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ORIGINAL REPORT

Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort Study

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ABSTRACT

Purpose

Frailty classifications of older patients with cancer have been developed to assist physicians in selecting cancer treatments and geriatric interventions. They have not been compared, and their performance in predicting outcomes has not been assessed. Our objectives were to assess agreement among four classifications and to compare their predictive performance in a large cohort of in- and outpatients with various cancers.

Patients and Methods

We prospectively included 1,021 patients age 70 years or older who had solid or hematologic malignancies and underwent a geriatric assessment in one of two French teaching hospitals between 2007 and 2012. Among them, 763 were assessed using four classifications: Balducci, International Society of Geriatric Oncology (SIOG) 1, SIOG2, and a latent class typology. Agreement was assessed using the κ statistic. Outcomes were 1-year mortality and 6-month unscheduled admissions.

Results

All four classifications had good discrimination for 1-year mortality (C-index ≥ 0.70); discrimination was best with SIOG1. For 6-month unscheduled admissions, discrimination was good with all four classifications (C-index ≥ 0.70). For classification into three (fit, vulnerable, or frail) or two categories (fit *v* vulnerable or frail and fit or vulnerable *v* frail), agreement among the four classifications ranged from very poor ($\kappa \leq 0.20$) to good ($0.60 < \kappa \leq 0.80$). Agreement was best between SIOG1 and the latent class typology and between SIOG1 and Balducci.

Conclusion

These four frailty classifications have good prognostic performance among older in- and outpatients with various cancers. They may prove useful in decision making about cancer treatments and geriatric interventions and/or in stratifying older patients with cancer in clinical trials.

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INTRODUCTION

The burden of cancer increases with aging worldwide.[1,2] Older patients with cancer raise therapeutic challenges, because they constitute a heterogeneous population with various combinations of comorbidities, disabilities, and geriatric syndromes that contribute to frailty. However, there is no consensus about the best means of measuring frailty. The two main approaches are the cumulative deficit model developed by Rockwood et al and the physical phenotype described by Fried.[3] Neither has been validated in the geriatric oncology setting. The International Society of Geriatric Oncology (SIOG) recommends a geriatric assessment (GA) to detect previously unidentified impairments, predict severe treatment-related toxicity and overall mortality, and improve cancer treatment selection.[4] Balducci et al[5] reported a system for classifying older patients with cancer based on their GA findings. They identified three groups: fit, vulnerable, and frail. Fit patients may benefit from standard cancer treatment, vulnerable patients from adapted care, and frail patients from palliative care.[6] Another classification, developed by Droz et al,[7] is used in the SIOG guidelines for older men with prostate cancer (named SIOG1 in this study); in its updated version (SIOG2), only

ASSOCIATED CONTENT

Appendix
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patients with an abnormal G8 screening test are evaluated.[8] Again, patients are categorized into one of three groups: fit, vulnerable, or frail. These classifications are based on clinical expertise and consensus.[5-8] They have not been compared, and their performance in predicting mortality and unscheduled admissions has not been assessed.[9-11] Recently, we used a statistical approach—latent class (LC) analysis—to combine GA components into homogeneous health profiles seen among older patients with cancer.[12] We identified four health profiles: relatively healthy (LC1), malnourished (LC2), cognitively and/or mood impaired (LC3), and globally impaired (LC4).

Our objectives were to compare these four frailty classifications in terms of both agreement and performance in predicting 1-year overall mortality and 6-month unscheduled admissions. We studied a large cohort of in- and outpatients with various cancers before treatment. We also assessed performance among subgroups defined by tumor site and metastatic status.

PATIENTS AND METHODS

Population

We used data from ELCAPA (Elderly Cancer Patients), a prospective cohort survey of consecutive patients age 70 years or older who had newly diagnosed cancer and were referred to one of the geriatric oncology clinics of two teaching hospitals in the Paris urban area, France, before cancer treatment decisions were made.[13] For our study (ELCAPA14), we selected the 763 patients recruited between 2007 and 2012 for whom the data used in all four classifications were available (Table 1).

Geriatric Assessment and Data Collection

At baseline, all patients underwent a GA, as described previously.[14] Domains and indicators used in the Balducci, SIOG1, SIOG2, and LC typology (LCT) classifications are listed in Table 1.[5-8,12,14-19] Data were not available for three of the geriatric syndromes used in Balducci, namely, osteoporosis, neglect and abuse, and failure to thrive, which were therefore disregarded. For other variables unavailable in our database, we used substitutes (Table 1). We considered the following confounders: outpatient or inpatient status at the GA, year of patient inclusion, planned treatment decision (palliative, curative, or not reported), and age (median, ≤ 80 $v >$ 80 years). In addition, given the previously reported greater prognostic value of metastatic status in breast and prostate malignancies, we also considered a composite variable combining tumor site and metastatic status, with nonmetastatic colorectal cancer as the reference category.[20]

Outcomes

The ability to predict overall 1-year mortality and 6-month unscheduled admissions was assessed for each classification. Vital status was determined from the medical records or public records office; unscheduled admissions were determined from medical records.

Statistical Analysis

Categorical variables are described as numbers and percentages and quantitative variables as mean (standard deviation [SD]) or median (range) depending on distribution. To assess agreement among the four classifications, we used the κ or weighted κ statistic, as appropriate[21,22]; 95% CIs were computed using the bootstrap method with 1,000 replicates. Level of agreement was assessed as follows: $\kappa \leq 0.20$, very poor; κ of 0.21 to 0.40, poor; κ of 0.41 to 60, moderate; κ of 0.61 to 80, good; and κ of 0.81 to 1.00, excellent. For all four classifications, we first considered three categories: fit, vulnerable, and frail. In the SIOG1 classification, patients in the too-sick and frail groups were pooled in the frail category. For the LCT, relatively healthy (LC1) patients were categorized as fit, malnourished (LC2) and those with cognitive and/or mood impairments (LC3) as vulnerable, and those with global impairment (LC4) as frail.[12] Then, we simplified the classification into two categories, by pooling fit and vulnerable patients and comparing them with frail patients and by pooling vulnerable and frail patients and comparing them with fit patients. For these last analyses, LC3 patients were categorized as either vulnerable or frail.[12]

The log-rank test was used for global comparisons of mortality across categories. The proportional hazards assumption was assessed using Schoenfeld residual plots and tests.[23] This assumption was met for all variables in the final models except in- or outpatient status. Stratified Cox models were developed to deal with this time-dependent variable. Models were adjusted for age, year of inclusion, final planned treatment strategy, and the composite variable combining tumor site and metastatic status.[20] Hazard ratios (HRs) and their 95% CIs were estimated. We assessed calibration (level of agreement between observed and predicted 1-year survival probabilities) using graphs and the slope test.[24] P values greater than .05 indicated good calibration. Discrimination (ability to separate patients with v without the outcome) was assessed using Harrell's C-index with bootstrapped 95% CIs and the Royston-Sauerbrei D statistic (95% CI).[25] C-index values of 0.60 to 0.69, 0.70 to 0.79, and 0.80 to 0.89 suggest moderate, good, and very good discrimination, respectively.[26] Higher D statistic values indicate better discrimination; no threshold is available.

Prevalences of 6-month unscheduled admissions were compared globally across categories using the χ^2 test. Then, we developed logistic models adjusted for age, year of inclusion, in- or outpatient status, tumor site and metastatic status, and final planned treatment strategy. Odds ratios (ORs) and their 95% CIs were estimated. Calibration and discrimination were assessed by the Hosmer-Lemeshow test and the area under the receiver operating characteristic curve.[27,28] We compared the prognostic value of the models using the Akaike information criterion and calibration and discrimination indices.[29]

Subgroup Analyses

We performed analyses to assess the prognostic performance of the classifications in subgroups of patients with colorectal (n = 146), breast (n = 136), or prostate cancer (n = 98). Models were adjusted for age, year of inclusion, and metastatic status. Final planned treatment strategy was not included in the models, because of its collinearity with metastatic status. We also performed analyses in subgroups of patients with nonmetastatic (n = 311) or metastatic disease (n = 328). All tests were two sided, and P values of .05 or less were considered significant. The false discovery rate method was chosen to adjust for pairwise comparisons. Analyses were performed using STATA software (version 13.0; STATA, College Station, TX).

