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The prognostic value of patient-reported Health-Related Quality of Life and Geriatric Assessment in predicting early death in 6769 older (≥ 70 years) patients with different cancer tumors

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ABSTRACT

Objectives: We aimed to determine the prognostic value of baseline Health-Related Quality Of Life (HRQOL) and geriatric assessment (GA) to predict three-month mortality in older patients with cancer undergoing treatment.
Methods: Logistic regressions analysed HRQOL, as measured with the EORTC Global Health Status (GHS) scale, and geriatric information prognostic for early mortality controlling for oncology variables. The assessment was established with the odds ratio (OR), 95% confidence interval (CI) and level of significance set at $p < 0.05$. Discriminative power was evaluated with area under the curve (AUC).
Results: In total, 6769 patients were included in the study, of whom 1259 (18.60%) died at three months. Our model showed higher odds of early death for patients with lower HRQOL (GHS, OR 0.98, 95% CI 0.98–0.99;

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$p < 0.001$), a geriatric risk profile (G8 Screening Tool, 1.94, 1.14–3.29; $p = 0.014$), cognitive decline (Mini Mental State Examination, 1.41, 1.15–1.72; $p = 0.001$), being at risk for malnutrition (Mini Nutritional Assessment–Short Form, 1.54, 1.21–1.98; p = 0.001), fatigue (Visual Analogue Scale for Fatigue, 1.45, 1.16–1.82; $p = 0.012$) and comorbidities (Charlson Comorbidity index, 1.23, 1.02–1.49; $p = 0.033$). Additionally, older age, poor ECOG PS and being male increased the odds of early death, although the magnitude differed depending on tumor site and stage, and treatment (all $p < 0.05$). Predictive accuracy increased with 3.7% when including HRQOL and GA in the model.

Conclusion: The results suggest that, in addition to traditional clinical measures, HRQOL and GA provide additional prognostic information for early death, but the odds differ by patient and tumor characteristics.

1. Introduction

Despite the growing population of older patients with cancer [1], solid evidence about optimal treatment for this specific population is often lacking. This lack is mainly driven by trial inclusion criteria which exclude older patients due to their unfavourable expected symptom burden and toxicity and the fact that the endpoints chosen are not always relevant for older patients [2–4].

It is important for health care professionals to understand the characteristics of this vulnerable population to guide clinical decision-making. Short-term mortality prediction is crucial to select the optimal treatment in older patients with cancer, especially for aggressive treatments where such patients may have an increased risk of mortality. Within surgery, for example, the higher risk of postoperative mortality for older patients should be weighed against the potential benefits [5]. Differences in mortality chances can be explained by differences in tumor type or stage, patient characteristics or treatment [6]. In older patients, these chances can also be attributed to the presence of comorbidities, disabilities, and geriatric syndromes [7], representing serious conditions such as falls and functional decline, common to older patients [8]. In oncology, a threshold of age 70 years is often applied to define the older population [9].

Geriatric Assessment (GA) is primarily used by clinicians to decide on the best treatment in the older population with cancer. GA is a multidimensional, interdisciplinary evaluation tool that allows the identification of a patient's general health status including medical, cognitive, social, nutritional and psychological parameters [10]. In addition, research has also shown that GA can aid in predicting early death in older patients with cancer [11]. Similarly, patient-reported HRQOL provides crucial information for predicting mortality [12–15]. However, corresponding evidence for older patients with cancer remains scarce [16].

Early death, defined in our study as occurring within three months of study initiation, is considered a relevant time frame for this cancer population; if mortality within this short time frame can be adequately predicted, this could have a major impact on baseline treatment decisions. Patients who die within this period most likely will not completely benefit from their treatment, although they might endure severe toxicity.

In this study we provide results of a secondary analysis investigating the prognostic value of HRQOL and GA, in addition to traditional socio-demographic and clinical measures, for predicting early death in an older patient population with cancer. As age-related conditions may increase the risk of early mortality, we hypothesize that information about these conditions, collected through a GA, and a patient's perception of its own HRQOL improves the accuracy in predicting survival on top of traditional tumor and socio-demographic variables.

2. Patients and methods

2.1. Data

The data analysed here is derived from a prospective, multicentre, observational cohort study involving 8451 patients from 22 Belgian hospitals (8 academic and 14 non-academic) from November 2012 to February 2015 with the primary aim to assess the adherence to geriatric assessment-based recommendations and subsequent actions undertaken in older patients with cancer [17]. Patients eligible for this study were at least 70 years of age and had a newly diagnosed, relapsed or progressive invasive solid tumor (or hematological malignancy) at the start of the study. Socio-demographic patient characteristics such as age, gender as well as living situation and presence or absence of professional homecare were collected. Oncologic parameters such as Eastern Cooperative Oncology Group—Performance Status (ECOG PS), tumor characteristics (type and stage using the TNM classification [18]), and treatment details (surgery/radiotherapy/hormonal therapy/chemotherapy/combination of therapies/other) were recorded. The ECOG PS scale ranges from 0 (fully active, able to carry out all pre-disease activities without restriction) to 4 (bedbound) and was dichotomised into good (0–1) versus poor (2–4) ECOG PS. The endpoint was survival at three months after study inclusion with a time window of two weeks before and after. The study was approved by the Ethics Committees of all hospitals involved.

2.2. The EORTC QLQ-C30 global health status scale

To assess HRQOL, the European Organization for Research and Treatment Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Global Health Status (GHS) scale was used as this was the only QLQ-C30 scale collected to address the primary analysis. The EORTC QLQ-C30 GHS scale consists of two questions, “How would you rate your overall health during the past week?” and “How would you rate your overall quality of life during the past week?” and are combined into one score, whereby a higher score indicates a better HRQOL. The GHS score is linearly transformed to a 0–100 score to facilitate statistical interpretation.

2.3. Geriatric assessment

At baseline, all patients underwent a geriatric screening test with the Geriatric 8 (G8) screening tool [19] applied by a trained health care worker [20]. This tool contains eight questions with a total score ranging from 0 and 17. This tool was developed to separate older patients with cancer without a geriatric risk profile (G8 > 14) from those that need to undergo geriatric assessment (G8 ≤ 14) to guide the tailoring of geriatric interventions and/or treatment decision-making [17].

