ESC HEART FAILURE
ESC Heart Failure (2022)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14175

ORIGINAL ARTICLE

Cardiovascular and metabolic determinants of quality of life in patients with cancer

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Abstract

Aims Maintaining quality of life (QoL) in patients with cancer has gathered significant interest, but little is known about its major determinants. We sought to identify determinants of QoL in patients undergoing cancer treatment as well as in treatment-naïve patients about to commence such therapy.

Methods and results QoL was assessed in 283 patients with cancer using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire. All patients underwent a battery of tests including physical examination, resting electrocardiogram, hand grip strength, and biochemistry assessment. Using multivariable logistic regression, we found that age [odds ratio (OR) 0.954, 95% confidence interval (CI) 0.916–0.994], resting heart rate (OR 1.036, 95% CI 1.004–1.068), hand grip strength (OR 0.932, 95% CI 0.878–0.990), and the presence of cachexia (OR 4.334, 95% CI 1.767–10.631) and dyspnoea (OR 3.725, 95% CI 1.540–9.010; all $P < 0.05$) remained independently predictive of reduced QoL.

Conclusions Therefore, it may be reasonable to address circumstances that are affecting muscle mass, body weight, and heart rate to maintaining QoL; however, prospective studies to test these endpoints are required.

Keywords Quality of life; Cancer

Received: 16 May 2022; Revised: 17 August 2022; Accepted: 15 September 2022
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Introduction

Clinical trials in oncology are mostly driven by survival and remission rates that have helped to improve both aspects in several types of cancer. These endpoints, however, largely neglect treatment effects surrounding cancer therapy itself like developing and/or treatable co-morbidities or psychosocial aspects. Chemotherapy regimens, for example, have made significant progress but are frequently associated with severe side effects that influence aspects of physical, emotional, and social life and therefore patients' quality of life (QoL). Although survival and remission rates are obviously important, patients usually wish to maintain their mobility, QoL, and independence throughout their treatment. These points are mounting in the palliative setting, where their achievement is becoming more difficult as the underlying disease

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advances. Maintaining QoL is therefore an important target during all periods of care for patients with cancer. The World Health Organization (WHO) has defined QoL as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns' (WHOQOL Group 1993). As such, health-related QoL (HRQoL) becomes more important and embraces various dimensions including, but not limited to, physical, psychological, and social aspects. In the following, we only use the term QoL.

QoL can be assessed using a vast array of different tools. Such tools are in most cases questionnaires that have been developed over the last decades and whose use depends on the underlying illness. In 1987, the European Organisation for Research and Treatment of Cancer (EORTC) developed a health-related questionnaire, aligned to the needs of cancer patients. The first version was refined continuously, and in 1993, the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) was finalized and validated.[1,2] It has been used in more than 2200 studies; however, the factors influencing QoL in cancer patients remain incompletely understood. The present study has been designed to establish a cardiovascular perspective of QoL in patients undergoing cancer treatment as well as in patients who are about to commence such therapy.

Materials and methods

Study population

Between September 2017 and March 2020, we prospectively enrolled 283 participants at the University of Göttingen Medical Centre and at Charité Medical School, Campus Benjamin Franklin, Berlin, both in Germany. Patients were identified by studying their medical records and eligible to participate in case of histologically confirmed malignant disease and an age of at least 18 years. There was no restriction in participation regarding patients' treatment status. The following criteria were defined as reasons for exclusion: (i) clinical signs of an acute infection, antibiotic treatment due to an infection, or fever defined as a temperature $>$ 38.0°C; (ii) severe cardiovascular disease, defined as coronary heart disease, prior myocardial infarction, chronic or acute heart failure, and severe valvular heart disease; (iii) severe chronic obstructive pulmonary disease (COPD), defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage $>$ II (except in lung cancer patients, all COPD GOLD stages were allowed); and (iv) any other cancer diagnosis in the 5 years preceding enrolment.

All participants underwent a standardized clinical evaluation, which included the acquisition of the patient's medical history, a physical examination, a resting electrocardiogram (ECG), blood collection, hand grip strength (HGS), and a QoL questionnaire (EORTC QLQ-C30).

The local ethics committees approved the study protocol, and written informed consent was obtained from all participants. The study was conducted according to the principles of the Declaration of Helsinki.

Blood collection

Patients underwent routine laboratory assessments including a full blood count, biochemistry, and kidney and liver function tests. In addition, serum and plasma samples were collected and immediately frozen at −80°C for later analysis. Full blood count and clinical chemistry parameters were analysed immediately by the local laboratory. High-sensitivity cardiac Troponin T (hs-Troponin T) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed using assays purchased from Roche Diagnostics (Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany).

