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Geriatric Oncology

# Predicting Chemotherapy Toxicity and Death in Older Adults with Colon Cancer: Results of MOST Study

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Colon cancer • Frailty markers • Grip strength • Geriatric assessment • Death • Chemotoxicity

## Abstract

***Purpose.*** Older patients with colon cancer (CC) are vulnerable to chemotherapy toxicity and death. Establishing simple scores specific for patients with CC to predict severe chemotoxicity or early death is needed to select the best treatment strategy.

***Subjects, Materials, and Methods.*** This prospective multicenter study included patients aged ≥70 years with CC receiving adjuvant or first-line metastatic chemotherapy. Frailty markers (nutrition, physical activity, energy, mobility, strength), comprehensive geriatric assessment (functional status, comorbidities, falls, nutrition, cognition, and depression), and usual laboratory parameters were collected. Logistic or Cox regression was used to examine at 500 days the association between frailty markers, comprehensive geriatric assessment, laboratory parameters, and grade 3–4 toxicity or death.

***Results.*** A total of 97 patients (median age, 79.0 years) received adjuvant (37.1%) or metastatic (62.9%) chemotherapy. During the first 500 days, grade 3–4 toxicity occurred in 49.5%, and 30% died. The predictive model for grade 3–4 toxicity combined (polychemotherapy × 3) + (hypoalbuminemia <32 g/L × 2) + (abnormal grip strength × 1.5) + C-reactive protein >11 mg/L + Eastern Cooperative Oncology Group performance status (ECOG-PS), cutoff score >3. The predictive model for death combined (metastasis × 5) + (age × 2) + alkaline phosphatase >100 IU/mL + sex (female) + abnormal grip strength + ECOG-PS, cutoff score >6. For chemotoxicity prediction, sensitivity was 81.6% and specificity 71.4%. For death prediction, sensitivity was 89.7% and specificity was 83.6%.

***Conclusion.*** These simple and efficient "ColonPrediscores" will help to better identify older patients with CC with increased risk of chemotherapy-related toxicity and/or death. ***The Oncologist*** 2020;25:e85–e93

**Implications for Practice:** The two scores assessed in this study, called "ColonPrediscores", offer a major advantage in that they do not need a previous complete geriatric assessment, which makes them an easy-to-use tool in oncologic settings.

## Introduction

Colon cancer (CC) is mainly a disease of older individuals, as median age at diagnosis is 70 years, and it represents the second cause for all cancer deaths [1]. The older cancer population is heterogeneous and requires specific workup in order to decide the best treatment strategy. Older patients seem to benefit from chemotherapy as much as younger ones [2]. However, older age is a risk factor for chemotherapy toxicities [3].

The International Society of Geriatric Oncology task force on comprehensive geriatric assessment (CGA) recommends implementation of a geriatric assessment for older patients with cancer to identify patients who may benefit from treatment as well as to detect conditions that may interfere with cancer therapy [4]. Some domains of CGA have been associated with cancer treatment toxicity (impairments in instrumental

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activities of daily living [IADL], comorbidity, depression, poor social support, and cognitive functioning) and all-cause mortality (impairments in basic and IADL nutritional status, comorbidities, depression) [5, 6]. However, a minority of patients with CC were included in these studies. In almost 1,000 older patients with cancer, one-fifth of whom had CC (21.4%), severe comorbidities and malnutrition were geriatrics parameters significantly associated with death [7]. Only two studies exclusively concern chemotherapy for colorectal cancer. Aparicio et al. [8] found in 123 patients that abnormal IADL score and Mini-Mental Status Examination were independently associated with chemotoxicity. Ramsdale et al. [9] showed in a very small sample of older patients that the vulnerable elders survey (VES-13) was the only significant predictive factor for death. To date, only two predictive scores for chemotherapy toxicity in older cancer patients (with 27% and 12% of whom had gastrointestinal cancers) have been published [10, 11]. Altogether, the scarcity of studies and the potential ceiling effects of CGA in CC highlight the need for the search of additional markers and specific scores [12–14].

The frailty phenotype in older adults described by Fried et al. [15] identified five markers: nutrition, mobility, strength, energy, and physical activity. Individuals exhibiting three or more of these characteristics were classified as frail, those with 1 or 2 as prefrail, and those with none as nonfrail. Regardless of the number of frailty markers, the presence of at least one of these markers conferred an increased risk (death, institutionalization, disability, mobility impairment, etc.) compared with patients with none [16–18]. In an oncology setting, Retornaz et al. [14]. found that more than 80% of older patients with cancer had at least one frailty marker including IADL or ADL disability, whereas 42% presented with at least one frailty marker without any IADL or ADL disability. Some frailty markers predicted treatment toxicity (low grip strength) [19] and risk of early death (nutrition and mobility) [20]. Thus, frailty phenotype could be a useful approach to detect potential vulnerability to cancer treatment and death in older patients with cancer.

