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RESEARCH ARTICLE

Cardiovascular health-related quality of life in cancer: a prospective study comparing the ESC HeartQoL and EORTC QLQ-C30 questionnaire

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Aims Health-related quality of life (HRQoL) is highly relevant in cancer and often assessed with the EORTC QLQ-C30. Cardiovascular HRQoL in cancer can be measured with the ESC HeartQoL questionnaire. We compared these instruments and examined their prognostic value.

Methods and results Summary scores for EORTC QLQ-C30 (0–100 points) and ESC HeartQoL (0–3 points) questionnaires were prospectively assessed in 290 patients with mostly advanced cancer (stage 3/4: 81%, 1-year mortality: 36%) and 50 healthy controls (similar age and sex). Additionally, physical function and activity assessments were performed. Both questionnaires demonstrated reduced HRQoL in patients with cancer versus controls (EORTC QLQ-C30: 67 ± 20 vs. 91 ± 11, $p < 0.001$; ESC HeartQoL: 1.8 ± 0.8 vs. 2.7 ± 0.4, $p < 0.001$). The instruments were strongly correlated with each other (summary scores [$r = 0.76$], physical [$r = 0.81$], and emotional subscales [$r = 0.75$, all $p < 0.001$]) and independently associated with all-cause mortality (best cut-offs: EORTC QLQ-C30 <82.69:

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hazard ratio [HR] 2.33, $p = 0.004$; ESC HeartQoL <1.50: HR 1.85, $p = 0.004$ – adjusted for sex, age, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide [NT-proBNP], high-sensitivity troponin T, cancer stage/type), with no differences in the strength of the association by sex (p-interaction > 0.9). Combining both questionnaires identified three risk groups with highest mortality in patients below both cut-offs (vs. patients above both cut-offs: HR 3.60, $p < 0.001$). Patients with results below both cut-offs, showed higher NT-proBNP and reduced physical function and activity.

Conclusions The EORTC QLQ-C30 and ESC HeartQoL – assessing cancer and cardiovascular HRQoL – are both associated with increased mortality in cancer patients, with even greater stratification by combing both. Reduced HRQoL scores were associated with elevated cardiovascular biomarkers and decreased functional status.

Keywords Quality of life • Cancer • EORTC QLQ-C30 • HeartQoL

Introduction

Health-related quality of life (HRQoL) is becoming increasingly important as cancer survival improves, thanks to novel anti-cancer therapies such as immune checkpoint inhibitors and targeted therapies.[1–4] The main factors influencing HRQoL in patients with cancer include symptoms, cancer stage, treatment status, psychosocial and spiritual factors, financial security, and social support.[5,6] Cardiovascular disease is increasingly recognized as a major health problem in patients with cancer, both at the time of initial diagnosis due to similar risk factors and after treatment[7–9] due to cancer-related factors, including metabolic and oxidative stress, increased cytokines and neurohormones, tissue hypoxia, oncometabolite, and the cardiovascular toxicity of some anti-cancer therapies.[10–12] Cardiovascular disease can also negatively impact the quality of life in patients with cancer.[13,14] Oncologists and cardiologists regularly assess the HRQoL in their patients with advanced disease, but both fields ask different questions for assessing this. Therefore, we prospectively tested in patients with mostly advanced cancer whether both a cancer-oriented HRQoL questionnaire (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30])[15] and a cardiovascular-oriented HRQoL questionnaire (Heart Quality of Life questionnaire [HeartQoL])[16,17] were associated with mortality independently and in a combined model, and whether both HRQoL (EORTC QLQ-C30 and HeartQoL) summary scores are associated with cardiovascular biomarkers, other patient-reported outcomes (appetite and pain), and physical functioning.

Methods

Patient population

Between November 2017 to March 2020, the EORTC QLQ-C30 and HeartQoL questionnaires were prospectively assessed in 290 hospitalized patients with cancer and 50 healthy controls at Charité-Universitätsmedizin, Berlin, Germany and the Medical University of Göttingen, Göttingen, Germany. Most common causes for hospital admission included the administration of anti-cancer therapy and cancer staging/diagnostics (both 40%). All patients with cancer had a histologically confirmed cancer diagnosis and no secondary cancer diagnosis within the previous 5 years before enrolment. Exclusion criteria included: (1) an acute infection (clinical signs or current antibiotic treatment), (2) significant cardiovascular disease (e.g. current or prior myocardial infarction or diagnosed heart failure), (3) diagnosed chronic obstructive pulmonary disease (COPD) with GOLD stage >II[18] (except in patients with lung cancer, in whom all GOLD stages were allowed). Controlled arterial hypertension or type 2 diabetes mellitus were no exclusion criteria for patients with cancer. For comparison, 50 healthy controls (1:6 ratio) of similar age and sex as patients with cancer, without significant cardiovascular disease or an acute infection, were included. As in patients with cancer, controlled arterial hypertension or type 2 diabetes mellitus were allowed in healthy controls. All healthy controls underwent the same study protocol as the patients with cancer. Advanced stage cancer was defined as: stage III/IV for Ann Arbor classification,[19] stage III/IV Union for International Cancer Control (UICC),[20] and stage III for Durie and Salmon classification.[21]