In addition to the G8, the following GA measures were collected at start of the study: Charlson Comorbidity Index (CCI) [21], Katz's Activities of Daily Living (ADL) [22], Lawton's instrumental Activities of Daily Living (iADL) [23], the Mini Mental State Examination (MMSE) [24], the Mini Nutritional Assessment–Short Form (MNA–SF) [25], the 15-item Geriatric Depression Scale (GDS15) [26], Visual Analogue Scales (VAS) for Pain and Fatigue, polypharmacy as measured by the number of different drugs (<5 versus ≥5) taken the week before treatment and the presence of falls in the past year (no falls versus at least one fall). The CCI categorizes comorbidities of patients on a scale from 0 to 37, where a score of zero indicates no comorbidities. Scores on the ADL

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Table 1
Distribution of baseline patient characteristics and *p*-value, assessing the statistical significant differences in patient characteristics, for those patients that died and were alive at three months (± 2 weeks).

	Patients who died within 3 months (± 2 weeks) after inclusion $N = 1259$ (18.60%)	Patients alive 3 months (± 2 weeks) after inclusion $N = 5510$ (81.40%)	*p*-value
Clinical and Socio-demographic variables			
Age (Mean(SD[a,b]))	80.33 (5.9)	78.37 (5.7)	<0.001
	1259 (100)	5510 (100)	
Gender			<0.001
Female	570 (45.27)	3110 (56.26)	
Male	689 (54.73)	2410 (43.74)	
Living situation			0.140
Home alone	422 (33.52)	1809 (32.83)	
Home with family member	74 (5.88)	320 (5.81)	
Home with partner	608 (48.29)	3043 (55.23)	
Institution (e.g. nursing home)	90 (7.15)	195 (3.54)	
Assisted living community apartment	44 (3.49)	91 (1.65)	
Other	15 (1.19)	48 (0.87)	
Unknown	6 (0.48)	4 (0.07)	
Professional homecare			0.004
No	605 (48.05)	2832 (51.40)	
Yes	647 (51.39)	2663 (48.33)	
Unknown	7 (0.56)	15 (0.27)	
Tumor type			<0.001
Solid tumor	1122 (89.12)	5098 (92.52)	
Hematological malignancy	137 (10.88)	412 (7.48)	
Treatment			<0.001
Chemotherapy	332 (26.37)	1028 (18.66)	
Surgery	127 (10.09)	1302 (23.63)	
Radiotherapy	94 (7.47)	323 (5.86)	
Hormonal therapy	26 (2.07)	232 (4.21)	
Combined therapy	372 (29.55)	2400 (43.56)	
Other	308 (24.46)	225 (4.08)	
Solid Tumor type			<0.001
Breast	77 (6.12)	1328 (24.10)	
Unknown primary site	42 (3.34)	31 (0.56)	
Digestive system	424 (33.68)	1664 (30.20)	
Genitourinary sites	169 (13.42)	870 (15.79)	
Gynecological sites	68 (5.40)	403 (7.31)	
Head and neck	49 (3.89)	206 (3.74)	
Musculoskeletal sites	16 (1.27)	47 (0.85)	
Skin	27 (2.14)	122 (2.21)	
Thorax	250 (19.86)	427 (7.75)	
Tumor stage			<0.001
I	31 (2.46)	819 (14.86)	
II	76 (6.04)	1235 (22.41)	
III	145 (11.52)	1248 (22.65)	
IV	788 (61.80)	1462 (26.53)	
NR[♯]	137 (10.88)	412 (7.48)	
Unknown	92 (7.31)	334 (6.06)	
Diagnosis			<0.001
Newly diagnosed	910 (72.28)	4421 (80.24)	
Relapsed/Progressed	349 (27.72)	1089 (19.76)	
ECOG Performance Status			<0.001
0–1 (good)	392 (31.14)	3930 (71.32)	
2–4 (poor)	866 (68.78)	1578 (28.64)	
Unknown	1 (0.08)	2 (0.04)	
HRQOL and geriatric variables			
EORTC GHS scale (Mean 0–100 (SD))	43.83 (22.21)	57.64 (22.29)	<0.001
	1052 (83.39)	3804 (69.11)	
G8 (0–17)			<0.001
> 14 (absence of a geriatric risk profile)	67 (5.32)	1924 (34.92)	
≤14 (presence of a geriatric risk profile)	1192 (94.68)	3586 (65.08)	
MMSE (0−30)			<0.001
≥24 (normal cognition)	657 (52.18)	2996 (54.37)	
<24 (cognitive impairment)	311 (24.70)	676 (12.27)	
Unknown	291 (23.11)	1838 (33.36)	
iADL (0–5 male/0–8 female)			<0.001
5 or 8 (independent)[c]	356 (28.28)	1796 (32.60)	
<5 or < 8 (dependent)	814 (64.65)	2191 (39.76)	
Unknown	89 (7.07)	1523 (27.64)	
ADL (6–24)			<0.001
6 (independent)	350 (27.80)	1816 (32.96)	
≥7 (dependent)	855 (67.91)	2190 (39.75)	
Unknown	54 (4.29)	1504 (27.30)	
MNA-SF (0–14)			<0.001
≥12 (normal nutrition)	119 (9.45)	1100 (19.96)	

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Table 1 (*continued*)

	Patients who died within 3 months (± 2 weeks) after inclusion N = 1259 (18.60%)	Patients alive 3 months (± 2 weeks) after inclusion N = 5510 (81.40%)	*p*-value
<12 (risk for malnutrition + malnourished)	1082 (85.94)	2913 (52.87)	
Unknown	58 (4.61)	1497 (27.17)	
GDS15 (0–15)			<0.001
≤4 (not at risk for depression)	520 (41.30)	2549 (46.26)	
>4 (at risk for depression)	489 (38.84)	1173 (21.29)	
Unknown	250 (19.86)	1788 (32.45)	
VAS Pain (0−10)			<0.001
0 (no pain)	497 (39.48)	1993 (36.17)	
>0 (presence of pain)	647 (51.39)	1931 (35.05)	
Unknown	115 (9.13)	1586 (28.78)	
VAS Fatigue (0–10)			<0.001
0 (no fatigue)	155 (12.31)	1064 (19.31)	
>0 (presence of fatigue)	966 (76.73)	2804 (50.89)	
Unknown	138 (10.86)	1642 (29.80)	
CCI (0–37)			<0.001
0 (no comorbidities)	278 (22.08)	1837 (33.34)	
≥1 (presence of comorbidities)	967 (76.81)	3636 (65.99)	
Unknown	14 (1.11)	37 (0.67)	
Polypharmacy			<0.001
0–4 number of drug	397 (31.53)	2663 (48.33)	
≥5 number of drug	828 (65.77)	2762 (50.13)	
Unknown	34 (2.70)	85 (1.54)	
Fall			<0.001
0 (no falls)	685 (54.41)	2635 (47.82)	
≥1 (presence of falls)	482 (38.28)	1345 (24.41)	
Unknown	92 (7.31)	1530 (27.77)	

[a] SD = Standard Deviation.

