



# Association of an impaired GH-IGF-I axis with cardiac wasting in patients with advanced cancer

Ann-Kathrin Fröhlich<sup>1,2,3,4</sup> · Jan Porthun<sup>1,4,5</sup> · Khawaja M. Talha<sup>6</sup> · Alessia Lena<sup>1,2,3,7</sup> · Sara Hadzibegovic<sup>1,2,3,7</sup> · Ursula Wilkenshoff<sup>1,7,8</sup> · Frederike Sonntag<sup>1,2,3,4</sup> · Anja Nikolski<sup>1,2,3,4</sup> · Luisa Valentina Ramer<sup>1,2,3,4</sup> · Tanja Zeller<sup>9,10,11</sup> · Ulrich Keller<sup>12,13,14</sup> · Lars Bullinger<sup>13,15</sup> · Stefan D. Anker<sup>2,3,16</sup> · Wilhelm Haverkamp<sup>2,3,16</sup> · Stephan von Haehling<sup>17,18</sup> · Wolfram Doehner<sup>2,3,4,19</sup> · Ursula Rauch<sup>1,2,7</sup> · Carsten Skurk<sup>1,7</sup> · John G. F. Cleland<sup>20</sup> · Javed Butler<sup>6,21</sup> · Andrew J. S. Coats<sup>22</sup> · Ulf Landmesser<sup>1,2,7,8</sup> · Mahir Karakas<sup>11,23</sup> · Markus S. Anker<sup>1,2,3,7</sup>

Received: 13 December 2023 / Accepted: 7 February 2024  
© The Author(s) 2024

## Abstract

**Background** Growth hormone (GH) resistance is characterized by high GH levels but low levels of insulin-like growth factor-I (IGF-I) and growth hormone binding protein (GHBP) and, for patients with chronic disease, is associated with the development of cachexia.

**Objectives** We investigated whether GH resistance is associated with changes in left ventricular (LV) mass (cardiac wasting) in patients with cancer.

**Methods** We measured plasma IGF-I, GH, and GHBP in 159 women and 148 men with cancer (83% stage III/IV). Patients were grouped by tertile of echocardiographic LVmass/height<sup>2</sup> (women, < 50, 50–61, > 61 g/m<sup>2</sup>; men, < 60, 60–74, > 74 g/m<sup>2</sup>) and by presence of wasting syndrome with unintentional weight loss (BMI < 24 kg/m<sup>2</sup> and weight loss ≥ 5% in the prior 12 months). Repeat echocardiograms were obtained usually within 3–6 months for 85 patients.

**Results** Patients in the lowest LVmass/height<sup>2</sup> tertile had higher plasma GH (median (IQR) for 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tertile women, 1.8 (0.9–4.2), 0.8 (0.2–2.2), 0.5 (0.3–1.6) ng/mL,  $p = 0.029$ ; men, 2.1 (0.8–3.2), 0.6 (0.1–1.7), 0.7 (0.2–1.9) ng/mL,  $p = 0.003$ ). Among women, lower LVmass was associated with higher plasma IGF-I (68 (48–116), 72 (48–95), 49 (35–76) ng/mL,  $p = 0.007$ ), whereas such association did not exist for men. Patients with lower LVmass had lower log IGF-I/GH ratio (women,  $1.60 \pm 0.09$ ,  $2.02 \pm 0.09$ ,  $1.88 \pm 0.09$ ,  $p = 0.004$ ; men,  $1.64 \pm 0.09$ ,  $2.14 \pm 0.11$ ,  $2.04 \pm 0.11$ ,  $p = 0.002$ ). GHBP was not associated with LVmass. Patients with wasting syndrome with unintentional weight loss had higher plasma GH and GHBP, lower log IGF-I/GH ratio, and similar IGF-I. Overall, GHBP correlated inversely with log IGF-I/GH ratio (women,  $r = -0.591$ ,  $p < 0.001$ ; men,  $r = -0.575$ ,  $p < 0.001$ ). Additionally, higher baseline IGF-I was associated with a decline in LVmass during follow-up ( $r = -0.318$ ,  $p = 0.003$ ).

**Conclusion** In advanced cancer, reduced LVmass is associated with increased plasma GH and reduced IGF-I/GH ratio, suggesting increasing GH resistance, especially for patients with wasting syndrome with unintentional weight loss. Higher baseline IGF-I was associated with a decrease in relative LVmass during follow-up.

---

Mahir Karakas and Markus S. Anker contributed equally to this work.

---

The last authorship is shared by Mahir Karakas and Markus S. Anker.

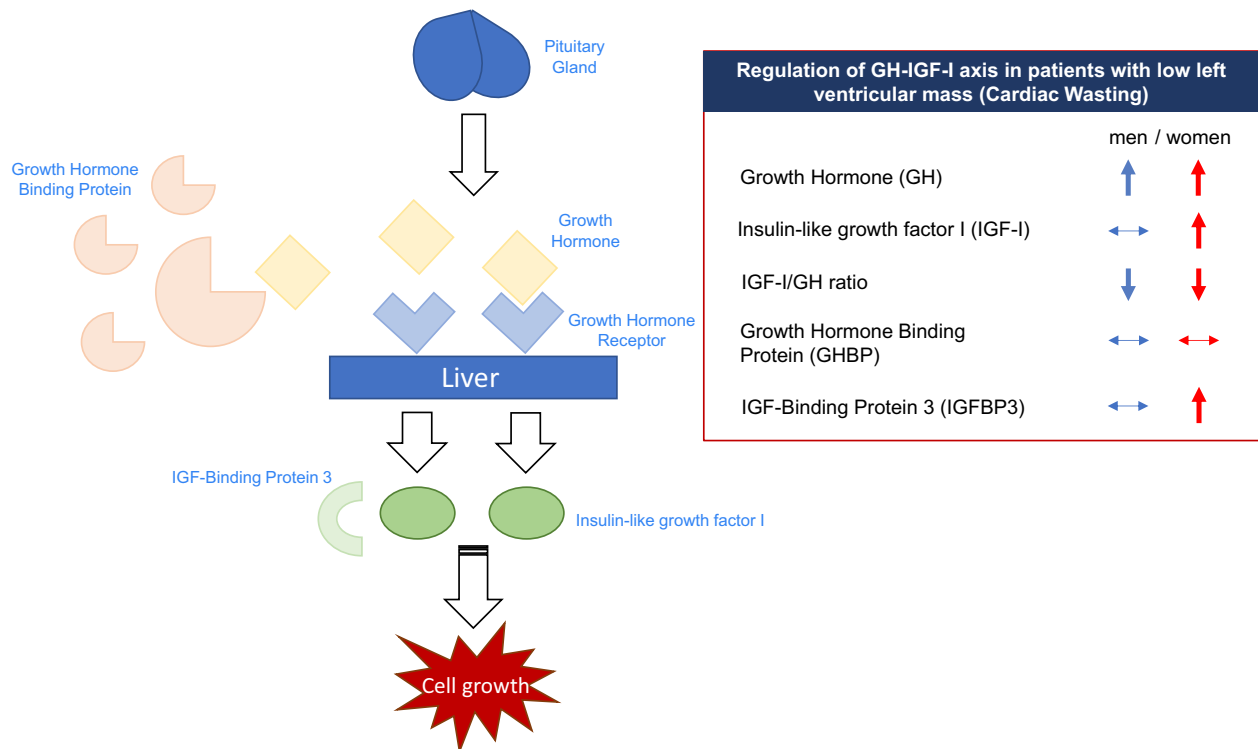
---

✉ Markus S. Anker  
markus.anker@charite.de

Extended author information available on the last page of the article.