Cardiovascular assessment

Following the recording of the medical history, a detailed physical examination including measurement of body weight and height was performed. Blood pressure of all patients was assessed according to current guidelines issued by the European Society of Cardiology (ESC) in a sitting position in a quiet environment after a rest of at least 5 min.[3] Three measurements were performed 2 min apart and results recorded as an average of the last two blood pressure readings. Measurements were performed using a boso medicus electronical sphygmomanometer (Bosch + Sohn GmbH und Co KG, Juningen, Germany). Twelve-lead ECGs were recorded in a supine position after a rest of at least 5 min using a MAC™ 3500 Resting ECG System (GE Healthcare, Chicago, IL, USA).

Physical strength was evaluated by measuring HGS, which was performed in a sitting position with the elbow flexed at 90°, whereas shoulder and wrist were in neutral position (0°) using a Jamar® Plus + Digital Hand Dynamometer (Performance Health Holding, Inc., Warrenville, IL, USA). HGS was evaluated in both hands, and the average of three tests of the stronger hand noted. Cachexia was defined as a weight loss of at least 5% within the last 12 months or a combination of 2% weight loss and a body mass index (BMI) $<$ 20 kg/m^2. In patients presenting with dyspnoea, its extent was described in analogy to the New York Heart Association (NYHA classification) used in patients with heart failure.

Quality of life

QoL was assessed once at the time of patients' inclusion using the EORTC QLQ-C30 questionnaire, Version 3.[1] The

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questionnaire contains functional scales (physical, role, cognitive, emotional, and social) and symptom scales (fatigue, pain, nausea and vomiting, dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and financial impact due to disease or treatment). In addition, the global health condition and patients' global QoL are gathered. Values between 0 and 100 can be reached. For the functional scales, higher values indicate a high level of functioning, whereas for the symptom scales, higher values indicate a higher symptom burden. The analysis of the gathered QoL data was done using a dedicated scoring manual.[4] Acquired data were compared with thresholds deemed to have clinical importance, based on a publication by Giesinger *et al*.[5] For further analysis, the study population was divided into two groups according to the median EORTC QLQ-C30 summary score, where a higher score indicates higher QoL.

Statistical analysis

Normally distributed data are expressed as mean ± standard deviation, whereas non-normally distributed data are expressed as median with interquartile range. Normal distribution was tested using the Shapiro–Wilk test. Data not following normal distribution were compared using the Mann–Whitney *U* and Kruskal–Wallis tests, as appropriate. For between-group comparisons in normally distributed data, Student's *t*-test and analysis of variance (ANOVA) testing were performed, as appropriate. For binary variables, intergroup comparisons were performed using the χ^2 test.

Univariable and multivariable logistic regression models were used to identify clinical determinants of QoL in patients with cancer. A *P*-value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics Version 26 for Windows [International Business Machines Corporation (IBM® Corp.), Armonk, NY 10504, USA].

Results

Study population characteristics

Patients' baseline characteristics are summarized in *Table 1*. The EORTC QLQ-C30 questionnaire was completed by all 283 patients. A total of 52.4% of the cohort were male; the mean age was 61.2 ± 13.0 years with age ranging from 20 to 87 years. A total of 60.8% of patients were suffering from a solid tumour, whereas the remaining 39.2% had malignant haematological diseases (*Figure 1*). Most cancer types in the

Table 1 Baseline characteristics of the study population divided by EORTC QLQ-C30 summary score median

	Study population (n = 283)		EORTC QLQ-C30 summary score < median (n = 141)		EORTC QLQ-C30 summary score ≥ median (n = 142)		*P*-values
Demographic data							
Age (years)	61.2 ± 13.0		60.7 ± 13.6		61.6 ± 12.5		0.576
Sex (male)	148 (52.3%)		63 (44.6%)		85 (59.9%)		**0.012**
Height (cm)	172 ± 9		171 ± 9		174 ± 9		**0.007**
Weight (kg)	75.7 ± 17.6		72.7 ± 17.3		78.6 ± 17.5		**0.004**
Body mass index (kg/m^2)	25.4 ± 4.8		24.84 ± 5.08		25.94 ± 4.53		0.055
Haematology and oncology data							
Solid tumour	172 (60.8%)		81 (57.4%)		91 (64.1%)		0.274
UICC stage	I = 3 (1.7%)	II = 8 (4.7%)	I = 1 (1.3%)	II = 3 (3.8%)	I = 2 (2.2%)	II = 5 (5.4%)	0.892
	III = 14 (8.1%)	IV = 147 (85.5%)	III = 6 (7.5%)	IV = 70 (86.5%)	III = 8 (8.7%)	IV = 77 (83.7%)	
Haematological neoplasia	111 (39.2%)		60 (42.6%)		51 (35.9%)		0.274
Ann-Arbor stage	I = 23 (22.8%)	II = 15 (14.9%)	I = 7 (11.2%)	II = 10 (16.6%)	I = 16 (31.3%)	II = 5 (9.8%)	0.052
	III = 25 (24.8%)	IV = 38 (37.6%)	III = 16 (26.7%)	IV = 23 (38.3%)	III = 9 (17.6%)	IV = 15 (29.4%)	
Deceased	110 (38.9%)		55 (39.0%)		55 (38.7%)		0.962
Treatment naïve	53 (18.7%)		23 (16.3%)		30 (21.1%)		0.361
Co-morbidities							
Cachexia	131 (46.3%)		79 (56.0%)		52 (36.6%)		**0.001**
Hypertension	120 (42.4%)		59 (41.8%)		61 (43.0%)		0.904
Anaemia	181 (64.0%)		101 (71.6%)		80 (56.3%)		**0.009**
Diabetes mellitus	26 (9.2%)		12 (8.5%)		14 (9.9%)		0.837
Current smoker	68 (24%)		43 (30.7%)		25 (17.6%)		**0.012**
Dyspnoea (NYHA class ≥ II)	49 (17.3%)		31 (22.0%)		18 (12.7%)		**0.003**