[b] NR = Not rated and applies to those patients with hematologic malignancies; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G8: geriatric 8 screening tool; MMSE: Mini Mental State Examination; iADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; MNA-SF: Mini Nutritional Assessment–Short Form; GDS: Geriatric Depression Scale; VAS: Visual Analogue Score; CCI: Charlson Comorbidity Index.

[c] score 5 for males and score 8 for females.

range from 6 (fully independent) to 24 (fully dependent) with dependency defined as a score > 6. The iADL summary score ranges from 0 to 8 for women and 0 to 5 for men, with the top scores indicating full independence. The Activities measured by the iADL differ from those measured by the ADL in that the former require more complex cognitive and motor skills and also measure a different level of independence. The MMSE is a 30-point questionnaire measuring cognitive impairment, where a score ≥ 24 points indicates normal cognition, 18–23 points mild impairment and ≤ 18 points significant impairment. The MNA–SF (score 0–14) is a validated screening tool that identifies geriatric patients aged 65 and above who are malnourished or at risk of malnutrition (< 12). Risk for depression is measured by the 15-item GDS–15 (score 0–15), with scores >4 indicating some degree of risk. The VAS for Fatigue is a self-reported measure consisting simply of a 10-cm line marked "no fatigue" at one end and "worst possible fatigue" at the other which the patient marks to indicate the degree of fatigue s/he is experiencing. The VAS for Pain is applied the same.

2.4. Statistical analysis

To assess significant differences in the distribution of patient characteristics between those who survived versus those who died at three months with a time window of two weeks, we used the *t*-test for normal distributed data, chi-square test for binary data and Kruskal-Wallis test for categorical data. Unknowns were omitted from this analysis.

Logistic regression models were used to assess the prognostic significance of baseline socio-demographic, clinical, HRQOL and GA characteristics for death at three months with a time window of two weeks. First, in the univariate model, each clinical (tumor type, treatment, tumor stage, diagnosis and ECOG PS), sociodemographic (age, gender, living situation, professional homecare), HRQOL (EORTC GHS scale) and GA variable (G8, MMSE, iADL, ADL, MNA-SF, GDS15, VAS Pain, VAS Fatigue, CCI, Polypharmacy and Falls) was independently assessed, with a level of significance (p) less than 0.05, to identify independent prognostic variables. A second univariate analysis was carried out whereby 100 bootstrap samples of the original dataset were drawn and missing values were imputed ($n = 20$), using multiple imputation chained equations (MICE) [27], in each of the bootstrap samples to produce robust estimates [28,29].

The final list of statistically significant ($p < 0.05$) parameters from the univariate level, derived from the imputed dataset, were included in an initial multivariate model and a backward selection was applied to eliminate nonsignificant parameters with a criterion of p greater than 0.05. Thereafter, a forward selection, with a criterion of p less than 0.05, was used to add the nonsignificant individual parameters from the univariate analysis in the final model obtained with backward selection. At last, we used a stepwise selection procedure to ensure that a final model was obtained in which no further parameters could be either removed or included. We performed two multivariate models: a multivariate model including socio-demographic and clinical variables alone, and a multivariate model including additionally HRQOL and GA variables.

The association was assessed with the odds ratio (OR), its 95% confidence interval (CI) and the *p*-value (set at 5%) of the Wald $\chi 2$ statistic. OR measures the strength of association between the independent variable and early death. An OR equal to 1 means that the independent variable does not affect the odds of early death. An OR > 1 means that the independent variable is associated with higher odds, while an OR < 1 means that the independent variable is associated with lower odds.

The reported OR of the HRQOL scale takes into consideration the clinically important difference, defined as the smallest difference in a score in the domain of interest which a patient perceives as beneficial and which would mandate a change in patient management [30]. Osoba and colleagues [31] defined a threshold of 10 points to categorise patients as improved stable or worsened on the EORTC QLQ–C30 scales and items. Similar thresholds have been reported for an older population with cancer [32]. Therefore OR for the EORTC GHS scale was calculated for every 10-point difference.

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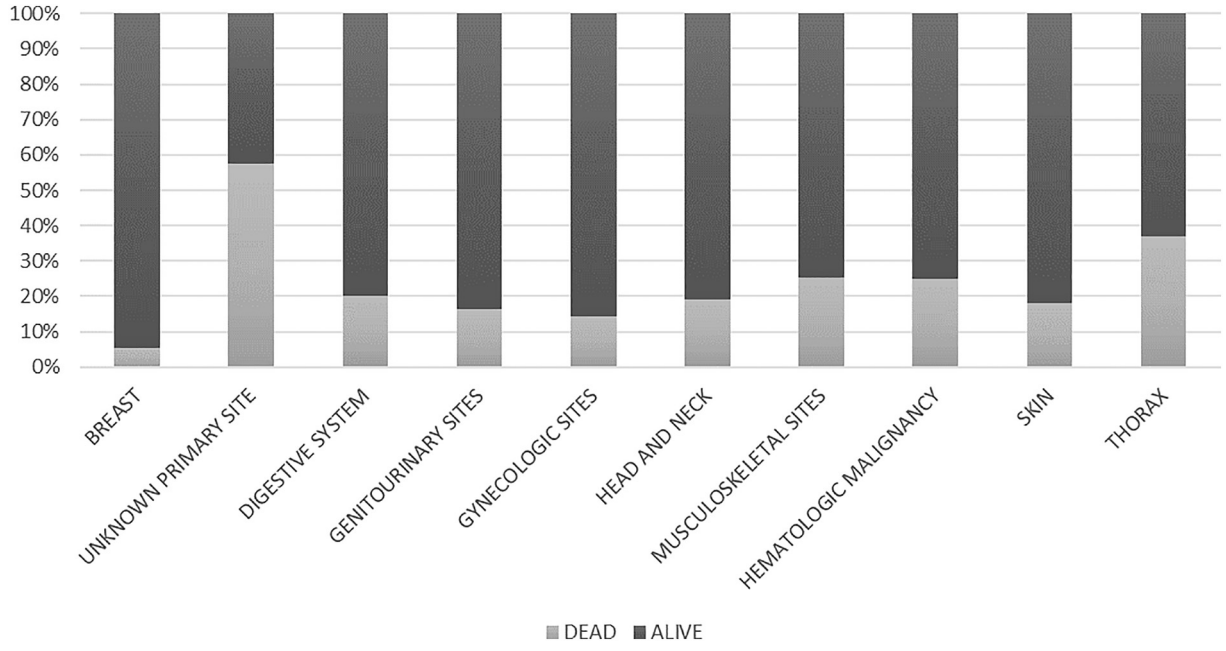

FIG. 1. The distribution of survival status per tumor type.