## Graphical abstract

## The indirect anabolic pathway of the GH-IGF-I axis

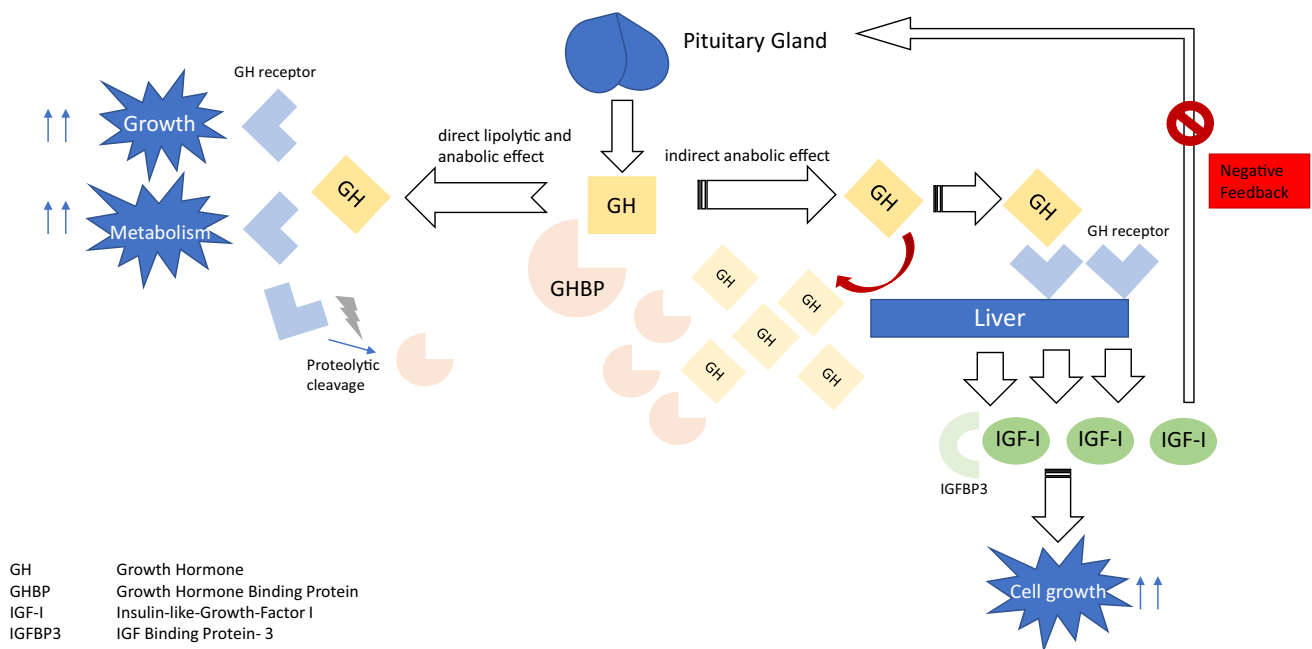


**Keywords** Left ventricular mass · Growth hormone · Insulin-like growth factor-I · Cardiology · Cancer · Echocardiography · Cachexia

## Introduction

Cardiac wasting—associated cardiomyopathy has recently been described in patients with advanced-stage cancer [1, 2] and was shown to be associated with reduced physical performance, increased all-cause mortality, and inflammation. In preclinical models, the loss of left ventricular (LV) mass has been attributed to cytokine-mediated inflammatory processes and malnutrition [2, 3]. The pathophysiological process in humans causing a remodelling process in the heart as well as an absolute decline of heart muscle tissue remains to be established. Chronic illnesses such as heart failure (HF) and cancer are often characterized by enhanced catabolism and malnutrition predisposing to loss of skeletal muscle mass (sarcopenia) and loss of fat and lean muscle mass with global weight loss (cachexia). The GH-IGF-I axis is an important regulator of the wasting processes in chronic heart failure [4–7]. The GH-IGF-I axis consists of a complex interplay of several stages in this hormonal

system (Fig. 1) [5, 8]. Growth hormone (GH) is periodically released from the pituitary gland and leads to the activation of both lipolysis and anabolic effects in the body, affecting men and women similarly. GH's main anabolic mediator is insulin-like growth factor I (IGF-I) that is mainly bound to IGF-Binding Protein 3 (IGFBP3) when circulating in the blood. GH itself is an important anabolic hormone that mediates several cardiometabolic processes but requires an adequate IGF-I response. Growth hormone binding protein (GHBP) is a surrogate marker for the amount of cellular GH receptors. Derived by proteolytic cleavage of the extracellular binding domain of the GH receptor, GHBP is structurally identical to the GH receptor ectodomain, and therefore both (GH receptor and GHBP) are in constant competition for GH. Depending on feedback mechanisms, GHBP can then either prolong the efficacy of GHBP-bound GH or exclude GH from binding to the GH receptor. In patients with chronic HF and GH treatment, IGF-I has been shown to positively correlate with LV mass [9]. Acquired



**Fig. 1** The GH-IGF-I axis (simplified); a simplified version of the human GH-IGF-I axis. GH, growth hormone; GHBP, growth hormone binding protein; IGF-I, insulin-like growth factor I; IGFBP3, IGF binding protein-3

GH resistance (as seen in cachectic HF patients) [10] is characterized by a shortage of cellular GH receptors (i.e., GHBP is reduced), elevated circulating GH, and low IGF-I [8, 11]. GH sensitivity, as represented by the IGF-I/GH ratio, is very important as isolated IGF-I levels alone cannot be interpreted. We hypothesized that GH resistance is also important in the development of cardiac wasting and designed this study to test this hypothesis in cancer patients.

## Methods

### Patient population

In a prospective single-center study, we enrolled 307 cancer patients (159 female, 148 male, advanced stage III/IV 83%) hospitalized at the oncology wards of Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin and Campus Virchow-Klinikum, with assessment of GH-IGF-I biochemical status. Of 332 prospectively examined cancer patients, we excluded 12 patients due to newly diagnosed cardiac dysfunction and 13 patients due to inadequate imaging quality that precluded assessment of LV mass. Recruitment took place between September 2017 and October 2020. At baseline, all patients where (A)  $\geq 18$  years of age, (B) had a histologically confirmed active cancer disease, and (C) had no other diagnosis of cancer in the previous 5 years. All patients provided written informed consent for participation in the study.

We excluded cancer patients with (A) significant cardiovascular (CV) disease such as myocardial infarction, coronary artery disease, major valvular defects, or a left ventricular ejection fraction (LVEF)  $< 50\%$  at baseline; (B) presence of acute, antibiotic-treated infection, and (C) all patients with chronic obstructive pulmonary disease GOLD stages  $\geq 3$  [12] were excluded from participation in the study—whereas all lung cancer patients could participate in the study, regardless of GOLD stage. The presence of uncomplicated type II diabetes mellitus (T2DM) and controlled arterial hypertension (RR  $< 160/100$  mmHg) were not reasons for exclusion. Cancer entities are displayed in Table S3.

### Study design

We assessed patients with mostly advanced cancer stage. Definition for advanced cancer stage was Union for International Cancer Control (UICC) [13] stage III and IV, the Ann Arbor [14] classification stage III and IV, and Durie and Salmon classification [15] stage III. The possibility of a follow-up examination was provided to every study participant preferably after 3–6 months (maximum 12 months) after baseline assessment. All cancer patients were grouped in tertiles of LV mass adjusted for height squared (height<sup>2</sup>) using sex-specific cut-offs [1, 16]. Additionally, cancer patients were grouped according to the presence/absence of wasting

**Table 1** Baseline characteristics of women with advanced-stage cancer

Measurement	All women <i>n</i> = 159	LV mass/ height <sup>2</sup> < 50.00 g/m <sup>2</sup> (1 <sup>st</sup> tertile, <i>n</i> = 53)	LV mass/ height <sup>2</sup> ≥ 50.00– < 61.15 g/m <sup>2</sup> (2 <sup>nd</sup> tertile, <i>n</i> = 53)	LV mass/ height <sup>2</sup> ≥ 61.15 g/m <sup>2</sup> (3 <sup>rd</sup> tertile, <i>n</i> = 53)	<i>p</i> -value, ANOVA
<b>Clinical variables</b>					
Age (years)	62 ± 1.1	53 ± 2.0###, ***	64 ± 1.6	68 ± 1.6	< 0.001
Body mass index, BMI (kg/m <sup>2</sup> )	24.1 ± 0.4	21.8 ± 0.6##, ***	24.5 ± 0.7	26.1 ± 0.7	< 0.001
Wasting syndrome with unintentional weight loss, <i>n</i> (%)	85 (54)	37 (70)***	29 (55)*	19 (36)	0.002
<b>Markers of the GH-IGF-I axis</b>					
Growth hormone, GH (ng/mL)	0.97 (0.35–2.55)	1.82 (0.86–4.17)#, *	0.82 (0.21–2.18)	0.51 (0.27–1.63)	0.029
Insulin-like growth factor-I, IGF-I (ng/ mL)	64.7 (40.7–97.4)	67.6 (48.2–115.9)**	71.6 (47.9–95.3)*	48.5 (34.9–75.5)	0.007
Log IGF-I/GH ratio	1.83 ± 0.05	1.60 ± 0.09##, *	2.02 ± 0.09	1.88 ± 0.09	0.004
Growth hormone binding protein, GHBP (pmol/L)	384 (138–663)	276 (144–627)	294 (132–696)	424 (125–685)	0.54
IGF-I binding protein 3, IGFBP3 (µg/mL)	1.82 ± 0.05	1.97 ± 0.09**	1.90 ± 0.08*	1.65 ± 0.08	0.022
<b>Cancer and anti-cancer therapy details</b>					
Cancer stage III/IV, <i>n</i> (%)	127 (79)	41 (77)	45 (85)	41 (77)	0.56
Solid cancer, <i>n</i> (%)	98 (62)	31 (58)	39 (74)	28 (53)	0.08
ECOG Performance Scale points	1.96 ± 0.09	1.68 ± 0.14	2.09 ± 0.16	2.09 ± 0.16	0.09
Karnofsky Index (%)	70.8 ± 1.6	74.5 ± 2.4	66.7 ± 2.9	69.1 ± 2.8	0.24
Systemic anti-cancer therapy naïve, <i>n</i> (%)	25 (16)	7 (13)	6 (11)	12 (23)	0.23
Cancer drugs caus- ing heart failure (ESC guidelines '22), <i>n</i> (%)	66 (42)	22 (42)	23 (43)	21 (40)	0.98
Cancer therapies associated with cardiomyopathy (AHA '22), <i>n</i> (%)	88 (55)	29 (55)	32 (60)	27 (51)	0.62
<b>Side diagnosis</b>					
Anemia, <i>n</i> (%)	109 (69)	36 (68)	31 (58)	42 (79)	0.08
Arterial hyperten- sion, <i>n</i> (%)	79 (50)	14 (26)###, ***	29 (55)	36 (68)	< 0.001
Hypercholester- olemia, <i>n</i> (%)	49 (31)	8 (15)##, *	23 (43)	18 (34)	0.004
Type II diabetes mellitus, <i>n</i> (%)	20 (13)	1 (2)#, **	8 (15)	11 (21)	0.008
Chronic kidney disease, <i>n</i> (%)	9 (6)	1 (2)	3 (6)	5 (9)	0.30
<b>Medication</b>					
ACE inhibitors/ ARBs, <i>n</i> (%)	41 (26)	8 (15)	16 (30)	17 (32)	0.09
Beta-blockers, <i>n</i> (%)	28 (18)	6 (11)	9 (17)	13 (25)	0.22