EORTC, European Organisation for Research and Treatment of Cancer; NYHA, New York Heart Association; QLQ-C30, Quality of Life Questionnaire Core 30; UICC, Union for International Cancer Control.
Data are expressed as mean ± standard deviation or number (percentage).
The bold values indicate significant *P*-values (defined as $P \leq 0.05$).

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Figure 1 Tumour type distribution in the studied population. ENT, ear–nose–throat.

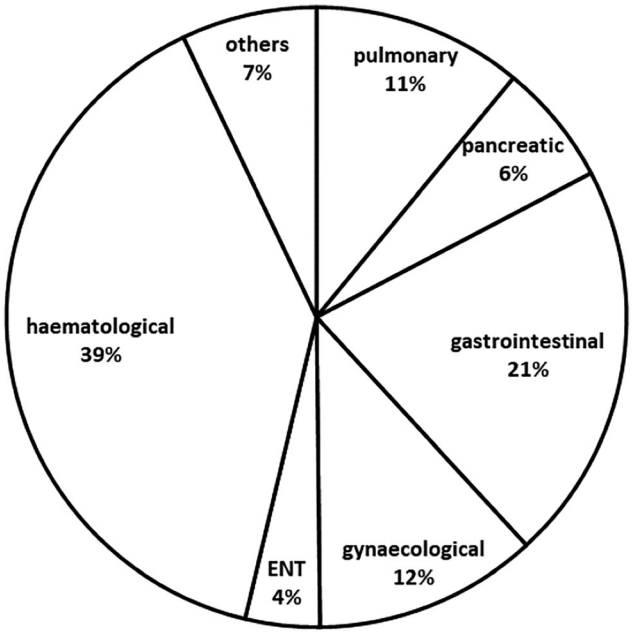

Table 2 Baseline characteristics of the study population divided by EORTC QLQ-C30 summary score median

	Study population (n = 283)	EORTC QLQ-C30 summary score < median (n = 141)	EORTC QLQ-C30 summary score ≥ median (n = 142)	P-values
Blood count				
Haemoglobin (g/dL)	11.7 ± 2.1	11.2 ± 2.1	12.2 ± 2.0	**<0.001**
Haematocrit (%)	34.7 ± 5.9	33.3 ± 5.9	36.1 ± 5.6	**<0.001**
Erythrocytes (x 10^6/μL)	3.90 ± 0.72	3.76 ± 0.74	4.05 ± 0.67	**0.001**
Platelets (x 10^3/μL)	238 (173–312)	242 (166–315)	236 (185–305)	0.999
Leucocytes (x 10^3/μL)	6.13 (4.63–8.51)	6.08 (4.49–8.29)	6.17 (4.64–8.58)	0.556
Clinical chemistry panel				
Sodium (mmol/L)	140 ± 3.4	139.11 ± 3.60	139.99 ± 3.22	**0.031**
Potassium (mmol/L)	4.0 ± 0.5	3.9 ± 0.5	4.0 ± 0.4	**0.003**
Iron (μmol/L)	12.2 (8.2–18.5)	11.4 (7.8–16.5)	13.4 (8.7–19.5)	0.125
Transferrin (g/L)	2.14 (1.82–2.52)	2.06 (1.66–2.45)	2.19 (1.97–2.55)	**0.007**
Transferrin saturation (%)	22 (15–35)	22.00 (14–35)	22.00 (16–35)	0.707
Ferritin (μg/L)	326 (99–432)	291.8 (108–523)	191.9 (88–376)	**0.020**
Creatinine (mg/dL)	0.84 ± 0.25	0.84 ± 0.28	0.84 ± 0.22	0.944
Albumin (g/L)	37 ± 5	36 ± 5	38 ± 5	**0.001**
CRP (mg/L)	6.7 (2–18.7)	9.2 (2.4–23.7)	5.5 (1.7–11.6)	**0.011**
Cardiac biomarkers				
Troponin T (ng/L)	8 (5–14)	10 (5–18)	8 (4–12)	**0.008**
NT-proBNP (ng/L)	189 (84–465)	231 (102–548)	155 (75–321)	**0.002**