The primary objective of this prospective longitudinal study was to develop two simple scores able predict grade 3–4 chemotoxicity and death during the 500 days follow-up period in a cohort of older patients with CC cancer by using CGA, frailty markers, laboratory data, and oncologic parameters.

## Subjects, Materials, and Methods

### Study Design

This multicenter prospective longitudinal study in eight oncologic centers included from October 2010 to January 2013, 97 patients with CC, aged 70 years and older, referred for adjuvant or first-line metastatic chemotherapy. The selection of the eligible patients was done in each center during the multidisciplinary team meeting. Eight oncologic centers participated in this study. Then, the research coordinator of each center approached the eligible patients. Unfortunately, we did not record the reasons for nonacceptance or the number of patients with exclusion criteria. We are not able to produce a flow diagram. Patients were excluded if they were terminally ill, had a life expectancy of less than 3 months, or had previously received any chemotherapy or hormone therapy regimen. All patients completed the informed consent form. The protocol was approved by the regional ethics committee and was conducted in accordance with the declaration of Helsinski, Good Clinical Practices, and local ethical and legal requirements (trial registration in ClinicalTrials.gov: MOST no. NCT02148731).

### Data Collection

The measurement tools were selected by a multidisciplinary team composed of geriatricians, oncologists, epidemiologists, and statisticians, based on a review of both the geriatric and oncology literature. The assessment was completed by a research coordinator using both self-report and performance-based measures, in addition to a medical chart review. Demographic data and oncologic parameters (stage of disease, metastasis location, chemotherapy regimen, K-ras mutation, and Eastern Cooperative Oncology Group [ECOG]) performance status) were collected. CGA consisted of basic activities of daily living (ADL) [21], IADL [22], comorbidities (the Cumulative Illness Rating Scale for Geriatrics [CIRS-G] [23], falls in the last 6 months, Mini Nutritional Assessment Short Form (MNA-SF) [24], Mini-Cog (cutoff score < 4) [25], and 4-item Geriatric Depression Scale (mini GDS) [26]. Lack of social support was defined as a negative answer to the question "Do you have a person who is able to take care of you if necessary?"

A frailty-related phenotype was used [14] to assess the five frailty domains defined by Fried [15]: (a) mobility: balance was considered abnormal if the patient was unable to balance on one leg for more than 5 seconds [27] or if the Timed Up and Go test [28] cutoff score was above 10 seconds; (b) grip strength: adjusted for sex and body mass index as described by Fried et al. [15]; (c) energy (visual scale assessed less than 3) [29]; (d) impaired physical activity (Canadian Study of Health and Aging Risk Factor Questionnaire assessed physical activities: no exercise or a low level of exercise was considered a positive marker of frailty for physical activity) [30]; and (e) impaired nutrition (losing more than 4 kg unintentionally during the last year [15] and/or decrease in food intake during the last 3 months whatever the cause) [31].

CGA and frailty markers were collected by a research coordinator.

Laboratory data (serum hemoglobin, lymphocyte count, serum creatinine clearance, serum albumin, C-reactive protein, and alkaline phosphatase levels) were recorded at inclusion.

Chemotherapy-induced side-effects were assessed at 3, 6, 9, and 12 months using the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 and collected by a research coordinator. Toxicities were graded on a 0–4 scale. Grade 3 or 4 toxicities, as well as any cause of death, were recorded.

### Statistical Analysis

Statistical analysis was performed using SPSS software, version 17.0 (SPSS, Chicago, IL). The association between death or toxicity and the dichotomous variables or the continuous variables was examined using the $\chi^2$ test or the Mann-Whitney *U* test, respectively. The relevant variables that reached a *p* value <.2 or that were of major interest were examined using multivariate logistic regression or Cox regression for toxicity or death, respectively; the optimal cut-point for the