RESULTS

Study Population

Of the 763 patients, 754 had information about vital status and 690 about 6-month unscheduled admissions (Fig 1). Mean age was 80 (SD, $\pm$ 5.7) years, 63.6% were outpatients, 52.4% were men, 19.1% had colorectal cancer, and 46.3% had metastatic disease. Other characteristics are listed in Appendix Table A1 (online only).

Agreement Among the Four Classifications

By univariable analysis, patient distribution differed significantly across the four classifications (all $P < .001$; Table 2). When we considered the following categories (fit, vulnerable, or frail; fit v

Table 1. Description of Four Classifications and Variables Used

Classification	Population and Methods	Original Definition	Variables Used in Study	Algorithm for Classifying Patients
Balducci and Beghe[5] (2000)	Population and methods: Developed for older patients with cancer, based on expert consensus (a priori) Validation: No formal validation of prognostic performance (no information on calibration or discrimination); observational studies found higher risk for death among frail or unfit older patients with cancer classified according to criteria derived from Balducci: Basso et al[9] (N = 117): median age, 75 years (range, 70 to 92 years); 59.9% men; various cancers before chemotherapy (lung, colorectal, ovarian, head and neck, other sites); 80.3% had locally advanced and inoperable tumors or metastatic disease Tucci et al[10] (N = 84): median age, 73 years (range, 66 to 89 years); 40.5% men; diffuse large-cell lymphoma; 66% had stage III to IV disease; 63% in intermediate-high– or high-risk category according to International Prognostic Index Ommundsen et al[11] (N = 178): median age, 80 years (range, 70 to 94 years); 43.0% men; colorectal cancer before elective surgery; 37.1% had stage III to IV disease	Age > 85 years Dependence for ≥ 1 ADLs (Katz) Dependence for ≥ 1 IADLs (Lawton) Presence of ≥ 3 comorbid conditions (CIRS-G) Presence of ≥ 1 geriatric syndromes: Dementia Delirium Depression Incontinence (continuous and irreversible) Falls (≥ 3 per month) Osteoporosis (history of pathologic fractures) Neglect and abuse Failure to thrive Decision rules for cancer treatment: Fit: standard treatment Vulnerable: adapted treatment and geriatric interventions Frail: palliative care	Age > 85 years ADL score (Katz; ≤ 5 of 6) IADL score (Lawton; ≤ 7 of 8) No. of severe (grade 3 to 4) comorbidities as assessed by CIRS-G (0, 1 to 2, or ≥ 3) Presence of ≥ 1 geriatric syndromes: Dementia (MMSE score < 24 of 30) Delirium Depression (yes or no) diagnosed via semistructured interview to identify criteria for major depressive episode from DSM-IV Urinary and/or fecal incontinence Falls: ≥ 1 in last 6 months	Fit: Age ≤ 85 years and no grade 3 to 4 comorbidity and ADL score > 5 of 6 and IADL score > 7 of 8 and no geriatric syndrome Vulnerable: Age ≤ 85 years and ADL score > 5 of 6 and no geriatric syndrome and 1 or 2 grade 3 to 4 comorbidities or IADL score ≤ 7 of 8 Frail: Age > 85 years and/or ≥ 3 grade 3 to 4 comorbidities and/or ADL score ≤ 5 of 6 and/or ≥ 1 geriatric syndrome

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Table 1. Description of Four Classifications and Variables Used (continued)

Classification	Population and Methods	Original Definition	Variables Used in Study	Algorithm for Classifying Patients
Droz et al[7] (SIOG1; 2010)	Population and methods: Developed based on expert consensus for older patients with prostate cancer (a priori) Validation: No validation of prognostic performance	Dependence for ≥ 1 ADL, except for incontinence (Katz) Dependence for ≥ 1 IADL (4 items of Lawton scale: ability to manage money, manage medications, use transportation, and use telephone) No. of grade 3 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) No. of grade 4 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) Nutritional status assessed based on weight loss during previous 3 months (good nutritional status, < 5% of weight loss; risk of malnutrition, weight loss 5% to 10%; severe malnutrition, weight loss > 10%) Terminal, bedridden Decision rules for cancer treatment: Fit: standard treatment (ie, as in younger patients) Vulnerable: standard treatment after resolution of any geriatric problems Frail: adapted treatment Too sick: symptomatic palliative treatment	ADL score (Katz; ≤ 5 of 6) IADL score (Lawton; ≤ 7 of 8) No. of grade 3 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) No. of grade 4 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) Malnutrition (absence, weight loss < 10% in last 6 months and < 5% in last month; at risk, weight loss 10% to 15% in last 6 months and/or 5% to 10% in last month; severe malnutrition, weight loss ≥ 15% in last 6 months and/or ≥ 10% in last month) Bedridden (ECOG PS, 4)	Fit: No grade 3 to 4 comorbidity and ADL score > 5 of 6 and IADL score > 7 of 8 and no malnutrition Vulnerable: No grade 4 comorbidity and ADL score > 5 of 6 and 1 grade 3 comorbidity or IADL score ≤ 7 of 8 or at risk for malnutrition Frail: ≥ 2 grade 3 comorbidities or 1 grade 4 comorbidity or ADL score ≤ 5 of 6 or severe malnutrition Too sick: ≥ 2 grade 4 comorbidities or ECOG PS of 4

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Table 1. Description of Four Classifications and Variables Used (continued)

Classification	Population and Methods	Original Definition	Variables Used in Study	Algorithm for Classifying Patients
Droz et al[8] (SIOG 2; 2014)	Population and methods: Developed based on expert consensus for older patients with prostate cancer (a priori) Validation: No validation of prognostic performance	Step 1: Abnormal G8 screening test (score ≤ 14 of 17) Step 2: Dependence for ≥ 1 ADLs, except for incontinence (Katz; ≤ 3 of 6; > 3 of 6) Dependence for ≥ 1 IADLs (4 items of Lawton scale: ability to manage money, manage medications, use transportation, and use telephone) No. of grade 2 comorbidities as assessed by CIRS-G (0 or ≥ 1) No. of grade 3 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) No. of grade 4 comorbidities as assessed by CIRS-G (0 or ≥ 1) Nutritional status assessed based on weight loss during previous 3 months (good nutritional status, < 5% of weight loss; risk of malnutrition, weight loss 5% to 10%; severe malnutrition, weight loss > 10%) Neuropsychological problems: depression, cognitive impairment Decision rules for cancer treatment: Fit: standard treatment, (ie, as in younger patients) Vulnerable: standard treatment after resolution of any geriatric problems Frail: adapted treatment	Step 1: Abnormal G8 screening test (score ≤ 14 of 17) Step 2: ADL score (Katz; ≤ 3 of 6; > 3 of 6) IADL score (Lawton; ≤ 7 of 8) No. of grade 2 comorbidities as assessed by CIRS-G (0 or ≥ 1) No. of grade 3 comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) No. of grade 4 comorbidities as assessed by CIRS-G (0 or ≥ 1) Malnutrition (absence, weight loss < 10% in last 6 months and < 5% in last month; at risk, weight loss 10% to 15% in last 6 months and/or 5% to 10% in last month; severe malnutrition, weight loss ≥ 15% in last 6 months and/or ≥ 10% in last month) Neuropsychological problems: Depression (yes or no) diagnosed via semistructured interview to identify criteria for major depressive episode from DSM-IV Cognitive impairment (MMSE score < 24 of 30)	Fit: G8 score > 14 of 17 Vulnerable: No grade 4 comorbidity and IADL score > 7 of 8 and MMSE ≥ 24 of 30 and 1 grade 3 comorbidity or ≥ 1 grade 2 comorbidity or at risk for malnutrition or ADL score 4 or 5 of 6 or depression Frail: ≥ 1 grade 4 comorbidity or ≥ 2 grade 3 comorbidities or IADL score ≤ 7 of 8 or MMSE score < 24 of 30 or severe malnutrition or ADL score ≤ 3 of 6

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Table 1. Description of Four Classifications and Variables Used (continued)