CRP, C-reactive protein; EORTC, European Organisation for Research and Treatment of Cancer; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QLQ-C30, Quality of Life Questionnaire Core 30.
Data are expressed as mean ± standard deviation. Non-normally distributed data are expressed as median (25% and 75% percentile).
The bold values indicate significant P-values (defined as $P \leq 0.05$).

study population were classified as advanced disease [Union for International Cancer Control (UICC) stage ≥ III 93.6%; Ann-Arbor stage ≥ III 62.4%]. Mean BMI was 25.4 ± 4.8 kg/m^2 (range 15.4–41.6 kg/m^2). The most common co-morbidities were anaemia (64.0%) followed by cachexia (46.3%), hypertension (42.4%), and diabetes mellitus (9.2%). Dyspnoea, equivalent to NYHA class II or higher, was reported by 17.3% of all patients. The follow-up was censored in October 2020. Until this point, a total of 110 (38.9%) patients had died.

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Quality of life

Patients were divided according to the median EORTC QLQ-C30 summary score with higher values indicating higher QoL. There were no significant differences with regard to age ($P = 0.58$), tumour type ($P = 0.27$), survival rate ($P = 0.96$), and therapy-naïve status ($P = 0.36$) between these two groups. Whereas cachexia ($P = 0.001$), anaemia ($P = 0.009$), status as current smoker ($P = 0.012$), and dyspnoea ($P = 0.003$) were more frequent in patients with lower QoL, no such difference

Table 3 Baseline characteristics of the study population divided by EORTC QLQ-C30 summary score median

	Study population ($n = 283$)	EORTC QLQ-C30 summary score < median ($n = 141$)	EORTC QLQ-C30 summary score ≥ median ($n = 142$)	*P*-values
Physical diagnostic				
Heart rate (b.p.m.)	75 ± 14	78 ± 15	72 ± 12	**<0.001**
BP systolic (mmHg)	129 ± 20	129 ± 21	129 ± 19	0.506
BP diastolic (mmHg)	79 ± 23	80 ± 12	78 ± 11	0.266
HGS (kg)	28.91 (22.49–37.25)	26.25 (20.61–34.73)	32.23 (24.16–39.86)	**<0.001**

BP, blood pressure; EORTC, European Organisation for Research and Treatment of Cancer; HGS, hand grip strength; QLQ-C30, Quality of Life Questionnaire Core 30.
Data are expressed as mean ± standard deviation. Non-normally distributed data are expressed as median (25% and 75% percentile).
The bold values indicate significant *P*-values (defined as $P \leq 0.05$).

Table 4 Quality of life characterization of the study population using EORTC QLQ-C30

