

RESEARCH ARTICLE



Association of altered body composition with cardiac wasting in cancer with and without cardiotoxic therapy

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Background and Purpose: In advanced cancer, associations among changes in body composition, cardiac wasting and prior cardiotoxic anticancer therapy have not been investigated.

Experimental Approach: Using bioelectrical impedance analysis (BIA), body composition was measured in 206 patients with mostly advanced cancer without known cardiovascular disease or infection (stage III/IV: 84%, prior cardiotoxic anticancer therapy: 55%). Left ventricular (LV) mass was assessed by transthoracic echocardiography and grouped by presence of cardiac wasting according to previously established sex-specific thresholds for LV mass adjusted for height² (<61 g/m² for women, <57 g/m² for men). BIA measurements (indexed to height²) included fat mass index (FMI), fat-free mass index (FFMI), skeletal muscle mass index (SMMI), visceral fat index (VFI), total body water index (TBWI) and extracellular water index (ECWI).

Key Results: Patients with cancer and cardiac wasting ($n = 88$) were younger (57 ± 15 vs 62 ± 13 years) and more often women (68% vs 29%) compared to those without cardiac wasting ($n = 118$). Patients with cardiac wasting had significantly lower FMI (−12%), FFMI (−14%), SMMI (−16%), VFI (−46%), TBWI (−13%) and ECWI (−14%). For women, FFMI was significantly associated with LV mass/height² ($r = 0.41$) and VFI for men ($r = 0.40$). In the multivariable linear regression analysis, FFMI was the

Abbreviations: BIA, bioelectrical impedance analysis; FFMI, fat-free mass index; FMI, fat mass index; GH, growth hormone; LV, left ventricular; PhA, phase angle; PPAR γ , peroxisome proliferator-activated receptor gamma; R, resistance; SMMI, skeletal muscle mass index; VFI, visceral fat index.

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strongest significant predictor of cardiac wasting, with no significant interaction by sex or previous cardiotoxic therapy.

Conclusions and Implications: Cardiac wasting in advanced cancer is associated with lower FFMI and VFI independent of prior cardiotoxic therapy.

KEYWORDS

cardiotoxicity, cachexia, cancer, cardiology, echocardiography, left ventricular mass

1 | INTRODUCTION

The clinical evaluation of body composition offers insights into nutritional and metabolic status beyond traditional anthropometric indices such as body mass index (BMI) (Brown et al., 2024). In oncology, both the distribution and quality of muscle and adipose tissue predict the ability to tolerate anticancer therapies (Prado et al., 2008), postoperative outcomes (Matsui et al., 2025) and survival (Feliciano et al., 2017). Sarcopenia, loss of skeletal muscle mass and function, is particularly prevalent among patients with cancer and has been associated with greater toxicity from chemotherapy, longer hospital stays and poorer prognosis for various malignancies (Miranda et al., 2024). Quantification of body composition allows clinicians to identify patients with a low muscle mass, which is associated with an adverse prognosis (Zhang et al., 2023), even when fat mass is increased and BMI is normal or high (Iyengar et al., 2015). Moreover, longitudinal assessment of body composition can help monitor disease progression and treatment-related changes, providing guidance for nutritional, pharmacologic and exercise interventions aimed at maintaining quality of life and improving survival (Lee et al., 2024).

Body composition can be measured using methods like bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT). BIA estimates body fat and lean mass by measuring tissue resistance to electrical currents, while dual-energy X-ray absorptiometry and CT scans provide information on bone density, fat distribution and muscle mass, with CT offering cross-sectional images of internal structures. In the oncologic setting, BIA is increasingly recognised as a useful, non-invasive method for detecting sarcopenia and monitoring changes in body composition (Aleixo et al., 2020). Recent studies have compared visceral fat area measurements obtained by BIA and CT in cohorts with gastric cancer, confirming the validity of serial BIA measurements (Haverkort et al., 2015).

As conditions such as heart failure and cancer progress, they are often complicated by catabolism, with a loss of skeletal muscle mass (sarcopenia) (Fang et al., 2023; Zhang et al., 2021; Zuo et al., 2023), fat mass and overall body mass (cachexia) (Baracos et al., 2018; Castiglione et al., 2023; Valentova et al., 2022). Cachexia is common in advanced stages of heart failure (5% to 15% of patients) and cancer (up to 50% to 80% of patients) (Khan et al., 2024).

Cardiac wasting, defined as a low left ventricular (LV) mass, has emerged as an under recognised complication of late-stage cancer. Pre-clinical evidence suggests that inflammatory cytokines, neurohormonal

What is already known?

- Patients with advanced cancer experience fatigue, reduced physical performance impaired quality of life and prognosis.
- This could in part be attributed to cardiac dysfunction.

What does this study add?

- Cardiac wasting is common in patients with advanced cancer.
- It is associated with changes in body composition, especially a reduction in lean body mass, independent of prior cardiotoxic therapy.

What is the clinical significance?

- Body composition changes could indicate the possibility of cardiac wasting.
- Cardiac wasting could contribute to symptoms in patients with advanced cancer.

disturbances, up-regulated proteolysis and metabolic alterations cause reductions in LV mass (Tian et al., 2010), but the precise clinical mechanisms are complex and unresolved (Wiggs et al., 2022). Cardiac wasting-associated cardiomyopathy has recently been described as a distinct cardiovascular syndrome, characterised by cardiac impairment, symptoms such as breathlessness and fatigue, decreased physical performance, poor quality of life and an adverse prognosis (Anker et al., 2021; Anker et al., 2024; Lena et al., 2023; Piepoli & Coats, 2013). Indeed, cardiac wasting in patients with cancer may lead to all the features of heart failure, with cardiac dysfunction being accompanied by systemic metabolic changes and reduced skeletal muscle mass and strength (Hadzibegovic et al., 2023).

Another important concern in cardio-oncology is cardiotoxicity induced by anti-cancer treatments (Lyon et al., 2022). Clinical manifestations can vary widely, from heart failure- and coronary

artery-related symptoms (such as shortness of breath, angina, fatigue, or swelling in legs and ankles) to arrhythmias and myocarditis, including myocarditis associated with immune checkpoint inhibitors (ICIs) (Lyon et al., 2022). Cardiotoxicity can occur both acutely and with a delayed onset months to years later (Cardinale et al., 2015; Serrano et al., 2023). Advanced patients with cancer exhibit an increased risk for both cardiotoxicity and cardiac wasting (Anker et al., 2021), mediated through direct myocardial injury or indirectly through systemic inflammation, metabolic disturbances and reduced physical activity (Baracos et al., 2018). The interplay between these conditions further exacerbates the risk of poor clinical outcome, chemotherapy intolerance and increased mortality. However, it is challenging to distinguish whether these conditions are interrelated or represent independent pathological processes.

Accordingly, we investigated the relationship between cardiac wasting and changes in BIA-based body composition in patients with advanced cancer and examined whether these associations differed between sexes and prior cardiotoxicity anticancer therapy.

2 | METHODS

2.1 | Recruitment

In this prospective single-centre study, we recruited 206 hospitalised patients with cancer (94 women, 84% with advanced stage cancer) from the Department of Oncology of the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin. Recruitment took place between January 2020 and February 2023. Out of the 224 initially screened patients, eight patients were excluded because of newly identified cardiac disease and because of poor imaging quality making assessment of LV mass unreliable. Eligible patients (i) were ≥ 18 years, (ii) had histologically confirmed active cancer and (iii) had no other cancer diagnosis in the past 5 years. Exclusion criteria were the following:- (i) cardiovascular disease such as myocardial infarction, coronary artery disease, major valve defects or a left ventricular ejection fraction (LVEF) $< 50\%$ at baseline (ii) acute, antibiotic-treated infection, (iii) chronic obstructive pulmonary disease (COPD) GOLD stages ≥ 3 , except for those with lung cancer who were included regardless of GOLD stage. Patients with controlled hypertension (BP $< 160/100$ mm Hg) and/or uncomplicated type II diabetes mellitus (T2DM) were not excluded. The main reasons for hospitalisation were as follows:- systemic anticancer therapy administration ($n = 117$), diagnostic examinations ($n = 55$), worsening clinical condition ($n = 14$), pain exacerbation ($n = 6$), shortness of breath ($n = 9$) and neurologic symptoms ($n = 5$). Patients with cancer were recruited regardless of whether they had previously been treated with cardiotoxic or non-cardiotoxic agents or not. Cardiotoxic anticancer agents were defined based on the most recent European Society of Cardiology guideline as drugs with the potential to cause heart failure (McDonagh et al., 2021a).

2.2 | Study protocol

The criteria for advanced cancer stages were based on the Union for International Cancer Control (UICC) stages III and IV (Bertero et al., 2018), the Ann Arbor classification stages III and IV (Carbone et al., 1971) and the Durie and Salmon classification stage III (Durie & Salmon, 1975). Patients were classified according to the presence of cardiac wasting, defined as LV mass adjusted for height squared (height^2) using gender-specific cutoffs ($< 61 \text{ kg/m}^2$ women, $< 57 \text{ kg/m}^2$ men) (Lena et al., 2023). Additionally, patients were classified based on the presence or absence of cachexia defined as a wasting syndrome with unintentional weight loss using the following criteria: body mass index (BMI) of less than 24.0 kg/m^2 at baseline and an unintentional weight loss of at least 5% over the previous 12 months (Fearon et al., 2011; Stewart Coats et al., 2016). Malnutrition was defined according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines as values of fat-free mass index (FFMI) $< 17 \text{ kg/m}^2$ in men and $< 15 \text{ kg/m}^2$ in women (Cederholm et al., 2017) (Arends et al., 2017). Previous medical history and medication at baseline were documented. The following clinical assessments were conducted:- anthropometric assessments (mid-arm and calf circumference; Lohman & Martorell, 1988), physical function (Karnofsky Performance Status [Karnofsky D, 1949] and Eastern Cooperative Oncology Group performance status [Oken et al., 1982]) and physical activity (hand-grip strength [HGS]; Hadzibegovic et al., 2023) and 6-min walking test (6MWT; Laboratories ATSCoPSfCPF, 2002). Water retention can lead to misinterpretation of lean mass values; therefore, the water retention status was documented using the oedema score (Mullens et al., 2018). The oedema score documents three components:- the presence of oedema in the lower extremities, pleural effusion and ascites. Lower extremity oedema is graded on a 5-point scale:- no oedema (0 points), trace oedema (1 point), oedema up to the ankle (2 points), up to the knee (3 points) and above the knee (4 points). Pleural effusion and ascites are each categorised into three levels:- none (0 points), minor (2 points; not amenable to puncture) and significant (3 points; amenable to puncture). This study received approval from the Ethics Committee of the Charité and was conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent.

2.3 | Bioimpedance analysis

Body composition was evaluated using the SECA mBCA 515 analyser (Seca GmbH & Co., KG, Hamburg, Germany), which operates with a $100 \mu\text{A}$ current across frequencies from 1 to 1000 kHz. The device features a platform with an integrated scale and a handrail system, equipped with six electrodes, two of which are selected based on the participant's height. Additional pairs of electrodes are located on the platform to contact the feet. This phase-sensitive eight-electrode system allows for segmental impedance measurement of the trunk and

each limb, measuring the left and right sides separately and then averaging them to ensure consistency between right-handed and left-handed individuals. All measurements followed the manufacturer's guidelines. The participants stood barefoot on the platform in an upright position with arms extended and holding the handrail. The device automatically initiated the measurement when proper contact was made with all electrodes, which lasted 15 s. The participant height was recorded using a wall-mounted stadiometer. Measurements were made between 9 AM and 1 PM in a non-fasting state with standardised clothing (hospital gown and underwear). Trained study centre personnel supervised all measurements. The body composition assessment included body weight and following bioelectrical impedance measures, which were also indexed by height squared (m^2): fat mass index (FMI, kg/m^2), fat-free mass index (FFMI, kg/m^2), skeletal muscle mass index (SMMI, kg/m^2), visceral fat index (VFI, L/m^2), total body water index (TBWI, L/m^2), extracellular water index (ECWI, L/m^2), resistance (R , Ω), reactance (X_c , Ω) and phase angle (PhA , $^\circ$). The fat mass/fat-free mass ratio was calculated by dividing total fat mass by total fat-free mass.

2.4 | Echocardiography and assessment of LV mass

All echocardiography studies were performed by experienced sonographers using a Vivid E90 echocardiography system (GE, Boston, USA). Subsequent analysis was performed by two independent investigators with a Tomtec analysis software (Unterschleissheim, Germany). To determine the LV mass, we used the Devereux formula, incorporating linear measurements of the LV wall thickness and LV diameter at end diastole in the parasternal long-axis view (Devereux & Reichek, 1977). Echocardiographic variables are presented as absolute values and adjusted for height squared (Lena et al., 2023; McDonagh et al., 2021b).

2.5 | Statistical analysis

The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology (Curtis et al., 2025). To assess whether variables followed a normal distribution, the Kolmogorov–Smirnov test and a visual inspection of the variables' distribution were employed. Differences between groups were evaluated using unpaired *t*-test and results for normally distributed data were expressed as mean $\pm$ standard deviation (SD). Frequency comparisons were conducted using the Chi-square test. Correlations between LV mass adjusted for height² and all BIA measurements were calculated using Pearson's correlation. A scatter plot was generated to visualise the correlations between the variables. We conducted a linear regression analysis using LV mass adjusted for height² as the outcome variable and BIA measurements as predictors. The multivariable model was adjusted for established prognostic factors in patients with cancer, including age (per 1-year increase), sex (male vs female), Charlson comorbidity index (CCI; per 1-point increase) and the presence of cachexia (yes vs no). In addition, systolic blood pressure (per 1 mmHg increase) was included as a cardiovascular parameter commonly used

in clinical assessment. The necessary assumptions for linear regression, including linearity, homoscedasticity, normality of residuals and multicollinearity, were methodically verified. Robust standard errors were utilised to address heteroscedasticity and to ensure more dependable inference. The goodness-of-fit for the linear regression model was assessed using adjusted R^2 and model performance was evaluated based on Akaike's Information Criterion (AIC). A significance level of $P < 0.05$ was applied for all statistical tests. The analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA) and SAS/STAT software version 9.4 (SAS Institute Inc). The graphical abstract was created using BioRender: Scientific Figure and Illustration Software.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY <http://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/2026 (Alexander et al., 2025).

3 | RESULTS

3.1 | Study population

The mean age of the cohort was 60 ± 14 years, 54% were men and 55% had been treated with cardiotoxic agents (Table 1). Eighty-one per cent of the patients had an oedema score of 1 point or less. In Table S1 cancer diagnoses are shown and Table S2 lists the cardiotoxic chemotherapeutic agents that were administered in this study cohort.

3.2 | Group stratification based on cardiac wasting

The patients with cardiac wasting were significantly younger (57 ± 15 vs 62 ± 13 years) and predominantly women (68% vs 29%; Table 1a). The patients with cardiac wasting had more often received anticancer therapy than the patients without cardiac wasting, but the proportions with cachexia were similar for those with and without cardiac wasting. Antihypertensive and antidiabetic therapies were more commonly administered in patients without cardiac wasting. Physical status (ECOG and Charlson comorbidity index) and physical function (hand grip strength and six-min walking test) were similar between groups with and without cardiac wasting (Table 1a). The patients with lower LV mass index had lower FMI, VFI, FFMI and SMMI compared to patients with higher LV mass index, whereas R and X_c were increased (Table 1b). For the entire cohort of patients, regardless of cardiac wasting, women had higher FMI than men, whereas BMI, FFMI, VFI, SMMI and PhA were higher in men (Table 2a). The pattern of differences in body composition between individuals with and without cardiac wasting was similar in women and men (Table 2b).

TABLE 1a Baseline characteristics of patients with cancer stratified by cardiac wasting.

Variable	All patients (n = 206)	Cardiac wasting (n = 88)	No cardiac wasting (n = 118)	P-value
Clinical variables				
Age (years)	60 ± 14	57 ± 15	62 ± 13	0.024
Men (n, %)	112 (54)	28 (32)	84 (71)	<0.001
Cancer stage III/IV (n, %)	171 (84)	76 (86)	95 (83)	0.34
Solid cancer (n, %)	162 (79)	70 (80)	92 (78)	0.78
Cardiotoxic agents (n, %)	114 (55)	54 (61)	60 (51)	0.13
Presence of cachexia (n, %)	112 (54)	47 (53)	65 (55)	0.81
Charlson comorbidity index (points)	6.5 ± 2.5	6.6 ± 2.4	6.5 ± 2.6	0.93
Systolic blood pressure (mmHg)	130 ± 18	129 ± 18	131 ± 18	0.35
LV mass adjusted for height ² (g/m ²)	63 ± 17	49 ± 8	75 ± 12	<0.001
Medications				
ACEi/ARBs (n, %)	53 (28)	18 (21)	40 (34)	0.034
Beta-blockers (n, %)	37 (18)	10 (11)	27 (23)	0.033
Treatments for diabetes (n, %)	18 (9)	3 (3)	15 (13)	0.019
Corticosteroids (n, %)	50 (24)	19 (22)	31 (26)	0.44
Clinical assessments				
ECOG performance status (points)	1.4 ± 1.0	1.3 ± 0.9	1.5 ± 1.0	0.34
Karnofsky performance status (%)	78 ± 14	79 ± 20	77 ± 14	0.26
Hand-grip strength (kg)	33.5 ± 12.7	31.5 ± 9.6	34.9 ± 13.1	0.049
Six-minute walking test (m)	457 ± 95	463 ± 93	452 ± 96	0.52
Mid-arm circumference (cm)	28 ± 4	27 ± 3	29 ± 4	0.001
Calf circumference (cm)	35 ± 4	35 ± 3	37 ± 4	0.003

Note: Normal distributed variables are presented as means ± SD and nominal variables as percent. Bold indicates statistical significance of $p < 0.05$. P-values for normal distributed variables are determined using unpaired *t*-test, and P-values for nominal variables are computed according to χ^2 test. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ECOG, Eastern Cooperative of Oncology Group.

TABLE 1b Bioimpedance analysis in patients with cancer stratified by cardiac wasting.

Variable	All patients (n = 206)	Cardiac wasting (n = 88)	No cardiac wasting (n = 118)	P-value
Weight (kg)	73.7 ± 15.9	66.1 ± 13.8	79.3 ± 15.1	<0.001
Height (m)	1.72 ± 0.11	1.70 ± 0.10	1.74 ± 0.11	0.014
Body mass index (kg/m ²)	24.8 ± 4.4	22.8 ± 4.2	26.3 ± 4.0	<0.001
Body surface area (Du Bois, m ²)	1.86 ± 0.23	1.76 ± 0.20	1.94 ± 0.22	<0.001
Fat mass index (kg/m ²)	7.3 ± 3.2	6.8 ± 3.1	7.7 ± 3.2	0.036
Fat-free mass index (kg/m ²)	17.5 ± 3.0	16.0 ± 2.7	18.7 ± 2.6	<0.001
Malnutrition: ESPEN guidelines ^a (n, %)	62 (30)	42 (48)	20 (17)	<0.001
Fat mass/fat-free mass ratio	0.427 ± 0.189	0.426 ± 0.194	0.427 ± 0.187	0.43
Skeletal muscle mass index (kg/m ²)	7.7 ± 1.8	6.9 ± 1.6	8.2 ± 1.8	<0.001
Visceral fat index (L/m ²)	0.73 ± 0.54	0.49 ± 0.37	0.91 ± 0.58	<0.001
Total body water index (L/m ²)	12.9 ± 2.1	11.9 ± 1.6	13.6 ± 2.1	<0.001
Extracellular body water index (L/m ²)	6.1 ± 0.8	5.6 ± 0.7	6.5 ± 0.8	<0.001
Resistance (Ω)	582 ± 103	630 ± 99	546 ± 91	<0.001
Reactance (Ω)	43.3 ± 10.9	46.7 ± 10.8	40.7 ± 10.3	<0.001
Phase angle (°)	4.2 ± 0.9	4.2 ± 0.9	4.3 ± 0.9	0.69

Note: Normal distributed variables are presented as means ± SD. P-values for normal distributed variables are determined using unpaired *t*-test. Bold indicates statistical significance of $p < 0.05$. ESPEN, European Society for Clinical Nutrition and Metabolism,

^aFFMI < 17 kg/m² in men and FFMI < 15 kg/m² in women.

TABLE 2a Bioimpedance analysis in women and men with cancer for the overall population with or without cardiac wasting.

Variable	All patients (n = 206)	Women (n = 94)	Men (n = 112)	P-value
Weight (kg)	73.7 ± 15.9	64.7 ± 12.2	81.0 ± 14.7	<0.001
Height (m)	1.72 ± 0.11	1.64 ± 0.08	1.79 ± 0.08	<0.001
Body mass index (kg/m ²)	24.8 ± 4.4	24.1 ± 4.5	25.5 ± 4.1	0.018
Body surface area (Du Bois, m ²)	1.86 ± 0.23	1.70 ± 0.16	1.99 ± 0.20	<0.001
Fat mass index (kg/m ²)	7.3 ± 3.2	8.5 ± 3.2	6.3 ± 2.8	<0.001
Fat-free mass index (kg/m ²)	17.5 ± 3.0	15.6 ± 2.5	19.2 ± 2.3	<0.001
Malnutrition: ESPEN guidelines ^a (n, %)	62 (30)	42 (45)	20 (18)	<0.001
Fat mass/fat-free mass ratio	0.427 ± 0.189	0.544 ± 0.179	0.328 ± 0.133	<0.001
Skeletal muscle mass index (L/m ²)	7.7 ± 1.8	6.4 ± 1.2	8.7 ± 1.5	<0.001
Visceral fat index (L/m ²)	0.73 ± 0.54	0.49 ± 0.37	0.94 ± 0.58	<0.001
Total body water index (L/m ²)	12.9 ± 2.1	11.7 ± 1.4	14.0 ± 1.9	<0.001
Extracellular water index (L/m ²)	6.1 ± 0.8	5.8 ± 0.7	6.4 ± 0.8	<0.001
Resistance (Ω)	582 ± 103	639 ± 94	534 ± 84	<0.001
Reactance (Ω)	43.3 ± 10.9	45.1 ± 11.3	41.8 ± 10.4	0.028
Phase angle (°)	4.2 ± 0.9	4.0 ± 0.7	4.4 ± 0.9	<0.001

Note: Normal distributed variables are presented as means ± SD. P-values for normal distributed variables are determined using unpaired t-test. Bold indicates statistical significance of $p < 0.05$. ESPEN, European Society for Clinical Nutrition and Metabolism.

^aFFMI < 17 kg/m² in men and FFMI < 15 kg/m² in women.

TABLE 2b Bioimpedance analysis in women and men with cancer stratified by cardiac wasting.

Variable	Women (n = 94)			Men (n = 112)		
	Cardiac wasting (n = 60)	No cardiac wasting (n = 34)	P-value	Cardiac wasting (n = 28)	No cardiac wasting (n = 84)	P-value
Weight (kg)	62.4 ± 11.4	68.7 ± 12.5	0.007	73.9 ± 15.3	83.7 ± 13.8	0.001
Height (m)	1.66 ± 0.08	1.61 ± 0.06	0.004	1.79 ± 0.07	1.78 ± 0.09	0.40
Body mass index (kg/m ²)	22.7 ± 4.0	26.4 ± 4.5	<0.001	23.0 ± 4.4	26.3 ± 3.6	<0.001
Body surface area (Du Bois, m ²)	1.69 ± 0.16	1.73 ± 0.16	0.21	1.92 ± 0.20	2.02 ± 0.19	0.017
Fat mass index (kg/m ²)	7.6 ± 2.8	10.1 ± 3.4	<0.001	4.9 ± 2.8	6.8 ± 2.6	0.002
Fat-free mass index (kg/m ²)	14.9 ± 2.4	16.6 ± 2.3	<0.001	18.1 ± 2.0	19.5 ± 2.3	0.006
Malnutrition: ESPEN guidelines ^a (n, %)	33 (55)	9 (26)	0.008	9 (32)	11 (13)	0.023
Fat mass/fat-free mass ratio	0.503 ± 0.167	0.617 ± 0.181	0.001	0.262 ± 0.138	0.350 ± 0.125	0.001
Skeletal muscle mass index (kg/m ²)	6.3 ± 1.2	6.6 ± 1.2	0.16	8.3 ± 1.3	8.9 ± 1.6	0.098
Visceral fat index (L/m ²)	0.30 ± 0.35	0.59 ± 0.40	0.041	0.61 ± 0.39	1.0 ± 0.59	<0.001
Total body water index (L/m ²)	11.3 ± 1.4	12.2 ± 1.2	<0.001	13.2 ± 1.5	14.2 ± 2.0	0.021
Extracellular water index (L/m ²)	5.5 ± 0.7	6.2 ± 0.6	<0.001	5.9 ± 0.7	6.6 ± 0.8	<0.001
Resistance (Ω)	658 ± 99	607 ± 73	0.010	569 ± 67	522 ± 86	0.010
Reactance (Ω)	46.9 ± 11.4	41.8 ± 10.2	0.014	45.9 ± 9.6	40.3 ± 10.3	0.012
Phase angle (°)	4.1 ± 0.8	3.9 ± 0.8	0.24	4.5 ± 1.0	4.4 ± 1.0	0.43

Note: Normal distributed variables are presented as means ± SD. P-values for normal distributed variables are determined using unpaired t-test. Bold indicates statistical significance of $p < 0.05$. ESPEN, European Society for Clinical Nutrition and Metabolism.

^aFFMI < 17 kg/m² in men and FFMI < 15 kg/m² in women.

3.3 | Stratification based on wasting syndrome with unintentional weight loss

The patients with and without cachexia were similar in age and sex, but those with cachexia had a higher Charlson comorbidity index and were

significantly more likely to have advanced cancer (stages III/IV; 90% vs 79%) and solid tumours (88% vs 71%; Table 3). LV mass index was similar between patients with and without cachexia. The patients with cachexia had lower FFMI and SMMI compared to those without cachexia but similar FMI and VFI (Table 3). PhA was lower in patients with cachexia.

TABLE 3 Baseline characteristics and body composition of patients with cancer stratified by cachexia.

Clinical variables	Cachexia (n = 94)	No cachexia (n = 112)	P-value
Age (years)	62 ± 13	59 ± 15	0.10
Men (n, %)	50 (53)	62 (55)	0.76
Cancer stage III/IV (n, %)	84 (90)	87 (79)	0.031
Solid cancer (n, %)	83 (88)	79 (71)	0.002
Cardiotoxic agents (n, %)	53 (56)	61 (55)	0.78
Charlson comorbidity index (points)	7.1 ± 2.3	6.1 ± 2.6	0.004
Systolic blood pressure (mm Hg)	128 ± 18	132 ± 18	0.059
LV mass adjusted for height ² (g/m ²)	63 ± 17	63 ± 17	0.63
Medication			
ACEi/ARBs (n, %)	28 (30)	30 (27)	0.63
Beta-blockers (n, %)	17 (18)	20 (18)	0.97
Treatments for diabetes (n, %)	8 (9)	10 (9)	0.92
Corticosteroids (n, %)	25 (27)	25 (22)	0.48
Clinical assessments			
ECOG performance status (points)	1.7 ± 0.9	1.1 ± 0.9	<0.001
Karnofsky performance status (%)	74 ± 13	81 ± 14	<0.001
Hand-grip strength (kg)	31.4 ± 12.0	35.3 ± 13.0	0.028
Six-minute walking distance (m)	429 ± 96	474 ± 91	0.015
Mid-arm circumference (cm)	26.9 ± 3.2	28.8 ± 3.9	<0.001
Calf circumference (cm)	34.8 ± 4.1	35.8 ± 4.3	0.066
Bioimpedance analysis			
Body mass index (BMI, kg/m ²)	23.8 ± 4.2	25.7 ± 4.4	0.001
Fat mass index (kg/m ²)	6.9 ± 3.1	6.9 ± 3.2	0.11
Fat-free mass index (kg/m ²)	17.1 ± 2.6	17.9 ± 3.2	0.046
Malnutrition: ESPEN guidelines ^a (n, %)	34 (36)	28 (25)	0.082
Fat mass/fat-free mass ratio	0.666 ± 0.188	0.436 ± 0.191	0.46
Skeletal muscle mass index (kg/m ²)	7.3 ± 1.6	8.0 ± 1.9	0.003
Visceral fat index (L/m ²)	0.67 ± 0.49	0.78 ± 0.57	0.12
Total body water index (L/m ²)	12.5 ± 1.8	13.2 ± 2.4	0.007
Extracellular water index (L/m ²)	6.0 ± 0.8	6.2 ± 0.9	0.031
Resistance (Ω)	596 ± 100	570 ± 104	0.033
Reactance (Ω)	42.7 ± 10.1	43.8 ± 11.6	0.47
Phase angle (°)	4.1 ± 0.9	4.4 ± 0.9	0.009

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ECOG, Eastern Cooperative of Oncology Group; ESPEN, European Society für Clinical Nutrition and Metabolism. Normal distributed variables are presented as means ± SD and nominal variables as percent. P-values for normal distributed variables are determined using unpaired t-test and P-values for nominal variables are computed according to χ^2 test. Bold indicates statistical significance of $p < 0.05$.

^aFFMI < 17 kg m⁻² in men and FFMI < 15 kg m⁻² in women.

3.4 | Association of bioelectrical impedance analysis (BIA) measurements and LV mass index

We observed moderate correlations between BIA measurements and LV mass index, except for PhA and fat mass/fat-free mass ratio (Table 4 and Figures 1a–f). Linear regression analysis showed that FFMI was the significantly strongest predictor of cardiac wasting, followed by FMI (Table 5a). Among women, FFMI showed significantly the strongest correlation with LV mass index (Table 4 and Figures S1A–F). In men, VFI

was most strongly associated with LV mass index (Table 4 and Figures S2A–F). FFMI was the strongest predictor of cardiac wasting whether or not patients received cardiotoxic therapies (Tables 5b and 5c). To reduce bias because of disease-related fluid shifts, such as oedema, pleural effusion or ascites, we conducted a sensitivity analysis by excluding patients with clinically relevant fluid retention assessed by the oedema score. The multivariable model remained robust after excluding patients with an oedema score ≥2 points and FFMI remained the strongest predictor of cardiac wasting.

TABLE 4 Pearson correlation for LV mass adjusted for height² versus bioelectrical impedance analysis (BIA) measurements. CI, confidence interval

BIA measurement	All patients (n = 206)		Women (n = 94)		Men (n = 112)	
	<i>r_s</i> (95% CI)	P-value	<i>r_s</i> (95% CI)	P-value	<i>r_s</i> (95% CI)	P-value
Body mass index (kg/m ²)	0.37 (0.24–0.48)	<0.001	0.33 (0.14–0.50)	0.001	0.34 (0.16–0.49)	<0.001
Fat mass index (kg/m ²)	0.16 (0.02–0.29)	0.024	0.34 (0.15–0.51)	<0.001	0.30 (0.12–0.46)	0.002
Fat-free mass index (kg/m ²)	0.45 (0.34–0.55)	<0.001	0.41 (0.22–0.56)	<0.001	0.25 (0.06–0.41)	0.009
Fat mass/fat-free mass ratio	0.03 (–0.11 to 0.17)	0.65	0.34 (0.14–0.50)	<0.001	0.26 (0.08–0.43)	0.006
Skeletal muscle mass index (kg/m ²)	0.34 (0.21–0.46)	<0.001	0.10 (–0.10 to 0.30)	0.33	0.21 (0.02–0.38)	0.029
Visceral fat index (L/m ²)	0.42 (0.30–0.53)	<0.001	0.22 (0.02–0.40)	0.032	0.40 (0.23–0.54)	<0.001
Total body water index (L/m ²)	0.38 (0.26–0.50)	<0.001	0.22 (0.02–0.41)	0.031	0.26 (0.08–0.43)	0.005
Extracellular water index (L/m ²)	0.41 (0.29–0.52)	<0.001	0.34 (0.15–0.51)	<0.001	0.22 (0.02–0.41)	0.031
Resistance (Ω)	–0.40 (–0.51 to –0.27)	<0.001	–0.25 (–0.43 to –0.05)	0.014	–0.29 (–0.45 to –0.11)	0.002
Reactance (Ω)	–0.25 (–0.38 to 0.12)	<0.001	–0.25 (–0.41 to 0.03)	0.026	–0.20 (–0.37 to –0.02)	0.034
Phase angle (°)	0.03 (–0.11 to 0.16)	0.73	–0.09 (–0.29 to 0.11)	0.40	–0.04 (–0.23 to 0.14)	0.64

Note: Bold indicates statistical significance of $p < 0.05$.

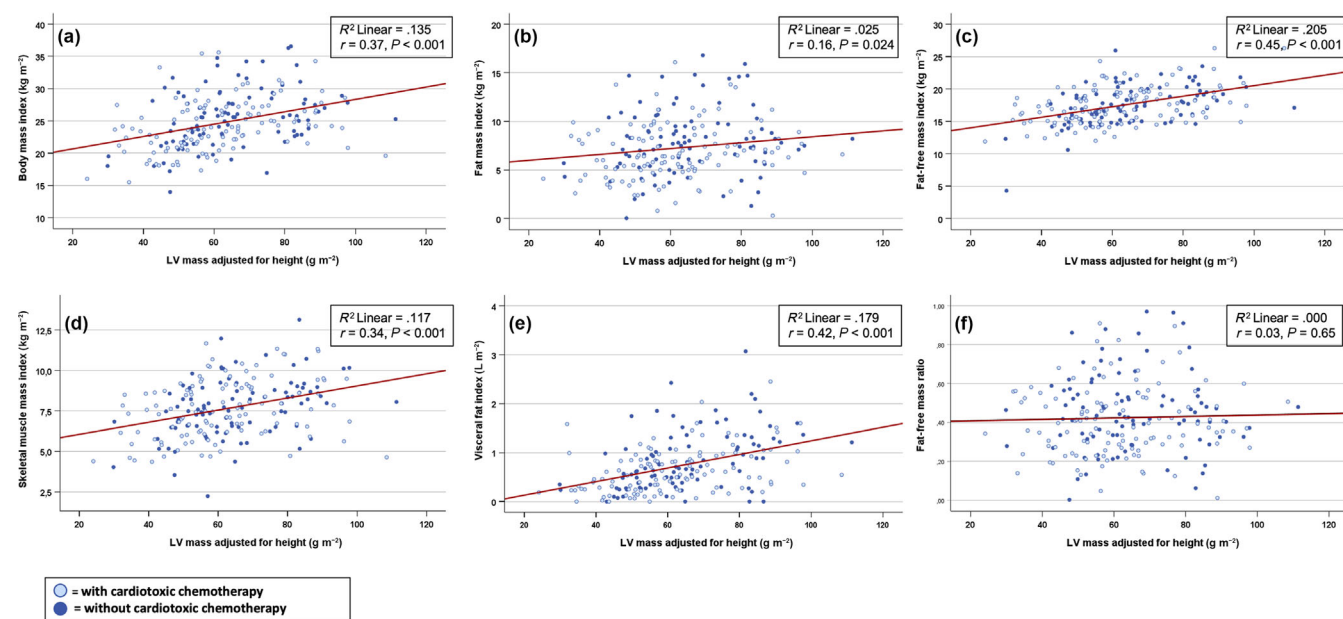


FIGURE 1 (a–f) Correlation of body mass index, fat mass index, free mass index, skeletal muscle mass index, visceral fat index and fat mass/fat-free mass ratio with LV mass adjusted for height² in all patients with cancer.

4 | DISCUSSION

This study provides the first systematic evaluation of body composition and cardiac wasting in patients with cancer. We found that BMI, fat mass (FMI), fat-free mass (FFMI) and visceral fat index (VFI) were all lower in patients with cardiac wasting. FFMI was most strongly associated with cardiac wasting, which was not modified by prior use of cardiotoxic anticancer therapy. In women, lower LV mass index was most strongly associated with a lower FFMI, while in men, it was more strongly linked to lower VFI.

Measuring body composition has aroused increasing interest as a method of assessing disease progression, the impact of therapy and

prognosis (Brown et al., 2024). Patients with cancer, depending on tumour site and extent of metastatic disease, frequently experience dysphagia, malabsorption, malnutrition and wasting syndromes. Wasting is often accompanied by an up-regulated inflammatory response that drives metabolic and hormonal alterations, promoting hypercatabolism and impaired cell regeneration (von Haehling, 2015). These detrimental consequences affect not only body weight and composition but also vital physiological functions, including digestion, thermoregulation, physical performance and overall quality of life.

Loss of muscle mass and strength, as observed in sarcopenic and cachectic patients, adversely affects prognosis. Hand grip strength, a surrogate marker of muscle quality and function, has been associated

TABLE 5 a Linear regression with LV mass adjusted for height² in all patients with cancer (*n* = 206). AIC, Akaike's Information Criterion; CI, confidence interval.

Variable	Univariable model					Multivariable model ^a				
	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value
1. Weight (kg)	0.10	0.33	0.34	0.21–0.48	<0.001	0.26	0.27	0.28	0.14–0.42	<0.001
2. Height (m)	<0.01	0.07	10.91	–10.65 to 32.48	0.32	0.24	–0.23	–36.51	–61.09 to –11.94	0.004
3. Body mass index (kg/m ²)	0.13	0.37	1.40	0.91–1.90	<0.001	0.32	0.33	1.27	0.86–1.67	<0.001
4. Fat mass index (kg/m ²)	0.02	0.16	0.82	0.11–1.53	0.011	0.28	0.29	1.49	0.88–2.10	<0.001
5. Fat-free mass index (kg/m ²)	0.20	0.45	2.50	1.82–3.19	<0.001	0.33	0.43	2.39	1.51–3.28	<0.001
6. Skeletal muscle mass index (kg/m ²)	0.11	0.34	3.09	1.91–4.27	<0.001	0.28	0.35	3.22	1.93–4.51	<0.001
7. Visceral fat index (L/m ²)	0.17	0.42	12.77	8.97–16.57	<0.001	0.26	0.25	7.49	3.04–11.94	0.001
8. Total body water index (L/m ²)	0.14	0.38	3.06	2.04–4.07	<0.001	0.29	0.35	2.76	1.71–3.80	<0.001
9. Extracellular water index (L/m ²)	0.16	0.41	7.83	5.40–10.25	<0.001	0.28	0.29	5.53	3.21–7.84	<0.001
10. Resistance (Ω)	0.15	–0.40	–0.06	–0.08 to –0.04	<0.001	0.28	–0.29	–0.05	–0.07 to –0.02	<0.001
11. Reactance (Ω)	0.06	–0.25	–0.38	–0.58 to –0.18	<0.001	0.22	–0.11	–0.17	–0.35 to 0.02	0.08
12. Phase angle (°)	<0.01	0.02	0.45	–2.07 to 2.96	0.72	0.22	0.07	1.29	–1.26 to 3.83	0.32

Note: Bold indicates statistical significance of *p* < 0.05.^aVariables 1–12 were adjusted separately for age (years), sex (male vs female), systolic blood pressure (mmHg), cachexia (yes vs no) and Charlson comorbidity index (points).

TABLE 5b Linear regression with LV mass adjusted for height² in patients with cancer with prior cardiotoxic agents (*n* = 114). AIC, Akaike's Information Criterion.

Variable	Univariable model				Multivariable model ^a						
	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value	AIC
1. Weight (kg)	0.08	0.30	0.32	0.13–0.51	0.001	0.24	0.26	0.28	0.08–0.47	0.020	944.680
2. Height (m)	<0.01	0.07	10.46	–19.15 to 40.07	0.47	0.21	–0.19	–29.95	–66.63 to 6.73	0.11	948.691
3. Body mass index (kg/m ²)	0.12	0.35	1.50	0.76–2.24	<0.001	0.28	0.31	1.33	0.68–1.98	<0.001	937.656
4. Fat mass index (kg/m ²)	0.01	0.15	0.87	–0.23 to 1.97	0.12	0.25	0.26	1.52	0.47–2.57	0.005	942.774
5. Fat-free mass index (kg/m ²)	0.18	0.44	2.49	1.53–3.46	<0.001	0.33	0.47	2.66	1.37–3.95	<0.001	930.016
6. Skeletal muscle mass index (kg/m ²)	0.08	0.30	2.82	1.14–4.49	0.001	0.24	0.34	3.21	0.98–5.44	0.005	943.743
7. Visceral fat index (L/m ²)	0.15	0.39	14.19	7.87–20.51	<0.001	0.23	0.22	7.97	–0.21 to 16.14	0.028	945.804
8. Total body water index (L/m ²)	0.12	0.36	2.91	1.49–4.34	<0.001	0.26	0.34	2.74	1.23–4.25	0.003	941.502
9. Extracellular water index (L/m ²)	0.15	0.40	7.78	4.45–11.12	<0.001	0.26	0.29	5.58	2.66–8.49	<0.001	940.688
10. Resistance (Ω)	0.11	–0.35	–0.06	–0.08 to –0.03	<0.001	0.30	–0.28	–0.04	–0.08 to 0.01	0.005	942.465
11. Reactance (Ω)	0.07	–0.27	–0.44	–0.72 to –0.15	0.003	0.22	–0.15	–0.23	–0.50 to 0.04	0.09	948.082
12. Phase angle (°)	0.08	0.30	0.32	0.13–0.51	0.001	0.19	0.01	0.15	–3.66 to 3.96	0.94	950.979

Note: Bold indicates statistical significance of *p* < 0.05.

^aVariables 1–12 were adjusted separately for age (years), sex (male vs female), systolic blood pressure (mmHg), cachexia (yes vs no) and Charlson comorbidity index (points).

TABLE 5c Linear regression with LV mass adjusted for height² in patients with cancer without prior cardiotoxic agents (*n* = 92). AIC, Akaike's Information Criterion.

Variable	Univariable model				Multivariable model ^a						
	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value	Adjusted R ²	Standardised coefficient	Regression coefficient	95% CI	P-value	AIC
1. Weight (kg)	0.12	0.36	0.35	0.16–0.55	0.001	0.24	0.26	0.27	0.04–0.49	0.015	748.396
2. Height (m)	<0.01	0.09	13.18	–18.53 to 44.88	0.35	0.24	–0.29	–44.13	–79.06 to –9.20	0.014	749.082
3. Body mass index (kg/m ²)	0.12	0.37	1.25	0.58–1.92	<0.001	0.32	0.35	1.22	0.63–1.80	<0.001	738.709
4. Fat mass index (kg/m ²)	<0.01	0.14	0.62	–0.33 to 1.57	0.20	0.28	0.31	1.44	0.59–2.29	0.001	744.019
5. Fat-free mass index (kg/m ²)	0.22	0.49	2.54	1.57–3.50	<0.001	0.30	0.41	2.18	0.91–3.44	0.001	740.621
6. Skeletal muscle mass index (kg/m ²)	0.15	0.40	3.40	1.74–5.05	<0.001	0.28	0.37	3.20	1.39–5.00	0.001	743.892
7. Visceral fat index (L/m ²)	0.19	0.45	11.44	6.63–16.25	<0.001	0.24	0.28	7.08	1.44–12.72	0.015	748.132
8. Total body water index (L/m ²)	0.17	0.42	3.22	1.78–4.66	<0.001	0.30	0.38	2.85	1.11–4.59	0.002	741.123
9. Extracellular water index (L/m ²)	0.16	0.41	7.62	4.04–11.20	<0.001	0.28	0.33	6.23	2.10–10.37	0.004	743.010
10. Resistance (Ω)	0.21	–0.46	–0.07	–0.10 to –0.04	<0.001	0.29	–0.37	–0.06	–0.09 to –0.02	0.001	742.790
11. Reactance (Ω)	0.04	–0.23	–0.32	–0.60 to –0.04	0.027	0.20	–0.12	–0.16	–0.46 to 0.14	0.29	753.566
12. Phase angle (°)	<0.01	0.08	1.15	–2.21 to 4.52	0.68	0.20	0.12	1.87	–1.96 to 5.69	0.33	753.536

Note: Bold indicates statistical significance of *p* < 0.05.^aVariables 1–12 were adjusted separately for age (years), sex (male vs female), systolic blood pressure (mmHg), cachexia (yes vs no) and Charlson comorbidity index (points).

with increased mortality in patients with advanced cancer (Hadzibegovic et al., 2023). Nutritional and metabolic derangements are also linked to reduced tolerance to anticancer therapies, increased treatment-related toxicity and poor survival (Brown et al., 2018). Consequently, the assessment of body composition should be of interest when developing and evaluating novel pharmacological and nonpharmacological interventions in oncology (Brown et al., 2024).

Patients with cancer may develop a specific form of wasting affecting the cardiac muscle (Barkhudaryan et al., 2017; Kazemi-Bajestani et al., 2019; Springer et al., 2014). In a prior study on cardiac wasting, we compared LV mass in patients who were therapy naïve, with those receiving non-cardiotoxic anticancer therapy and those who underwent cardiotoxic treatment (Lena et al., 2023). LV mass index was similar across all three groups. Our results now show that FFMI is most strongly associated with cardiac wasting independent of previous anticancer treatment.

This supports the concept of cardiac wasting as an independent entity in patients with cancer. The first evidence of cardiac wasting in humans with cancer emerged from autopsy studies (Barkhudaryan et al., 2017; Calamelli et al., 2023; Springer et al., 2014). Histopathological analyses revealed cardiomyocyte atrophy, oedema and fibrosis. These findings support initial preclinical studies on cardiac wasting in mouse cancer models (Cosper & Leinwand, 2011; Tian et al., 2010; Zhou et al., 2010). Accordingly, there is a need for increased awareness of cardiac remodelling during tumour progression, independent of cardiotoxic chemotherapy.

Notably, there was no significant interaction with prior cardiotoxic treatment. Although cardiotoxic agents have been proposed to accelerate cardiac wasting by inducing oxidative damage in cardiomyocytes and disrupting mitochondrial function, thereby triggering cell death and protein degradation (Octavia et al., 2012), this effect seems not to be evident in our cohort. The status of the study population was similar, with most participants not being severely limited, as reflected by Eastern Cooperative of Oncology Group performance status, suggesting that cardiac wasting in this context likely represents subclinical damage. Alternatively, the absence of an observable effect may relate to the early timing of assessment, as none of the patients exhibited manifest cardiovascular disease or clinical signs of cardiotoxicity. These findings warrant further investigation in longitudinal studies to clarify potential delayed effects of cardiotoxic therapy on cardiac wasting over time. Further research is also required to elucidate whether cardiac wasting is associated with major adverse cardiovascular events (MACE) and whether specific treatments can prevent or reverse cardiac wasting and improve outcomes.

In a previous study involving 300 patients with advanced cancer, only 30% met the criteria for cachexia (Lena et al., 2023). In our current study, the prevalence of cachexia (54%) was higher but there was no difference in LV mass index in patients with or without cachexia. These findings support the hypothesis that cardiac wasting might only partially depend on cachexia and might be more associated to specific metabolic changes occurring in late-stage cancer. However, lower FMI, FFMI and skeletal muscle mass index (SMMI) were all associated with cardiac wasting, suggesting a generalised loss of metabolically

active tissues. Lower FFMI was slightly more strongly related to cardiac wasting, but the ratio of FMI to FFMI was not, suggesting that the reduction in FMI and FFMI might be more or less in step. FFMI showed also a stronger correlation than the muscle-specific SMMI. Because FFMI reflects not only lean tissue but also total body water and the mass of nonskeletal organs (Prado & Heymsfield, 2014), this observation could indicate that cardiac atrophy is part of a broader, systemic 'multi-organ' wasting process or may reflect an advanced stage of overall systemic wasting, induced by mediators released from tumour cells, metastatic lesions and activated immune cells (Lena et al., 2026).

Although there were some possibly sex-related differences in the relationship between body composition and cardiac wasting, these differences were modest and should be confirmed in other patient cohorts. Women had higher FMI, but lower FFMI compared to men, similar to findings in healthy individuals (Franssen et al., 2014; Kyle et al., 2003; Pichard et al., 2000). Both men and women with cancer and cardiac wasting had a lower FMI and FFMI.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggest that values of FFMI $<17 \text{ kg/m}^2$ in men and FFMI $<15 \text{ kg/m}^2$ in women indicate malnutrition (Cederholm et al., 2017) (Arends et al., 2017). Our findings indicate that patients with cancer with lower LV mass are affected, with malnutrition being more pronounced among women. Skeletal muscle mass index, excluding organs such as the heart, was similar between the two groups. We believe these findings align with the observation that our patients were relatively physically active, as reported in their evidence-based assessments. Thus, our results may indicate a catabolic state in patients with cardiac wasting rather than 'disuse' atrophy, consistent with the changes described in patients with cancer cachexia (Baracos et al., 2018; Frohlich et al., 2024).