Study protocol

All study participants were asked to self-complete the EORTC QLQ-C30 and HeartQoL questionnaire at the time of study inclusion (baseline). The HeartQoL consists of 14 items – five questions regarding physical activities and nine regarding emotional wellbeing. Each question can be answered on a 4-point Likert scale ('none, a little, some, and a lot' of limitation), resulting in a score of 0–3 points. The EORTC QLQ-C30 summary score was calculated according to Husson *et al.*[22] and the HeartQoL summary score as described by Oldridge *et al.*[16,17] For comparison, the following evidence-based assessments were performed at baseline: physical function (Eastern Cooperative Oncology Group [ECOG] performance status[23] and Karnofsky Performance Status [KPS][24]), patient-reported outcomes (visual analogue scale for appetite[25] and pain[26]), and nutrition (Mini Nutritional Assessment [MNA][27]), physical activity (maximum handgrip strength [HGS],[28] 4 m gait speed,[29] 10-step stair-climbing power test[30] and 6-min walk test[31]), and sampling for blood biomarkers (including high-sensitivity troponin T [hsTnT], N-terminal pro-B-type natriuretic peptide [NT-proBNP], haemoglobin, and estimated glomerular filtration rate). Additionally, we obtained a medical history from each patient and performed a physical examination. Left ventricular ejection fraction was calculated by echocardiography with the modified Simpson's biplane method (Vivid E90, GE, Boston, MA, USA). A written informed consent form was signed by all study participants. Patients were followed though regular interrogation of electronic hospital records and

telephone contact. The study protocol was approved by the local ethics committees and complied with the Declaration of Helsinki principles.

Statistical analysis

Continuous data with normal distributions are described by the mean ± standard deviation (SD) and non-normal distributions are described with the median and interquartile range (IQR). Categorical variables are shown as absolute numbers and percentages. Unpaired *t*-test and analysis of variance (ANOVA) with Fisher's post hoc test were used as a parametric hypothesis test and Mann–Whitney U test and Kruskal–Wallis test with Dunn–Bonferroni test as non-parametric hypothesis tests. With regard to contingency tables, we used Chi-squared tests as mean of comparison, unless at least one cell assignment was smaller than five, then Fisher's exact test was used.[32]

All patients were followed up for survival until October 2020 for a minimum of 120 days. Survival between groups was compared using univariable and multivariable Cox proportional-hazard regression models, presented as hazard ratios (HRs) with 95% confidence intervals (CI). We calculated the best prognostic cut-off with the most significant split for either summary score (i.e. for EORTC QLQ-C30 and HeartQoL separately) using the standardized log-rank test. The combination of both summary scores and their respective cut-offs led to three risk groups: high risk group (patients below the cut-off in EORTC QLQ-C30 AND HeartQoL), medium risk (patients below the cut-off in either EORTC QLQ-C30 OR HeartQoL), and low risk (patients above the cut-off in EORTC QLQ-C30 AND HeartQoL). For illustrative purposes we constructed Kaplan–Meier curves. For all analyses a *p*-value <0.05 was considered as statistically significant. For statistical analysis IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Co., Armonk, NY, USA) was used.

Results

Study population

Patients with cancer ($n = 290$) and healthy controls ($n = 50$) had similar age and sex. Baseline characteristics and clinical data are shown in *Tables 1* and *2*. Patients with cancer more often had type 2 diabetes mellitus and anaemia, higher heart rates, as well as higher values of hsTnT and NT-proBNP, compared with healthy controls. Diuretic, beta-blocker, steroid, opioid, and antidepressant medications were more often used in patients with cancer. Specific cancer types of the recruited patients are shown in online supplementary *Table Appendix S1*.

Correlation analysis of EORTC QLQ-C30 and HeartQoL

EORTC QLQ-C30 and HeartQoL summary scores and subscales were lower in patients with cancer than healthy controls (online supplementary *Table S2*, *Figure 1*). Correlations between EORTC QLQ-C30 and HeartQoL summary scores ($r = 0.76$, $p < 0.001$; *Figure 2A*), physical subscales ($r = 0.81$, $p < 0.001$; *Figure 2B*) and emotional subscales ($r = 0.75$, $p \leq 0.001$; *Figure 2C*) were strong.

Survival analysis and risk assessment – separate assessment of EORTC QLQ-C30 and HeartQoL

During up to 33 months of observation (mean 15 months), 121 (42%) patients died. One-year mortality was 36% (95% CI 30–42%) and 2-year mortality was 45% (95% CI 38–51%). EORTC QLQ-C30 and HeartQoL summary scores were associated with all-cause mortality in both univariable and multivariable Cox survival analysis (adjusted for age, sex, cancer stage, cancer type) (*Table 3*). The EORTC QLQ-C30 physical functioning, role functioning, fatigue, pain, and appetite loss subscales, but not the other EORTC QLQ-C30 subscales, were independently associated with mortality. The HeartQoL physical, but not emotional, subscale was independently associated with mortality (online supplementary *Table S3*). Sex had no significant impact on the strength of the associations of either summary score with mortality (both: $p > 0.9$ for interaction).

The best prognostic cut-point for EORTC QLQ-C30 summary score was found to be <82.69 and 222 (77%) patients with cancer were below that cut-point (*Figure 3A*). The best prognostic cut-point for HeartQoL summary score was found to be <1.50 and 106 (37%) of patients with cancer were below that cut-point (*Figure 3B*). For EORTC QLQ-C30 and HeartQoL, those patients that were below the cut-points versus those patients that were above showed reduced physical function (ECOG and KPS), patient-reported outcomes (less appetite and more pain), nutrition (MNA), physical activity (HGS, gait speed, stair-climbing power, 6-min walking distance), higher heart rates, and elevated cardiovascular biomarkers (including hsTnT and NT-proBNP) (*Tables 1* and *4*).

Survival analysis and risk assessment – combined analysis of EORTC QLQ-C30 and HeartQoL

Patients with cancer with EORTC QLQ-C30 scores <82.69 and HeartQoL scores <1.50 (high-risk group) had higher mortality than patients with EORTC QLQ-C30 scores <82.69 or HeartQoL scores <1.50 (medium risk group) or patients with EORTC QLQ-C30 scores ≥82.69 and HeartQoL scores ≥1.50 (low-risk group, *Table 3*, *Figure 3C*). Patients with cancer in the high-risk group were more likely to be female, had more often received previous anti-cancer therapy, and had higher levels of hsTnT and NT-proBNP in comparison to the other risk groups (all $p < 0.05$, *Table 2*). For the combination of EORTC QLQ-C30 and HeartQoL, those patients that were in the high-risk group (compared to medium and low risk) showed reduced physical function, patient-reported outcomes, nutrition, physical activity, and elevated cardiovascular biomarkers (*Table 5*).