	Study population ($n = 283$)	TCI	EORTC QLQ-C30 summary score < median ($n = 141$)	EORTC QLQ-C30 summary score ≥ median ($n = 142$)	*P*-values
Global health status/ QoL scale (QL)	49.53 ± 22.52 50 (33.33–66.67)		35.34 ± 17.56 33.3 (25–50)	63.32 ± 17.52 66.67 (50–75)	**<0.001**
Functional scales					
Physical (PF)	66.20 ± 27.48 73.33 (46.67–86.67)	83	51.64 ± 27.16 53.33 (33.33–73.33)	80.66 ± 18.86 86.67 (71.67–93.33)	**<0.001**
Role (RF)	52.59 ± 35.94 50 (16.67–83.33)	58	30.50 ± 30.27 33.33 (0–50)	74.53 ± 26.46 83.33 (66.67–100)	**<0.001**
Cognitive (CF)	76.80 ± 25.76 83.33 (66.67–100)	75	62.65 ± 27.23 66.67 (50–83.33)	90.84 ± 13.83 100 (66.67–100)	**<0.001**
Emotional (EF)	63.19 ± 28.18 66.67 (41.67–83.33)	71	44.86 ± 23.39 41.67 (25–66.67)	81.40 ± 19.36 83.33 (66.67–100)	**<0.001**
Social (SF)	55.89 ± 33.75 66.67 (33.33–83.33)	58	36.17 ± 30.01 33.33 (16.67–50)	75.47 ± 24.68 83.33 (66.67–100)	**<0.001**
Symptom scales					**<0.001**
Fatigue (FA)	48.00 ± 28.65 44.44 (33.33–67.67)	39	69.47 ± 20.42 66.67 (55.56–88.89)	28.53 ± 18.89 33.33 (11.11–44.44)	**<0.001**
Nausea and vomiting (NV)	11.90 ± 19.75 0 (0–100)	8	19.42 ± 24.29 16.67 (0–33.33)	4.49 ± 9.32 0 (0–0)	**<0.001**
Pain (PA)	32.39 ± 33.44 33.33 (0–50)	25	49.64 ± 33.55 50 (16.67–83.33)	14.89 ± 22.16 0 (0–33.33)	**<0.001**
Dyspnoea (DY)	32.51 ± 34.66 33.33 (0–66.67)	17	49.40 ± 37.07 33.33 (0–66.67)	15.60 ± 21.66 0 (0–33.33)	**<0.001**
Insomnia (SL)	37.22 ± 34.79 33.33 (0–66.67)	50	53.72 ± 35.33 66.67 (33.33–66.67)	20.57 ± 25.40 0 (0–33.33)	**<0.001**
Loss of appetite (AP)	32.39 ± 39.91 33.33 (0–66.67)	50	52.04 ± 38.09 66.67 (0–100)	12.29 ± 21.24 0 (0–33.33)	**<0.001**
Constipation (CO)	16.37 ± 29.76 0 (0–33.33)	50	25.18 ± 35.86 0 (0–33.33)	6.86 ± 17.14 0 (0–0)	**<0.001**
Diarrhoea (DI)	15.78 ± 28.73 0 (0–33.33)	17	23.50 ± 33.92 0 (0–33.33)	8.27 ± 19.98 0 (0–0)	**<0.001**
Financial impact (FI)	22.22 ± 30.72 0 (0–33.33)	17	28.54 ± 34.18 0 (0–66.67)	15.60 ± 24.74 0 (0–33.33)	**0.001**
QLQ summary score	68.25 ± 19.55 71.15 (54.96–83.25)		52.42 ± 14.18 54.96 (40.83–64.19)	83.96 ± 8.09 83.08 (77.38–90.96)	**<0.001**

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life; TCI, threshold for clinical importance.
Data are expressed as mean ± standard deviation. Non-normally distributed data are expressed additionally as median (25% and 75% percentile).
The bold values indicate significant *P*-values (defined as $P \leq 0.05$).

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was observed for hypertension (P = 0.90) and diabetes (P = 0.84). A trend towards lower BMI was recorded for patients with lower QoL (P = 0.055; *Table 1*). Laboratory findings for the two groups are given in *Table 2*. Haemoglobin, haematocrit, erythrocyte count, transferrin, sodium, and potassium values were significantly reduced in patients with lower QoL (all $P < 0.05$). In contrast, ferritin, C-reactive protein (CRP), and cardiac biomarkers were significantly lower in patients with a QoL summary score above or equal the median (all $P < 0.05$) (*Table 2*). Whereas there were no significant differences in blood pressure, the heart rate was lower and the HGS higher in patients with a QoL summary score above or equal to the median than in the comparison group (both $P < 0.001$) (*Table 3*).

Determinants of quality of life

Results of the EORTC QLQ-C30 in the study population divided by the QLQ-C30 summary score are given in *Table 4*. Patients with a summary score above or equal to the median had consistently better functional status and overall lower symptom burden (all $P < 0.05$). *Figure 2* illustrates functional and symptom scales in direct comparison between the two groups. Comparing these data with thresholds of clinical importance published by Giesinger *et al.*, the studied population showed clinically important variations in physical, role, emotional, and social functions (*Table 4*). From a symptomatic point of view, patients were primarily affected by fatigue, pain, nausea, and vomiting, as well as dyspnoea and loss of appetite. Finally, the study population was burdened by the financial impact of their individual disease.

Using univariable logistic regression, we found that female sex, lower body weight, lower height, the presence of cachexia, night sweats, current smoking, NHYA class $\geq$ II, and the presence of anaemia were all associated with lower QoL (all $P < 0.005$). The same was true for different laboratory parameters like sodium, potassium, albumin, haemoglobin, and haematocrit in which decreasing values were associated with lower QoL. Increasing values in hs-Troponin T and NT-proBNP were also associated with lower QoL (*Table 5*). In addition, univariable logistic regression showed heart rate, heart rate $\geq$ 75 b.p.m., and HGS to be significantly associated with lower QoL.

Adjusting for clinically relevant parameters, multivariable logistic regression showed age, heart rate, HGS, and the presence of cachexia and dyspnoea to be independent predictors of a lower QoL (*Table 5*). No material change was noted when variables were entered into the model with EORTC QLQ-C30 summary score entered as continuous dependent variable.

Figure 2 Comparative quality of life scores in tumour patients. The two groups are built by using the median summary score. Left: Values are reflecting functional scales. Higher values result in better 'performance'. Right: Values are reflecting symptom scales. Higher values mean higher symptom burden. All components demonstrated statistically significant differences ($P < 0.05$). EORTC, European Organisation for Research and Treatment of Cancer.