VFI was observed to be lower in men with lower LV mass while there was a slight difference in VFI between women with and without cardiac wasting. Accumulation of visceral adipose tissue is commonly associated with cardiovascular risk (Shibata et al., 2021), type 2 diabetes (Feng et al., 2022) and metabolic syndrome (Neeland et al., 2019). Therefore, low visceral fat is generally considered beneficial for health. However, extremely low levels of visceral fat, particularly in the presence of cancer, may be disadvantageous: in a database of 507 patients with upper gastrointestinal cancers, those with low visceral fat content had a worse prognosis, suggesting that visceral fat might play a protective role possibly as a metabolic energy reserve (Harada et al., 2015). A retrospective study of 215 patients with advanced oesophageal cancer demonstrated that maintaining adequate levels of visceral fat during neoadjuvant chemotherapy was associated with improved clinical outcomes (Onishi et al., 2024). Our results may offer further insight into the obesity paradox, which has been particularly described in chronic conditions such as heart failure and cancer (Simati et al., 2023). Visceral fat may serve as an important metabolic reserve (Obomanu et al., 2025). This is noteworthy, as our results show that the average BMI in our study cohort ranged from normal weight to pre-obese and visceral fat appeared similar between the cachectic and non-cachectic groups. We observed main differences in reduced lean mass and skeletal

muscle mass index. It remains unclear whether cardiac wasting precedes or follows general body wasting. A causal inference cannot be made, as multiple confounding factors would need to be considered. Fröhlich et al. demonstrated that cardiac wasting in advanced cancer is closely linked to elevated plasma growth hormone (GH) levels and a reduced **insulin-like growth factor 1 (IGF-I)/GH** ratio, indicating acquired GH resistance. The increase in serum GH drives enhanced lipolysis, most notably the depletion of visceral fat. Mechanistically, this lipolytic shift is mediated via down-regulation of the lipid droplet-associated protein FSP27 and subsequent impairment of **peroxisome proliferator-activated receptor gamma (PPAR γ ; NR1C3)** activity, resulting in increased breakdown of triglycerides into glycerol and fatty acids. This metabolic maladaptation has been reported as a central mechanism underlying cardiac wasting, facilitating the loss of cardiac mass (Tian et al., 2010). Therapeutically, ghrelin receptor agonists, such as **anamorelin**, have been discussed as modulators of cachexia and cardiac wasting in heart failure patients (Nagaya et al., 2004). Preclinical and early clinical studies showed direct cardioprotective actions, including improved ventricular function and reduced catabolic signalling (Nagaya et al., 2004). In patients with cancer, the ROMANA 1–3 trials showed improvements in body weight and anorexia–cachexia symptoms; however, no functional benefit was observed (Currow et al., 2017; Takayama et al., 2016). Consequently, anamorelin is not approved for cancer cachexia in Europe and the United States (Sato et al., 2025). Selective PPAR γ agonists may beneficially reprogramme metabolic and inflammatory transcriptional networks, improving systemic energy homeostasis and insulin sensitivity, while avoiding the adverse effects commonly associated with full agonists, such as fluid retention and disproportionate adipogenic weight gain (Doshi et al., 2010). In this setting, selected PPAR γ activation may preserve both cardiac and skeletal muscle integrity (Gilde & Van Bilsen, 2003; Rubio-Ruiz et al., 2024). So far, selected PPAR γ agonists have not been fully validated in clinical trials with cancer-associated cardiac cachexia (Ding et al., 2025). Overall, these findings suggest that GH-driven increases in metabolic rate play a key role in cardiac tissue loss and they highlight the GH/IGF axis as a promising target for future cardio-oncology treatments. However, this is only one part of a broader inflammatory and endocrine process, and further research is needed to clarify this complexity in patients with cancer with cardiac wasting.

Phase angle (PhA) has previously been linked to mortality in patients with lung cancer (Shi et al., 2022) and predicts cancer cachexia in head and neck cancer (Stegel et al., 2016). In our study, although PhA was not associated with cardiac wasting, it was lower in patients with cachexia compared to those without. This may be because of the fact, when stratified by LV mass, both groups had similar comorbidities and physical status, as indicated by the Charlson comorbidity index and event-reported outcomes, with cachexia being present in 50%.

4.1 | Study limitations

We acknowledge that various malignancies, anticancer treatments and bed rest may influence body composition but have recruited a

real-world cohort here reflecting patients encountered in clinical practice. The two groups, with and without cardiac wasting, differed in terms of sex and age distribution as well as comorbidities and the use of medications, in particular antihypertensive and antidiabetic therapies. These differences may, at least in part, account for the observed changes in body composition and should be considered as a potential confounding factor on cardiac wasting. In addition, the malignancy-associated factors, including dysphagia and malnutrition, may be challenging to distinguish from the effects of systemic inflammation on body composition and their specific contribution on cardiac wasting warrants further investigation in subsequent studies. We included individuals with controlled arterial hypertension and type 2 diabetes mellitus, only excluding those with cardiovascular disease to prevent bias from preexisting conditions. Future research could focus specifically on patients with cancer who also have significant cardiovascular disease. Additionally, this study did not track changes in body composition over time, an area that warrants further investigation.

Despite these limitations, we believe that BIA is a valuable method for assessing body composition in research and clinical practice, complementary to other measures such as weight, BMI or skin-fold thickness.

5 | CONCLUSION

Low LV mass in patients with advanced cancer is associated with altered body composition, particularly fat-free mass index (FFMI), independent of prior cardiotoxic anticancer treatment. These findings offer deeper insights into the mechanisms of cancer-related wasting syndrome that could potentially lead to overt clinical cardiomyopathy, heart failure and arrhythmias. Further trials are required to determine the existence and nature of any potential causal relationship between altered body composition and cardiac wasting in cancer and to identify effective treatments with a favourable effect on outcomes.

AUTHOR CONTRIBUTIONS

Sara Hadzibegovic: Writing—review and editing; conceptualization; writing—original draft; methodology; formal analysis; investigation; data curation; visualization; funding acquisition; validation. **Jonathan L. Hella:** Formal analysis; investigation; data curation; visualization; writing—review and editing; formal analysis; investigation; data curation; visualization; writing—review and editing; resources. **Jan Porthun:** Writing—review and editing; formal analysis; data curation; visualization; validation. **Alessia Lena:** Writing—review and editing; formal analysis; investigation; data curation; visualization. **Danara Krug:** Writing—review and editing; investigation; data curation. **Iulia Baluta:** Writing—review and editing; investigation; data curation. **Ursula Wilkenschoff:** Writing—review and editing. **Amir A. Mahabadi:** Writing—review and editing. **Matthias Totzeck:** Writing—review and editing. **Tienush Rassaf:** Writing—review and editing. **Stefan D. Anker:** Writing—review and editing; resources; funding acquisition; writing—review and editing. **Wolfram Doehner:** Writing—review and editing. **Ulrich Keller:** Writing—review and editing; resources. **Lars**

Bullinger: Writing—review and editing; resources. **Dominik P. Modest:** Writing—review and editing; formal analysis; data curation; visualization; validation; writing—review and editing. **Barry J. A. Laird:** Writing—review and editing. **Richard J. E. Skipworth:** Writing—review and editing. **John G. F. Cleland:** Writing—review and editing. **Christian Oeing:** Writing—review and editing. **Stephan von Haehling:** Writing—review and editing. **Ulf Landmesser:** Writing—review and editing; resources. **Markus S. Anker:** Writing—review and editing; supervision; conceptualization; methodology; formal analysis; resources; data curation; project administration; funding acquisition; investigation.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the BJP guidelines for [Design and Analysis](#) and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

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