reported an AUC below 0.6 (0.52 and 0.54, respectively).[15,16] Only 2 studies (with respectively 120 and 106 patients) evaluated both the CARG and CRASH scores: the AUCs were 0.68 and 0.77 for the CARG score, and 0.65 and 0.77 for the CRASH score.[17,18] To the best of our knowledge, the ELCAPA cohort is the largest in which the CARG and CRASH scores have been simultaneously evaluated. The median patient age in the ELCAPA cohort (79) is higher than those of the aforementioned studies. Combined with the higher proportion of patients with gastrointestinal or genito-urinary cancer, and the smaller proportion of patients with PS 0-1 in this study, this could contribute to the lack of predictivity of these scores in the current population. Patients included in the ELCAPA cohort are referred for a GA before chemotherapy and are not representative of all older patients with cancer undergoing chemotherapy. Interestingly, a new predictive score for chemotherapy toxicities has been published by Kim et al after the end of data collection,[25] thus it has not been tested in the present study.

Cancer type, functional status, and comorbidities have already been reported as predictive factors for chemotherapy toxicity in older adults with cancer.[26-29] In our cohort, an ECOG-PS of 3 or 4 was not predictive of severe toxicity. However, this might be due to (i) the small number of patients with a high PS in our study population, and (ii) anticipation of a risk of toxicity by the patients' oncologists (only 37% of

Table 1. General characteristics of the study population and associations with grade ≥3 adverse events.

	Total (*n* = 248)	Grade 3, 4, or 5 adverse events		*P*[a]
		No (*n* = 99)	Yes (*n* = 149)	
Age (years), median (IQR)	79 [76-82] (*0*)	80 [76-83]	78 [75-82]	**.03**
Sex (male), *n* (%)	138 (56) (*0*)	51 (52)	87 (58)	.29
Primary cancer, *n* (%)	(*0*)			**.002**
Colorectal	53 (21)	32 (32)	21 (14)	
Gastrointestinal other than colorectal	69 (28)	25 (25)	44 (30)	
Breast	37 (15)	18 (18)	19 (13)	
Genitourinary tract	68 (27)	18 (18)	50 (34)	
Other	21 (9)	6 (6)	15 (10)	
Metastases, *n* (%)	155 (63) (*0*)	55 (56)	100 (68)	**.05**
ECOG PS, *n* (%)	(*2*)			**.004**
0	59 (24)	36 (36)	23 (16)	
1	92 (37)	29 (29)	63 (43)	
2	65 (26)	21 (21)	44 (30)	
3	27 (11)	12 (12)	15 (10)	
4	3 (1)	1 (1)	2 (1,4)	
Polychemotherapy, *n* (%)	144 (58) (*0*)	55 (56)	89 (60)	.51
Primary chemotherapy dose reduction, *n* (%)	59 (24)	25 (25)	34 (23)	.66
MAX2 index, *n* (%)	(*0*)			**.03**
0	87 (35)	42 (42)	45 (30)	
1	121 (49)	38 (38)	83 (56)	
2	40 (16)	19 (19)	21 (14)	
Diastolic blood pressure, median (IQR)	75 [67-82] (*34*)	75 [70-82]	72 [65-82]	.11
Hemoglobin (g/dL), median (IQR)	11.9 [11-13] (*3*)	12 [11-13]	12 [11-13]	.98
Neutrophil count (/mm^3), median (IQR]	4571 [3337-6400] (*78*)	4489 [3410-6400]	4700 [3240-6300]	.67
Lymphocyte count (/mm^3), median (IQR)	1557 [1101-2037] (*84*)	1650 [1235-2220]	1443 [1100-2000]	.86
Albumin	35 [30-39.1] (*30*)	36.5 [32-40]	33.6 [29.1-38]	.01
Creatinine clearance rate (mL/min), median (IQR) (*10*)				
Calculated with the Cockroft equation	60 [49-76]	62 [48-76]	60 [49-75]	.47
Calculated with the MDRD equation	79 [61-97]	80 [61-96]	77 [61-97]	.95
Calculated with Jelliffe's equation	60 [45-71]	61 [44-70]	60 [46-71]	.79
LDH (IU/L), median (IQR)	204 [169-322] (*106*)	217 [169-332]	203 [168-316]	.91
CRP (mg/L), median (IQR)	15 [5-41] (*64*)	10 [4-26]	19 [6-59]	.10
CRP/albumin ratio, median (IQR) (*72*)	0.4 [0.1-1.4]	0.2 [0.1-0.6]	0.5 [0.2-2]	.06

The MAX2 score is an estimate of the frequency of severe adverse events for a given chemotherapy regimen.
[a]In a Pearson chi-squared test or Student's t test, as appropriate; significant results ($P < .05$) are given in bold; number of missing data for each value is presented in brackets and in italic.
Abbreviations: CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LDH, lactate dehydrogenase.

the PS 3 or 4 patients received polychemotherapy, vs. 61% of PS 0-2 patients). In the same way, MAX2 index of 2 was not associated with chemotherapy toxicities, but only 16% of patients received a high-risk chemotherapy regimen based on MAX2 index calculation. Interestingly, the presence of severe comorbidities was not an independent predictive factor of toxicity in both CARG and CRASH studies,[5,8] but was also associated with chemotherapy toxicities in other studies.[27,30]

Overweight and obesity have also been reported as factors that protect against chemotherapy toxicity in older patients.[31] This might be due to under-exposure to chemotherapy in patients with a body surface area of more than 2 m^2 (the limit for chemotherapy dose calculation) or in patients with a different distribution between fat and lean body masses,[32] or a protective effect of obesity among older patients with chronic disease (already described as the "obesity paradox" in cardiovascular diseases[33] and in oncology[34]).

The present study had several limitations. Adverse events were recorded retrospectively, which could have led to classification bias. However, the frequencies of severe adverse events were similar to those in the literature. The proportion of missing data (especially for the CRASH score) might have led to underestimate of the scores' predictive value through a lack of statistical power. Another limitation was the use of substitutive variables for 2 components of CARG score. Lastly, the single-center mode of recruitment means that our predictive model lacks external validity.

Table 2. Results of the GA and associations with grade ≥3 adverse events.

Domain evaluated	Score or scale	Total (*n* = 248)	Grades 3, 4, or 5 adverse events		
			No (*n* = 99)	Yes (*n* = 149)	*P*[a]
Functional status	ADL ≤ 5, *n* (%)	34 (14) (*5*)	12 (12)	22 (15)	.48
	IADL < 7, *n* (%)	104 (43) (*4*)	38 (39)	66 (45)	.38
	Hearing impairment, *n* (%)	104 (42) (*1*)	43 (43)	61 (41)	.73
Mobility	TGUG time >20 s, *n* (%)	43 (20) (*36*)	16 (18)	27 (22)	.41
	≥ 1 fall in the previous 6 months, *n* (%)	62 (25) (*1*)	27 (27)	35 (24)	.52
	Walking outside unaided, *n* (%)	177 (73) (*7*)	76 (78)	101 (71)	.23
Nutritional status	BMI, *n* (%)	(*3*)			**.005**
	- 22-24.9	68 (28)	20 (20)	48 (33)	
	- <22	55 (22)	20 (20)	35 (24)	
	- 25-29.9	88 (36)	39 (40)	49 (33)	
	- ≥30	34 (14)	19 (19)	15 (10)	
	MNA (out of 30), median (IQR]	23 [20-26] (*16*)	24 [21-27]	23 [20-26]	**.05**
	Serum albumin level (g/dL), median (IQR)	35 [30-39] (*30*)	36 [32-40]	34 [29-38]	**.01**
Cognitive status	MMSE score ≤24, *n* (%)	29 (16) (*66*)	10 (15)	19 (17)	.68
	Pre-existing cognitive impairment, *n* (%)	12 (4.9) (*5*)	5 (*5*)	7 (*5*)	.88
Emotional status	Mini-GDS ≥1, *n* (%)	64 (28) (*17*)	20 (21)	44 (32)	.07
	Clinical depressive syndrome, *n* (%)	58 (25) (*14*)	16 (17)	42 (30)	**.03**
Comorbidities	CIRS-G score (out of 56), median (IQR)	12 [9-16] (*30*)	12 [9-14]	13 [10-16]	**.003**
	≥1 grade 3 or 4 CIRS-G comorbidities	125 (57) (*30*)	37 (43)	88 (67)	**.001**
	Number of medications taken daily, median (IQR)	5 [3-8] (*5*)	4 [3-8]	6 [3-8]	.28
Social environment	Patients living alone at home, *n* (%)	78 (32) (*0*)	32 (32)	46 (31)	.81
	Number of children, median (IQR)	2 [1-3] (*27*)	2 [2-3]	2 [1-3]	.09

[a]In a Pearson chi-squared test or Student's t test, as appropriate; significant results ($P < .05$) are given in bold; number of missing data for each value is presented in brackets and in italic.
Abbreviations: ADL, activities of daily living; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale-Geriatrics. IADL, instrumental activities of daily living; IQR, interquartile range; Mini-GDS, Mini Geriatric Depression Scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; TGUG, timed get-up-and-go test.

Conclusion

Severe chemotherapy adverse events are frequent among older patients. Neither the CARG score nor the CRASH score predicted the risk of severe chemotherapy toxicity in the ELCAPA cohort of patients aged 70 or over with solid tumors referred for a pretherapeutic GA. Our analysis showed that the main predictors of severe adverse events were an intermediate ECOG PS, the type of cancer, the MAX2 index, and the presence of severe comorbidities, while a high BMI was a protective factor. Thus, the decision to initiate (or not) chemotherapy in an older patient with a solid tumor might already include an assessment of the risk of chemotherapy toxicity but should also encompass an evaluation of the treatment benefit-risk ratio, the results of a GA, and the overall prognosis, in accordance with the patient's wishes. As recommended by the International Society of Geriatric Oncology, a GA might help to (i) identify the patient's vulnerabilities, (ii) predict and anticipate adverse events, and (iii) increase the safety of chemotherapy after the identified vulnerabilities have been corrected.

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Table 3. Severe adverse events observed during chemotherapy.

					n	**%**
Severe adverse events (CARG analysis)					150	60
Severe adverse events (CRASH analysis)					126	51
Severe hematologic adverse events (CRASH analysis)					26	10
Severe non-hematologic adverse events (CRASH analysis)					119	48
Adverse events	Grade 3		Grade 4		Grade 5	
	n	%	*n*	%	*n*	%
Hematologic adverse events	57	23	24	10	2	1
Anemia	31	13	4	2	—	—
Neutropenia	20	8	7	3	—	—
Thrombopenia	9	4	10	4	—	—
Febrile neutropenia	3	1	3	1	2	1
Non-hematologic adverse events	101	41	17	7	7	3
Fatigue	36	15	3	1	—	—
Anorexia	19	8	—	—	—	—
Infection	17	7	7	3	6	2
Nausea/vomiting	16	6	1	1	1	1
Neuropathy	13	5	—	—	—	—
Diarrhea	7	3	1	1	—	—
Mucositis	5	2	—	—	—	—
Acute kidney failure	3	1	—	—	—	—
Palmar-plantar syndrome	2	1	—	—	—	—
Thrombosis	—	—	2	1	—	—
Bleeding	—	—	2	1	—	—

Abbreviations: CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients.

Table 4. A multivariate model for predicting grade ≥3 chemotherapy-associated adverse events.

	aOR[a]	**95%CI**		***P***[a]
Type of cancer (reference: colorectal cancer)				
Gastrointestinal cancer (other than colorectal)	3.7	1.5	8.9	**.003**
Breast cancer	7.1	2.1	24.7	**.002**
Genitourinary tract cancer	7.1	2.5	19.8	**<.001**
Other cancer	7.6	1.7	32.7	**.007**
ECOG PS (reference: PS 0)				
1-2	2.4	1.1	5.6	**.04**
3-4	1.1	0.3	3.6	.88
One or more grade 3 or 4 comorbidites (CIRS-G)	3.7	1.8	7.7	**<.001**
BMI class (reference: 22-25 kg/m²)				
<22 kg/m²	0.6	0.2	1.5	.24
>25 kg/m²	0.3	0.1	0.8	**.01**
>30 kg/m²	0.3	0.1	0.8	**.02**
MAX2 index (reference: a index of 0)				
1	2.4	1.1	5.2	**.02**
2	0.9	0.3	2.6	.78
Area under curve [95%CI]	0.78 [0.72-0.85]			

Significant results are given in bold. The MAX2 score is an estimate of the frequency of severe adverse events for a given chemotherapy regimen.
[a]In a multivariate logistic regression for severe adverse events, adjusted for all the other variables in the table; Wald's test for *P*-value estimation.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale-Geriatric; ECOG PS, Eastern Cooperative Oncology Group performance status.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: M.F., E.P., S.C., C.T., J.P., S.B.-G., F.C.-P., P.C. Provision of study material or patients: M.F., E.P., G.B., A.-L.S., C.T., P.C. Collection and/or assembly of data: M.F., G.B. Data analysis and interpretation: M.F., F.C.-P., P.C. Manuscript writing: All authors. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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