Classification	Population and Methods	Original Definition	Variables Used in Study	Algorithm for Classifying Patients
Ferrat et al[12] (2016)	Population and methods: Developed based on cohort of older patients with various cancers, using LC analysis and expert consensus Validation: Validation of prognostic performance in prospective cohort of older patients with cancer: Ferrat et al[12] (N = 821): median age, 80 years (range, 76 to 84 years); 52% male; various cancer sites (colorectal, breast, prostate, upper GI tract or liver, urinary system, hematologic malignancies, other); 43.1% had metastatic disease	Inadequate social environment (yes or no) defined as absence of primary caregiver or adequate support at home or strong circle of family and friends able to meet needs of patient at time of evaluation Malnutrition (≥ 1 of following criteria recommended by French National Authority for Health: at least 10% weight loss in 6 months or 5% in 1 month and/or BMI < 21 kg/m^2 and/or MNA score < 17 of 30 and/or serum albumin level < 35 g/L) Depression (yes or no) diagnosed via semistructured interview to identify criteria for major depressive episode from DSM-IV Cognitive impairment (MMSE score < 24 of 30) No. of severe (grade 3 to 4) comorbidities as assessed by CIRS-G (0, 1, or ≥ 2) Functional impairment (Katz; ADLscore ≤ 5 of 6) Age > 80 years Tumor site (colorectal, breast, prostate, upper GI or liver, other urologic malignancies, hematologic malignancies, other) Metastatic status (M0, M1/Mx, NA, or not reported) In- or outpatient status at time of GA	Same variables	Class assignment using posterior class membership probabilities from scoring rule (available from authors) LC1: relatively healthy Low probabilities of GA indicator impairments Higher probabilities of nonmetastatic cancer, breast or prostate cancer, age ≤ 80 years, and outpatient status at time of GA LC2: malnourished Characterized chiefly by high probability of malnutrition Higher probabilities of digestive cancer, metastatic disease, age ≤ 80 years, and outpatient status at time of GA LC3: cognitively and/or mood impaired Higher probabilities of cognitive and functional impairments, depressive mood, inadequate social environment, and ≥ 1 severe comorbidities compared with LC1 and LC2; in contrast, probabilities of malnutrition, functional impairment, and having ≥ 2 severe comorbidities are lower than in LC4 Higher probabilities of breast cancer or tumors in other category (ovary, uterus, lung, head and neck, skin, thyroid, and unknown primary location), nonmetastatic disease, age > 80 years, and outpatient status at time of GA LC4: globally impaired High probabilities of functional and cognitive impairments, depressive mood, malnutrition, and severe comorbidities; compared with both LC1 and LC2, LC4 is also associated with higher probability of inadequate social environment Higher probabilities of upper GI tract or liver cancer, metastatic disease, age > 80 years, and inpatient status at time of GA

Abbreviations: ADL, Activity of Daily Living; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (fourth edition); ECOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; IADL, Instrumental Activity of Daily Living; LC, latent class; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; NA, not applicable.

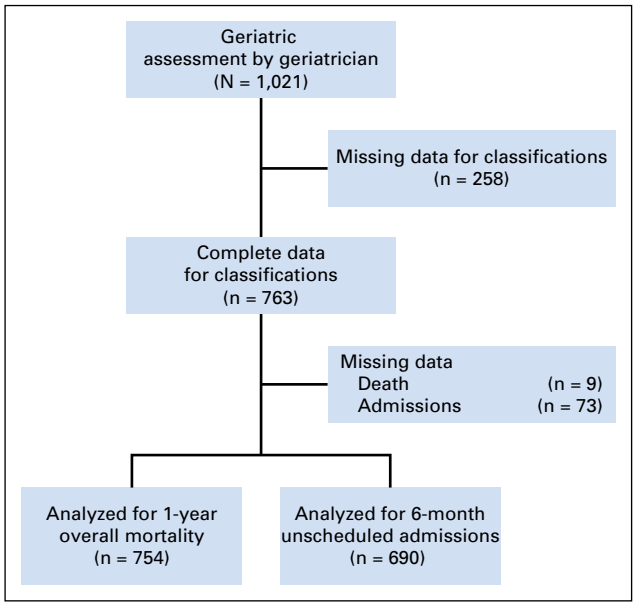

Fig 1. Flow diagram of participants.

vulnerable or frail; and fit or vulnerable *v* frail), agreement was very poor to poor between LCT and Balducci and between Balducci and SIOG2 (Table 3). Agreement was very poor to moderate between LCT and SIOG2 and between SIOG1 and SIOG2. Agreement was moderate to good between LCT and SIOG1 and between Balducci and SIOG1.

Prognostic Performance of the Four Classifications

Univariable analysis showed significant associations linking each of the four classifications to overall 1-year mortality and to 6-month unscheduled admissions (all $P < .001$; Tables 4 and 5). Risks for death and admission increased steadily from the lowest to highest category with all classifications (trend $P < .001$).

Vulnerable and frail or frail/too-sick patients according to Balducci or SIOG1 or SIOG2 had a higher 1-year mortality rate compared with fit patients (Table 4). Similarly, with LCT, 1-year mortality was higher in the LC2 (malnourished), LC3 (cognitively and/or mood impaired), and LC4 (globally impaired) categories. All four multivariable models showed good calibration (all $P > .20$; Table 4; Appendix Fig A1, online only) and good discrimination (C-index ≥ 0.70). Discrimination and calibration were best with SIOG1, followed by LCT.

The risk of 6-month unscheduled admissions was higher in the vulnerable, frail, and frail/too-sick categories according to Balducci or SIOG1 and in the LC2, LC3, and LC4 categories (Table 5), compared with fit patients. With SIOG2, only frail patients were at higher risk for this outcome. All four multivariable models had good calibration (all $P > .20$) and discrimination (C-index ≥ 0.70). Discrimination was similar for the four models.

Subgroup Analyses

Discrimination indices varied according to tumor site (Appendix Tables A2 and A3, online only). For 1-year overall mortality, discrimination was moderate to good in patients with colorectal cancer and very good in those with breast or prostate cancer, with all four classifications. SIOG1 and SIOG2 performed best in patients with colorectal or breast cancer, whereas performance indices were slightly better for LCT in patients with prostate cancer.

For admissions, discrimination was good in patients with colorectal or prostate cancer and very good in those with breast cancer, with all four classifications. SIOG1 and SIOG2 performed best in patients with colorectal or breast cancer, whereas LCT and SIOG2 had slightly better performance indices in patients with prostate cancer. All models displayed good calibration. Discrimination was very good for mortality (C-index = 0.82 to 0.84) and good for hospitalizations (C-index = 0.79 to 0.80) in patients without metastases but only moderate for both outcomes (C-index = 0.65 to 0.69) in patients with metastases (Appendix Table A4, online only).

DISCUSSION

The four frailty classifications performed well in predicting 1-year mortality, with slightly better performance for SIOG1, followed by LCT. Performance in predicting 6-month unscheduled admissions was similar for the four classifications. However, agreement among the four classifications was poor to moderate.

Performance of the classifications varied across tumor sites. For predicting mortality, discrimination was very good for prostate and breast cancers and lower for colorectal cancer. For predicting unscheduled admissions, discrimination was very good in patients with breast cancer. None of the four classifications performed best for all three tumor sites.

To our knowledge, no previous study has compared the prognostic performance of these four frailty classifications in geriatric oncology patients. In keeping with our findings, previous studies have reported that older patients with various types of cancer were at higher risk of death if they were categorized as unfit or frail using Balducci.[9-11] Among patients categorized as fit by SIOG1, SIOG2, and LCT, 40% to 50% were classified as frail by Balducci. This discrepancy is probably ascribable to differences in the GA components used to define frailty (eg, malnutrition [not used in Balducci] and older age [used only in Balducci and LCT]). The Balducci classification may tend to overdiagnose frailty, because the risk for mortality seems lower in frail patients using Balducci (51%) than in frail patients according to the three other classifications (55% to 81%).