**Table 1.** Patients characteristics ($n$ = 97)

| Characteristics | $n$ (%) |
|---|---|
| Female | 49 (50.5) |
| Age, median (25th–75th percentile), yr | 79.0 (74.5–83.0) |
| BMI, mean (SD), kg/m$^2$ | 24.4 ± 3.8 |
| Chemotherapy | |
| Adjuvant | 36 (37.1) |
| Metastatic | 61 (62.9) |
| Protocol of chemotherapy | |
| Monochemotherapy | |
| 5-fluoro-uracile | |
| Adjuvant | 18 (18.6) |
| Metastatic | 12 (12.4) |
| Erbitux, metastatic | 1 (1.0) |
| Polychemotherapy | |
| Oxaliplatin +5-fluoro-uracile | |
| Adjuvant | 17 (17.5) |
| Metastatic | 25 (25.8) |
| Oxaliplatin +5-fluoro-uracile + avastin, metastatic | 3 (3.1) |
| Oxaliplatin +5-fluoro-uracile + erbitux, metastatic | 3 (3.1) |
| Irinotecan +5-fluoro-uracile, metastatic | 12 (12.4) |
| Irinotecan +5-fluoro-uracile + avastin, metastatic | 5 (5.2) |
| Irinotecan +5-fluoro-uracile + erbitux, metastatic | 1 (1.0) |
| Primary tumor resected | 69 (71.1) |
| Emergency surgery | 17 (17.5) |
| K-Ras mutation (only for metastatic) | |
| Yes | 25 (45.5) |
| No | 18 (32.7) |
| Unknown | 19 (34.5) |
| UICC stage | |
| II | 14 (15.0) |
| III | 29 (31.2) |
| IV | 50 (53.8) |
| Metastasis location | |
| Liver | 51 (83.6) |
| Lung | 16 (26.2) |
| Peritoneum | 10 (16.4) |
| Lymph node | 9 (14.8) |
| Bone | 4 (6.6) |
| Pleura | 1 (1.6) |
| Number of metastatic location sites | |
| 1 | 41 (42.2) |
| 2 | 18 (18.6) |
| 3 | 4 (4.1) |
| Percentage of normal hepatic parenchyma replaced by tumor | |
| <25% | 23 (54.8) |
| >25% | 19 (45.2) |
| ECOG-PS | |
| >0 | 18 (21.4) |
| Comprehensive geriatric assessment | |
| Lack of social support | 9 (9.3) |
| Comorbidities (3 or more) | 31 (32.3) |
| Functional status | |
| Abnormal ADL | 26 (26.8) |
| Abnormal IADL | 59 (61.5) |
| Cognitive impairment (Mini COG) | 33 (34.0) |
| At risk of malnutrition (MNA-SF) | 60 (61.9) |
| 6-mo history of falls | 14 (14.4) |
| Depression (4 items GDS) | 36 (37.1) |
| At least 1 CGA impairment | 87 (89.7) |
| At least 3 CGA impairment | 56 (57.7) |
| Frailty markers | |
| Nutrition: lost more than 4 kg and/or loss of appetite | 71 (73.2) |
| Mobility: one leg stand <5 seconds and/or abnormal TUG | 63 (64.9) |
| Strength: abnormal grip strength adjusted for BMI and sex | 43 (44.8) |
| Impaired physical activity | 28 (28.9) |
| Energy <3 (VAS) | 5 (5.2) |
| At least 1 frailty marker | 89 (91.7) |
| At least 3 frailty markers | 35 (36.1) |
| Grade 3 to 4 toxicity | |
| 3 mo | 27 (27.8) |
| 6 mo | 22 (22.7) |
| 9 mo | 18 (18.6) |
| 12 mo | 11 (11.3) |
| Death | |
| Days 0–60 | 5 (17.2) |
| Days 61–500 | 24 (82.8) |
| Cause of death | |
| Tumor progression | 19 (65.5) |
| Other | 6 (20.7) |
| Not reported | 4 (13.8) |
| Laboratory variables, mean ± SD | |
| Hemoglobin (g/dL) | |
| Female | 11.0 ± 1.4 |
| Male | 12.3 ± 1.3 |
| Lymphocyte count (G/L) | 1.02 ± 1.91 |
| C-reactive protein (mg/L) | 28.1 ± 32.9 |
| Creatinine clearance (µmol/L) | 65.6 ± 22.8 |
| Alkaline phosphatase (UI/L) | 185 ± 252 |
| Albumin g/L | 34.4 ± 7.0 |

Data are expressed as number (%) unless otherwise indicated.
Abbreviations: ADL, activities of daily living; BMI, body mass index; CGA, comprehensive geriatric assessment; GDS, geriatric depression scale; IADL, instrumental activities of daily living; MNA SF, mini nutritional assessment short form; MNA-SF, short-form mini nutritional assessment; TUG, time up and go; UICC, Union for International Cancer Control; VAS, visual analog scale.

continuous variables was determined using the Youden index. The combined set of risk factors with the highest sensitivity and specificity (estimated using the receiver operating

characteristic [ROC] curve), the best goodness of fit (estimated using the Hosmer-Lemeshow test or the −2 log likelihood for toxicity or death, respectively) was selected and internally validated using the bootstrap methodology. The risk score for each factor was the rounded adjusted odds ratio and hazard ratio, for toxicity or death risk, respectively. Some risk scores were adjusted to insure an optimal sensitivity and/or specificity. Interactions among the selected factors were evaluated by introducing interaction terms to the model one at a time in the multivariate logistic regression or Cox regression for toxicity or death, respectively. No significant interaction was found between the different risk factors of each model, implying that they were independent. The sum of the score values was calculated for each patient and a cutoff point was estimated using the Youden index. Differences between groups were estimated with logistic regression or Kaplan-Meier analysis for toxicity or death, respectively.