**Table 1** (continued)

Measurement	All women <i>n</i> = 159	LV mass/ height <sup>2</sup> < 50.00 g/m <sup>2</sup> (1 <sup>st</sup> tertile, <i>n</i> = 53)	LV mass/ height <sup>2</sup> ≥ 50.00–< 61.15 g/m <sup>2</sup> (2 <sup>nd</sup> tertile, <i>n</i> = 53)	LV mass/ height <sup>2</sup> ≥ 61.15 g/m <sup>2</sup> (3 <sup>rd</sup> tertile, <i>n</i> = 53)	<i>p</i> -value, ANOVA
Anticoagulants, <i>n</i> (%)	6 (4)	2 (4)	2 (4)	2 (4)	1.00
Diuretics, <i>n</i> (%)	30 (19)	3 (6)***	10 (19)	17 (32)	<b>0.003</b>
Antidepressants, <i>n</i> (%)	25 (16)	11 (21)	8 (15)	6 (11)	0.45
Opioids, <i>n</i> (%)	43 (27)	9 (17)	19 (36)	15 (28)	0.08
Corticosteroids, <i>n</i> (%)	46 (29)	12 (23)	18 (34)	16 (30)	0.47

vs. 2<sup>nd</sup> tertile: # < 0.05, ## < 0.01, ### < 0.001

vs. 3<sup>rd</sup> tertile: \* < 0.05, \*\* < 0.01, \*\*\* < 0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BSA, body surface area; ECOG, Eastern Co-operative of Oncology Group [22]; Karnofsky Index [23]; ESC, European Society of Cardiology cardio-oncology guidelines 2022 [24]; AHA, American Heart Association 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [25]; ANOVA *p*-value/chi-squared ( $\chi^2$ ) test for comparison between LV mass-tertile 1, LV mass-tertile 2, and LV mass-tertile 3 of female cancer patients. Normal distributed variables are presented as means  $\pm$  SEM, non-normally distributed variables as median (interquartile range) and nominal variables as *n* (%), *p*-values < 0.05 are bold

syndrome with unintentional weight loss at baseline defined as body mass index (BMI) < 24.0 kg/m<sup>2</sup> and weight loss of at least 5% during the previous 12 months [17–19]. The study was approved by the Ethics Committee of the Charité and conducted in accordance with the Declaration of Helsinki.

### Echocardiography and LV mass

Echocardiographic examination and analysis were performed by three experienced echocardiographers in minimum dual control principle with a Vivid E90 echocardiography device (GE, Boston, USA) utilizing Tomtec analyzing software (Unterschliessheim, Germany). To calculate LV mass, we applied the Devereux [20] formula, using the linear measurements of left ventricular wall thickness and left ventricular diameter at end-diastole in parasternal long axis view. All echocardiographic variables are shown as absolute values or adjusted for height [2, 21].

### Blood sampling

We collected venous blood samples of the patients in the mornings. Hormonal parameters of the GH-IGF-I axis were analyzed using ELISA: growth hormone (Roche, assay range 30–50.000 pg/mL inter coefficient of variation (CV)%, 2.23–4.73), growth hormone binding protein (R&D Systems, assay range, 125–80.000 pg/mL, inter CV%, 4.53–6.78), IGFBP3 (Roche, assay range, 0–5000 ng/mL, inter CV%, 8.9–10.66), IGF-I (Roche, assay range, 0–4.0 ng/mL, inter CV%, 3.54–8.31).

### Statistical analyses

To determine normal distribution of variables, we used the Kolmogorov–Smirnov test. To assess between-group differences, Fisher post hoc tests and one-way analysis of variance were used. We presented mean  $\pm$  standard error (SEM) for normally distributed values when appropriate. For non-normally distributed variables, we displayed the data as median and interquartile range (IQR) and used the Mann–Whitney *U* test as well as the Kruskal–Wallis test, as appropriate. The chi-square test was used to compare frequencies. We calculated the best cut-off to predict LV mass change during follow-up for IGF-I using ROC analysis.

A *p*-value < 0.05 was considered statistically significant in all analyses. Analyses for this paper were generated using SAS/STAT software version 9.4 (SAS Institute, Inc), Stata (StataCorp. 2021, Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC.), and SPSS software version 26.0 (IBM Corp).

## Results

### Baseline characteristics

A total of 307 patients with mostly advanced-stage cancer were included in this study (52% female, mean age 62  $\pm$  1 years (SEM)), mean BMI was 24.6  $\pm$  0.3 kg/m<sup>2</sup> (SEM), and 152 (50%) were cachectic. Baseline characteristics are displayed in Tables 1 and 2.

**Table 2** Baseline characteristics of men with advanced-stage cancer

Measurement	All men <i>n</i> = 148	LV mass/ height <sup>2</sup> < 59.58 g/m <sup>2</sup> (1 <sup>st</sup> tertile, <i>n</i> = 48)	LV mass/ height <sup>2</sup> ≥ 59.58–< 74.06 g/ m <sup>2</sup> (2 <sup>nd</sup> tertile, <i>n</i> = 51)	LV mass/ height <sup>2</sup> ≥ 74.06 g/m <sup>2</sup> (3 <sup>rd</sup> tertile, <i>n</i> = 49)	<i>p</i> -value, ANOVA
<b>Clinical variables</b>					
Age (years)	62 ± 1.1	63 ± 2.4	61 ± 1.8	63 ± 1.6	0.53
Body mass index, BMI (kg/m <sup>2</sup> )	25.1 ± 0.4	22.4 ± 0.5###, ***	26.4 ± 0.6	26.4 ± 0.7	< 0.001
Wasting syndrome with unintentional weight loss, <i>n</i> (%)	67 (45)	32 (67)##, **	17 (33)	18 (37)	0.001
<b>Markers of the GH-IGF-I axis</b>					
Growth hormone, GH (ng/mL)	0.91 (0.26–2.34)	2.11 (0.77–3.22)##, **	0.56 (0.12–1.65)	0.70 (0.19–1.89)	0.003
Insulin-like growth factor-I, IGF-I (ng/ mL)	73.6 (46.6–107.2)	73.4 (49.6–108.8)	78.3 (51.8–113.4)	68.9 (42.6–107.7)	0.98
Log IGF-I/GH ratio	1.95 ± 0.06	1.64 ± 0.09###, **	2.14 ± 0.11	2.04 ± 0.11	0.002
Growth hormone binding protein, GHBP (pmol/L)	325 (108–857)	413 (159–972)	233 (95–598)	293 (89–950)	0.44
IGF-I binding protein 3, IGFBP3 (µg/mL)	1.45 ± 0.05	1.41 ± 0.08	1.49 ± 0.08	1.47 ± 0.08	0.75
<b>Cancer and anti-cancer therapy details</b>					
Cancer stage III/IV, <i>n</i> (%)	127 (86)	43 (90)	44 (86)	40 (82)	0.54
Solid cancer, <i>n</i> (%)	72 (49)	28 (58)	18 (35)	26 (53)	0.05
ECOG Performance Scale points	1.49 ± 0.09	1.54 ± 0.17	1.25 ± 0.15	1.67 ± 0.17	0.18
Karnofsky Index (%)	76.2 ± 1.6	72.7 ± 3.0	81.6 ± 2.5	73.9 ± 2.8	0.05
Systemic anti-cancer therapy naïve, <i>n</i> (%)	16 (11)	7 (15)	5 (10)	4 (8)	0.55
Cancer drugs caus- ing heart failure (ESC guidelines '22), <i>n</i> (%)	72 (49)	27 (56)	23 (45)	22 (45)	0.46
Cancer therapies associated with cardiomyopathy (AHA '22), <i>n</i> (%)	99 (67)	36 (75)	35 (69)	28 (57)	0.17
<b>Side diagnosis</b>					
Anemia, <i>n</i> (%)	113 (76)	42 (86)##	32 (63)	39 (80)	0.014
Arterial hypertension, <i>n</i> (%)	65 (44)	21 (44)	19 (37)	25 (51)	0.39
Hypercholester- olemia, <i>n</i> (%)	23 (16)	5 (10)	7 (14)	11 (22)	0.26
Type II diabetes mellitus, <i>n</i> (%)	23 (16)	7 (15)	8 (16)	8 (16)	1.00
Chronic kidney disease, <i>n</i> (%)	12 (8)	2 (4)	3 (6)	7 (14)	0.17
<b>Medication</b>					
ACE inhibitors/ ARBs, <i>n</i> (%)	37 (25)	9 (19)	11 (22)	17 (35)	0.17
Beta-blockers, <i>n</i> (%)	25 (17)	9 (19)	6 (11)	10 (21)	0.48