Although the four classifications showed limited agreement overall, they performed well in predicting both study outcomes, with SIOG1 and LCT performing best. This finding may be explained by the good prognostic value of the GA parameters used. SIOG1 was developed for older men with prostate cancer but performed well in our overall population and in our subgroups, especially those with breast or prostate cancer, suggesting that the GA components used in this classification may predict poor outcomes for many tumor sites.[7] In keeping with this possibility, several studies have shown that malnutrition, Activities of Daily Living, Instrumental Activities of Daily Living, and comorbidities are associated with death in older patients with cancer.[20,30,31] Because malnutrition has a strong prognostic value in older patients with cancer, its absence from the Balducci classification may explain the slightly lower performance of

Table 2. Comparisons of Patient Distribution Across Four Classifications (N = 763)

Classification*	Classification No. (%)											
	Balducci				SIOG 1					SIOG 2			
	Fit (n = 98; 12.9%)	Vulnerable (n = 114; 14.9%)	Frail (n = 551; 72.2%)	*P*†	Fit (n = 148; 19.4%)	Vulnerable (n = 237; 31.1%)	Frail (n = 291; 38.1%)	Too Sick (n = 87; 11.4%)	*P*†	Fit (n = 136; 17.8%)	Vulnerable (n = 114; 15%)	Frail (n = 513; 67.2%)	*P*†
LC typology				< .001					< .001				< .001
LC1: relatively healthy (n = 231; 30.3%)	70 (30.3)	50 (21.7)	111 (48.0)		113 (48.9)	104 (45.0)	14 (6.1)	0 (0.0)		103 (44.6)	60 (26.0)	68 (29.4)	
LC2: malnourished (n = 254; 33.3%)	28 (11.0)	62 (24.4)	164 (64.6)		34 (13.4)	113 (44.5)	99 (39.0)	8 (3.1)		33 (13.0)	51 (20.1)	170 (66.9)	
LC3: cognitively and/or mood impaired (n = 104; 13.6%)	0 (0.0)	1 (1.0)	103 (99.0)		1 (1.0)	17 (16.3)	69 (66.3)	17 (16.4)		0 (0.0)	0 (0.0)	104 (100.0)	
LC4: globally impaired (n = 174; 22.8%)	0 (0.0)	1 (0.6)	173 (99.4)		0 (0.0)	3 (1.6)	109 (62.6)	62 (35.6)		0 (0.0)	3 (1.7)	171 (98.3)	
SIOG1				< .001									< .001
Fit (n = 148; 19.4%)	83 (56.1)	0 (0.0)	65 (43.9)							73 (49.3)	68 (46.0)	7 (4.7)	
Vulnerable (n = 237; 31.1%)	11 (4.6)	90 (38.0)	136 (57.4)							51 (21.5)	40 (16.9)	146 (61.6)	
Frail (n = 291; 38.1%)	4 (1.4)	22 (7.6)	265 (91.1)							12 (4.1)	6 (2.1)	273 (93.8)	
Too sick (n = 87; 11.4%)	0 (0.0)	2 (2.3)	85 (97.7)							0 (0.0)	0 (0.0)	87 (100.0)	
SIOG2				< .001									
Fit (n = 136; 17.8%)	54 (39.7)	33 (24.3)	49 (36.0)										
Vulnerable (n = 114; 15%)	38 (33.3)	11 (9.7)	65 (57.0)										
Frail (n = 513; 67.2%)	6 (1.2)	70 (13.6)	437 (85.2)										

Abbreviations: LC, latent class; SIOG, International Society of Geriatric Oncology.
*Percentages reading across each classification row equal 100%.
†*P* values obtained using x^2 test corrected by false discovery rate method for pairwise comparisons.

Table 3. Concordance Between Four Classifications (N = 763)

Classification	Classification Cohen's κ Coefficient (95% CI)*									
	LC Typology				Balducci			SIOG1		
	LC1 *v* LC2/ LC3 *v* LC4	LC1 *v* LC2/ LC3/LC4	LC1/LC2/ LC3 *v* LC4	LC1/LC2 *v* LC3/LC4	Fit *v* Vulnerable *v* Frail	Fit *v* Vulnerable/Frail	Fit/Vulnerable *v* Frail	Fit *v* Vulnerable *v* Frail	Fit *v* Vulnerable/Frail	Fit/Vulnerable *v* Frail
Balducci										
Fit *v* vulnerable *v* frail	0.24 (0.20 to 0.27)†	—	—	—	—	—	—			
Fit *v* vulnerable/frail	—	0.30 (0.23 to 0.37)†	—	—	—	—	—			
Fit/vulnerable *v* frail	—	—	0.20 (0.17 to 0.24)‡	0.35 (0.31 to 0.40)†	—	—	—			
SIOG 1										
Fit *v* vulnerable *v* frail/too sick	0.46 (0.41 to 0.50)§	—	—	—	0.48 (0.42 to 0.53)§	—	—			
Fit *v* vulnerable/ frail/too sick	—	0.47 (0.40 to 0.54)§	—	—	—	0.62 (0.54 to 0.69)‖	—			
Fit/vulnerable *v* frail/too sick	—	—	0.45 (0.39 to 0.50)§	0.63 (0.57 to 0.68)‖	—	—	0.41 (0.34 to 0.46)§			
SIOG2										
Fit *v* vulnerable *v* frail	0.31 (0.27 to 0.36)†	—	—	—	0.39 (0.33 to 0.45)†	—	—	0.50 (0.45 to 0.54)§	—	—
Fit *v* vulnerable/frail	—	0.43 (0.36 to 0.51)§	—	—	—	0.37 (0.28 to 0.46)†	—	—	0.41 (0.32 to 0.49)§	—
Fit/vulnerable *v* frail	—	—	0.10 (0.05 to 0.14)‡	0.15 (0.09 to 0.20)‡	—	—	0.10 (0.02 to 0.17)‡	—	—	0.17 (0.10 to 0.23)‡

Abbreviations: LC, latent class; SIOG, International Society of Geriatric Oncology.
*κ (for two categories) or weighted κ statistics (for three categories with w = |i-j|) and 95% CIs using bootstrap method (n = 1,000 replicates).
†Poor agreement (0.21 to 0.40).
‡Very poor agreement (≤ 0.20).
§Moderate agreement (0.41 to 0.60).
‖Good agreement (0.61 to 0.80).

Table 4. Estimated Value of Four Classification Models in Predicting 1-Year Mortality (n = 754)

Classification	No. (%) of Patients	No. (%) of Events	P*	HR (95% CI)†	AIC	Test of Calibration Slope (P)‡	C-index (bootstrapped 95% CI)	Royston-Sauerbrei D (95% CI)
Balducci			< .001, < .001		3,085.6	.90	0.74 (0.72 to 0.77)	1.40 (1.20 to 1.60)
Fit	97 (12.9)	11 (11.3)		1.00 (reference)				
Vulnerable	113 (14.9)	31 (27.4)		1.91 (0.95 to 3.85)				
Frail	544 (72.2)	278 (51.1)		2.94 (1.59 to 5.43)				
SIOG1			< .001, < .001		3,050.3	.88	0.77 (0.74 to 0.79)	1.83 (1.59 to 2.07)
Fit	147 (19.5)	19 (12.9)		1.00 (reference)				
Vulnerable	234 (31.1)	66 (28.2)		1.75 (1.03 to 2.97)				
Frail	286 (37.9)	167 (58.4)		3.31 (2.00 to 5.50)				
Too sick	87 (11.5)	68 (78.2)		6.12 (3.45 to 10.85)				
SIOG2			< .001, < .001		3,076.1	.84	0.75 (0.73 to 0.78)	1.45 (1.25 to 1.65)
Fit	134 (17.8)	11 (8.2)		1.00 (reference)				
Vulnerable	112 (14.8)	28 (25.0)		2.08 (1.02 to 4.22)				
Frail	508 (67.4)	281 (55.3)		3.69 (1.97 to 6.89)				
LC typology			< .001, < .001		3,065.3	.92	0.76 (0.73 to 0.78)	1.66 (1.42 to 1.90)
Relatively healthy	227 (30.1)	27 (11.9)		1.00 (reference)				
Malnourished	252 (33.4)	110 (43.6)		2.15 (1.34 to 3.47)				
Cognitively and/or mood impaired	103 (13.7)	44 (42.7)		2.66 (1.54 to 4.61)				
Globally impaired	172 (22.8)	139 (80.8)		4.84 (2.82 to 8.31)				

Note: Percent of patients expressed in columns; percent of events expressed in lines.
Abbreviations: AIC, Akaike information criterion; HR, hazard ratio; LC, latent class; SIOG, International Society of Geriatric Oncology.
*First *P* value is from log-rank test; second is for trend.
†All Cox models were stratified on in- or outpatient status and adjusted for composite variable, including tumor site and metastatic status, age, year of inclusion, and treatment decision (palliative, curative, or not reported).
‡*P* values from test of slope of regression of pseudovalues for event probabilities on predicted event probabilities at 1 year.

this tool in predicting 1-year mortality. Reported benefits of nutritional intervention include better treatment response and fewer chemotherapy adverse effects.[31,32]

As compared with SIOG1, SIOG2 involves two steps (patients with a G8 score > 14 are considered fit and not evaluated further) and no longer includes a too-sick category.[8] We found that these changes failed to significantly improve prognostic performance. However, because the GA is time consuming and not available everywhere, SIOG2 may be useful in busy practices. The slightly better discrimination of SIOG1, which does not include chronologic age, suggests that this parameter may have no place in the core set. Finally, the comparison between the four classifications suggests that the optimal set of GA components may include at least disability, number of severe comorbidities, and malnutrition.