## Results

### Patients

Ninety seven patients (median age 79.0 years; range, 70–90) received either adjuvant ($n$ = 36, 37.1%) or first-line metastatic (61, 62.9%) chemotherapy (Table 1). Almost one-third received monotherapy.

### Geriatric Assessment and Frailty Markers Results

See Table 1. One-third of patients had more than three comorbidities. A total of 61.5% and 26.8% of patients, respectively, had IADL and ADL disabilities. Cognitive disorders and depression were observed in 34.0% and 37.1% of the patients, respectively. The most prevalent frailty markers were malnutrition (73.2%), mobility (64.9%), and strength (44.8%). Almost 90% of the patients presented at least one frailty marker, whereas 36.1% were frail (three or more frailty markers).

### Chemotherapy Toxicities and Death

During the first 500 days, grade 3–4 toxicity occurred in 49 patients (50.5%) and death occurred in 29 (30.0%). The 60-day mortality occurred in five patients (17.2%; Table 1). Grade 3–4 hematologic and nonhematologic toxicity occurred in 34.0 and 44.3% of the patients, respectively (Table 2). The most common hematologic toxicities were anemia (36.1%) and neutropenia (26.8%). The most common nonhematologic toxicities were fatigue (63.9%), neuropathy (44.3%), and nausea (43.3%).

### Factors Associated with Chemotherapy Toxicity and Death

The risk factors associated with grade 3–4 toxicity in univariate analysis were metastatic chemotherapy, polychemotherapy, impaired grip strength, increased C-reactive protein and alkaline phosphatase levels, and decreased lymphocytes count and hypoalbuminemia (Table 3). The risk factors associated with death were age, sex (female), metastatic chemotherapy, ECOG-PS, depression, impaired mobility and grip strength, increased C-reactive protein and alkaline phosphatase levels, and decreased hemoglobin, creatinine clearance, and hypoalbuminemia. In multivariate logistic regression, variables independently associated with toxicity were albuminemia <32 g/L, polychemotherapy, abnormal grip strength, C reactive protein >11 mg/L, and ECOG-PS >0 (odds ratio: 3.94, 2.06, 2.18, 1.90, and 0.43, respectively). In Cox regression, variables independently associated with death were chemotherapy for metastatic disease, age > 82 years, alkaline phosphatase >100 IU/mL, sex (female), ECOG-PS, and abnormal grip strength (hazard ratio: 12.80, 5.20, 2.64, 1.68, 1.67, and 1.11, respectively; Table 4).

**Table 2.** Treatment-related adverse events (grade 3–4)

| Toxicity type | $n$ (%) |
|---|---|
| Hematologic | |
| Hemoglobin | 35 (36.1) |
| ANC | 26 (26.8) |
| WBC | 20 (20.6) |
| Platelets | 19 (19.6) |
| Infection with abnormal ANC | 4 (4.1) |
| Nonhematologic | |
| Fatigue | 62 (63.9) |
| Neuropathy | 43 (44.3) |
| Nausea | 42 (43.3) |
| Diarrhea | 33 (34.0) |
| Infection with normal ANC | 15 (15.5) |
| Thrombosis, embolism | 7 (7.2) |

Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell count.

### Predictive Model for Chemotherapy Toxicity and Death

The predictive model for grade 3–4 toxicity combined (albumin <32 g/L × 5) + (polychemotherapy × 3) + (abnormal grip strength × 2) + (C-reactive protein >11 mg/L × 2) + ECOG-PS >0, cutoff score > 3. The predictive model for death combined (chemotherapy metastatic × 5) + (age > 82 years × 2.5) + alkaline phosphatase >100 IU/mL + sex (female) + ECOG-PS >0 + abnormal grip strength, cutoff score > 6. Characteristics of both models are described Table 4 and Figures 1 and 2. No significant interaction between the variables was found. Both models showed a high goodness of fit (Hosmer-Lemeshow test: $\chi^2$ = 5.751 $p$ = .569, −2 log likelihood = 203, $\chi^2$ = 47.7, $p$ < .0001 for toxicity or death model, respectively) and a good discrimination ability (area under the ROC curve = 0.774 ± 0.051; 95% CI, 0.674–0.855; $p$ < .0001) and 0.925 ± 0.028 (95% CI, 0.849–0.970; $p$ < .0001) for toxicity or death model, respectively (Table 5). Supplemental Data Table 1 describes the ability of the stratified risk score to predict chemotherapy toxicity.