Discussion

Given the increasingly recognized intersection of cancer and cardiovascular disease,[33–35] along with the greater use of

Table 1 Baseline characteristics of patients with cancer and controls

	Controls ($n = 50$)	Patients with cancer ($n = 290$)	*p*-value	Patients with cancer with HeartQoL <1.50 ($n = 106$)	Patients with cancer with HeartQoL ≥1.50 ($n = 184$)	*p*-value	Patients with cancer with EORTC QLQ-C30 <82.69 ($n = 222$)	Patients with cancer with EORTC QLQ-C30 ≥82.69 ($n = 68$)	*p*-value
Clinical characteristics									
Age, years	60 ± 9	61 ± 14	0.42	63 ± 14	61 ± 14	0.11	61 ± 14	62 ± 13	0.09
Male sex, *n* (%)	24 (48)	148 (51)	0.69	45 (43)	103 (56)	**0.026**	105 (47)	43 (63)	**0.021**
BMI, kg/m^2	25 ± 4	25 ± 5	0.56	25 ± 5	26 ± 5	0.29	25 ± 5	26 ± 4	0.30
Cancer stage, *n* (%)									
I	N/A	21 (7)	N/A	5 (5)	16 (9)	0.21	10 (5)	11 (16)	**0.001**
II	N/A	34 (12)	N/A	10 (9)	24 (13)	0.36	24 (11)	10 (15)	0.38
III	N/A	41 (14)	N/A	13 (12)	28 (15)	0.49	33 (15)	8 (12)	0.52
IV	N/A	194 (67)	N/A	78 (74)	116 (63)	0.066	155 (70)	39 (57)	0.056
Cancer type: solid, *n* (%)	N/A	170 (59)	N/A	67 (63)	103 (56)	0.23	132 (60)	38 (56)	0.60
Anti-cancer therapy naive, *n* (%)	N/A	66 (23)	N/A	14 (13)	52 (28)	**0.003**	41 (18)	25 (37)	**0.002**
Current smoker, *n* (%)	13 (27)	56 (19)	0.25	23 (22)	33 (18)	0.45	47 (21)	9 (13)	0.14
Cardiovascular parameters									
LVEF, %	67 ± 3	63 ± 6	**<0.001**	64 ± 7	62 ± 6	**0.026**	64 ± 7	62 ± 6	**0.024**
Heart rate, bpm	59 ± 10	75 ± 13	**<0.001**	77 ± 13	74 ± 13	**0.011**	76 ± 14	71 ± 11	**0.002**
Systolic blood pressure, mmHg	134 ± 15	129 ± 19	0.084	126 ± 21	131 ± 18	**0.028**	128 ± 19	134 ± 19	0.025
Diastolic blood pressure, mmHg	86 ± 10	79 ± 12	**<0.001**	78 ± 13	79 ± 10	0.595	79 ± 12	79 ± 10	0.832
Laboratory parameters									
Haemoglobin, g/dl	14.4 ± 1.2	11.5 ± 2.1	**<0.001**	11.0 ± 2.1	11.9 ± 2.1	**<0.001**	11.2 ± 2.1	12.7 ± 1.9	**<0.001**
eGFR, ml/min	85 ± 12	87 ± 21	0.5	73 ± 19	77 ± 14	**0.048**	75 ± 17	77 ± 15	0.43
hsTnT, ng/L	7 [5–8]	9 [5–15]	**<0.001**	13 [8–23]	8 [4–12]	**<0.001**	11 [6–17]	7 [4–12]	**0.002**
NT-proBNP, ng/L	64 [50–148]	207 [84–508]	**<0.001**	362 [124–732]	171 [76–372]	**<0.001**	229 [94–541]	168 [73–336]	**0.019**
Secondary diagnoses, *n* (%)									
Arterial hypertension	19 (38)	133 (46)	0.30	51 (48)	82 (45)	0.56	105 (47)	28 (41)	0.38
Diabetes mellitus type 2	0 (0)	36 (12)	**0.005**	16 (15)	20 (11)	0.29	29 (13)	7 (10)	0.55
Hypercholesterolaemia	31 (62)	93 (32)	**<0.001**	32 (30)	61 (33)	0.6	66 (30)	27 (40)	0.12
Anaemia	1 (2)	190 (66)	**<0.001**	75 (71)	115 (63)	0.15	158 (71)	32 (47)	**<0.001**
Previous stroke	0 (0)	12 (4)	0.28	6 (6)	6 (3)	0.32	11 (5)	1 (2)	0.21
Medications on examination day, *n* (%)									
ACE-I/ARBs	8 (16)	79 (27)	0.092	29 (27)	50 (27)	0.97	58 (26)	21 (31)	0.44
Beta-blockers	1 (2)	59 (20)	**0.001**	26 (25)	33 (18)	0.18	49 (22)	10 (15)	0.19
Diuretics	1 (2)	56 (19)	**0.001**	29 (27)	27 (15)	**0.008**	45 (20)	11 (16)	0.45
Opioids	0 (0)	53 (18)	**<0.001**	29 (28)	24 (13)	**0.002**	48 (22)	5 (7)	**0.007**
Antidepressants	0 (0)	31 (11)	**0.013**	18 (17)	13 (7)	**0.008**	28 (13)	3 (4)	0.055
Steroids	0 (0)	77 (27)	**<0.001**	32 (30)	45 (25)	0.29	59 827)	18 (27)	0.99