**Table 2** (continued)

Measurement	All men <i>n</i> = 148	LV mass/ height <sup>2</sup> < 59.58 g/m <sup>2</sup> (1 <sup>st</sup> tertile, <i>n</i> = 48)	LV mass/ height <sup>2</sup> ≥ 59.58–< 74.06 g/ m <sup>2</sup> (2 <sup>nd</sup> tertile, <i>n</i> = 51)	LV mass/ height <sup>2</sup> ≥ 74.06 g/m <sup>2</sup> (3 <sup>rd</sup> tertile, <i>n</i> = 49)	<i>p</i> -value, ANOVA
Anticoagulants, <i>n</i> (%)	6 (4)	1 (2)	0	5 (10)	<b>0.023</b>
Diuretics, <i>n</i> (%)	26 (18)	8 (17)	7 (14)	11 (22)	0.55
Antidepressants, <i>n</i> (%)	17 (12)	6 (13)	6 (12)	5 (10)	0.95
Opioids, <i>n</i> (%)	28 (19)	11 (23)	5 (10)	12 (25)	0.11
Corticosteroids, <i>n</i> (%)	55 (37)	22 (46)	19 (37)	14 (29)	0.23

vs. 2<sup>nd</sup> tertile: # < 0.05, ## < 0.01, ### < 0.001

vs. 3<sup>rd</sup> tertile: \* < 0.05, \*\* < 0.01, \*\*\* < 0.001

ACE, angiotensin-converting enzyme, ARB, angiotensin II receptor blocker; BSA, body surface area; ECOG, Eastern Co-operative of Oncology Group; ESC, European Society of Cardiology cardio-oncology guidelines 2022; AHA, American Heart Association 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure; ANOVA *p*-value/chi-squared ( $\chi^2$ ) test for comparison between LV mass-tertile 1, LV mass-tertile 2, and LV mass-tertile 3 of male cancer patients. Normal distributed variables are presented as means  $\pm$  SEM, non-normally distributed variables as median (interquartile range), and nominal variables as *n* (%), *p*-values < 0.05 are bold

### Group stratification by left ventricular mass

Patients were grouped by LVmass/height<sup>2</sup> tertiles, as assessed by transthoracic echocardiography (tertiles females, < 50.00 g/m<sup>2</sup>, 50.00–< 61.15 g/m<sup>2</sup>, ≥ 61.15 g/m<sup>2</sup>; tertiles males, < 59.85 g/m<sup>2</sup>, 59.85–< 74.06 g/m<sup>2</sup>, ≥ 74.06 g/m<sup>2</sup>; Tables 1 and 2). Patients in the lowest tertile were younger, had a lower BMI, and more frequently demonstrated wasting syndrome with unintentional weight loss. Cancer stage, cardiotoxic anti-cancer therapies [24, 25], and presence of solid cancer were similar in all three groups. Cancer patients in the lowest tertile showed higher levels of GH and lower log IGF-I/GH ratio (Fig. 2A, B). LV mass is significantly associated with the IGF-I/GH ratio (Pearson correlation coefficient, 0.203, *p* < 0.001). In a multivariate model, markers of the GH-IGF-I axis are significant predictors for the LV mass ( $R^2 = 0.079$ ; Beta(IGF-I) = –0.101, *p* = 0.12; Beta(GH) = –0.193, *p* < 0.001; Beta(IGF-I/GH) = 0.167, *p* = 0.007; Beta(GHBP) = 0.143, *p* = 0.04). Among females, lower LV mass was associated with higher levels of IGF-I, whereas such association did not exist for males. GHBP and IGFBP3 were not associated with reduced LV mass, whereas in all cancer patients, GHBP negatively correlated with log IGF-I/GH ratio (Fig. 3). When adjusting for age (log(IGF-I/GH)/age ratio vs. GHBP), the correlation remained significant (female, *p* < 0.001; male, *p* < 0.001).

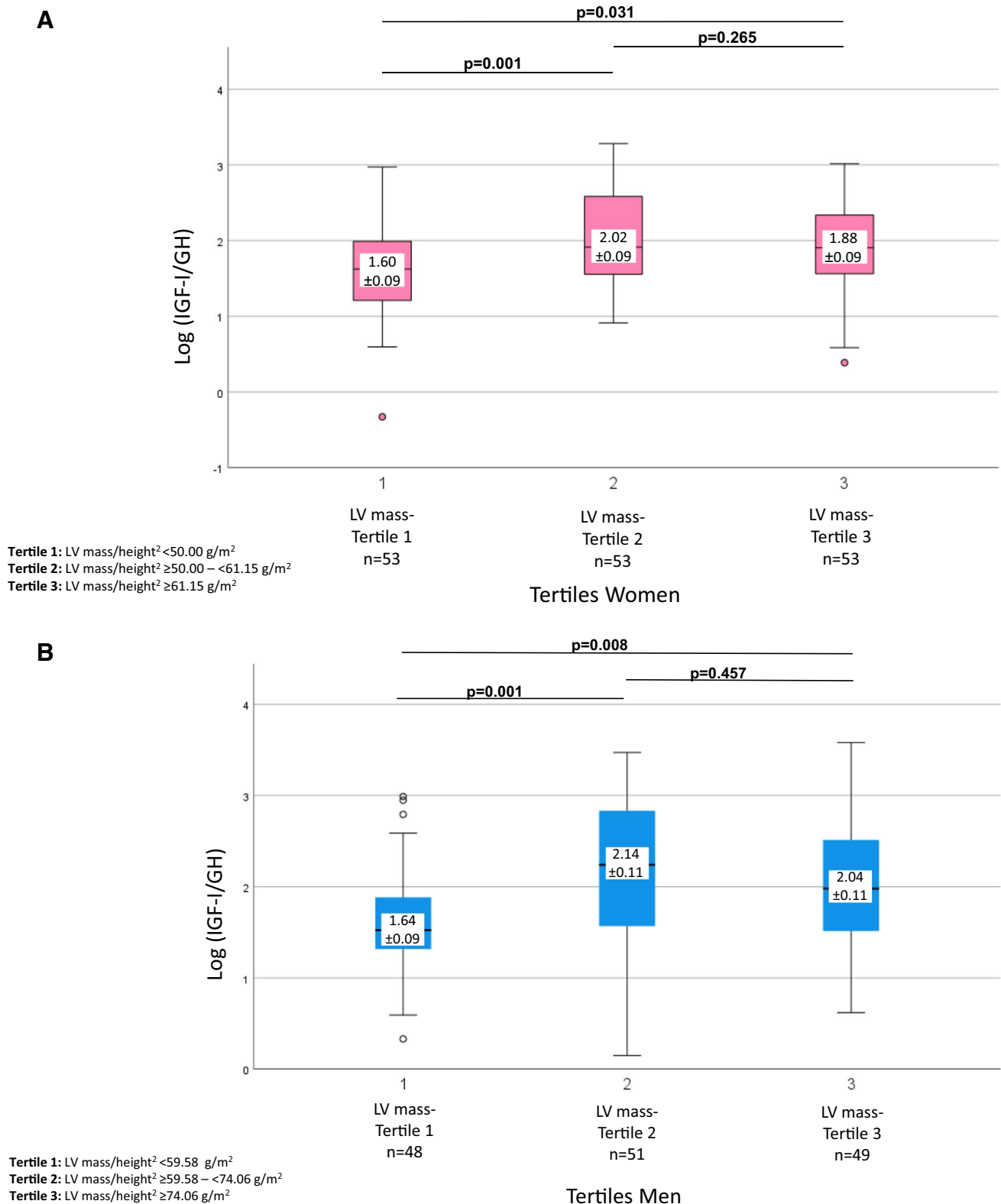
### Group stratification by wasting syndrome with unintentional weight loss

Women and men were stratified by presence or absence of wasting syndrome with unintentional weight loss and

baseline characteristics are provided in Table 3. Cachectic cancer patients in general less frequently had hypercholesterolemia, T2DM, and arterial hypertension. Patients with vs. without wasting syndrome with unintentional weight loss had higher GH and GHBP, lower log IGF-I/GH ratio, and similar levels of IGF-I and IGFBP3. Cancer patients with wasting syndrome with unintentional weight loss had lower LV mass and LV mass/height<sup>2</sup> than patients without. There was no difference in cancer stage or administration of cardiotoxic anti-cancer therapies regarding presence of wasting syndrome with unintentional weight loss.