## Discussion

Predicting chemotoxicity and death is one of the main issues for oncologists when they prescribe chemotherapy in older patients, particularly in the adjuvant setting. Our study suggests that for patients greater than 70 years of age with CC, among the numerous geriatric, oncologic, and laboratory parameters, easy-to-obtain variables such as albumin, polychemotherapy, grip strength, C-reactive protein, and ECOG-PS predicted chemotoxicity, whereas chemotherapy for metastatic disease, age, alkaline phosphatase, sex, ECOG-PS, and grip strength

**Table 3.** Patient characteristics for toxicity or death

| Characteristics | Toxicity, Mean ± SD | | | Death, *n* (%) | | |
|---|---|---|---|---|---|---|
| | No | Yes | *p* value | No | Yes | *p* value |
| Sex | | | | | | |
| Male | 24 (51.1) | 24 (49.0) | | 35 (57.4) | 9 (31.0) | |
| Female | 23 (48.9) | 25 (51.0) | <.999 | 16 (42.6) | 20 (69.0) | .025[a] |
| Chemotherapy | | | | | | |
| Adjuvant | 25 (53.2) | 11 (22.4) | | 32 (52.5) | 1 (3.4) | |
| Metastatic | 22 (46.8) | 38 (77.2) | .003[a] | 29 (47.5) | 28 (96.6) | <.0001[a] |
| Monotherapy | 22 (46.8) | 8 (16.3) | | 20 (32.8) | 10 (34.5) | |
| Polytherapy | 25 (53.2) | 41 (83.7) | .002[a] | 41 (67.2) | 19 (65.5) | <.999 |
| ECOG-PS | | | | | | |
| 0 | 36 (85.7) | 39 (79.6) | | 52 (85.2) | 21 (72.4) | |
| 1–3 | 6 (14.3) | 10 (20.4) | .671[a] | 9 (14.8) | 8 (27.6) | .146[a] |
| Cormorbidies (3 or more) | | | | | | |
| No | 31 (67.4) | 33 (67.3) | | 39 (65.0) | 22 (75.9) | |
| Yes | 15 (32.6) | 16 (32.7) | <.999 | 21 (35.0) | 7 (24.1) | .340 |
| Abnormal ADL | | | | | | |
| No | 39 (83.0) | 31 (63.3) | | 45 (73.8) | 21 (72.4) | |
| Yes | 8 (17.0) | 18 (36.7) | .039[a] | 16 (26.2) | 8 (27.6) | <.999 |
| Abnormal IADL | | | | | | |
| No | 20 (42.6) | 17 (35.4) | | 26 (43.3) | 9 (31.0) | |
| Yes | 27 (57.4) | 31 (64.6) | .532 | 34 (56.7) | 20 (69.0) | .355 |
| Cognitive impairment | | | | | | |
| No | 31 (66.0) | 30 (63.8) | | 38 (64.4) | 20 (69.0) | |
| Yes | 16 (34.0) | 17 (36.2) | <.999 | 21 (35.6) | 9 (31.0) | .812 |
| Malnutrition | | | | | | |
| No | 19 (40.4) | 17 (34.7) | | 23 (37.7) | 11 (37.9) | |
| Yes | 28 (59.6) | 32 (65.3) | .674 | 38 (62.3) | 18 (62.1) | <.999 |
| 6-mo history of falls | | | | | | |
| No | 38 (80.9) | 44 (89.8) | | 55 (90.2) | 24 (82.8) | |
| Yes | 9 (19.1) | 5 (10.2) | .256 | 6 (9.8) | 5 (17.2) | .323 |
| Depression | | | | | | |
| No | 31 (66.0) | 30 (61.2) | | 41 (67.2) | 15 (51.7) | |
| Yes | 16 (34.0) | 19 (38.8) | .675 | 20 (32.8) | 14 (48.2) | .171[a] |
| Impaired nutrition | | | | | | |
| No | 11 (23.4) | 14 (28.6) | | 19 (31.1) | 7 (24.1) | |
| Yes | 36 (76.6) | 35 (71.4) | .645 | 42 (68.9) | 22 (75.9) | .621 |
| Impaired mobility | | | | | | |
| No | 16 (34.0) | 18 (36.7) | | 26 (42.6) | 7 (24.1) | |
| Yes | 31 (66.0) | 31 (63.3) | .833 | 35 (57.4) | 22 (75.9) | .106[a] |
| Impaired grip strength | | | | | | |
| No | 30 (63.8) | 22 (45.8) | | 37 (61.7) | 11 (37.9) | |
| Yes | 17 (32.6) | 26 (54.2) | .100[a] | 23 (38.3) | 18 (62.1) | .043[a] |
| Impaired physical activity | | | | | | |
| No | 31 (66.0) | 37 (75.5) | | 46 (75.4) | 20 (69.0) | |
| Yes | 16 (34.0) | 12 (24.5) | .371 | 15 (24.6) | 9 (31.0) | .612 |
| Abnormal energy | | | | | | |
| No | 45 (95.7) | 45 (93.8) | | 59 (98.3) | 25 (86.2) | |
| Yes | 2 (4.3) | 3 (6.3) | <.999 | 1 (1.7) | 4 (13.8) | .037 |