Normal distributed variables are presented as mean ± standard deviation, non-parametric variables as median [interquartile range], nominal variables as *n* (%).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; hsTnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; N/A, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Baseline characteristics according to combined EORTC QLQ-C30 and HeartQoL risk score

	Patients with cancer with EORTC QLQ-C30 ≥82.69 and HeartQoL ≥1.50 (*n* = 67)	Patients with cancer with EORTC QLQ-C30 ≥82.69 or HeartQoL ≥1.50 (*n* = 118)	Patients with cancer with EORTC QLQ-C30 < 82.69 and HeartQoL <1.50 (*n* = 105)	*p*-value
Clinical characteristics				
Age, years	61 ± 13	60 ± 14	63 ± 14	0.22
Male sex, *n* (%)	43 (64)	60 (51)	45 (43)**	**0.024**
BMI, kg/m^2	26 ± 4	26 ± 5	25 ± 5	0.50
Cancer stage, *n* (%)				
I	11 (16)	5 (4)**	5 (5)*	**0.004**
II	9 (13)	16 (14)	9 (9)	0.45
III	8 (12)	20 (17)	13 (12)	0.52
IV	39 (60)	77 (65)	78 (74)*	0.082
Cancer type: solid, *n* (%)	37 (55)	67 (57)	66 (63)	0.53
Anti-cancer therapy naive, *n* (%)	24 (36)	29 (25)	13 (12)***†	**0.001**
Current smoker, *n* (%)	9 (13)	24 (21)	23 (22)	0.36
Cardiovascular parameters				
LVEF, %	61 ± 6	63 ± 6	64 ± 5*	**0.037**
Heart rate, bpm	71 ± 11	75 ± 15	78 ± 13**	**0.006**
Systolic blood pressure, mmHg	133 ± 19	130 ± 16	126 ± 21*	**0.029**
Diastolic blood pressure, mmHg	79 ± 10	79 ± 11	78 ± 13	0.869
Laboratory parameters				
Haemoglobin, g/dl	12.7 ± 1.9	11.4 ± 2***	10.9 ± 2.1***	**<0.001**
eGFR, ml/min	77 ± 15	78 ± 14	73 ± 19	0.074
hsTnT, ng/L	7 [4–12]	8 [5–13]	13 [8–23]****††††	**<0.001**
NT-proBNP, ng/L	169 [72–339]	175 [76–411]	363 [123–770]**†††	**<0.001**
Secondary diagnoses, *n* (%)				
Arterial hypertension	28 (42)	54 (46)	51 (49)	0.69
Diabetes mellitus type 2	7 (10)	13 (11)	16 (15)	0.54
Hypercholesterolaemia	26 (40)	36 (31)	31 (30)	0.39
Anaemia	31 (46)	85 (72)***	74 (70)**	**0.001**
Previous stroke	1 (2)	5 (4)	6 (6)	0.40
Medications on examination day, *n* (%)				
ACE-I/ARBs	21 (31)	29 (25)	29 (28)	0.61
Beta-blockers	10 (15)	23 (20)	26 (25)	0.28
Diuretics	11 (16)	16 (14)	29 (28)††	**0.023**
Opioids	5 (8)	19 (16)	29 (28)**†	**0.002**
Antidepressants	3 (5)	10 (9)	18 (17)*	**0.019**
Steroids	17 (25)	29 (25)	31 (30)	0.68

Normal distributed variables are presented as mean ± standard deviation, non-parametric variables as median [interquartile range], nominal variables as *n* (%).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; hsTnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ vs. EORTC QLQ-C30/HeartQoL 0 point.
†$p < 0.05$, ††$p < 0.01$, †††$p < 0.001$, ††††$p < 0.0001$ vs. EORTC QLQ-C30/HeartQoL 1 point.

patient-reported outcomes in clinical care,[36,37] there is a need to understand the distribution and prognostic significance of common HRQoL measures in a cancer population. To the best of our knowledge, this is the first time that the main European Society of Cardiology (ESC) questionnaire for assessing cardiovascular HRQoL of cancer patients (i.e. the HeartQoL questionnaire) was prospectively tested and validated in patients with solid and haematologic cancers and compared with the commonly used oncology HRQoL questionnaire (i.e. the EORTC QLQ-C30 questionnaire). The distributions of the HRQoL measures, as might be expected, were much worse in patients with cancer, as compared with healthy controls. However, the significant prognostic associations of these instruments with survival highlight their importance and both questionnaires provide additional and relevant information for the assessment of patients with cancer. Moreover, while the tools were highly correlated, they both independently stratified mortality risk and the combination of the two questionnaires led to even greater stratification. Additionally, patients with reduced