### Follow-up analysis

Eight-five cancer patients (41 female, 44 male) had a follow-up assessment after a mean of 153  $\pm$  16 days. During that time, LV mass declined by on average –18.8  $\pm$  2.6 g (i.e., –9.2  $\pm$  1.5% [SEM]). Thirty-nine patients (46%) had a reduction of LV mass by  $\geq$  10%. Higher IGF-I baseline values were associated with a reduction of LV mass at follow-up (univariate *r* = –0.318, *p* = 0.003; multiple linear regression model standardized coefficient (Beta) –0.308, *p* = 0.02—adjusted for sex, age, BMI, and GHBP, Table S1/ Fig. 4). Best IGF-I cut-off for LV mass change prediction was  $\geq$  98.22 ng/mL. Patients with lower vs. higher IGF-I levels were older, had a similar BMI and frequency of wasting syndrome with unintentional weight loss, higher LV mass at baseline and GHBP levels, lower IGFBP3 and IGF-I/GH ratio, and similar levels of GH (Table S2). Further, when adjusting for age, the log (IGF-I)/age ratio vs. relative change of LV mass (%) significantly correlate (*r* = –0.314, *p* = 0.003).

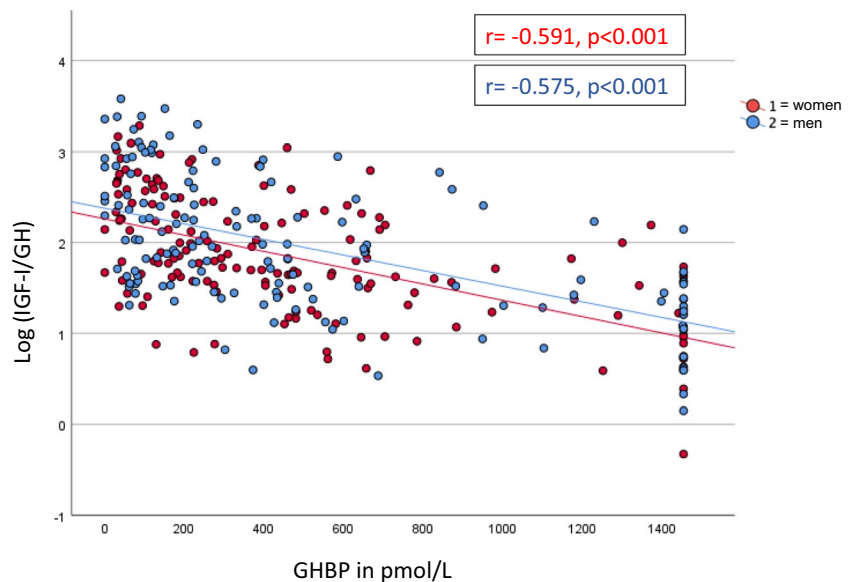


**Fig. 2** **A** LV mass according to tertiles of log(IGF-I/GH) in women; **A** compares the ratio of Log (IGF-I/GH) in dependence of LV mass adjusted for height squared tertiles in women. GH, growth hormone; IGF-I, insulin-like growth factor I; Log (IGF-I/GH), log insulin-like growth factor I/growth hormone ratio; LV, left ventricular. **B** LV mass

according to tertiles of log(IGF-I/GH) in men; **B** compares the ratio of Log (IGF-I/GH) in dependence of LV mass adjusted for height squared tertiles in men. GH, growth hormone; IGF-I, insulin-like growth factor I; Log (IGF-I/GH), log insulin-like growth factor I/growth hormone ratio; LV, left ventricular



**Fig. 3** Relationship between ratio of insulin-like growth factor-I (IGF-I) to growth hormone (GH) (log IGF-I/GH ratio) vs. growth hormone binding protein (GHBP in pmol/L) in patients with cancer; displays the correlation of Log (IGF-I/GH) ratio with the growth hormone binding protein in our cohort. GH, growth hormone; GHBP, growth hormone binding protein; IGF-I, insulin-like growth factor I; Log (IGF-I/GH), log insulin-like growth factor I/growth hormone ratio



## Discussion

This analysis provides new insights into the regulation of the GH-IGF-I axis with regard to the LV mass of cancer patients. We found that reduced LV mass (i.e., cardiac wasting) in patients with mostly advanced-stage cancer is associated with an imbalance in the GH-IGF-I axis. Low LV mass was associated with higher GH levels (with mostly stable GHBP and IGF-I levels observed across LV mass tertiles) and lower log IGF-I/GH ratio, indicating a state of acquired GH resistance in these patients. Overcoming GH resistance therapeutically may be beneficial for cancer patients with cardiac wasting-associated cardiomyopathy.

Cardiac wasting is known to occur in patients with chronic HF [26] and is attributed to chronic inflammatory processes, oxidative and metabolic stress, as well as severe malnutrition. Patients with advanced-stage cancer show similar systemic metabolic abnormalities as chronic HF patients marked by severe cachexia [27–29] and suffer from cardiac wasting without overt LV dysfunction, at least when standard criteria like LVEF are considered [1]. Previous studies have demonstrated a link between imbalance in the GH-IGF-I axis and worsening cachexia in patients with advanced-stage cancer [30]. The current study found an inverse relationship between LV mass and circulating GH levels and IGF-I/GH ratio indicative of an acquired GH resistance. GHBP levels were consistent across all LV mass tertiles in men and women. Interestingly, increased levels of markers of the GH-IGF-I axis have previously been linked to incidence of breast cancer [31]. IGF-I is found to promote tumor growth [32–34] and prevent cell apoptosis [35, 36], including skeletal muscle cells. GH levels are also known to

be much higher in untreated vs. treated heart failure patients [37]. These findings suggest that GH resistance is present in cancer patients with cardiac wasting and may potentially contribute towards cardiac wasting-associated cardiomyopathy, although a causal relationship remains to be determined.

We stratified our findings based on sex to account for differences in baseline LV mass and potential effects of sex-specific endocrine systems. Women were found to have significantly lower levels of GH and IGF-I with increased LV mass. A variable GH-IGF-I axis response has been reported previously in the setting of hormone replacement therapy in women and men [38]. No significant differences in GHBP levels were found across LV mass tertiles among men or women. Among men, a similar trend was observed between GH and LV mass tertiles; however, no significant difference in IGF-I levels was observed for men across the LV mass spectrum. These findings of different IGF-I patterns in men and women may be attributed to inherent sex-specific differences in responsiveness to GH levels [38]. Additionally, high IGF-I levels at baseline were a predictor for LV mass loss at follow-up. Several studies have reported reduced sensitivity of exogenous GH analogue supplementation in stimulating circulating IGF-I in GH-deficient women compared to men [39]. It can be reasonably inferred that the variable trends in IGF-I levels with increasing GH levels in women across LV mass tertiles may not be of special cancer-specific clinical significance as levels predictably remained lower than those observed in men. Previous studies in gastrointestinal cancer, for instance, reported low GH levels and low log IGF-I/GH ratio in combination with normal IGF-I levels [5, 30, 40]. Consequently, the reported normal IGF-I levels but high

**Table 3** Baseline characteristics of cachectic and non-cachectic women ( $n=159$ ) and men ( $n=148$ ) (wasting syndrome with unintentional weight loss defined as weight loss  $\geq 5\%$  in the last 12 months and BMI  $< 24$  kg/m<sup>2</sup>)