The discriminative power was assessed with the area under the curve (AUC). Several AUC were calculated to account for potential multicollinearity [33] as previous analyses on the same dataset revealed strong correlation between the GHS scale, ECOG PS and several GA scales [32].

Four AUC were calculated; one for clinical and socio-demographic variables retained in the final model; one for clinical, socio-demographic and GA variables retained in the final model; one for clinical, socio-demographic and HRQOL variables retained in the final model and one for clinical, socio-demographic, GA and HRQOL variables retained in the final model.

Finally, a nomogram [34] was developed to visualize the outcomes of the final multivariate model and to assess the probability of dying at month three for an individual patient. When developing nomograms, individual patient's score for each variable will be calculated. The sum of the scores can predict the three-month mortality for an individual patient. A nomogram can be used to facilitate the interpretation and the communication with the patient.

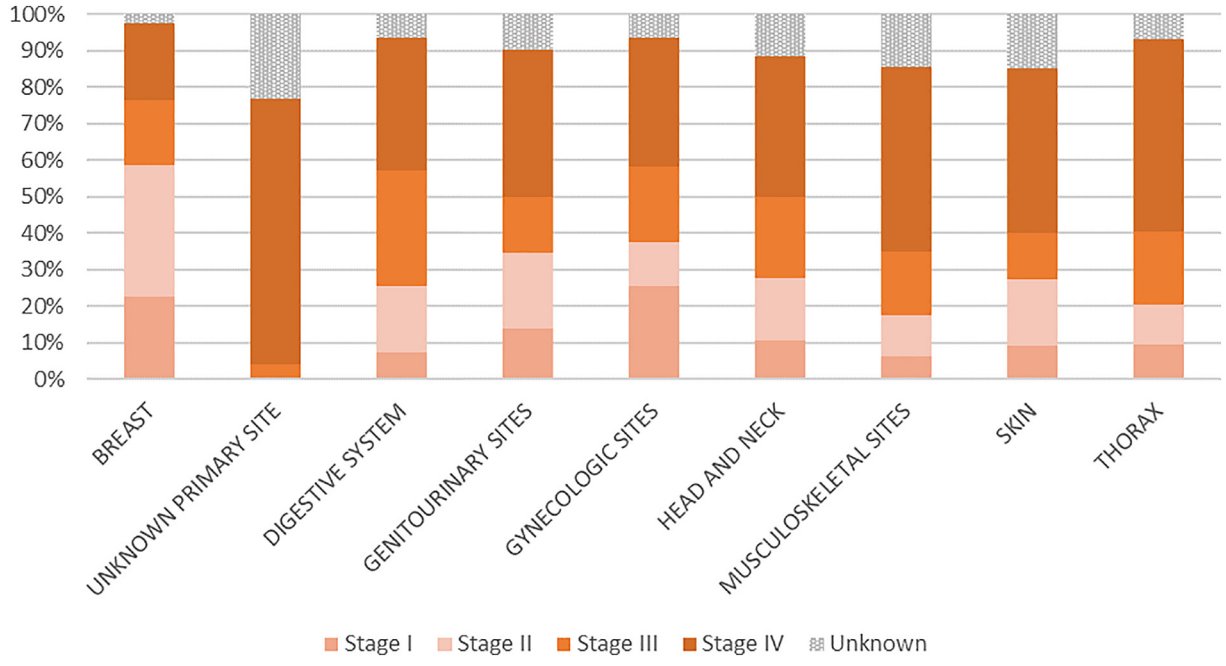

FIG. 2. The distribution of cancer stage per tumor type[Π]. [Π]Since the staging system is not used for most hematologic malignancies, this cancer group was omitted from the figure.

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Table 2
Univariate regression analyses to assess the association between socio- demographic, HRQOL and geriatric measures and survival status before and after multiple imputation.