(continued)

**Table 3.** (continued)

| Characteristics | Toxicity, Mean ± SD | | | Death, *n* (%) | | |
|---|---|---|---|---|---|---|
| | No | Yes | *p* value | No | Yes | *p* value |
| Age, median (25th–75th percentile) | 77.5 (74.0–82.0) | 80.0 (74.0–83.0) | .705 | 83.0 (80.5–85.0) | 79.0 (74.5–83.0) | <.0001[a] |
| Hemoglobin (g/dL) | | | | | | |
| Male | 12.2 ± 1.3 | 12.4 ± 1.2 | .836 | 12.7 ± 1.2 | 11.5 ± 1.1 | .006[a] |
| Female | 11.0 ± 1.1 | 11.1 ± 1.6 | .849 | 10.8 ± 1.34 | 11.5 ± 1.4 | .111[a] |
| Lymphocytes count (G/L) | 2.36 ± 2.12 | 1.67 ± 1.64 | .186[a] | 2.09 ± 2.01 | 1.92 ± 1.96 | .349 |
| C-reactive protein (mg/L) | 22.5 ± 32.1 | 30.5 ± 30.3 | .113[a] | 16.2 ± 19.4 | 55.2 ± 41.1 | <.0001[a] |
| Creatinine clearance (mL/min) | 68.0 ± 22.7 | 63.1 ± 23.0 | .288 | 68.2 ± 23.5 | 58.0 ± 21.1 | .102[a] |
| Alkaline phosphatase (IU/L) | 178 ± 261 | 193 ± 249 | .182[a] | 123 ± 114 | 320 ± 393 | .001[a] |
| Albumin (g/L) | 35.1 ± 6.7 | 33.8 ± 7.3 | .081[a] | 34.6 ± 7.2 | 33.2 ± 6.7 | .174[a] |

Statistical analysis was performed using the $\chi^2$ test for categorical variables or the Mann-Whitney *U* test for continuous variables.
[a]Denotes variables used for multivariate analysis.
Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.