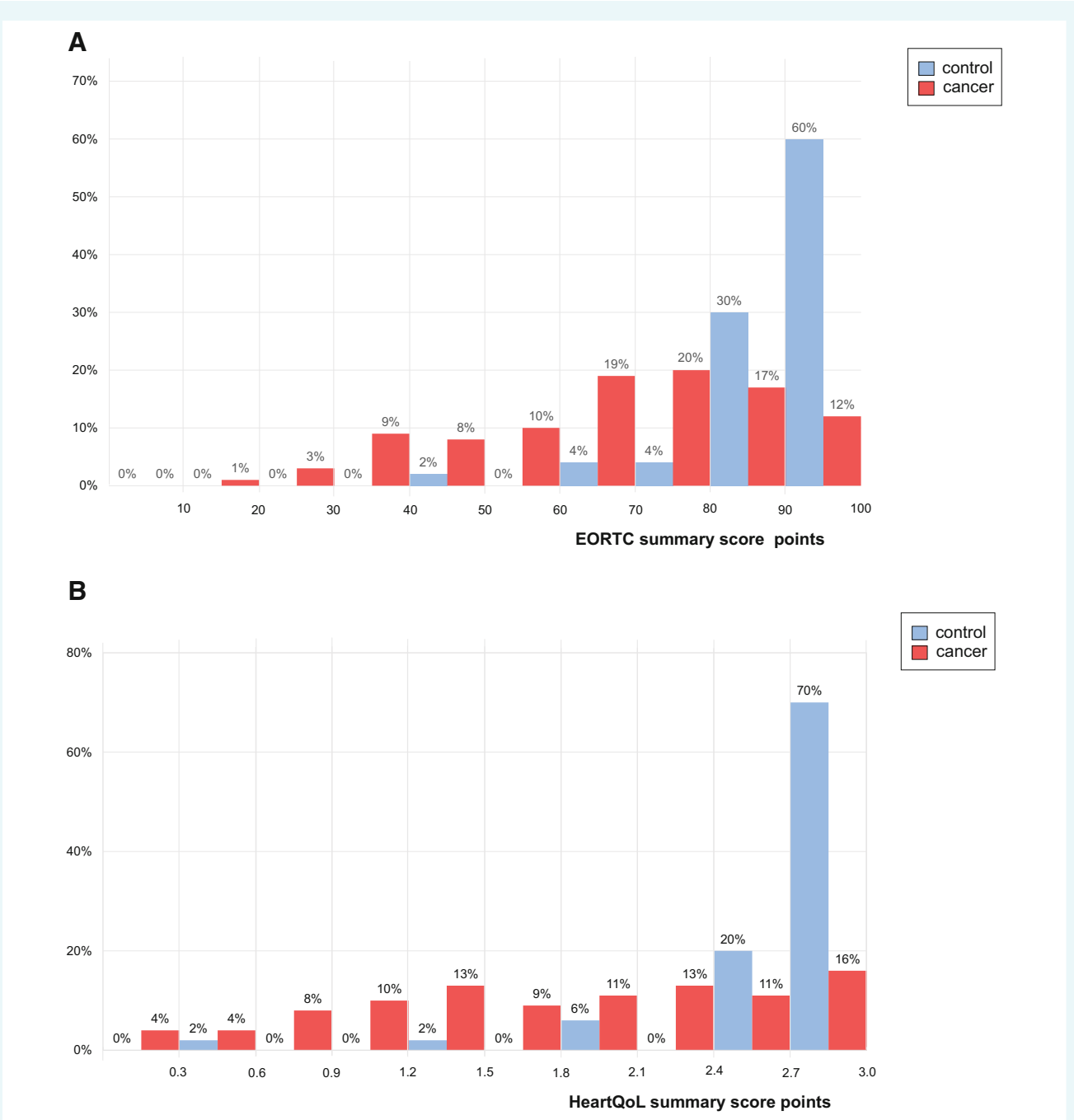

Figure 1 (*A*) Distribution of EORTC QLQ-C30 summary score in cancer patients and controls. (*B*) Distribution of HeartQoL summary score in cancer patients and controls.

EORTC QLQ-C30 and HeartQoL summary scores had reduced physical function, worse appetite and pain, as well as poorer nutrition, physical activity, higher heart rates, and they showed elevated cardiovascular biomarkers.

Health-related quality of life measurements as a reflection of patients' symptom burden and daily life restrictions have an increasingly prominent role as an important outcome in clinical trials for patients with cancer.[38–40] As we show here and have shown before,[41–43] patients with cancer in general have higher cardiac distress than healthy controls reflected by slightly lower left ventricular ejection fraction, higher resting heart rates and elevated cardiac biomarkers (even though significant cardiovascular disease was an exclusion criterion in this study and patients with cancer more often used beta-blockers). Other commonly observed problems in patients with advanced cancer include whole body wasting/cachexia and malnutrition[44–46] as well as muscle wasting and