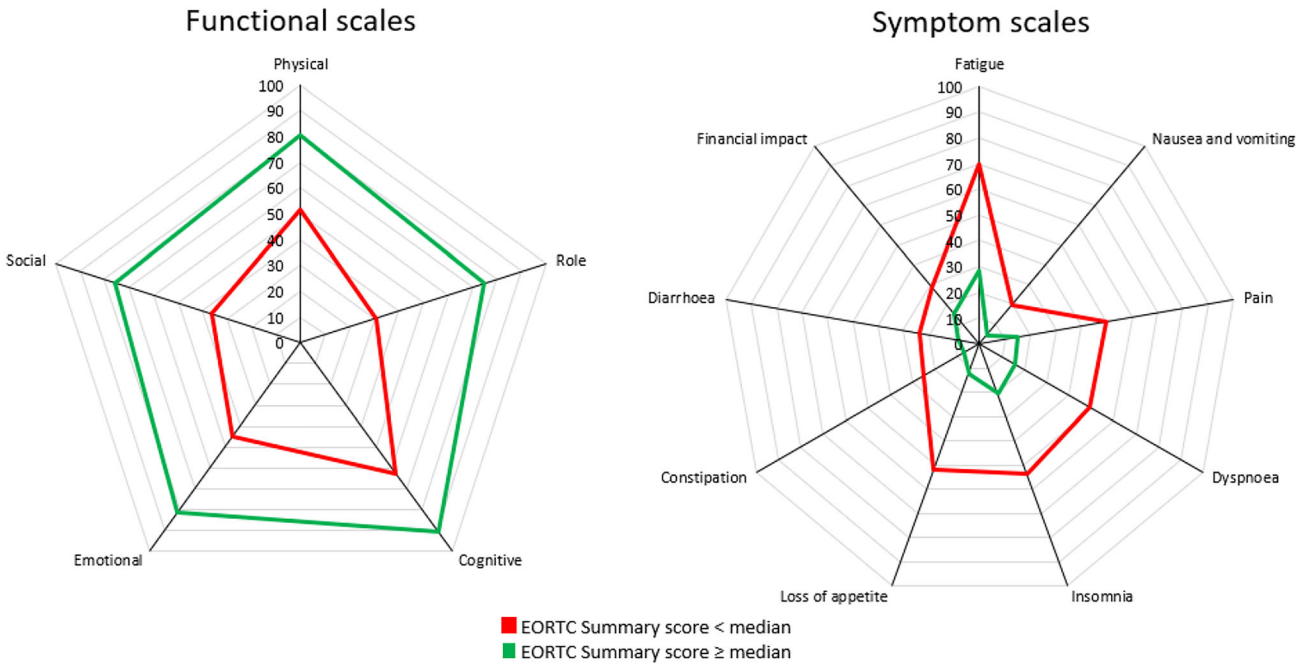

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Table 5 Univariable and multivariable analyses for prediction of low QoL

Variable	Odds ratio (95% CI)	*P*-values
Univariable models		
Age (1 year increase)	0.995 (0.977–1.013)	0.575
Sex (male)	0.542 (0.338–0.868)	**0.011**
Currently alive (present)	0.989 (0.613–1.594)	0.962
Solid tumour (present)	0.757 (0.469–1.221)	0.253
Treatment naïve (present)	0.728 (0.399–1.328)	0.728
Height (1 cm increase)	0.966 (0.941–0.991)	**0.008**
Weight (1 kg increase)	0.980 (0.967–0.994)	**0.005**
BMI (1 kg/m^2 increase)	0.953 (0.907–1.001)	0.057
Night sweat (present)	2.614 (1.457–4.689)	**0.001**
Cachexia (present)	2.266 (1.401–3.665)	**0.001**
Hypertension (present)	0.955 (0.596–1.531)	0.850
Anaemia (present)	1.957 (1.194–3.207)	**0.008**
Diabetes mellitus (present)	0.850 (0.379–1.910)	0.695
Current smoker (present)	2.075 (1.183–3.638)	**0.011**
Dyspnoea (present)	3.062 (1.505–6.227)	**0.002**
(NYHA class ≥ II)		
Sodium (1 mmol/L increase)	0.926 (0.862–0.994)	**0.034**
Potassium (1 mmol/L increase)	0.451 (0.262–0.774)	**0.004**
Haemoglobin (1 g/dL increase)	0.786 (0.697–0.886)	<**0.001**
Haematocrit (1 unit increase)	0.919 (0.880–0.959)	<**0.001**
Erythrocytes	0.556 (0.394–0.784)	**0.001**
Platelets	1.000 (0.998–1.002)	0.816
Leucocytes	0.990 (0.953–1.028)	0.608
Ferritin (10 μg/L increase)	1.004 (0.999–1.008)	0.096
TSAT (1 unit increase)	1.003 (0.992–1.015)	0.589
Albumin (1 g/L increase)	0.922 (0.878–0.969)	**0.001**
Log Troponin T (1 SD increase)	2.323 (1.554–5.001)	**0.014**
Log NT-proBNP (1 SD increase)	2.030 (1.258–3.275)	**0.004**
Log CRP (1 SD increase)	1.518 (1.067–2.161)	**0.020**
Heart rate (1 b.p.m. increase)	1.033 (1.014–1.051)	**0.001**
Heart rate ≥ 75 b.p.m. (present)	1.858 (1.155–2.989)	**0.011**
HGS (1 kg increase)	0.955 (0.932–0.979)	<**0.001**
Multivariable model[a]		
Age (years)	0.954 (0.916–0.994)	**0.025**
Cachexia (present)	4.334 (1.767–10.631)	**0.001**
Dyspnoea (present)	3.725 (1.540–9.010)	**0.004**
(NYHA class ≥ II)		
HR (1 b.p.m. incrase)	1.036 (1.004–1.068)	**0.025**
HGS (1 kg increase)	0.932 (0.878–0.990)	**0.022**