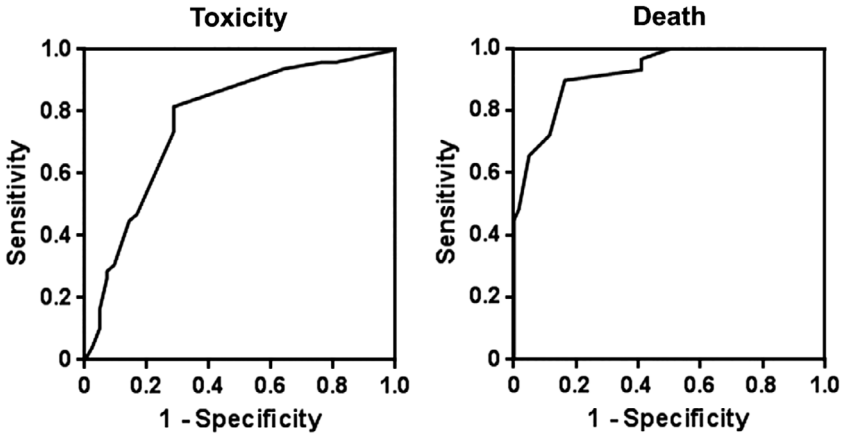


**Figure 1.** Receiver operating characteristic curve analysis of the predictive models of toxicity or death.

**Table 4.** Multivariate logistic regression and Cox regression analysis for toxicity or death, respectively

| Risk factor | Prevalence *n* (%) | Toxicity *n* (%) | AOR | 95% CI | *p* value | Score | Cutoff |
|---|---|---|---|---|---|---|---|
| Albumin <32 g/L | 25 (25.8) | 17 (77.3) | 3.94 | 0.60–25.87 | .103 | 5 | >3 |
| Polychemotherapy | 66 (68.0) | 41 (63.1) | 2.06 | 0.58–7.34 | .095 | 3 | |
| Abnormal grip strength | 43 (44.3) | 26 (65..4) | 2.18 | 0.65–7.36 | .197 | 2 | |
| C-reactive protein >11 mg/L | 36 (37.1) | 24 (77.4) | 1.90 | 0.47–7.63 | .346 | 2 | |
| ECOG-PS >0 | 18 (18.6) | 10 (62.5) | 0.43 | 0.06–2.98 | .451 | 1 | |
| **Risk factor** | **Prevalence *n* (%)** | **Death *n* (%)** | **AHR** | **95% CI** | ***p* value** | **Score** | **Cutoff** |
| Chemotherapy metastatic | 61 (62.9) | 28 (49.1) | 12.80 | 1.60–102.3 | .020 | 5 | >6 |
| Age > 82 yr | 27 (27.8) | 19 (73.1) | 5.20 | 2.17–12.47 | .0002 | 2.5 | |
| Alkaline phosphatases >100 IU/mL | 41 (42.3) | 21 (56.8) | 2.64 | 0.98–7.13 | .067 | 1 | |
| Sex (female) | 49 (50.5) | 20 (43.5) | 1.68 | 0.69–4.04 | .189 | 1 | |
| ECOG-PS >0 | 18 (18.6) | 8 (47.1) | 1.67 | 0.63–4.44 | .273 | 1 | |
| Abnormal grip strength | 43 (44.3) | 18 (43.9) | 1.11 | 0.48–2.57 | .877 | 1 | |

Abbreviations: AHR, adjusted hazard ratio; AOR, adjusted odds ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status.

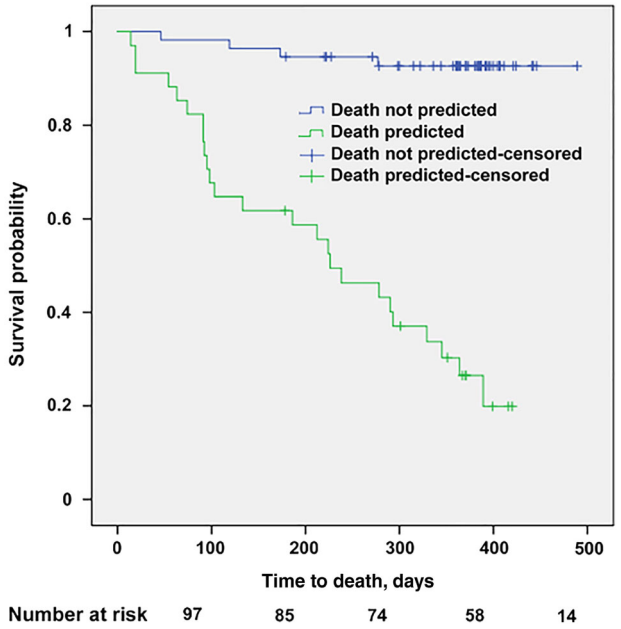


**Figure 2.** Kaplan-Meier analysis of the predictive model of death.

predicted death. A cutoff value >3 for toxicity and > 6 for death provided a good sensitivity (81.6 and 89.7%, respectively) and specificity (71.4 and 83.6%, respectively). Both models showed a robust goodness of fit (Hosmer-Lemeshow test: $\chi^2$ = 5.751, $p$ = .569 and –2 log likelihood = .203, $\chi^2$ = 47.7, $p$ < .0001, for toxicity and death, respectively).

Only two studies have developed a predictive model for chemotoxicity in older populations with cancer. With data from more than 500 aged patients with various types of cancer, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score [11] was constructed along 2 subscores: hematological (H) toxicity and nonhematological (NH) toxicity. In their model, predictors of H toxicity were IADL score, lactate dehydrogenase levels, and diastolic blood pressure, and predictors of NH toxicity were Eastern Cooperative Oncology Group performance, Mini-Mental Status score, and Mini-Nutritional Assessment score, associated with a chemotherapy risk for both toxicities (H and NH). The CRASH score identified 4 risk categories of severe toxicity categories: low, medium-low, medium-high, and high. In 500 older patients with cancer, 53% of which had grade 3–5 chemotoxicity, Hurria et al. [10] developed a predictive model for grade 3–5 toxicity. Geriatric assessment variables (hearing impairment, fall, assistance in taking medications, limited walk, decreased social activities), laboratory test values (hemoglobin, creatinine clearance), and patient (age), tumor (gastrointestinal or genitourinary tumor), and treatment characteristics (standard dosing of chemotherapy, polychemotherapy) identified older adults at low, intermediate, or high risk of chemotherapy toxicity. These two studies included various types of cancer and chemotherapy whereas the proportion of CC was less than 25%. In addition, half the patients in one study [10] or more than two-thirds in the other [11] were classified as intermediate risk, which lead to uncertainty for the oncologist when making treatment decisions. The scores of the present study identify two categories of older patients with CC: low- and high-risk group, thus simplifying the decision-making process.