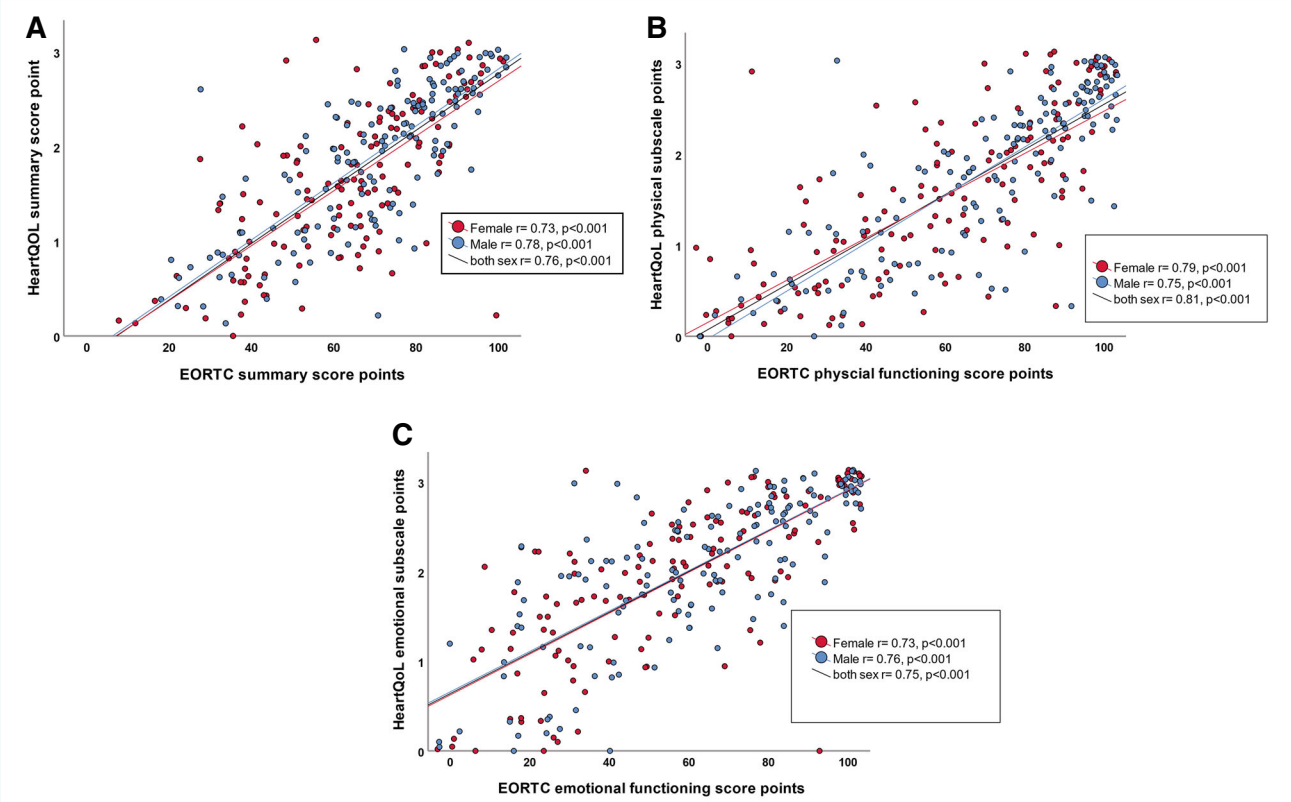

Figure 2 (*A*) Correlation between HeartQoL and EORTC QLQ-C30 summary score. (*B*) Correlation between HeartQoL physical subscale and EORTC QLQ-C30 physical functioning score. (*C*) Correlation between HeartQoL emotional subscale and EORTC QLQ-C30 emotional functioning score.

Table 3 Cox regression survival analysis (patients with cancer, $n = 290$)

	Univariable model			Multivariable model[a]					
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	Harrell's C	AIC	BIC
EORTC QLQ-C30 summary score (per 10 points)	1.14	1.04–1.23	**0.004**	1.12	1.01–1.24	**0.033**	0.667	884.06	913.11
HeartQoL summary score (per 0.3 points)	1.11	1.03–1.19	**0.004**	1.09	1.00–1.18	**0.042**	0.672	884.36	913.41
EORTC QLQ-C30 summary score <82.69 (yes vs. no)	2.47	1.46–4.18	**0.001**	2.33	1.31–4.12	**0.004**	0.687	849.29	871.07
HeartQoL summary score <1.50 (yes vs. no)	1.87	1.31–2.68	**0.001**	1.85	1.22–2.81	**0.004**	0.685	880.34	909.39
Combined model (high risk vs. low risk group)	2.99	1.72–5.22	**<0.001**	3.60	1.89–6.85	**<0.001**	0.693	462.03	486.88
Combined model (medium risk vs. low risk group)	1.56	1.06–2.29	**0.024**	1.57	1.01–2.42	**0.044**	0.667	713.02	739.95
Combined model (high risk vs. medium risk group)	1.98	1.12–3.50	**0.018**	1.90	1.02–3.54	**0.043**	0.716	405.27	430.77

AIC, Akaike's information criterion; BIC, Bayesian information criterion; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, cancer stage, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, sex and solid cancer vs. haematological cancer as strata.

sarcopenia.[47,48] Improving and maintaining HRQoL is one of the main goals of modern-day medicine. Considering the association of HRQoL and physical functioning, maintaining, and strengthening physical strength and endurance might be an important aspect to encourage perceived self-efficacy and resilience.[49] This may be an important area for future intervention trials.

Assessment of HRQoL is not routinely performed in every patient with cancer.[50] This is unfortunate, as it has been shown by Basch *et al.*[51] that routine use of patient-reported outcomes in cancer care not only improves patients' HRQoL, but also increased the duration with which they adhered to chemotherapy protocols and even improved 5-year mortality. Many different physical, psychological, and social factors influence HRQoL in patients with cancer. In addition to the improved efficacy of anti-cancer therapy, support from friends and family, financial security, and hope for recovery can also positively impact patients' HRQoL.[52] There are

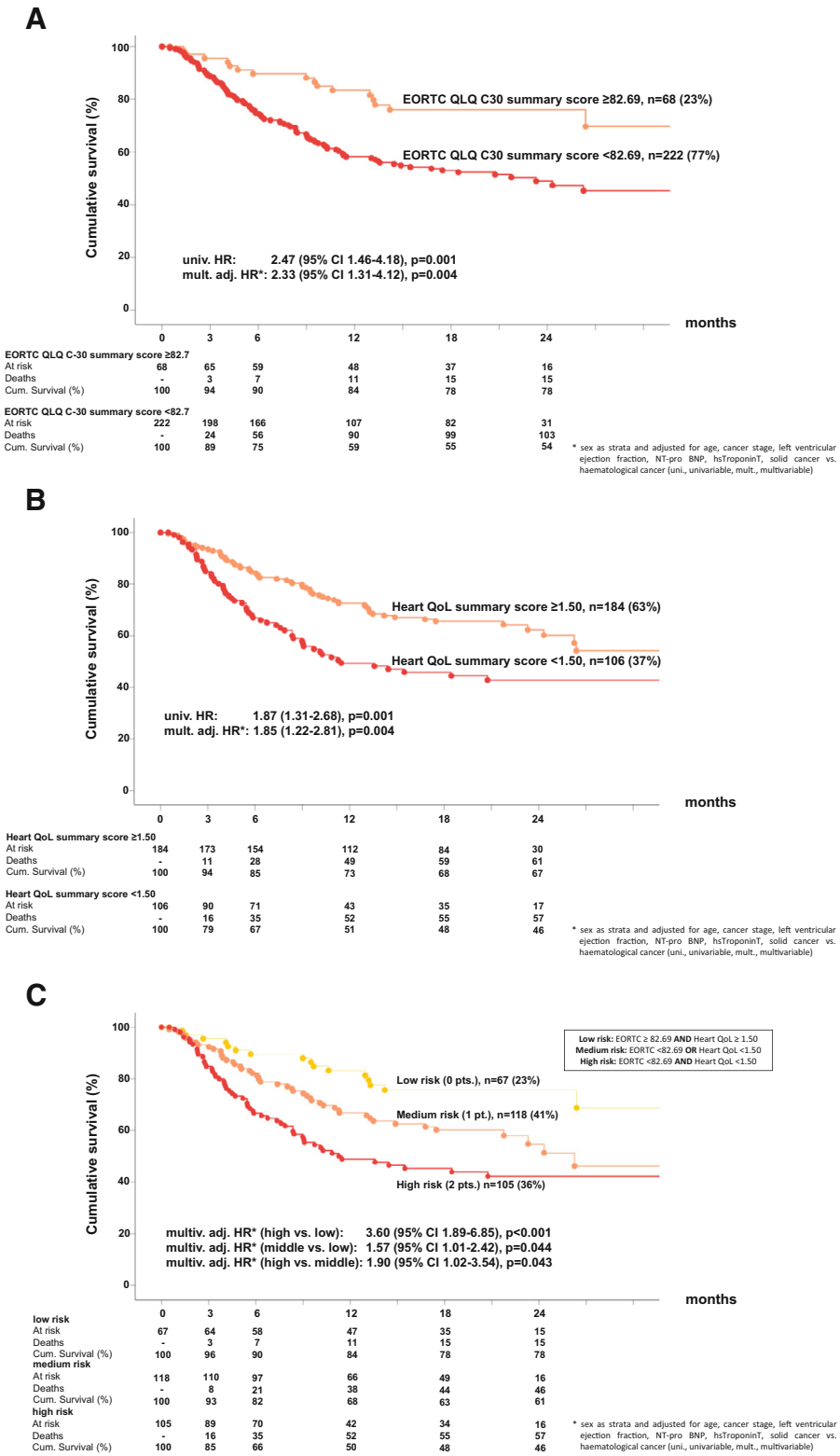

Figure 3 (*A*) Survival analysis in 290 cancer patients according to EORTC QLQ-C30 risk group. (*B*) Survival analysis in 290 cancer patients according to HeartQoL risk group. (*C*) Survival analysis in 290 cancer patients according to combined EORTC QLQ-C30 and HeartQoL risk group. CI, confidence interval; HR, hazard ratio; mult., multivariable; uni., univariable. *Sex as strata and adjusted for age, cancer stage, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, solid cancer versus haematological cancer.

Table 4 Functional testing and patient-reported outcomes in patients with cancer below and above calculated cut-offs of HeartQoL and EORTC QLQ-C30

Functional testing and patient-reported outcome	Patients with cancer with HeartQoL <1.50 (*n* = 106)	Patients with cancer with HeartQoL ≥1.50 (*n* = 184)	*p*-value	Patients with cancer with EORTC QLQ-C30 <82.69 (*n* = 222)	Patients with cancer with EORTC QLQ-C30 ≥82.69 (*n* = 68)	*p*-value
ECOG performance scale, points	2.1 ± 0.9	0.9 ± 0.8	**<0.001**	1 [1–2]	0 [0–1]	**<0.001**
Karnofsky index, %	70 ± 16	87 ± 12	**<0.001**	77 ± 16	91 ± 10	**<0.001**
Visual analogue scale appetite, mm	43 ± 28	64 ± 29	**<0.001**	51 ± 30	78 ± 23	**<0.001**
Visual analogue scale pain, mm	15 [3–50]	4 [0–24.5]	**0.002**	10 [0–38.5]	0 [0–20]	**0.016**
Mini nutritional assessment, points	19.3 ± 4.3	22.8 ± 3.5	**<0.001**	20.7 ± 4.2	24.4 ± 2.6	**<0.001**
Maximum handgrip strength, Newton	290 ± 107	356 ± 112	**<0.001**	321 ± 113	378 ± 111	**0.001**
4-m gait speed, m/s	0.93 ± 0.36	1.26 ± 0.32	**<0.001**	1.12 ± 0.37	1.27 ± 0.33	**0.006**
Stair-climbing power, W	320 ± 163	435 ± 199	**0.005**	381 ± 181	471 ± 220	**0.021**
6-min walking distance, m	367 ± 116	457 ± 84	**<0.001**	424 ± 103	466 ± 82	**0.007**

Normal distributed variables are presented as mean ± standard deviation, non-parametric variables as median [interquartile range].
ECOG, Eastern Cooperative Oncology Group.

Table 5 Functional testing and patient-reported outcomes in patients with cancer below and above calculated cut-offs of combined EORTC and HeartQoL risk score

Functional testing and patient-reported outcome	Patients with cancer with EORTC QLQ-C30 ≥82.69 and HeartQoL ≥1.50 (*n* = 67)	Patients with cancer with EORTC QLQ-C30 ≥82.69 or HeartQoL ≥1.50 (*n* = 118)	Patients with cancer with EORTC QLQ-C30 <82.69 and HeartQoL <1.50 (*n* = 105)	*p*-value
ECOG performance scale, points	0 [0–1]	1 [1–2]****	2 [1–3]****,††††	**<0.001**
Karnofsky index, %	91 ± 10	85 ± 10*	71 ± 16****,††††	**<0.001**
Visual analogue scale appetite, mm	78 ± 23	57 ± 30****	43 ± 28****,††	**<0.001**
Visual analogue scale pain, mm	14 ± 23	18 ± 24	27 ± 29*	**0.017**
Mini nutritional assessment, points	24 ± 3	22 ± 4****	19 ± 4****,††††	**<0.001**
Maximum handgrip strength, Newton	374 ± 111	346 ± 112	290 ± 107****,††	**<0.001**
4-m gait speed, m/s	1.27 ± 0.33	1.25 ± 0.31	0.93 ± 0.36****,††††	**<0.001**
Stair-climbing power, W	471 ± 220	413 ± 182	320 ± 163**,†	**0.008**
6-min walking distance, m	466 ± 82	450 ± 85	367 ± 116****,††††	**<0.001**