	Univariate Analysis before imputed for the unknowns		Univariate Analysis after imputed for the unknowns	
	OR (CI)	*p*-value	OR (CI)	*p*-value
Socio-demographic and clinical variables				
Age	1.06 (1.05;1.07)	<0.001	1.06 (1.05;1.07)	<0.001
Gender				
Female	1.00		1.00	
Male	1.56 (1.37;1.76)	<0.001	1.56 (1.37;1.76)	<0.001
Living situation				
Home alone	1.00	-	1.00	
Home with family member	0.99 (0.75;1.30)	0.950	0.99 (0.75;1.30)	0.955
Home with partner	0.86 (0.75;0.98)	0.027	0.86 (0.75;0.98)	0.029
Institution (e.g. nursing home)	1.98 (1.51;2.59)	<0.001	1.98 (1.51;2.60)	<0.001
Assisted living community apartment	2.07 (1.42;3.02)	<0.001	2.07 (1.42;3.02)	<0.001
Other	1.33 (0.74;2.41)	0.331	1.34 (0.75;2.42)	0.326
Unknown	6.43 (1.79;22.67)	0.004	-	-
Professional homecare				
No	1.00		1.00	
Yes	1.12 (0.99;1.27)	0.065	1.13 (0.97;1.29)	0.067
Unknown	2.15 (0.87;5.30)	0.095	-	-
Tumor type				
Solid tumor	1.00		1.00	
Hematologic malignancy	1.51 (1.24;1.86)	<0.001	1.51 (1.24;1.86)	<0.001
Treatment				
Surgery	1.00		1.00	
Combined	1.59 (1.28;1.97)	<0.001	1.59 (1.28;1.97)	<0.001
Radiotherapy	2.98 (2.23;4.00)	<0.001	2.98 (2.23;4.00)	<0.001
Hormonal therapy	1.14 (0.74;1.79)	0.568	1.14 (0.74;1.79)	0.568
Chemotherapy	3.31 (2.65;4.13)	<0.001	3.31 (2.65;4.13)	<0.001
Other	14.04 (10.92;18.03)	<0.001	14.03 (10.92;18.03)	<0.001
Solid Tumor type				
Breast	1.00		1.00	
Unknown primary site	23.36 (13.92;39.22)	<0.001	23.36 (13.92;39.22)	<0.001
Digestive system	4.39 (3.41;5.66)	<0.001	4.39 (3.41;5.66)	<0.001
Genitourinary sites	3.35 (2.53;4.44)	<0.001	3.35 (2.53;4.44)	<0.001
Gynecological sites	2.91 (2.06;4.11)	<0.001	2.91 (2.06;4.11)	<0.001
Head and neck	4.10 (2.78;6.04)	<0.001	4.10 (2.78;6.04)	<0.001
Musculoskeletal sites	5.87(3.18;10.83)	<0.001	5.87 (3.18;10.83)	<0.001
Hematologic malignancy	5.73 (4.25;7.74)	<0.001	5.73 (4.25;7.74)	<0.001
Skin	3.81 (2.37;6.14)	<0.001	3.81 (2.37;6.14)	<0.001
Thorax	10.09 (7.64;13.33)	<0.001	10.09 (7.64;13.33)	<0.001
Tumor stage				
I	1.00		1.00	
II	1.63 (1.06;2.49)	0.026	1.62 (1.06;2.49)	0.018
III	3.07 (2.06;4.57)	<0.001	2.90 (1.97;4.27)	<0.001
IV	14.06 (9.73;20.36)	<0.001	12.21 (8.51;17.51)	<0.001
NR[a]	8.78 (5.84;13.20)	<0.001	8.06 (5.44;11.94)	<0.001
Unknown	7.28 (4.75;11.14)	<0.001	-	-
Diagnosis				
Newly diagnosed	1.00		1.00	
Relapsed/Progressed	1.56 (1.35;1.79)	<0.001	1.56 (1.35;1.79)	<0.001
ECOG Performance Status				
0–1 (good)	1.00		1.00	
2–4 (poor)	5.50 (4.81;6.28)	<0.001	5.49 (4.80;6.27)	<0.001
Unknown	5.01 (0.45;55.40)	0.189	-	-
HRQOL and geriatric measures				
EORTC GHS scale	0.99 (0.99;0.99)[b]	<0.001	0.99 (0.99;0.99)	<0.001
G8 (0–17)				
>14 (absence of a geriatric risk profile)	1.00		1.00	
≤14 (presence of a geriatric risk profile)	9.54 (7.41;12.28)	<0.001	9.54 (7.41;12.28)	<0.001
MMSE (0–30)				
≥24 (normal cognition)	1.00		1.00	
<24 (cognitive impairment)	2.09 (1.79;2.46)	<0.001	2.40 (2.06;2.80)	<0.001
Unknown	0.72 (0.62;0.84)	<0.001	-	-
iADL (0–5 male/0–8 female)				
5 or 8 (independent)[c]	1.00		1.00	
<5 or < 8 (dependent)	1.87 (1.63;2.15)	<0.001	2.29 (1.99;2.64)	<0.001
Unknown	0.29 (0.23;0.38)	<0.001	-	-
ADL (6–24)				
6 (independent)	1.00		1.00	
≥7 (dependent)	2.02 (1.76;2.33)	<0.001	2.24 (1.95;2.58)	<0.001
Unknown	0.18 (0.14;0.25)	<0.001	-	-
MNA-SF (0–14)				
≥12 (normal nutrition)	1.00		1.00	
<12 (risk for malnutrition + malnourished)	3.43 (2.80;4.20)	<0.001	3.43 (2.81;4.20)	<0.001
Unknown	0.35 (0.26;0.49)	<0.001	-	-

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Table 2 (*continued*)

	Univariate Analysis before imputed for the unknowns		Univariate Analysis after imputed for the unknowns	
	OR (CI)	*p*-value	OR (CI)	*p*-value
GDS15 (0–15)				
≤4 (not at risk for depression)	1.00		1.00	
>4 (at risk for depression)	2.04 (1.77;2.35)	<0.001	2.40 (2.08;2.77)	<0.001
Unknown	0.69 (0.58;0.81)	<0.001	-	-
VAS Pain (0–10)				
0 (no pain)	1.00		1.00	
>0 (presence of pain)	1.34 (1.18;1.53)	<0.001	1.48 (1.29;1.69)	<0.001
Unknown	0.29 (0.23;0.36)	<0.001	-	-
VAS Fatigue (0–10)				
0 (no fatigue)	1.00		1.00	
>0 (presence of fatigue)	2.36 (1.96;2.84)	<0.001	2.72 (2.27;3.29)	<0.001
Unknown	0.58 (0.45;0.73)	<0.001	-	-
CCI (0–37)				
0 (no comorbidities)	1.00		1.00	
≥1 (presence of comorbidities)	1.77 (1.52;2.03)	<0.001	1.75 (1.52;2.03)	<0.001
Unknown	2.50 (1.33;4.68)	0.004	-	-
Polypharmacy				
0–4 number of drugs	1.00		1.00	
≥5 number of drugs	2.01 (1.76;2.30)	<0.001	2.01 (1.76;2.29)	<0.001
Unknown	2.68 (1.77;4.04)	<0.001	-	-
Fall				
0 (no falls)	1.00		1.00	
≥1 (presence of falls)	1.37 (1.21;1.58)	<0.001	1.52 (1.32;1.75)	<0.001
Unknown	0.23 (0.18;0.29)	<0.001	-	-

[a] NR = Not rated and applies to those patients with hematologic malignancies.
[b] Based on a 10- point difference on the EORTC GHS scale.
[c] Score 5 for males and score 8 for females. ECOG-PS: Eastern Cooperative Oncology Group–Performance Status; G8: geriatric 8 screening tool; MMSE: Mini Mental State Examination; iADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; MNA-SF: Mini Nutritional Assessment–Short Form; GDS: Geriatric Depression Scale; VAS: Visual Analogue Score; CCI: Charlson Comorbidity Index.

3. Results

In total, 8451 patients were enrolled in the study, of whom 1244 were excluded from the final analysis because no follow-up data on their survival were collected. A further 1027 patients were excluded as their survival status was collected outside the time window. As the number of patients with ophthalmic tumors was too small ($n = 3$) to draw meaningful conclusion, this type was omitted from further analysis. In addition, we removed those patients with cancer of the central nervous system (=59) as tumor staging for this tumor type is defined differently. This left a total of 6769 patients included in the study, of whom 5510 (81.40%) were still alive at three months and 1259 (18.60%) had died at three months.