Discrimination varied with tumor site and metastatic status. Discrimination was poorer in groups with a worse prognosis (ie, those with colorectal cancer; 1-year mortality, 40% *v* 30% and 18% in prostate and breast cancers, respectively) and metastatic disease (60% *v* 23% in nonmetastatic disease). Poorer discrimination in colorectal cancer has also been reported with the G8.[33-35] Prognostic performance is known to vary with patient characteristics and outcomes.[36,37] However, there is no obvious explanation for the consistently poorer discrimination among patients with a worse prognosis. Conceivably, specific frailty factors associated with prognosis may be missing, and/or cutoffs of GA parameters or frailty may require adjustment according to tumor site and stage. For example, severity of malnutrition is probably more relevant in colorectal cancer than presence or absence of malnutrition. Also, the prognostic performance of GA parameters may be better for tumors associated with relatively long life expectancies, leading to better discrimination compared with tumors of higher lethality.[36,38]

Our findings suggest these four classifications developed by expert consensus (SIOG1, SIOG2, and Balducci) or statistical modeling (LCT) provide prognostic information useful in guiding treatment decisions, stratifying patients in clinical trials, and detecting impairments amenable to intervention. However, decisions should also take into account physician and patient preferences and risk of toxicities. Cancer treatment decision rules based on the Balducci and SIOG classifications have been suggested. However, the discrepancies and performance variability across classifications indicate a need for better characterization of frailty according to tumor site and disease stage. GA parameters assessing malnutrition severity and mobility, if possible with their change over time, may deserve to be added.[39,40] The final step would consist in randomized trials to assess the impact of classifications on decision making and patient outcomes such as mortality and toxicities.[37,38]

The diversity of our patient population reflects everyday practice and supports the general applicability of our findings. The assessment of GA domains using validated scales indicates that our results are probably applicable to other health care institutions. We adjusted the main analyses for confounders including the final treatment decision, which may have affected the two study outcomes. Our analyses in the three subgroups of patients with the most common cancers strengthen the external validity of our findings.

Regarding limitations, the absence of three of the geriatric syndromes described in the Balducci classification and the use of substitutes for other unavailable variables may have resulted in classification bias. However, the substitutes were similar to the original variables. Finally, data on toxicities were not available.

In conclusion, despite poor to moderate agreement among the four frailty classifications of older patients with cancer (Balducci, SIOG1, SIOG2, and LCT), performance in predicting 1-year

Table 5. Estimated Value of Four Classification Models in Predicting Unscheduled 6-Month Admissions (n = 690)

Classification	No. (%) of Patients	Admissions No. (%)		*P**	OR (95% CI)†	AIC	Calibration (*P*)‡	AUC (95% CI)
		No (n = 434)	Yes (n = 279)					
Balducci				< .001, < .001		742.2	.39	0.78 (0.74 to 0.82)
Fit	95 (13.8)	77 (18.4)	18 (6.6)		1.00 (reference)			
Vulnerable	106 (15.4)	70 (16.7)	36 (13.3)		2.43 (1.17 to 5.04)			
Frail	489 (70.9)	272 (64.9)	217 (80.1)		2.33 (1.25 to 4.36)			
SIOG1				< .001, < .001		739.5	.85	0.78 (0.75 to 0.82)
Fit	142 (20.6)	115 (27.5)	27 (10.0)		1.00 (reference)			
Vulnerable	213 (30.9)	132 (31.5)	81 (29.9)		2.24 (1.28 to 3.92)			
Frail	262 (38.0)	130 (31.0)	132 (48.7)		2.82 (1.56 to 5.13)			
Too sick	73 (10.5)	42 (10.0)	31 (11.4)		2.17 (0.96 to 4.94)			
SIOG2				< .001, < .001		743.0	.48	0.78 (0.74 to 0.81)
Fit	134 (19.4)	109 (26.0)	25 (9.2)		1.00 (reference)			
Vulnerable	107 (15.5)	75 (17.9)	32 (11.8)		1.25 (0.63 to 2.47)			
Frail	449 (65.1)	235 (56.1)	214 (79.0)		2.04 (1.14 to 3.66)			
LC typology				< .001, < .001		746.0	.97	0.78 (0.74 to 0.81)
Relatively healthy	216 (31.3)	172 (41.1)	47 (16.2)		1.00 (reference)			
Malnourished	233 (33.8)	127 (30.3)	106 (39.1)		1.81 (1.02 to 3.20)			
Cognitively and/or mood impaired	87 (12.6)	50 (11.9)	37 (13.7)		2.33 (1.11 to 4.90)			
Globally impaired	154 (22.3)	70 (16.7)	84 (31.0)		2.01 (0.93 to 4.37)			

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; LC, latent class; OR, odds ratio; SIOG, International Society of Geriatric Oncology.
*First *P* value is from log-rank test; second is for trend.
†All Cox models were stratified on in- or outpatient status and adjusted for composite variable, including tumor site and metastatic status, age, year of inclusion, and treatment decision (palliative, curative, or not reported).
‡Hosmer-Lemeshow test for G = 10 groups.

overall mortality and 6-month unscheduled admissions was consistently good when evaluated in a large cohort of in- and outpatients with untreated cancer at various sites. The observed variations in agreement and performance across tumor sites suggest means of optimizing performance and better characterizing frailty. Studies of clinical impact are needed to determine whether classifications deserve to be integrated into the cancer treatment decision-making process.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Stewart BW, Wild CP (eds): World Cancer Report 2014. Lyon, France, International Agency for Research on Cancer, 2014
2. Binder-Foucard F, Bossard N, Delafosse P, et al: Cancer incidence and mortality in France over the 1980-2012 period: Solid tumors. Rev Epidemiol Sante Publique 62:95-108, 2014
3. Hurria A, Dale W, Mooney M, et al: Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol 32:2587-2594, 2014
4. Wildiers H, Heeren P, Puts M, et al: International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 32:2595-2603, 2014
5. Balducci L, Beghe C: The application of the principles of geriatrics to the management of the older person with cancer. Crit Rev Oncol Hematol 35: 147-154, 2000
6. Balducci L, Extermann M: Management of cancer in the older person: A practical approach. Oncologist 5:224-237, 2000
7. Droz JP, Balducci L, Bolla M, et al: Management of prostate cancer in older men: Recommendations of a working group of the International Society of Geriatric Oncology. BJU Int 106:462-469, 2010
8. Droz JP, Aapro M, Balducci L, et al: Management of prostate cancer in older patients: Updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol 15:e404-e414, 2014
9. Basso U, Tonti S, Bassi C, et al: Management of frail and not-frail elderly cancer patients in a hospital-based geriatric oncology program. Crit Rev Oncol Hematol 66:163-170, 2008
10. Tucci A, Ferrari S, Bottelli C, et al: A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer 115:4547-4553, 2009
11. Ommundsen N, Wyller TB, Nesbakken A, et al: Frailty is an independent predictor of survival in older patients with colorectal cancer. Oncologist 19: 1268-1275, 2014
12. Ferrat E, Audureau E, Paillaud E, et al: Four distinct health profiles in older patients with cancer: Latent class analysis of the prospective ELCAPA cohort. J Gerontol A Biol Sci Med Sci 71:1653-1660, 2016
13. Caillet P, Canoui-Poitrine F, Vouriot J, et al: Comprehensive geriatric assessment in the decision-making

process in elderly patients with cancer: ELCAPA study. J Clin Oncol 29:3636-3642, 2011

14. Katz S, Ford AB, Moskowitz RW, et al: Studies of illness in the aged: The index of ADL—A standardized measure of biological and psychosocial function. JAMA 185:914-919, 1963

15. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-198, 1975

16. Haute Autorité de Santé: Nutritional Support Strategy for Protein-Energy Malnutrition in the Elderly. http://www.has-sante.fr/portail/upload/docs/application/pdf/malnutrition_elderly_guidelines.pdf

17. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (ed 4). Washington, DC, American Psychiatric Association, 1994

18. Miller MD, Towers A: A Manual of Guidelines for Scoring the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Pittsburgh, PA, University of Pittsburgh, 1991

19. Lawton MP, Brody EM: Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 9:179-186, 1969

20. Ferrat E, Paillaud E, Laurent M, et al: Predictors of 1-year mortality in a prospective cohort of elderly patients with cancer. J Gerontol A Biol Sci Med Sci 70:1148-1155, 2015

21. Trikalinos AT, Balion CM: Chapter 9. : Options for summarizing medical test performance in the absence of a "gold standard", in Chang SM, Matchar DB, Smetana GW, et al (eds): Methods Guide for Medical Test Reviews. Rockville, MD, Agency for Healthcare Research and Quality, 2012

22. Cohen J: A coefficient of agreement for nominal scales. Educ Psychol Meas 20:27-46, 1960. www.garfield.library.upenn.edu/classics1986/A1986AXF2600001.pdf

23. Grambsch PM, Therneau TM: Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515-526, 1994. www.ics.uci.edu/~staceyah/112-203/Grambsch_Therneau-Biometrika-1994.pdf

24. Royston P, Altman DG: External validation of a Cox prognostic model: Principles and methods. BMC Med Res Methodol 13:33, 2013

25. Royston P, Sauerbrei W: A new measure of prognostic separation in survival data. Stat Med 23:723-748, 2004

26. Yourman LC, Lee SJ, Schonberg MA, et al: Prognostic indices for older adults: A systematic review. JAMA 307:182-192, 2012

27. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, NY, John Wiley and Sons, 1989

28. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29-36, 1982

29. Bozdogan H: Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. Psychometrika 52:345-370, 1987. http://link.springer.com/article/10.1007/BF02294361

30. Puts MT, Hardt J, Monette J, et al: Use of geriatric assessment for older adults in the oncology setting: A systematic review. J Natl Cancer Inst 104:1133-1163, 2012

31. Extermann M, Hurria A: Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 25:1824-1831, 2007

32. Blanc-Bisson C, Fonck M, Rainfray M, et al: Undernutrition in elderly patients with cancer: Target for diagnosis and intervention. Crit Rev Oncol Hematol 67:243-254, 2008

33. Hamaker ME, Jonker JM, de Rooij SE, et al: Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: A systematic review. Lancet Oncol 13:e437-e444, 2012

34. Liuu E, Canouï-Poitrine F, Tournigand C, et al: Accuracy of the G-8 geriatric-oncology screening tool for identifying vulnerable elderly patients with cancer according to tumour site: The ELCAPA-02 study. J Geriatr Oncol 5:11-19, 2014

35. Martinez-Tapia C, Canoui-Poitrine F, Bastuji-Garin S, et al: Optimizing the G8 screening tool for older patients with cancer: Diagnostic performance and validation of a six-item version. Oncologist 21:188-195, 2016

36. Bamias A, Tzannis K, Beuselinck B, et al: Development and validation of a prognostic model in patients with metastatic renal cell carcinoma treated with sunitinib: A European collaboration. Br J Cancer 109:332-341, 2013

37. Moons KG, Altman DG, Vergouwe Y, et al: Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 338:b606, 2009

38. Corre R, Greillier L, Le Caër H, et al: Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non–small-cell lung cancer: The phase III randomized ESOGIA-GFPC-GECP 08-02 study. J Clin Oncol 34:1476-1483, 2016

39. Pamoukdjian F, Lévy V, Sebbane G, et al: Slow gait speed is an independent predictor of early death in older cancer outpatients: Results from a prospective cohort study. J Nutr Health Aging 2016. DOI:10.1007/s12603-016-0734-x

40. Soubeyran P, Fonck M, Blanc-Bisson C, et al: Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 30:1829-1834, 2012

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Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort Study

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Appendix

The ELCAPA (Elderly Cancer Patients) Study Group is composed of three geriatricians (P. Caillet, M. Laurent, and E. Paillaud), one oncologist (Ch. Tournigand), one radiation oncologist (J.-L. Lagrange), three epidemiologists (F. Canouï-Poitrine, S. Bastuji-Garin, and E. Audureau), one pharmacist (P.A. Natella), one biostatistician (L. Segaux), one clinical research medical physician (N. Reinald), and two clinical research assistants (R. Ibrahim and E. Jan).

Table A1. Patient Demographic and Clinical Characteristics (N = 763)

Characteristic	No. (%)
Outpatient status	485 (63.6)
Age, years	
Mean	80.3
SD	5.7
> 80	353 (46.3)
Male sex	400 (52.4)
Tumor site	
Colorectal	146 (19.1)
Upper GI tract or liver	121 (15.9)
Breast	136 (17.8)
Prostate	98 (12.8)
Other urologic malignancy	114 (14.9)
Hematologic malignancy	63 (8.3)
Other	85 (11.1)
Metastatic status (n = 708)	
M0	311 (43.9)
M1	328 (46.3)
Mx	6 (0.9)
NA	63 (8.9)
Treatment decision	
Curative	310 (40.6)
Palliative	366 (48.0)
Not reported	87 (11.4)
Inadequate social support*	154 (20.2)
Timed GUG test score ≥ 3 and/or > 20 s (n = 761)	346 (45.5)
ECOG PS	
0-1	377 (49.4)
2	130 (17.0)
≥ 3	256 (33.6)
ADL score ≤ 5 of 6	261 (34.2)
IADL score ≤ 7 of 8 (n = 725)	468 (64.6)
Malnutrition†	394 (51.6)
Malnutrition (n = 721)	
Weight loss < 10% in last 6 months and < 5% in last month	517 (71.7)
10% to 15% in last 6 months and/or 5% to 10% in last month	105 (14.6)
≥ 15% in last 6 months and/or ≥ 10% in last month	99 (13.7)
MMSE score < 24 of 30	211 (27.7)
Depression (DSM-IV)	222 (29.1)
Delirium	23 (3.0)
≥ 1 fall in last 6 months (n = 743)	244 (32.8)
Urinary and/or fecal incontinence (n = 760)	141 (18.6)
No. of grade 3 comorbidities (CIRS-G; n = 695)	
Median	1
Range	0-8
No. of grade 4 comorbidities (CIRS-G; n = 695)	
Median	0
Range	0-4
Abnormal G8 score (≤ 14 of 17)	627 (82.2)

Abbreviations: ADL, Activity of Daily Living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (fourth edition); ECOG PS, Eastern Cooperative Oncology Group performance status; IADL, Instrumental Activity of Daily Living; MMSE; Mini Mental State Examination; MNA, Mini Nutritional Assessment; NA, not applicable; SD, standard deviation.

*Absence of primary caregiver or adequate support at home or strong network of family and friends able to meet needs of patient at time of evaluation.

†≥ One of following criteria: at least 10% weight loss in 6 months or 5% in 1 month and/or body mass index < 21 kg/m^2 and/or MNA score score < 17 of 30 and/or serum albumin < 35 g/L.

Table A2. Estimated Value of Four Classifications for Predicting 1-Year Mortality in Patients With Colorectal, Breast, or Prostate Cancer