Measurement	All patients $n=307$	Women with wasting syndrome with unintentional weight loss $n=85$	Women without wasting syndrome with unintentional weight loss $n=74$	$p$ -value	Men with wasting syndrome with unintentional weight loss $n=67$	Men without wasting syndrome with unintentional weight loss $n=81$	$p$ -value
<b>Clinical variables</b>							
Age (years)	62 $\pm$ 0.8	61 $\pm$ 1.6	63 $\pm$ 1.6	0.43	62 $\pm$ 1.9	63 $\pm$ 1.4	0.92
Body mass index, BMI (kg/m <sup>2</sup> )	24.6 $\pm$ 0.3	20.5 $\pm$ 0.3	28.3 $\pm$ 0.5	<b>&lt; 0.001</b>	21.3 $\pm$ 0.3	28.3 $\pm$ 0.4	<b>&lt; 0.001</b>
<b>Cancer and anti-cancer therapy details</b>							
Cancer stage III/IV, $n$ (%)	254 (83)	71 (84)	56 (76)	0.24	58 (87)	69 (85)	0.82
Solid cancer, $n$ (%)	170 (55)	54 (64)	44 (60)	0.63	41 (61)	31 (38)	<b>0.008</b>
ECOG Performance Scale points	1.73 $\pm$ 0.07	2.18 $\pm$ 0.13	1.70 $\pm$ 0.12	<b>0.008</b>	1.81 $\pm$ 0.16	1.22 $\pm$ 0.11	<b>0.002</b>
Karnofsky Index (%)	73.4 $\pm$ 1.1	66.6 $\pm$ 2.3	75.5 $\pm$ 1.9	<b>0.005</b>	70.3 $\pm$ 2.8	80.9 $\pm$ 1.7	<b>0.001</b>
Systemic anti-cancer therapy naïve, $n$ (%)	41 (13)	12 (14)	13 (18)	1.00	5 (8)	11 (14)	0.59
Cancer drugs causing heart failure (ESC guidelines '22), $n$ (%)	138 (45)	38 (45)	28 (38)	0.42	31 (46)	41 (51)	0.60
Cancer therapies associated with cardiomyopathy (AHA '22), $n$ (%)	187 (61)	52 (61)	36 (49)	0.11	45 (67)	54 (67)	0.95
<b>Laboratory variables</b>							
Growth hormone, GH (ng/mL)	0.94 (0.27–2.42)	1.45 (0.49–3.78)	0.54 (0.25–1.63)	<b>0.029</b>	1.79 (0.66–3.28)	0.53 (0.17–1.88)	<b>&lt; 0.001</b>
Insulin-like growth factor-I, IGF-I (ng/mL)	69.2 (44.3–100.3)	63.6 (43.9–95.3)	68.4 (37.4–98.2)	0.56	69.0 (47.2–112.3)	80.7 (50.6–107.1)	0.37
Log IGF-I/GH ratio	1.89 $\pm$ 0.04	1.68 $\pm$ 0.08	2.00 $\pm$ 0.07	<b>0.003</b>	1.68 $\pm$ 0.09	2.15 $\pm$ 0.07	<b>&lt; 0.001</b>
Growth hormone binding protein, GHBP (pmol/L)	331 (128–668)	444 (194–760)	272 (64–640)	<b>0.038</b>	431 (220–1455)	216 (84–470)	<b>&lt; 0.001</b>
IGF-I binding protein 3, IGFBP3 ( $\mu$ g/mL)	1.66 $\pm$ 0.04	1.85 $\pm$ 0.07	1.83 $\pm$ 0.08	0.86	1.45 $\pm$ 0.07	1.47 $\pm$ 0.06	0.87
<b>Side diagnosis</b>							
Anemia, $n$ (%)	222 (72)	65 (77)	44 (60)	<b>0.026</b>	56 (84)	57 (70)	0.08
Arterial hypertension, $n$ (%)	144 (47)	31 (37)	48 (65)	<b>0.001</b>	24 (36)	41 (51)	0.09

**Table 3** (continued)

Measurement	All patients <i>n</i> = 307	Women with wasting syndrome with unintentional weight loss <i>n</i> = 85	Women without wasting syndrome with unintentional weight loss <i>n</i> = 74	<i>p</i> -value	Men with wasting syndrome with unintentional weight loss <i>n</i> = 67	Men without wasting syndrome with unintentional weight loss <i>n</i> = 81	<i>p</i> -value
Hypercholesterolemia, <i>n</i> (%)	72 (24)	23 (27)	26 (35)	0.30	6 (9)	17 (21)	0.07
Type II diabetes mellitus, <i>n</i> (%)	43 (14)	6 (7)	14 (19)	<b>0.032</b>	7 (10)	16 (20)	0.17
Chronic kidney disease, <i>n</i> (%)	21 (7)	2 (2)	7 (10)	0.08	5 (8)	7 (9)	1.00
<b>Medication</b>							
ACE inhibitors/ARBs, <i>n</i> (%)	78 (25)	16 (19)	25 (34)	<b>0.045</b>	10 (15)	27 (33)	<b>0.013</b>
Beta-blockers, <i>n</i> (%)	53 (17)	8 (9)	20 (27)	<b>0.006</b>	9 (13)	16 (20)	0.38
Anticoagulants, <i>n</i> (%)	12 (4)	0	6 (8)	<b>0.009</b>	3 (5)	3 (4)	1.00
Diuretics, <i>n</i> (%)	56 (18)	9 (11)	21 (28)	<b>0.005</b>	8 (12)	18 (22)	0.13
Antidepressants, <i>n</i> (%)	42 (14)	14 (17)	11 (15)	0.83	6 (9)	11 (14)	0.45
Opioids, <i>n</i> (%)	71 (23)	23 (27)	20 (27)	1.00	16 (24)	12 (15)	0.21
Corticosteroids, <i>n</i> (%)	101 (33)	20 (24)	26 (35)	0.12	23 (34)	32 (40)	0.61
<b>Echocardiographic variables</b>							
Left ventricular (LV) mass (g)	183 ± 3	144 ± 5	169 ± 4	<b>&lt; 0.001</b>	195 ± 7	225 ± 5	<b>&lt; 0.001</b>
LV mass adjusted to height <sup>2</sup> (g/m <sup>2</sup> )	62 ± 1	53 ± 2	62 ± 2	<b>&lt; 0.001</b>	62 ± 2	71 ± 2	<b>&lt; 0.001</b>

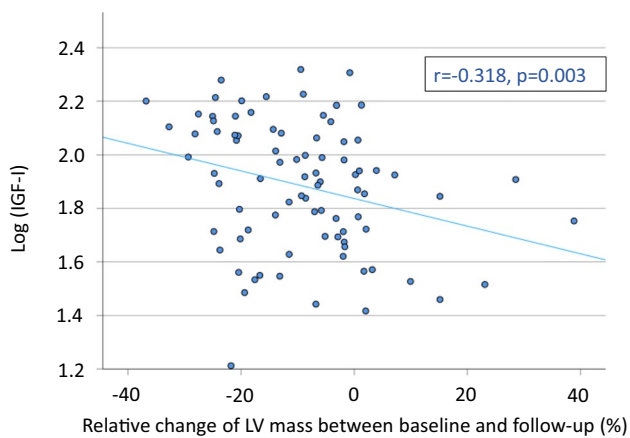
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BSA, body surface area; ECOG, Eastern Co-operative of Oncology Group; ESC, European Society of Cardiology cardio-oncology guidelines 2022; AHA, American Heart Association 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure; *t*-test *p*-value/chi-squared ( $\chi^2$ ) test for comparison between patients with wasting syndrome with unintentional weight loss vs. without. Normal distributed variables are presented as means ± SEM, non-normally distributed variables as median (interquartile range), and nominal variables as *n* (%), *p*-values < 0.05 are bold

GH levels for our study suggest presence of a secondary catabolic state and point towards an independent loss of LV mass in the context of whole body wasting. This clinical scenario may also resemble untreated heart failure. [2]

We found a high prevalence of wasting syndrome with unintentional weight loss across all LV mass tertiles, with increasing frequency of wasting syndrome with unintentional weight loss with worsening LV mass across both sexes. Since the link between cachexia and acquired GH resistance has previously been established [7, 10, 41], we performed a secondary analysis where patients were classified by the presence or absence of wasting syndrome with unintentional weight loss to assess the GH-IGF-I axis in patients with vs. without. We found that men and women with wasting syndrome with unintentional weight loss had significantly higher levels of GH and GHBP and lower IGF-I/GH ratio compared to men and women without wasting syndrome with unintentional weight loss, with no

significant differences between IGF-I levels. Wasting syndrome with unintentional weight loss leads to a reactionary increase in GH and if IGF-I fails to respond the wasting gets worse—therefore, it is hard to interpret an IGF-I level without knowing the GH level first.

Moreover, patients with wasting syndrome with unintentional weight loss also had significantly lower LV mass compared with patients without. This can potentially be explained by a greater degree of progression of GH resistance in patients who have developed wasting syndrome with unintentional weight loss, compared to patients without. Moreover, acquired GH resistance has been associated with age-mediated loss of skeletal muscle mass (i.e., primary sarcopenia) in geriatric patients [42]. These findings suggest that cancer-related wasting syndrome with unintentional weight loss and cardiac wasting, although modulated by similar mechanisms, can occur independently of each other, or occur sequentially after each other [43, 44].



**Fig. 4** Correlation of relative change in LV mass (%) vs. insulin-like growth factor-I (log(IGF-I)) at baseline in 85 patients with cancer with follow-up; the change of LV mass over time of 85 patients with cancer in dependence of IGF-I levels at baseline. Log (IGF-I/GH), log insulin-like growth factor I/growth hormone ratio; LV, left ventricular

We excluded patients with active, antibiotic-treated infection to reduce the possible catabolic effects of an acute systemic immune response influencing the GH-IGF-I axis [45]. However, chronic inflammation is persistent and progressive in patients with advanced-stage cancer and is known to contribute towards wasting processes [46]. It is still to be determined if inflammation predates the development of GH resistance. However, here we show that blunting of GH's anabolic activity with GH resistance is associated with loss of LV mass (i.e., cardiac wasting).