Table 1 shows the distribution of patients in terms of socio-demographic, clinical, HRQOL and GA variables. The GHS and GA scores for those patients who died at three months were significantly worse than those who were alive. (See Appendix Fig. 1 for more summary statistics). The median time from diagnosis to study initiation was 11 days for those patients who died versus 16 days for those alive at three months. The cause of death was disease related for 80% of the patients included in the analysis, 7% died due to complication of the therapy and 13% due to other causes (mainly comorbidity). For a more detailed distribution per treatment please see Appendix Fig. 2.

Fig. 1 shows the three-month mortality rate per tumor type. The highest proportion of deaths was reported among patients with unknown primary site cancer (58%), followed by thorax cancers (37%). Patients with breast cancer had the lowest mortality (5%) and were used as the reference group in our models. Patients with breast cancer included mainly patients with good ECOG PS.

Fig. 2 shows the distribution in terms of cancer stage per tumor type. The results show that, among those reported, advanced cancers (Stage IV) were most heavily represented in the group with unknown primary site cancer (73%), followed by thorax (53%) and musculoskeletal (51%) cancers.

Table 2 tabulates the results of the univariate analysis assessing the association between baseline patient characteristics and early death at three months. Except for professional home care, all baseline characteristics were statistically significantly associated ($p < 0.05$) with three-month death. The odds of experiencing early death increased for those patients who stayed in an institution (OR = 1.98; $p < 0.001$) or an assisted living community apartment (OR = 2.07; $p < .001$) compared to those patients who lived alone at home. For patients who lived with a partner the odds decreased (OR = 0.86; $p = 0.027$). The odds of experiencing early death increased fivefold for patients with a poor baseline ECOG performance status (OR = 5.50; $p < 0.001$) compared to those with a good baseline ECOG performance status. The table shows that for each 10-point increase in the baseline GHS score the odds of early death decreased by 1% (1–0.99). A poorer assessment on any of the geriatric measures at baseline increased the odds of early death significantly (all $p < 0.001$). Similar associations were reported when the dataset was imputed for missing values.

Table 3 shows the results of the two final multivariate models after applying the selection procedures to the initial multivariate models. The first model contains only the socio-demographic and clinical variables. Older age, being male and poor ECOG PS at baseline increased the odds of experiencing early death. This increased risk was also seen for those patients who had a higher stage tumor (stage III; OR = 2.09; $p = 0.001$ or IV; OR = 7.04; $p < 0.001$) compared to those whose tumor was at a more favourable stage I. Patients who underwent any treatment involving more than just surgery, except for those with hormonal treatment ($p = 0.307$), had increased odds of experiencing early death compared to the surgery group, which was the reference group in our study.

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The second model included, in addition to the clinical and socio-demographic variables, the HRQOL and GA measures. Besides poor baseline GHS, a geriatric risk profile (G8), a cognitive decline (MMSE), being at risk for malnutrition or being malnourished (MNA-SF), fatigue (VAS Fatigue) and having comorbidities (CCI) at baseline were all statistically significantly ($p < 0.05$) associated with increased odds for early death at three months after treatment decision.

AUC results show that the discriminative power for survival prediction increased from 0.8125 to 0.8426, a relative moderate increase of 3.7%, when including HRQOL and GA variables on top of socio-demographic and clinical variables. The AUC was 0.8283 when only GA variables were included in the model and 0.8204 when only HRQOL was included on top of socio-demographic and clinical variables.

Fig. 3 displays the nomogram for predicting death at month-three using the estimates of the final multivariate model (see Table 3) including socio-demographic, clinical, HRQOL and GA variables. This particular example shows the risk of dying at month three for an 80-year old female with a good ECOG-PS and the following clinical (breast tumor, stage III) and geriatric characteristics (presence of a geriatric risk profile, normal cognition, normal nutrition, presence of fatigue and comorbidities) and EORTC Global Health Score of 60 scheduled for chemotherapy. The individual score for each of the variables are identified with the red vertical lines. The total score is around 20.5 points. For this patient, the probability of dying at month three is about 10% when relying on the estimates of our model.

Table 3
The results of the final multivariate regression analyses to assess the association between socio- demographic, HRQOL and geriatric measures and mortality.

	Multivariate Analysis with socio-demographic and clinical variables		Multivariate Analysis with socio-demographic, clinical, HRQOL and GA variables	
	OR (CI)	*p*-value	OR (CI)	*p*-value
Socio-demographic and clinical variables				
Age	1.04 (1.02;1.05)	<0.001	1.03 (1.02;1.05)	<0.001
Gender				
Female	1.00		1.00	
Male	1.23 (1.04;1.45)	0.014	1.32 (1.09;1.59)	0.001
Treatment				
Surgery	1.00		1.00	
Combined	1.25 (0.97;1.60)	0.077	1.14 (0.86;1.51)	0.356
Radiotherapy	1.42 (1.01;1.99)	0.054	1.29 (0.88;1.88)	0.188
Hormonal therapy	0.76 (0.46;1.27)	0.307	0.72 (0.41;1.26)	0.250
Chemotherapy	1.46 (1.11;1.91)	0.006	1.23 (0.91;1.66)	0.179
Other	4.52 (3.38;6.06)	<0.001	3.81 (2.75;5.29)	<0.001
Solid Tumor type				
Breast	1.00		1.00	
Unknown primary site	5.38 (2.91;9.96)	<0.001	5.32 (2.69;10.51)	<0.001
Digestive system	2.62 (1.93;3.56)	<0.001	2.35 (1.67;3.31)	<0.001
Genitourinary sites	1.76 (1.25;2.47)	0.001	1.97 (1.35;2.88)	<0.001
Gynecological sites	1.92 (1.30;2.84)	0.001	2.08 (1.35;3.22)	0.001
Head and neck	2.38 (1.52;3.74)	<0.001	2.40 (1.46;3.93)	<0.001
Musculoskeletal sites	2.70 (1.33;5.51)	0.006	2.48 (1.13;5.49)	0.024
Hematologic malignancy	2.96 (1.02;8.59)	0.046	2.22 (0.67;7.27)	0.185
Skin	1.82 (1.05;3.14)	0.032	2.36 (1.28;4.35)	0.006
Thorax	4.86 (3.46;6.83)	<0.001	4.02 (2.74;5.88)	<0.001
Tumor stage				
I	1.00		1.00	
II	1.51 (0.98;2.32)	0.061	1.33 (0.82;2.17)	0.241
III	2.09 (1.39;3.16)	0.001	1.84 (1.15;2.91)	0.010
IV	7.04 (4.75;10.45)	<0.001	5.91 (3.80;9.20)	<0.001
NR[a]	-	-	-	-
ECOG Performance Status				
0–1 (good)	1.00		1.00	
2–4 (poor)	4.27 (3.68;4.96)	<0.001	2.25 (1.89;2.69)	<0.001
HRQOL and geriatric measures				
EORTC GHS scale			0.98 (0.98;0.99)[b]	<0.001
G8 (0–17)				
>14 (absence of a geriatric risk profile)			1.00	
≤14 (presence of a geriatric risk profile)			1.94 (1.14;3.29)	0.014
MMSE (0–30)				
≥24 (normal cognition)			1.00	
<24 (cognitive decline)			1.41 (1.15;1.72)	0.001
MNA-SF (0–14)				
≥12 (normal nutrition)			1.00	
<12 (risk for malnutrition + malnourished)			1.54 (1.21;1.98)	0.001
VAS Fatigue (0–10)				
0 (no fatigue)			1.00	
>0 (presence of fatigue)			1.45 (1.16;1.82)	0.001
CCI (0–37)				
0 (no comorbidities)			1.00	
≥1 (presence of comorbidities)			1.23 (1.02;1.49)	0.033

[a] NR = Not rated and applies to those patients with hematologic malignancies.
[b] Based on a 10- point difference on the EORTC GHS scale. ECOG-PS: Eastern Cooperative Oncology Group–Performance Status; G8: Geriatric 8 screening tool; MMSE: Mini Mental State Examination; MNA-SF: Mini Nutritional Assessment–Short Form.

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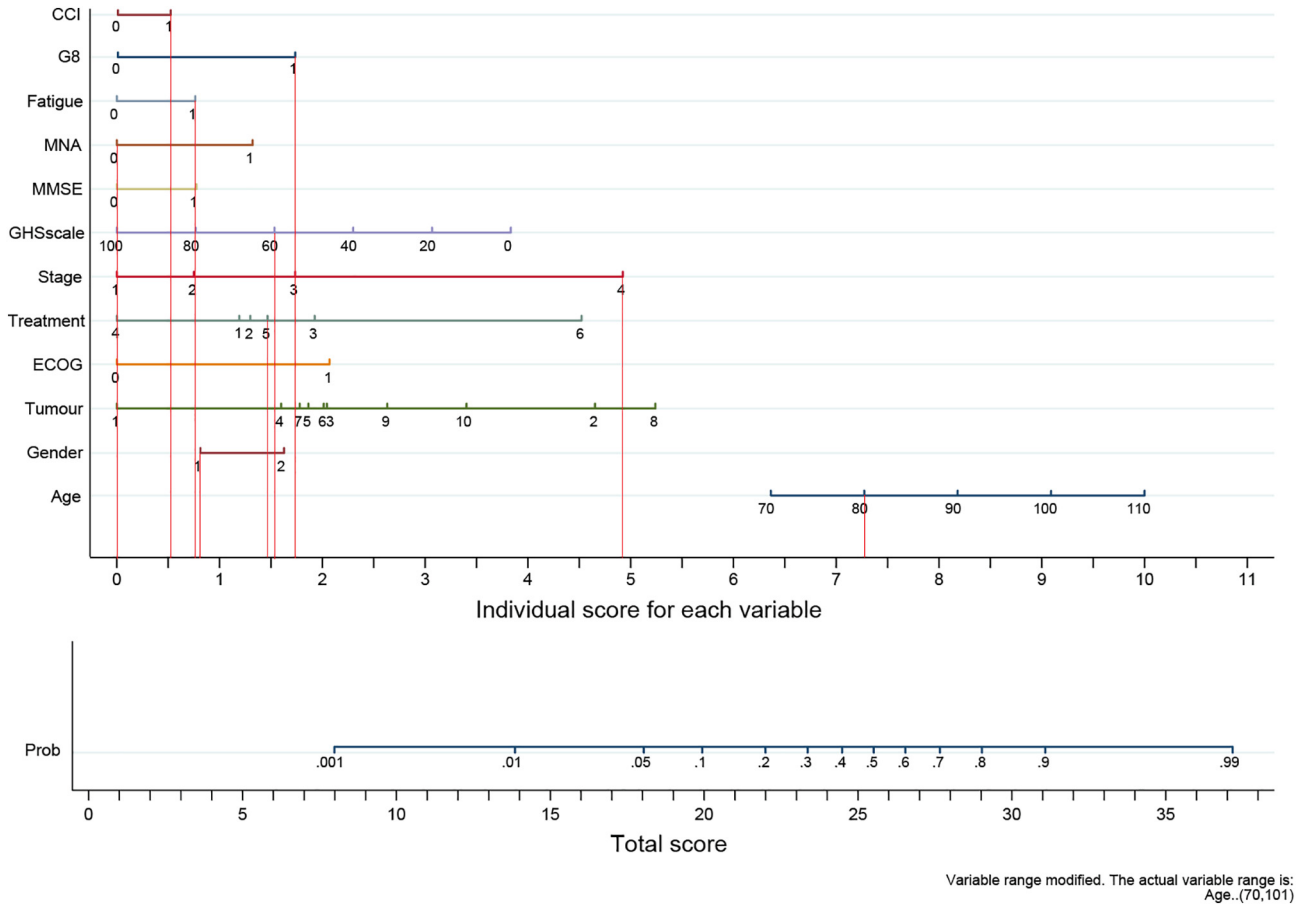

Fig. 3. Nomogram for predicting survival status at three months using the estimates of the final multivariate model with socio-demographic, clinical, HRQOL and GA variables. CCI; Charlson Comorbidity index, 0 = no comorbidities, 1 = comorbidities. G8; G8 screening tool, 0 = absence of a geriatric risk profile, 1 = presence of a geriatric risk profile. Fatigue; Visual Analogue Scale for Fatigue, 0 = no fatigue, 1 = presence of Fatigue. MNA; Mini Nutritional Assessment – Short Form, 0 = normal nutrition, 1 = risk for malnutrition + malnourished. MMSE; Mini Mental State Examination, 0 = normal cognition, 1 = cognitive decline. GHSscale; EORTC Global Health Status scale, 100 = good global health, 0 = poor global health Stage; TNM Classification, 1 = Stage I, 2 = Stage II, 3 = Stage III, 4 = Stage IV. Treatment; 1 = Surgery, 2 = Combined, 3 = Radiotherapy, 4 = Hormonal therapy, 5 = Chemotherapy, 6 = Other. ECOG; Eastern Cooperative Oncology Group - Performance Scale, 0 = good, 1 = poor. Tumor type; 1 = Breast, 2 = Unknown Primary Site, 3 = Digestive System, 4 = Genitourinary sites, 5 = Gynecologic sites, 6 = Head and Neck, 7 = Musculoskeletal sites, 8 = Hematologic Malignancy 9 = Skin, 10 = Thorax. Gender; 1 = Female, 2 = Male. This tool is not applicable to a person with a hematologic malignancy.

4. Discussion

In this study we investigated the prognostic value of HRQOL and GA on top of traditional measures in predicting early death. Our study showed that the odds of experiencing early death increased for those patients with a lower quality-of-life (low GHS score), a geriatric risk (high G8 score), a cognitive decline (low MMSE score), signs of malnutrition or malnourishment (low MNA-SF score), fatigue (high VAS Fatigue score) and the presence of comorbidities (high CCI score) at the start of study. Including above HRQOL and GA information next to age, gender, stage and ECOG-PS improved the accuracy in prediction early death for an individual patient.

The observation that G8 is a strong prognostic predictor for early death has been shown in several previous studies [35,36] and confirms the discriminatory power of a G8 score to identify those older patients who are less likely to benefit from standard care [37]. The existing literature [38,39] also confirms the prognostic value of MNA–SF for one-year mortality in patients older than 70 years. That both the G8 and MNA-SF are prognostic for early death can be explained by the fact that the G8 consists of most items (appetite changes, weight loss, mobility, neuropsychological problems, body mass index, medication, and self-rated health) of the MNA-SF. However, to our knowledge the present study is the first to report VAS Fatigue scores to be prognostic for post-treatment mortality in older patients with cancer, although previous studies have indicated self-reported fatigue to be prognostic for survivalin a heterogeneous sample of younger patients with cancer [40–42].

The association between poor ECOG PS and shorter survival in older patients was also reported in previous study [43], even next to GA measures [44]. However this association does not always hold as reported by Soubeyran et al. [12] This might be explained by potential multicollinearity between ECOG PS and several GA measures as they address similar health domains and are strongly correlated. The strong correlation found in this study between G8 and ADL ($r = 0.62$) and G8 and iADL ($r = 0.61$) might also explain why both ADL and iADL became insignificant in the multivariate model and G8 was retained in the model offering stronger prognostic information, as reported through the OR, than ALD and iADL. Similarly, it is well known that there is a strong correlation between ECOG PS and the EORTC–GHS scale [25]. After including GHS and GA measures in our multivariate model, the OR of ECOG PS became smaller. The reported OR of the GHS scale is smaller than those of the dichotomized GA measures and ECOG PS addressing similar health domains. This can be explained by the fact that the GHS score is divided into much smaller intervals (10 points on the 0–100 scale) than the other measures, which are dichotomized into only two groups. For any dichotomized measure, a shift from one subgroup to the other will result in a much bigger change in the status of the patient.

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The cause of death was disease-related for 80% of the cases. This high proportion of deaths related to cancer and not the treatment received might explain why treatment was not a strong prognostic variable for early death. Only patients who had other therapies had increased odds of dying than the surgery group. The latter included mainly skin tumors with high survival probabilities, while more than half of patients receiving other therapies had stage IV cancer and poor ECOG PS or had cancer with unknown primary site (CUP), all known to be associated with poor survival.

To our knowledge, our analysis is the first to offer insight into three-month mortality in a very large heterogeneous sample of older patients with different cancers. That said, our study presents some limitations. First, setting the cut-off at three months gives us a relatively close outcome horizon. However, our dataset included patients with a very poor survival prognosis (80% were cancer-related deaths) and included cancers (e.g., CUP) with a median life expectancy of only three months [45]. Patients dying within three months of receiving treatment are very unlikely to receive any benefit irrespective of the cause of death, be it side-effects from treatment, cancer progression, or any other factor and the treatment might do more harm than good [46,47]. Nonetheless, concrete plans are currently being made to update the median follow-up period of the study population to focus more on treatment-related factors associated with overall survival.

Another limitation is that our study included patients with a variety of cancer types making our findings might may be less "actionable" for clinicians working within specific tumor settings and treatment characteristics. Notwithstanding, our dataset included a relatively large proportion (29%) of older patients with poor ECOG PS scores, a population that is frequently excluded from clinical research that leads to the development of evidence-based treatment guidelines. This makes our findings more applicable to a broader older population with cancer.

Finally, to demonstrate the usability and to safeguard the interpretability of the nomograms by clinicians, interactions terms were not considered in this model. Patients with certain tumors were more likely to have late stage disease (stage III or IV) than others in our dataset. Including these interaction terms would further improve the prognostic performance of the nomogram. Further internal and external validation using an independent adequately powered patient cohort will further strengthen the applicability.

In conclusion, our study shows that, when it comes to deciding optimal treatment for an older patient with cancer, a comprehensive picture, including HRQOL and GA information, should preferably be taken into consideration. Our study demonstrates that baseline HRQOL and GA can aid in predicting which patients run a higher risk of early death. Being able to predict three-month overall survival is very important for taking oncological decisions. Given the large sample size featured in this study, the predictors identified likely represent true predictors. If the risk of dying within three months is high, the use of aggressive anticancer treatments such as chemotherapy or extensive surgery/radiotherapy may be contraindicated. External validation can be helpful, however, and may allow the construction of a formal calculator that can individually predict three-month overall survival for all older patients with cancer requiring treatment.

Author contributions

CQ, HW and CK were responsible for the conception and design of this study. CQ, HW and CK designed the statistical aspects of this study. LD, PRD, IDG, FC, CF, FC, VV, CB, DB, SL, GD, HVDB, JCG, DS, KG, BP, CL, RVR, PS, GJ, JPP, KV, ML, JF, KM, JPL and HW provided study materials or patients. HW and CK collected and assembled data. CQ, HW, CK, analysed and interpreted the data and contributed to the writing of the report. All authors approved the final version.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2020.03.017.

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