Classification	No. (%) of Patients	No. (%) of Events	*P**	HR (95% CI)†	AIC	Calibration Slope (*P*)‡	C-index (Bootstrapped 95% CI)	Royston-Sauerbrei D (95% CI)
Colorectal cancer (n = 146)								
Balducci			.002, .002		454.8	.31	0.65 (0.59 to 0.72)	1.01 (0.56 to 1.46)
Fit	16 (11.0)	1 (6.3)		1.00 (reference)				
Vulnerable	25 (28.1)	7 (28.0)		7.39 (0.90 to 60.84)				
Frail	105 (71.9)	51 (48.6)		8.24 (1.12 to 60.60)				
SIOG1			< .001, < .001		447.1	.27	0.70 (0.63 to 0.76)	1.20 (0.77 to 1.63)
Fit	17 (11.6)	1 (5.9)		1.00 (reference)				
Vulnerable	48 (32.9)	11 (22.9)		4.85 (0.62 to 37.81)				
Frail	70 (48.0)	39 (55.7)		12.15 (1.65 to 89.42)				
Too sick	11 (7.5)	8 (72.7)		13.55 (1.65 to 111.17)				
SIOG2			< .001, .001		437.9	.29	0.71 (0.65 to 0.77)	1.28 (0.83 to 1.73)
Fit	14 (9.6)	2 (14.3)		1.00 (reference)				
Vulnerable	21 (14.4)	0 (0.0)		NA				
Frail	111 (76.0)	57 (51.4)		3.91 (0.91 to 16.74)				
LC typology			< .001, < .001		448.7	.42	0.69 (0.62 to 0.76)	1.29 (0.82 to 1.76)
Relatively healthy	22 (15.1)	4 (18.2)		1.00 (reference)				
Malnourished	71 (48.6)	18 (25.4)		0.97 (0.31 to 3.08)				
Cognitively and/or mood impaired	19 (13.0)	9 (47.4)		3.23 (0.91 to 11.48)				
Globally impaired	34 (23.3)	28 (82.4)		4.07 (1.17 to 14.15)				
Prostate cancer (n = 97)								
Balducci			< .001, .001		152.0	.19	0.88 (0.82 to 0.94)	2.77 (1.71 to 3.83)
Fit	23 (23.7)	1 (4.3)		1.00 (reference)				
Vulnerable	19 (19.6)	0 (0.0)		NA				
Frail	55 (56.7)	28 (50.9)		5.95 (0.75 to 47.25)				
SIOG1			< .001, < .001		161.4	.19	0.85 (0.76 to 0.93)	2.46 (1.46 to 3.46)
Fit	34 (35.0)	3 (8.8)		1.00 (reference)				
Vulnerable	29 (29.9)	3 (10.3)		1.52 (0.30 to 7.81)				
Frail	22 (22.7)	13 (59.1)		4.05 (0.97 to 16.81)				
Too sick	12 (12.4)	10 (83.3)		6.21 (1.10 to 35.11)				
SIOG2			< .001, < .001		158.6	.53	0.86 (0.78 to 0.93)	2.73 (1.67 to 3.79)
Fit	46 (47.4)	2 (4.3)		1.00 (reference)				
Vulnerable	10 (10.3)	3 (30.0)		3.85 (0.63 to 23.66)				
Frail	41 (42.3)	24 (58.5)		5.73 (1.16 to 28.24)				
LC typology			< .001, < .001		154.0	.84	0.88 (0.81 to 0.94)	3.18 (1.98 to 4.38)
Relatively healthy	59 (60.8)	3 (5.1)		1.00 (reference)				
Malnourished	9 (9.3)	4 (44.4)		4.79 (0.92 to 24.96)				
Cognitively and/or mood impaired	2 (2.1)	0 (0.0)		NA				
Globally impaired	27 (27.8)	22 (81.5)		23.40 (3.24-168.78)				
Breast cancer (n = 134)								
Balducci			.020, .022		151.4	.11	0.85 (0.77 to 0.94)	2.16 (1.36 to 2.96)
Fit	25 (18.7)	0 (0.0)		NA				
Vulnerable	16 (11.9)	2 (12.5)		0.93 (0.21 to 4.2)				
Frail	93 (69.4)	22 (23.7)		1.00 (reference)				
SIOG1			< .001, < .001		154.4	.18	0.87 (0.78 to 0.95)	2.54 (1.60 to 3.48)
Fit	45 (33.6)	2 (4.4)		1.00 (reference)				
Vulnerable	46 (34.3)	5 (10.9)		2.06 (0.91 to 24.57)				
Frail	32 (23.9)	11 (34.4)		4.72 (0.89 to 50.81)				
Too sick	11 (8.2)	6 (54.5)		6.73 (0.89 to 50.81)				
SIOG2			< .001, .007		149.3	.49	0.87 (0.80 to 0.95)	2.36 (1.54 to 3.14)
Fit	34 (25.4)	0 (0.0)		NA				
Vulnerable	26 (19.4)	1 (3.9)		0.28 (0.03 to 2.30)				
Frail	74 (55.2)	23 (31.1)		1.00 (reference)				
LC typology			< .001, < .001		155.8	.35	0.86 (0.78 to 0.94)	2.07 (1.31 to 2.83)
Relatively healthy	78 (58.2)	5 (6.4)		1.00 (reference)				
Malnourished	18 (13.4)	5 (27.8)		3.29 (0.76 to 14.24)				
Cognitively and/or mood impaired	30 (22.4)	8 (26.7)		3.12 (0.76 to 12.80)				
Globally impaired	8 (6.0)	6 (75.0)		3.06 (0.51 to 18.17)				

Note: Percent of patients expressed in columns; percent of events expressed in lines.
Abbreviations: AIC, Akaike information criterion; HR, hazard ratio; LC, latent class; NA, not applicable; SIOG, International Society of Geriatric Oncology.
*First *P* value is from log-rank test for heterogeneity; second is for trend.
†All Cox models were stratified on in- or outpatient status and adjusted for metastatic status, age, and year of inclusion.
‡*P* values testing whether slope of regression of pseudovalues for event probabilities on predicted event probabilities over all time points at 1 year.

Table A3. Estimated Value of Four Classifications for Predicting 6-Month Unscheduled Admissions in Patients With Colorectal, Breast, or Prostate Cancer

Classification	No. (%) of Patients	Admissions No. (%)		P*	OR (95% CI)†	AIC	Calibration(P)‡	AUC (95% CI)
		No	Yes					
Colorectal cancer (n = 135)								
Balducci				.017, .008		168.9	.91	0.79 (0.72 to 0.87)
Fit	16 (11.9)	11 (18.0)	5 (6.8)		1.00 (reference)			
Vulnerable	21 (15.6)	13 (21.3)	8 (10.8)		1.98 (0.42 to 9.36)			
Frail	98 (72.6)	37 (60.7)	61 (82.4)		5.80 (1.56 to 9.36)			
SIOG1				.007, .001		164.1	.36	0.81 (0.74 to 0.89)
Fit	17 (12.6)	13 (21.3)	4 (5.4)		1.00 (reference)			
Vulnerable	44 (32.6)	23 (37.7)	21 (28.4)		3.02 (0.77 to 11.82)			
Frail	65 (48.1)	23 (37.7)	42 (56.8)		8.70 (2.16 to 35.09)			
Too sick	9 (6.7)	2 (3.3)	7 (9.5)		51.97 (3.60 to 749.36)			
Droz2				.023, .078		170.7	.86	0.80 (0.72 to 0.87)
Fit	14 (10.4)	7 (11.5)	7 (9.5)		1.00 (reference)			
Vulnerable	21 (15.5)	15 (24.6)	6 (8.11)		0.36 (0.08 to 1.71)			
Frail	10 (74.1)	39 (63.9)	61 (82.4)		1.59 (0.41 to 6.12)			
LC typology				.136, .038		175.1	.48	0.77 (0.69 to 0.85)
Relatively healthy	21 (15.6)	13 (21.3)	8 (10.8)		1.00 (reference)			
Malnourished	66 (48.9)	32 (52.5)	34 (48.9)		1.24 (0.34 to 4.50)			
Cognitively and/or mood impaired	17 (12.6)	5 (8.2)	12 (16.2)		5.78 (0.94 to 35.68)			
Globally impaired	31 (23.0)	11 (18.0)	20 (27.0)		2.16 (0.35 to 13.20)			
Prostate cancer (n = 92)								
Balducci				.360, .159		80.3	.27	0.73 (0.59 to 0.87)
Fit	23 (25.0)	20 (28.2)	3 (14.3)		1.00 (reference)			
Vulnerable	19 (20.7)	15 (21.1)	4 (19.0)		3.29 (0.52 to 20.98)			
Frail	50 (54.3)	36 (50.7)	14 (66.7)		4.49 (0.87 to 23.22)			
SIOG1				.109, .253		80.9	.32	0.73 (0.59 to 0.87)
Fit	34 (37.0)	29 (40.9)	5 (23.8)		1.00 (reference)			
Vulnerable	27 (29.3)	21 (29.6)	6 (28.6)		2.77 (0.62 to 12.46)			
Frail	22 (23.9)	13 (18.3)	9 (42.8)		12.72 (0.99 to 162.74)			
Too sick	9 (9.8)	8 (11.3)	1 (4.8)		14.10 (0.17 to 1157.24)			
SIOG2				.080, .032		75.7	.77	0.78 (0.64 to 0.91)
Fit	46 (50.0)	40 (56.3)	6 (28.6)		1.00 (reference)			
Vulnerable	10 (10.9)	7 (9.9)	3 (14.3)		4.58 (0.50 to 41.63)			
Frail	36 (39.1)	24 (33.8)	12 (57.1)		12.14 (1.82 to 81.09)			
LC typology				.002, .012		73.2	.50	0.79 (0.65 to 0.92)
Relatively healthy	59 (64.1)	52 (73.2)	7 (33.3)		1.00 (reference)			
Malnourished	8 (8.7)	3 (4.2)	5 (23.8)		15.42 (1.82 to 130.26)			
Cognitively and/or mood impaired	2 (2.2)	2 (2.8)	0 (0.0)		NA			
Globally impaired	23 (25.0)	14 (19.7)	9 (42.9)		40.23 (1.06 to 1529.86)			
Breast cancer (n = 124)								
Balducci				.084, .063		128.7	.94	0.82 (0.73 to 0.90)
Fit	26 (21.0)	24 (25.5)	2 (6.6)		1.00 (reference)			
Vulnerable	16 (12.9)	11 (11.7)	5 (16.7)		5.04 (0.68 to 37.45)			
Frail	82 (66.1))	59 (62.8)	23 (76.7)		3.37 (0.59 to 19.20)			
SIOG1				.044, .020		127.6	.94	0.83 (0.75 to 0.91)
Fit	43 (34.7)	39 (41.5)	4 (13.3)		1.00 (reference)			
Vulnerable	44 (35.5)	30 (31.9)	14 (46.7)		5.04 (1.29 to 19.65)			
Frail	26 (21.0)	18 (19.1)	8 (26.7)		2.65 (0.48 to 14.64)			
Too sick	11 (8.9)	7 (7.5)	4 (13.3)		2.79 (0.31 to 24.90)			
SIOG2				< .001, .001		121.1	.99	0.85 (0.78 to 0.93)
Fit	34 (27.4)	31 (33.0)	3 (10.0)		1.00 (reference)			
Vulnerable	25 (20.2)	24 (25.5)	1 (3.3)		0.24 (0.02 to 2.80)			
Frail	65 (52.4)	39 (41.5)	26 (86.7)		3.74 (0.79 to 17.57)			
LC typology				.111, .028		131.1	.73	0.82 (0.73 to 0.91)
Relatively healthy	75 (60.5)	61 (64.9)	14 (46.7)		1.00 (reference)			
Malnourished	16 (12.9)	12 (12.8)	4 (13.3)		0.41 (0.06 to 2.98)			
Cognitively and/or mood impaired	26 (21.0)	18 (19.1)	8 (26.7)		2.01 (0.46 to 8.88)			
Globally impaired	7 (5.6)	3 (3.2)	4 (13.3)		0.38 (0.02 to 5.65)			

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; LC, latent class; NA, not applicable; OR, odds ratio; SIOG, International Society of Geriatric Oncology.

*First *P* values obtained from χ^2 or Fisher's exact test. Second *P* value is for trend.

†All models were adjusted for in- or outpatient status, metastatic status, age, and year of inclusion.

‡Hosmer-Lemeshow test for G = 10 groups.

Table A4. Calibration and Discrimination Values for Predicting 1-Year Overall Mortality and 6-Month Unscheduled Admissions in Patients With and Without Metastases

Outcome	Classification			
	Balducci	SIOG1	SIOG2	LC Typology
1-year overall mortality				
No metastases (M0; n = 311)*				
Calibration slope (*P*)†	.66	.65	.83	.37
C-index (bootstrapped 95% CI)	0.83 (0.79 to 0.87)	0.83 (0.79 to 0.87)	0.82 (0.78 to 0.87)	0.84 (0.80 to 0.89)
Royston-Sauerbrei D (bootstrapped 95% CI)	1.85 (1.44 to 2.26)	2.01 (1.56 to 2.46)	1.80 (1.39 to 2.21)	2.04 (1.61 to 2.47)
Metastases (M1; n = 328)*				
Calibration slope (*P*)†	.43	.61	.34	.23
C-index (bootstrapped 95% CI)	0.65 (0.61 to 0.68)	0.69 (0.65 to 0.73)	0.66 (0.63 to 0.70)	0.67 (0.63 to 0.71)
Royston-Sauerbrei D (bootstrapped 95% CI)	0.85 (0.60 to 1.10)	1.30 (1.01 to 1.59)	0.92 (0.67 to 1.17)	1.10 (0.83 to 1.37)
6-month unscheduled hospitalizations				
No metastases (M0; n = 311)‡				
Calibration (*P*)§	.14	.84	.92	.97
AUC (95% CI)	0.79 (0.74 to 0.85)	0.80 (0.74 to 0.85)	0.80 (0.74 to 0.85)	0.79 (0.74 to 0.85)
Metastases (M1; n = 328)‡				
Calibration (*P*)§	.74	.61	.37	.29
AUC (95% CI)	0.67 (0.61 to 0.73)	0.68 (0.62 to 0.74)	0.66 (0.60 to 0.72)	0.66 (0.60 to 0.73)

Abbreviations: AUC, area under the curve; LC, latent class; SIOG, International Society of Geriatric Oncology.
*No. (%) of events: no metastases, 74 (23.2%); metastases, 200 (59.7%).
†*P* values testing slope of regression of pseudovalues for event probabilities on predicted event probabilities over all time points at 1 year.
‡No. (%) of admissions: no metastases, 98 (32.6%); metastases, 140 (46.5%).
§Hosmer-Lemeshow test for G = 10 groups.

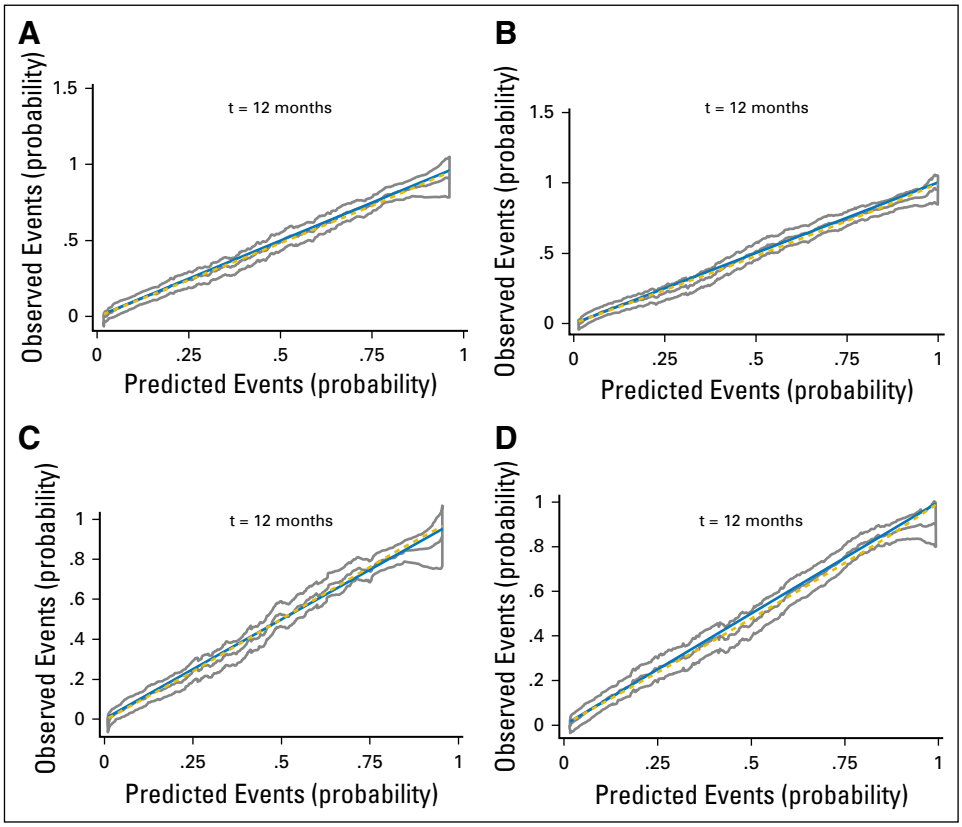

Fig A1. Calibration curves with their 95% CIs and tests of slope of the four classification models used to predict 1-year overall mortality in overall population: (A) Balducci, (B) SIOG1 (C) SIOG2, and (D) latent class typology.