Normal distributed variables are presented as means ± SD, non-parametric variables as median (interquartile range).
*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$ vs. EORTC QLQ-C30/HeartQoL 0 point.
†$p < 0.05$, ††$p < 0.01$, ††††$p < 0.0001$ vs. EORTC QLQ-C30/HeartQoL 1 point.

practical limitations to the implementation of HRQoL questionnaires, including time pressure and skepticism concerning assessment and interpretation of different HRQoL questionnaires.[53,54] Nevertheless, HRQoL measurements have proven to be good predictors of survival in patients with cancer and a key indicator of patient wellbeing.[55–59] Thus, they can be used for the evaluation of prognosis in patients with cancer and can help the clinician and patient to choose from different treatment options.[55,57]

Previous studies using the EORTC QLQ-C30 questionnaire have documented the extensive deterioration of HRQoL in patients with cancer[60] and its prognostic relevance.[22,57,61,62] On the other hand, the HeartQoL questionnaire was originally developed and validated in patients with ischaemic cardiomyopathy,[16,17] coronary artery disease, and heart failure[63] as a heart-specific HRQoL measure. Because it was designed to be applicable across a broad spectrum of cardiovascular conditions, it is more generic than other cardiovascular instruments, such as the Seattle Angina Questionnaire[64] or the Kansas City Cardiomyopathy Questionnaire,[65] which enabled it to be relevant to patients with cancer. To the best of our knowledge this is the first study to test the HeartQoL questionnaire in patients with cancer. We have found that not only the HeartQoL summary score, but also the two subscales (physical and emotional) were lower in patients with cancer than in controls – with strong correlation between HeartQoL and EORTC

QLQ-C30 summary scores and subscales. A lower HeartQoL summary score was associated with increased cardiac biomarkers and elevated heart rates in patients with cancer, suggesting that cardiac distress was higher in these patients. The increase in cardiac biomarkers was not due to significant cardiovascular disease or acute infection, since they were both exclusion criteria at the time of HRQoL assessment. This increase of cardiac biomarkers was most likely multifactorial. We found that patients with a reduced HeartQoL summary score were less frequently anti-cancer therapy naïve and had reduced kidney function, and both may contribute to elevated cardiac biomarkers. Interestingly, a reduced EORTC QLQ-C30 summary score was also associated with elevated cardiac biomarkers, in particular natriuretic peptides and myocardial necrosis markers. Likewise, these patients were also less frequently chemotherapy naïve, but kidney function was not reduced. For both questionnaires, lower points in the summary score were associated with worse outcome in other self-reported outcomes such as appetite and pain scale, less physical strength in functioning tests and worse perception of physicians in assessments like ECOG and KPS.

Since both questionnaires identified two distinct cohorts of patients with reduced HRQoL, combining both questionnaires resulted in three risk groups (high, medium, low risk group). The new obtained stratified risk assessment integrates the advantages of both questionnaires. Patients in the highest risk group had the highest mortality and highest level of cardiac biomarkers. Since elevated cardiovascular biomarkers are also known to be associated with subsequent development of cardiotoxicity,[66–68] the combination of both questionnaires could even help to identify patients with a higher risk of cardiotoxicity in the future.

On average, it took our patients about 5 min to fill out the HeartQoL questionnaire (14 questions) and 10 min to fill out the EORTC QLQ-C30 questionnaire (30 questions). Still, since both questionnaires were filled out by patients without staff assistance, filling out these questionnaires did not influence the clinical routine of staff. If only one questionnaire is used, it is noteworthy that the HeartQoL had a lower response time, while the longer EORTC QLQ-C30 quantified a broader range of health status characteristics. Thus, preference should depend on the goals of the providers, as both were prognostic of subsequent survival.

The self-completion of these two HRQoL questionnaires could help to improve patient management and identify those patients that need additional care. Psychosocial, resilience, and physical training interventions have been effective in improving HRQoL.[69–71] In this scenario, patients with cancer could benefit from a combined self-assessment of their cancer related as well as their cardiovascular HRQoL by inducing inter-disciplinary interventions targeting self-care abilities, physical capacity, and mental wellbeing.

Limitations

A limitation of this study is that our focus was on hospitalized patients that mostly presented with advanced cancer – but at the same time we therefore show the results here of a real-world cohort. In future studies the HeartQoL questionnaire should also be tested in different cohorts of patients with cancer including those with significant pre-existing cardiovascular disease, earlier cancer stages (including treatment naïve patients with good prognosis), ambulatory treatment, and acute infections. In this cohort, patients had several different cancer entities, also representing a real-world scenario, but validation of these results should also be performed in each cancer entity separately. In this study we used all-cause mortality in all analysis since today autopsies are rarely performed in patients with cancer and death adjudication in patients with cancer is rarely possible, since these patients often die at home, in palliative care settings, or in hospices with complex clinical presentation.[72] Still, a detailed cause of death analysis should be considered when possible. Future studies could also be directed at improving HRQoL as measured by EORTC QLQ-C30 and HeartQoL through targeted interventions.

Conclusion

EORTC QLQ-C30 and HeartQoL questionnaires both predicted mortality in patients with cancer with even greater stratification by combing the two. EORTC QLQ-C30 and HeartQoL questionnaires are associated with physical function, patient-reported outcomes, nutrition, physical activity, and elevated cardiovascular biomarkers. Using the EORTC QLQ-C30 and HeartQoL questionnaires more often in patients with cancer could improve patient management in clinical care.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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