Anabolic interventions—specifically in the context of cardiac wasting-associated cardiomyopathy of cancer patients or as part of cancer cachexia therapies [47, 48]—could provide such direct evidence. Clinical trials in advanced cancer and cancer cachexia per se should monitor cardiac effects of these interventions in detail.

In recent studies conducted by our group, we investigated the presence of cardiac cachexia in advanced-stage cancer patients and the risk of developing a HF-like syndrome in the setting of cardiac wasting-associated cardiomyopathy [1, 2, 49]; however, studies have been limited in the assessment of the underlying mechanisms and prognostic value of already known risk factors. As described earlier, higher levels of circulating IGF-I levels have been associated with improved myocardial mass with GH supplementation in patients with chronic HF, although trial results have been variable in terms of improvement in hard clinical endpoints [9, 50, 51]. Cardiac wasting-associated cardiomyopathy is a separate entity that may behave differently to augmentation of the GH-IGF-I axis, but that remains to be proven. Alterations in GH-IGF-I axis observed with changes in LV mass

may serve as a sensitive screening tool for earlier detection of cardiac wasting-associated cardiomyopathy in patients with cancer to allow for earlier implementation of appropriate treatment measures.

### Study limitations

This was a prospective cross-sectional study that enrolled patients from one center using standardized assessments. Still, causality cannot be inferred from those studies. Although we found no significant difference in LV mass loss in anti-cancer treatment naïve and treated patients, it might be desirable to study whether specific anti-cancer therapies could influence LV mass. We did not exclude patients with controlled arterial hypertension nor T2DM in an intention to show a real-world cohort of cancer patients—but those patients could be excluded in future studies. We excluded all patients with significant cardiovascular disease at baseline with the intent to not bias the analyses by such underlying diseases—further studies in the future could therefore exclusively investigate those patients with cancer that already demonstrate significant cardiovascular disease. While our study monitored the longitudinal change of LV mass over time by echocardiography, we did not measure longitudinal changes in GH-IGF-I axis over time, and therefore this could be of great interest for future studies.

### Conclusion

Low LV mass in patients with advanced-stage cancer is associated with an impaired state of the GH-IGF-I axis in both men and women, indicating presence of acquired GH resistance in many of these patients with cardiac wasting. These observations provide further insights into the underlying mechanism of a cancer-related wasting syndrome with unintentional weight loss, and particularly cardiac wasting in patients with cancer, which can result in a cardiomyopathy, leading to impaired exercise capacity and worsening symptoms and quality of life. Further prospective studies are warranted to ascertain a potential causal relationship between acquired GH resistance and cardiac wasting, and to explore related interventions to center-act or prevent cardiac wasting-associated cardiomyopathy in advanced cancer.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00392-024-02400-x>.

**Funding** Open Access funding enabled and organized by Projekt DEAL. This study was partly funded by the German Centre for Cardiovascular Research through research support to Dr Hadzibegovic, Dr

S. Anker, and Dr M. Anker. TZ is supported by the German Center of Cardiovascular Research (DZHK, FKZ: 81Z0710102).

## Declarations

**Conflict of interest** Dr Wilkenschhoff is supported by a Clinical Fellowship Grant from the Berlin Institute of Health; and has received speaker fees and/or contributions to congresses from Abbott, AstraZeneca, Bayer, Berlin Chemie, Bristol Myers Squibb, GE Healthcare, Pfizer, Philips, and Servier, all outside the submitted work.

Dr Zeller has received support from the German Centre for Cardiovascular Research (FKZ 81Z1710101 and FKZ 81Z0710102).

Dr Karakas is supported by a Clinician Scientist Professorship Grant from the Else Kroener-Fresenius-Foundation; and has received personal fees and grant support from Daiichi-Sankyo, Adrenomed, Sphingotec, and Vifor Pharma, all outside the submitted work, and is a part-time employee of 4TEEN4 Pharmaceuticals.

Dr Keller has served on advisory boards for Roche, Janssen-Cilag, Celgene, Takeda, Bristol Myers Squibb, Gilead, Hexal, Pfizer, AstraZeneca, and Pentixapharm; has received clinical research support from Janssen-Cilag, Novartis, Takeda, Bristol Myers Squibb, Roche, and Pfizer; and has received travel support from Roche, Bristol Myers Squibb, Gilead, Takeda, Janssen-Cilag, and Celgene.

Dr Bullinger has received honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi-Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer, Roche, Sanofi, and Seattle Genetics; and has received research support from Bayer and Jazz Pharmaceuticals.

Dr S. Anker has received grants and personal fees from Vifor and Abbott Vascular; and has received personal fees for consulting, trial committee work, and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards Lifesciences, Faraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave, all outside the submitted work; and is named co-inventor of 2 patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but does not benefit personally from the related issued patents.

Dr Butler has received personal fees/fees as consultant from Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, and Vifor. Dr Coats has received honoraria and/or speaker fees from AstraZeneca, Boehringer Ingelheim, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia, and Viatrix.

Dr Landmesser has received institutional research grants from Amgen, Bayer, and Novartis; and has received speaker or consulting honoraria from AstraZeneca, Bayer, Boehringer, Amgen, Sanofi, Novartis, and Novo Nordisk.

Dr M. Anker has received personal fees from Servier, outside the submitted work.

Dr Zeller is listed as co-inventor of an international patent on the use of a computing device to estimate the probability of myocardial infarction (International Publication Number WO2022043229A1). TZ is shareholder of the ART.EMIS GmbH Hamburg.

Dr von Haehling has been paid a consultant for and/or received honoraria payments from AstraZeneca, Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Pharmacosmos, Respicardia, Roche, Servier, Sorin, and Vifor. He also reports research support from Amgen, AstraZeneca, Boehringer Ingelheim,

Innovative Medicines Initiative (IMI), and the German Center for Cardiovascular Research (DZHK).

Dr. Doehner reports consulting fees and speaker honoraria from Aimediq, Bayer, Boehringer Ingelheim, Boston Scientific, Cardiomatics, Lilly, Medtronic, and Vifor Pharma; travel support from Pharmacosmos; and research support to the Institute from EU (Horizon2020), German Ministry of Education and Research, German Center for Cardiovascular Research, Boehringer Ingelheim, and Vifor Pharma.

Dr Cleland reports personal fees from Abbott, Amgen, Novartis, Medtronic, Idorsia, Servier, AstraZeneca, Biopeutics, Torrent, and Respicardia; grants and personal fees from Bayer, Bristol Myers Squibb, Pharmacosmos, Vifor, Johnson & Johnson, Myokardia, and Viscardia; and personal fees and non-financial support from Boehringer Ingelheim and NI Medical.

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.


**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

- Lena A et al (2023) Clinical and prognostic relevance of cardiac wasting in patients with advanced cancer. *J Am Coll Cardiol* 81:1569–1586
- Anker MS et al (2021) Advanced cancer is also a heart failure syndrome: a hypothesis. *J Cachexia Sarcopenia Muscle* 12:533–537
- Tian M et al (2010) Cardiac alterations in cancer-induced cachexia in mice. *Int J Oncol* 37:347–353
- Bentham J, Rodriguez-Arnan J, Ross RJ (1993) Acquired growth hormone resistance in patients with hypercatabolism. *Horm Res* 40:87–91
- Ross RJ, Chew SL (1995) Acquired growth hormone resistance. *Eur J Endocrinol* 132:655–660
- Anker SD et al (1997) Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 96:526–534
- Doehner W et al (2001) Leptin, insulin sensitivity and growth hormone binding protein in chronic heart failure with and without cardiac cachexia. *Eur J Endocrinol* 145:727–735
- Ross RJ (1999) The GH receptor and GH insensitivity. *Growth Horm IGF Res* 9 Suppl B:42–45 (discussion 45–46)
- Osterziel KJ et al (1998) Randomised, double-blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy. *Lancet* 351:1233–1237
- Anker SD et al (2001) Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. *J Am Coll Cardiol* 38:443–452
- Trobec K, von Haehling S, Anker SD, Lainscak M (2011) Growth hormone, insulin-like growth factor 1, and insulin signaling—a pharmacological target in body wasting and cachexia. *J Cachexia Sarcopenia Muscle* 2:191–200