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HGS, hand grip strength; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; TSAT, transferrin saturation.
[a]Adjusted for age, sex, solid tumour, treatment naïve, BMI, cachexia, dyspnoea (NYHA ≥ II), albumin, HR, HGS, and anaemia.
The bold values indicate significant *P*-values (defined as $P \leq 0.05$).

Discussion

The aim of this study was to quantitate the influence of parameters deemed clinically relevant on QoL. We found that a number of clinical factors contribute to reduced QoL in our multivariate model, notably younger age, the presence of cachexia and dyspnoea, higher heart rate, and lower HGS, all of which remained independently associated with lower values in the EORTC QLQ-C30 even after adjusting for several confounders. Some factors may be targets for specific therapies that could be added to cancer treatment algorithms.

The EORTC QLQ-C30 has proven to be a valuable tool in the assessment of QoL in patients with cancer,[6–8] in whom reduced QoL has been well established by several previous studies.[9–11] Different studies have identified pain, fatigue, and limitations in social and physical functions as primary determinants of reduced QoL.[12,13] Whilst oncological assessment tools are understandably focusing on cancer-specific complaints for assessing QoL, we sought to establish a cardiological perspective. This approach is reasonable not only because cancer and cardiovascular diseases are the two leading causes of death but also because there is gross overlap between the two disease groups in terms of their underlying mechanisms and risk factors.[14] Therefore, it is not surprising that cancer patients develop cardiovascular perturbations independent of whether a cancer-specific therapy has been commenced or whether patients are still chemotherapy naïve.[15]

Like in patients with cancer, QoL is significantly reduced in patients with heart failure, a clinical syndrome that can manifest as a result of cardiotoxic chemotherapies. Because heart failure has 1 year mortality rates up to 17%, its prognosis is per se comparable with several types of cancer.[16] The comparison between cancer and heart failure is advisable not only because of the interplay of both diseases but also because of the known impaired QoL.[17] Improvements in QoL in patients with heart failure remain extremely challenging due to a lack of efficacy of most standard medications in this regard. Our group has investigated heart failure medications on their effectiveness at improving exercise capacity and QoL. However, the results with respect to QoL were disappointing with ivabradine, supplementation of intravenous iron, and exercise training being the only therapies to effectively improve QoL as well as exercise capacity.[18] Interestingly, it was not possible to reveal a positive effect of heart rate reduction using beta-blockers. The fact that iron deficiency and elevated heart rate influence QoL in patients with heart failure is known, but now we were able to demonstrate this parallelism in cancer patients with regard to the interplay between increased heart rate and impaired QoL.[19–21] Interestingly, in both conditions—cancer and heart failure—an increased heart rate is associated not only with reduced QoL but also with higher mortality.[22–24] Therefore, it appears beneficial to initiate heart rate-modulating medications in patients with cancer as well. Unfortunately, evidence from clinical trials to support this view is not currently available outside the area of heart failure and cardiovascular disease.

Whereas heart rate is important for haemodynamic considerations, iron availability is essential for mobility due to its pivotal roles in skeletal muscle and myocardial respiration as well as in erythropoiesis. Muscle wasting can determine exercise capacity and thus mobility.[25,26] In the absence of detailed body composition analyses, weight loss and therefore cachexia can serve as surrogate markers for the loss of muscle and fat mass. Cachexia is a common co-morbidity in heart failure and cancer patients. Its prevalence varies due

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to inconsistent definitions and reaches 10–39% in heart failure patients.[27] Comparable prevalence data exist for patients with colorectal (22–55%) and lung cancer (46%), which is well in line with the prevalence of cachexia in the present study of 46.3%.[28,29]

The relationship between cachexia and QoL as well as that between cachexia and increased mortality is described for patients with cancer and patients with heart failure.[30–33] There are some explanatory approaches that show possible causes of an association between cachexia and reduced QoL: (i) Cachexia leads to a loss of muscle mass, which may result in a reduced physical capacity, fatigue, and dyspnoea.[34,35] (ii) Cachexia leads to reduced cancer treatment efficacy and to an increase in treatment side effects.[36] Due to the multifactorial genesis, a multimodal therapeutic approach is required. This is reinforced by the fact that studies that only followed one therapeutic approach gave negative results. Cachexia therapy is based on combating the underlying tumour disease and is supplemented by measures to improve food tolerance, nutritional advice, and physical activity or training. The latter seems to be important not only to oppose cachexia but also to improve muscle strength. Although cancer-specific treatment is usually felt as a passive procedure, physical activity or exercise training can be influenced by the patient, resulting in improved self-esteem and consequently improved QoL.[37–39] It is important to emphasize that physical activity and exercise training are usually not considered harmful at any point during cancer treatment.[40,41] The meaning of muscle strength was also observed in our study, where a reduced HGS was associated with a lower QoL, which is in line with other studies.[42–44] Marques *et al*. see a possible connection between reduced HGS and reduced QoL in the fact that the HGS represents the total muscle mass and a reduced muscle mass may lead to a loss of activity and autonomy.[45] On the other hand, reduced HGS may be interpreted just as a common pathway that reflects the overall condition of the individuum. There is evidence that pain, for example, negatively affects muscle mass.[46] Pain itself notoriously affects QoL as mentioned before. Besides QoL, HGS was proven to be associated with different outcome parameters. In the field of surgery, reduced HGS was associated with an increased incidence of complications and longer hospital stays.[47] In cancer patients, it was also associated with an increased mortality.[48] Apart from the already mentioned, our results reveal that dyspnoea influences QoL in cancer patients directly. This is particularly important because data from the National Hospice Study have shown that 70.2% of terminally ill cancer patients report dyspnoea. Interestingly, 23.9% of these patients did not have any underlying cardiac or respiratory disease nor lung or pleural cancer involvement. Therefore, breathlessness has been attributed to the poor overall health status commonly encountered in advanced malignant disease.[49] Indeed, dyspnoea is associated with reduction in QoL as confirmed in many studies and as is easily understandable for a feeling of intense tightening in the chest, air hunger, or breathlessness.[50,51] Besides the use of oxygen and the prescription of morphine derivatives, it should be searched for treatable causes. For example, if there is heart failure as a result of tumour therapy, heart failure treatment can be initiated and diuretics can be administered to address signs of pulmonary venous congestion.

Interestingly, in our study, there were no differences in terms of survival between patients with reduced QoL and patients with higher QoL. Although this finding seems initially counterintuitive, it has to be taken into account that only 38% of cancer patients were dying from cancer itself, whereas the majority died due to other causes like cardiovascular diseases accordingly to Sturgeon *et al*.[52] However, we cannot exclude that this finding in our cohort may be a chance finding.

In summary, increased heart rate, cachexia, and muscle strength represent important measures and therapeutic targets for improving QoL in patients with advanced cancer. Clinical trials are warranted to tackle these problems. Another interesting possibility embraces the treatment of iron deficiency, even though it was not associated with reduced QoL in the present study, likely due to the equal distribution of iron deficiency prevalence between patients with lower and higher QoL. Dyspnoea as a treatment target may be directly associated with muscle loss and reduced exercise capacity or with increased heart rate.

Limitations

Some limitations need to be addressed. First, the current study included all-comers of a regional cancer centre specialized in the treatment of gastroenterological and haematological cancers. The all-comer status resulted in a lot of patients who were on a second- or even third-line therapy. Therefore, most of the patients received cardiotoxic chemotherapy at the time of inclusion or in the past. However, our study aimed to assess determinants of QoL from a cardiologist perspective in cancer patients independently of the chemotherapy they received. Second, symptoms like pain, nausea, and vomiting were not included in the statistical analysis regarding determinants of QoL because they are already part of the EORTC QLQ-C30 questionnaire and their inclusion would result in selection bias. Third, we did not perform analyses of echocardiography parameters and QoL, because patients with relevant cardiovascular disease were excluded as per study design.

Conclusions

Our study shows that age, heart rate, HGS, and the presence of cachexia and dyspnoea are independent predictors of

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reduced QoL. It is therefore desirable that these parameters are routinely screened for during oncological consultation to start interventions as early as possible in order to maintain patients' QoL as long as possible. Other parameters affecting QoL outside the present study such as pain, nausea, or vomiting should of course not be neglected. Further investigations are needed to evaluate the impact of heart rate-modulating medications in the setting of cancer.

Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest with respect to this work.

Funding

This research received no external funding.

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