Several prospective studies in oncology have demonstrated the predictive value of frailty markers for treatment toxicities. In two studies of older patients with CC, patients with at least three markers had higher risks of developing postoperative major complications [32] and early death [33]. Whatever the number of frailty markers, it appears that some markers have their own predictive value. In the older cancer population, abnormal nutrition and poor mobility were significantly predictive for early deaths [7, 34, 35]. Grip strength was also identified as an independent variable that predicted chemotoxicity [36] and various adverse outcomes such as functional decline and postoperative morbimortality [37–39]. The International Database Inquiry on Frailty data from five studies of aging including almost 15,000 participants examined the importance and the interrelation of each frailty markers in explaining differences among participants. Researchers concluded that grip strength had the highest contribution overall in explaining differences among participants across the samples [40]. Our study confirms the usefulness of grip strength to predict outcomes in older patients with CC.

Today, CGA is recommended for older patients with cancer to identify the patients who may benefit from treatment and may be hurt by treatment as well as conditions that may interfere with cancer treatment [4]. However, implementation of CGA in oncologic setting presents some limitations. CGA is time consuming, costly in terms of resources, and is not standardized [1]. Furthermore, some studies suggest than CGA would have a ceiling effect and is unable to detect vulnerability in a relatively highly functional population seen in oncology. In our model, simple laboratory data, frailty, and oncologic parameters are sufficient to complete the risk scores of both toxicity and death independently of a previous CGA [13, 41].

In fit patients with stage III colon cancer, adjuvant chemotherapy regimens with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabin and oxaliplatin (CAPOX) are the standard of care, with a 5-year disease-free survival rate of 73.3% [42, 43]. For patients with metastatic colon cancer, several chemotherapy regimens can be administered at first line. The most frequently prescribed regimens are FOLFOX and FOLFIRI, combined with either antiangiogenic drugs or anti-epidermal growth factor receptor monoclonal antibodies (for KRAS-wild-type patients). The median overall survival of these various regimens exceeds 20 months [44–46]. Hence, assessing the risk of chemotherapy toxicity in the adjuvant and first-line metastatic settings are a major concern for oncologists because of the relatively good prognosis of these categories of patients with colon cancer.

An important strength of this study is that it is the first one to propose two simple, efficient models able to predict toxicity and death specifically for patients with CC. Also, the variables used do no depend upon clinicians or nurses, can be objectively quantified, and do not rely on patient's interview in a context of possible cognitive impairment. There are limitations to this study. First, the number of patients was relatively small and treatment regimens were large. However, our study population was homogeneous, grouping patients with CC from several centers, thus reflecting the whole population. This study focused on grade 3–4 toxicity. However, some grade 2 toxicities (diarrhea, neuropathy) may also be relevant to the geriatric population. Finally,

**Table 5.** Characteristics of the predictive models for toxicity or death.

| Risk | AUC ROC curve ± SD | 95% CI | *p* value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| Toxicity | 0.774 ± 0.051 | 0.674–0.855 | <.0001 | 81.6 | 71.4 |
| Death | 0.925 ± 0.028 | 0.849–0.970 | <.0001 | 89.7 | 83.6 |

Abbreviations: AUC, area under the cure; CI, confidence interval; ROC, receiver operating characteristic.

although the models were internally validated using the bootstrap methodology, an external validation cohort would be helpful to assess the potential of our scores as predictors for both chemotoxicity and death in older patients with CC.

## Conclusion

In geriatric oncology, optimal management of older patients with cancer is challenging, as the assessment of the underlying vulnerability guides decision making. We demonstrate, using an homogeneous colon cancer cohort, that two simple scores combining patient characteristics and tumoral and biological indexes are powerful to predict severe chemotoxicity and death. These "ColonPrediscores" offer a major advantage in that they do not need a previous complete geriatric assessment, which makes them an easy-to-use tool in oncologic settings. An external validation of these scores is currently ongoing in an independent cohort.

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## Disclosures

**Francois Morvan:** Novartis, Pfizer (SAB, ET, H). The other authors indicated no financial relationships.

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