12. Marçõa R et al (2018) Classification of chronic obstructive pulmonary disease (COPD) according to the new Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017: comparison with GOLD 2011. *COPD* 15:21–26
13. Bertero L et al (2018) Eighth edition of the UICC Classification of Malignant Tumours: an overview of the changes in the pathological TNM classification criteria-what has changed and why? *Virchows Arch* 472:519–531
14. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 31:1860–1861
15. Durie BG, Salmon SE (1975) A clinical staging system for multiple myelom. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 36:842–854
16. Lauer MS, Anderson KM, Larson MG, Levy D (1994) A new method for indexing left ventricular mass for differences in body size. *Am J Cardiol* 74:487–491
17. Fearon K et al (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 12:489–495
18. Bauer J et al (2019) Sarcopenia: a time for action. An SCWD position paper. *J Cachexia Sarcopenia Muscle* 10:956–961
19. Stewart Coats AJ et al (2016) Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 7:355–365
20. Devereux RB, Reichek N (1977) Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 55:613–618
21. McDonagh TA et al (2022) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 24:4–131
22. Oken MM et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649–655
23. Karnofsky DA, Burchenal JH, Escher GC (1950) Chemotherapy of neoplastic diseases. *Med Clin North Am* 34:439–458 (illust)
24. Lyon AR et al (2022) 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 43:4229–4361
25. Heidenreich PA et al (2022) 2022 AHA/ACC/HFSA Guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 145:e876–e894
26. Ciccoira M, Kalra PR, Anker SD (2003) Growth hormone resistance in chronic heart failure and its therapeutic implications. *J Card Fail* 9:219–226
27. Peixoto da Silva S, Santos JMO, Costa ESMP, Gil da Costa RM, Medeiros R (2020) Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia Sarcopenia Muscle* 11:619–635
28. Pototschnig I et al (2023) Interleukin-6 initiates muscle- and adipose tissue wasting in a novel C57BL/6 model of cancer-associated cachexia. *J Cachexia Sarcopenia Muscle* 14:93–107
29. Zhang Q et al (2021) Association of systemic inflammation with survival in patients with cancer cachexia: results from a multicentre cohort study. *J Cachexia Sarcopenia Muscle* 12:1466–1476
30. Bing C (2005) Insight into the growth hormone-insulin-like growth factor-I axis in cancer cachexia. *Br J Nutr* 93:761–763
31. Pazaitou-Panayiotou K et al (2007) Growth hormone-binding protein is directly and IGFBP-3 is inversely associated with risk of female breast cancer. *Eur J Endocrinol* 156:187–194
32. Boguszewski CL, Boguszewski M (2019) Growth hormone's links to cancer. *Endocr Rev* 40:558–574
33. Kaleko M, Rutter WJ, Miller AD (1990) Overexpression of the human insulinlike growth factor I receptor promotes ligand-dependent neoplastic transformation. *Mol Cell Biol* 10:464–473
34. Rodriguez-Tarduchy G, Collins MK, García I, López-Rivas A (1992) Insulin-like growth factor-I inhibits apoptosis in IL-3-dependent hemopoietic cells. *J Immunol* 149:535–540
35. Resnicoff M et al (1995) The insulin-like growth factor I receptor protects tumor cells from apoptosis in vivo. *Cancer Res* 55:2463–2469
36. Resnicoff M, Burgaud JL, Rotman HL, Abraham D, Baserga R (1995) Correlation between apoptosis, tumorigenesis, and levels of insulin-like growth factor I receptors. *Cancer Res* 55:3739–3741
37. Anand IS et al (1989) Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation* 80:299–305
38. Span JP, Pieters GF, Sweep CG, Hermus AR, Smals AG (2000) Gender difference in insulin-like growth factor I response to growth hormone (GH) treatment in GH-deficient adults: role of sex hormone replacement. *J Clin Endocrinol Metab* 85:1121–1125
39. Drake WM et al (1998) Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. *J Clin Endocrinol Metab* 83:3913–3919
40. Huang Q, Nai YJ, Jiang ZW, Li JS (2005) Change of the growth hormone-insulin-like growth factor-I axis in patients with gastrointestinal cancer: related to tumour type and nutritional status. *Br J Nutr* 93:853–858
41. Niebauer J et al (1998) Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J Am Coll Cardiol* 32:393–397
42. Ferrari U et al (2021) IGF-I/IGFBP3/ALS deficiency in sarcopenia: low GHBP suggests GH resistance in a subgroup of geriatric patients. *J Clin Endocrinol Metab* 106:e1698–e1707
43. Florea VG et al (2004) Wasting of the left ventricle in patients with cardiac cachexia: a cardiovascular magnetic resonance study. *Int J Cardiol* 97:15–20
44. Florea VG et al (2002) The cardiac component of cardiac cachexia. *Am Heart J* 144:45–50
45. Martín AI, Priego T, Moreno-Ruperez Á, González-Hedström D, Granado M, López-Calderón A (2021) IGF-1 and IGFBP-3 in Inflammatory Cachexia. *Int J Mol Sci* 22(17):9469
46. Refsgaard Holm M et al (2019) Fibroblast growth factor 21 in patients with cardiac cachexia: a possible role of chronic inflammation. *ESC Heart Fail* 6:983–991
47. Takayama K, Takiguchi T, Komura N, Naito T (2023) Efficacy and safety of anamorelin in patients with cancer cachexia: post-hoc subgroup analyses of a placebo-controlled study. *Cancer Med* 12:2918–2928
48. Ebner N, Anker SD, von Haehling S (2019) Recent developments in the field of cachexia, sarcopenia, and muscle wasting: highlights from the 11th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 10:218–225
49. Springer J et al (2014) Prevention of liver cancer cachexia-induced cardiac wasting and heart failure. *Eur Heart J* 35:932–941
50. Isgaard J et al (1998) A placebo-controlled study of growth hormone in patients with congestive heart failure. *Eur Heart J* 19:1704–1711
51. Fazio S et al (1996) A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. *N Engl J Med* 334:809–814

## Authors and Affiliations

Ann-Kathrin Fröhlich<sup>1,2,3,4</sup> · Jan Porthun<sup>1,4,5</sup> · Khawaja M. Talha<sup>6</sup> · Alessia Lena<sup>1,2,3,7</sup> · Sara Hadzibegovic<sup>1,2,3,7</sup> · Ursula Wilkenshoff<sup>1,7,8</sup> · Frederike Sonntag<sup>1,2,3,4</sup> · Anja Nikolski<sup>1,2,3,4</sup> · Luisa Valentina Ramer<sup>1,2,3,4</sup> · Tanja Zeller<sup>9,10,11</sup> · Ulrich Keller<sup>12,13,14</sup> · Lars Bullinger<sup>13,15</sup> · Stefan D. Anker<sup>2,3,16</sup> · Wilhelm Haverkamp<sup>2,3,16</sup> · Stephan von Haehling<sup>17,18</sup> · Wolfram Doehner<sup>2,3,4,19</sup> · Ursula Rauch<sup>1,2,7</sup> · Carsten Skurk<sup>1,7</sup> · John G. F. Cleland<sup>20</sup> · Javed Butler<sup>6,21</sup> · Andrew J. S. Coats<sup>22</sup> · Ulf Landmesser<sup>1,2,7,8</sup> · Mahir Karakas<sup>11,23</sup> · Markus S. Anker<sup>1,2,3,7</sup> 

<sup>1</sup> Charité – University Medicine Berlin corporate member of Free University Berlin and Humboldt-University Berlin, Berlin, Germany

<sup>2</sup> German Centre for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany

<sup>3</sup> Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany

<sup>4</sup> Department of Cardiology, Angiology and Intensive Care Medicine Campus Virchow Clinic, German Heart Center Charité, Berlin, Germany

<sup>5</sup> Norwegian University of Science and Technology, Campus Gjøvik, Gjøvik, Norway

<sup>6</sup> Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

<sup>7</sup> Department of Cardiology, Angiology and Intensive Care Medicine Campus Benjamin Franklin, German Heart Center Charité, Hindenburgdamm 30, 12200 Berlin, Germany

<sup>8</sup> Berlin Institute of Health, Charité – University Medicine Berlin, Berlin, Germany

<sup>9</sup> University Center of Cardiovascular Science, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

<sup>10</sup> Clinic for Cardiology, University Heart and Vascular Centre Hamburg, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

<sup>11</sup> German Centre for Cardiovascular Research, Partner Site HH/Kiel/HL, Hamburg, Germany

<sup>12</sup> Department of Hematology, Oncology and Cancer Immunology, Charité – University Medicine Berlin, Campus Benjamin Franklin, Berlin, Germany

<sup>13</sup> German Cancer Consortium (DKTK), Partner Site Berlin, a partnership between DKFZ and Charité-Universitätsmedizin Berlin, Berlin, Germany

<sup>14</sup> Max Delbrück Center, Berlin, Germany

<sup>15</sup> Department of Hematology, Oncology, and Tumor Immunology, Charité – University Medicine Berlin corporate member of Free University Berlin and Humboldt University Berlin, Berlin, Germany

<sup>16</sup> Department of Cardiology Campus, Virchow Clinic of German Heart Center Charité, Charité – University Medicine Berlin, Berlin, Germany

<sup>17</sup> Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany

<sup>18</sup> German Centre for Cardiovascular Research (DZHK), Partner Site Göttingen, Göttingen, Germany

<sup>19</sup> Centre for Stroke Research, Berlin, Charité-Universitätsmedizin, Berlin, Germany

<sup>20</sup> School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK

<sup>21</sup> Baylor Scott and White Research Institute, Dallas, TX, USA

<sup>22</sup> Heart Research Institute, Sydney, Australia

<sup>23</sup> Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany