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Prognostic Impact of Pretherapeutic Hemoglobin Levels on All-cause Mortality in Cardiooncology

ANNA HOHNECK[1,2], STEPHANIE ROSENKAIMER[1], TINA SIEBURG[1], JAKOB HOLZWARTH[1], RALF D. HOFHEINZ[3], IBRAHIM AKIN[1,2], MARTIN BORGGREFE[1,2] and STEFAN GERHARDS[1]

[1]First Department of Medicine (Cardiology), University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, European Centre for AngioScience (ECAS), Mannheim, Germany;
[2]DZHK (German Centre for Cardiovascular Research) partner site Heidelberg/Mannheim, Mannheim, Germany;
[3]Third Department of Medicine (Hematology and Oncology), Interdisciplinary Tumor Center Mannheim (ITM), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Abstract. *Background/Aim: We investigated the prognostic impact of hemoglobin (Hb) levels in tumour patients receiving routine cardiological surveillance during anti-cancer treatment. The aim of the study was to identify independent predictors of all-cause mortality in a cardio-oncological collective. Patients and Methods: A total of 551 patients (273 males, 278 females) were enrolled in the Mannheim Registry for Cardiooncology and were included in the present analysis. Median follow-up was 41 months (95% CI=40-43). Results: Patients were grouped according to a pretherapeutic Hb-threshold (determined by ROC analysis) into cohorts with Hb<11.4 g/dl (n=232, 42.1%) and Hb >11.4 g/dl (n=319, 57.9%). Patients with lower Hb levels were older at the time of first diagnosis (63.8±14.4 vs. 59.9±15.4 years, p=0.003) and were more likely to have advanced tumour stages (92 (39.7%) vs. 83 (26.0%), p=0.0007). There were no differences regarding cardiovascular comorbidities such as hypertension or diabetes, while chronic kidney disease was more common in patients with lower Hb. Anticoagulants were used more often in patients with lower Hb (88 (37.9%) vs. 84 (26.3%), p=0.01). Left ventricular ejection fraction (LVEF) was lower in patients with Hb <11.4 g/dl (51.9±11.0% vs. 55.1±9.7%, p=0.003). Correlation analysis revealed a significant correlation of Hb levels and LVEF (R^2=0.07, p<0.0001). During follow-up, a total of 140 patients (25.4%) were deceased, with significantly more deaths occurring in the group of patients with low Hb values [108 (46.6%) vs. 32 (10.0%), p<0.0001]. In multivariable analysis, Hb was identified as independent predictor for mortality (OR=5.3, CI=0.41-0.89, p<0.0001). Conclusion: Low Hb levels were identified as an independent predictor of mortality in patients with cancer. There was a significant correlation of Hb and LVEF, suggesting that low Hb values are not solely due to anaemia, but rather reflect the severity of cancer.*

Anaemia is a common finding in patients with cancer. The prevalence is influenced by tumour entity, stage of disease, patient age, comorbidities and anti-cancer treatment strategies (1, 2). Generally, cancer-related anaemia (CRA) is considered as normocytic and normochromic within the category of anaemia of chronic diseases (3). CRA may reduce performance status and quality of life. Depending on the severity of CRA, dyspnea and palpitations can occur (4). In patients with concomitant cardiovascular (CV) diseases, who present with similar symptoms, CRA may aggravate symptoms. Anaemia is also common in patients with heart failure (HF), which is associated with poor outcome (5).

CRA might be due to suppression of the bone marrow by infiltration of the tumour or reduced production of erythropoietin by inflammatory cytokines and relative iron deficiency, as well as myelosuppressive effects of radiation and/or chemotherapy (6, 7). Diseases in need of repeated blood transfusions, such as myelodysplastic syndrome, thalassemia or sickle cell anaemia are associated with poor survival due to secondary iron overload (8, 9). While some years ago, patients with coronary artery disease (CAD) and anaemia were more generously transfused, nowadays one is becoming more and more restrictive towards red blood cell (RBC) transfusions, as higher mortality rates have been observed (10). The American Association of Blood Banks (AABB), therefore, recommends a restrictive hemoglobin

Correspondence to: Dr. Anna Lena Hohneck, First Department of Medicine – Cardiology, University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel: +49 6213832204, Fax: +49 6213832172, e-mail: annalena.hohneck@umm.de

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(Hb) transfusion threshold down to as low as 7 g/dl, which is safe in most clinical settings (11). However, whether this restricted transfusion practice should also be applied in patients with CRA is unclear. We investigated the significance of pretherapeutic Hb levels in a cohort of patients undergoing anti-cancer treatment under regular cardiological surveillance.

Patients and Methods

A total of 551 patients undergoing anti-cancer treatment under regular cardiological surveillance, were enrolled in the ongoing MAnnheim Registry for CardioOncology (MARCO) database, which was established in 2016. All patients gave written informed consent and were followed over a median of 41 months (95% CI=40-43). The study was conducted as observational trial in the First Department of Medicine (Cardiology), University Medical Centre Mannheim, Germany. The study design complies with the declaration of Helsinki and was approved by the local ethical committee, Medical Ethics Commission II, Faculty of Medicine Mannheim, University of Heidelberg, Germany. Data were analyzed anonymously. Data protection was in accordance with the EU Data Protection Directive.

Demographic and clinical characteristics. Baseline demographic and clinical characteristics were acquired by a questionnaire and on the basis of the clinical charts of the electronic hospital system. Baseline characteristics comprised sex, age, BMI and date of first diagnosis of the tumour disease. Clinical characteristics included CV risk factors such as hypertension, diabetes, nicotine consumption and concomitant diseases (CAD, HF or chronic kidney disease (CKD) defined as glomerular filtration rate (GFR) <60 ml/min/1.73m^2) and concomitant drug treatment.

Transthoracic echocardiography. Echocardiographic examinations were performed periodically prior to cancer treatment and thereafter every 3 to 6 months, using Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) or iE33 (Philips Medical Systems, Andover, USA). Two experienced cardiologists acquired and interpreted the results. Images were digitally stored for offline use, and data were analyzed using GE Echo PAC PC analysis software.

Assessment of cardiac chamber size and function was performed using standard M-mode, 2D and color Doppler imaging (12). Left ventricular ejection fraction (LVEF) was calculated using the Simpson's method. Left atrial (LA) measurements were performed in end-systole in the apical two- and four-chamber (2Ch and 4Ch) views. Echocardiographic measurements of diastolic function were performed following the recommendation for the evaluation of LV diastolic function by echocardiography (13). Mitral inflow signal was assessed from the apical 4Ch view by placing the sample volume at the level of the mitral leaflet tips. Tissue Doppler-derived diastolic mitral annular velocity (E') was measured at the septal and lateral corner of the mitral annulus in the apical 4Ch view. Tricuspid valve regurgitation jet maximum velocity (TR Vmax) was measured by continuous wave (CW) Doppler from the apical 4Ch view or subcostal view. Longitudinal systolic movement was assessed with M-Mode to determine both mitral (MAPSE) and tricuspid annulus plane systolic excursion (TAPSE), measuring the distance of the annular movement between end-diastole and end-systole. The presence and extent of pericardial effusion was assessed in the subxiphoid view.

Primary endpoint. Primary endpoint was all-cause mortality. Changes in LVEF or TAPSE served as secondary outcome measures.

Laboratory parameters. Laboratory values included creatinine (mg/dl), GFR (ml/min/1.73m^2), thyroid stimulating hormone (TSH, U/l), glycated hemoglobin (HbA1c, %), Hb (g/dl) and Vitamin D (Vit. D, ng/ml). Blood samples were collected before treatment start under fasting conditions to provide reliable values.

Statistical analysis. All data are presented as a mean±standard deviation. Continuous variables were compared using a two-tailed Student's t-test for parametric and Mann–Whitney *U*-test for non-parametric variables. Categorical variables were compared with the χ^2 test. All results were considered statistically significant when $p<0.05$.

Receiver operating characteristic (ROC) curves were used to find the optimal cut-off value for Hb, maximizing the sum of sensitivity and specificity with help of the Youden-Index.

Multivariable analysis was performed with logistic regression analysis using block entry of the following variables, which showed the strongest correlation in univariate analysis: advanced tumour disease, palliative treatment, age at first diagnosis, breast cancer, haematological diseases, tumours of the hepatopancreaticobiliary (HPB) system, Vit. D, surgical treatment, and cancer treatment with gemcitabine or tyrosine kinase inhibitors, provided to have a R^2 >0.02 in univariate analysis.

Analyses were performed with Statistical 1 Package for Social Sciences (SPSS for windows 24.0, Chicago, IL, USA) and GraphPad Prism 8.0 (Graphpad Software, Inc., California, USA).

Results

A total of 551 patients (273 males, 278 females) were included in the analysis. Mean age at the time of first cancer diagnosis was 61.6±15.1 years. All patients underwent cancer treatment, either with conventional chemotherapeutic agents or a combination of different drugs, in 38% chemotherapy was combined with radiotherapy. One third of the patients were diagnosed at an advanced tumour stage (31.8%). Forty-eight percent of patients received palliative intended treatment. A total of 15% had a secondary neoplasm and 8% a relapse of their initial diagnosis. Breast cancer was found most frequently (25%), followed by haematological (12%) and gastrointestinal tumours (11%). CV concomitant diseases were relatively frequent: 59% had hypertension, 37% were suffering from CKD and 15% were diagnosed with HF. 28% were active smokers and 17% had diabetes. Complete tumour and patient characteristics are outlined in Table I.

ROC analysis was performed to determine the cut-off value for Hb (with maximizing the sum of sensitivity and specificity) correlating best with the primary endpoint. Hb <11.4 g/dl (sensitivity 79%, specificity 61%; AUC 0.75, $p<0.0001$) was detected as a threshold (Figure 1).

The cohort was subsequently divided, into Hb <11.4 g/dl (n=232, 42.1%) and Hb >11.4 g/dl (n=319, 57.9%). Patients with lower Hb were older at the time of first diagnosis

Table I. *Baseline characteristics, demographics and drug treatment details of included patients. A comparative analysis was performed for Hb <11.4 g/dl and >11.4 g/dl.*

	All patients (n=551)	Hb <11.4 g/dl (n=232, 42.1%)	Hb >11.4 g/dl (n=319, 57.9%)	*p*-Value (univariate)	R^2
Gender, m (%)	273 (49.5)	107 (46.1)	166 (52.0)	0.17	-
Age at first diagnosis	61.6±15.1	63.8±14.4	59.9±15.4	**0.003**	0.02
Advanced tumor disease (metastasized)	175 (31.8)	92 (39.7)	83 (26.0)	**0.0007**	0.02
Relapse	44 (8.0)	17 (7.3)	27 (8.5)	0.64	-
Secondary tumor	91 (16.5)	39 (16.8)	52 (16.3)	0.87	-
Palliative treatment	263 (47.7)	148 (63.8)	115 (36.1)	**<0.0001**	0.08
Karnofsky-Index	77.3±18.9	75.2±19.3	78.9±18.5	**0.02**	0.009
Tumour entities, n (%)					
Breast cancer	136 (24.7)	38 (16.4)	98 (30.7)	**<0.0001**	0.03
Haematological	66 (12.0)	40 (17.2)	26 (8.2)	**0.001**	0.02
Gastrointestinal	59 (10.7)	27 (11.6)	32 (10.0)	0.55	-
Lung	51 (9.3)	23 (9.9)	28 (8.8)	0.65	-
Kidney/Urothelium	38 (6.9)	19 (8.2)	19 (6.0)	0.31	-
Dermatological	32 (5.8)	10 (4.3)	22 (6.9)	0.20	-
Prostate	31 (5.6)	16 (6.9)	15 (4.7)	0.27	-
Lymphoma	30 (5.4)	6 (2.6)	24 (7.5)	**0.01**	0.01
Melanoma	21 (3.8)	4 (1.7)	17 (5.3)	**0.03**	0.009
Sarcoma	18 (3.3)	11 (4.7)	7 (2.2)	0.10	-
Gynaecological	18 (3.3)	12 (5.2)	6 (1.9)	0.03	0.009
ORL	17 (3.1)	6 (2.6)	11 (3.4)	0.56	-
HPB	15 (2.7)	12 (5.2)	3 (0.9)	**0.003**	0.02
Cerebral	9 (1.6)	3 (1.3)	6 (1.9)	0.59	-
CUP	3 (0.5)	1 (0.4)	2 (0.6)	0.76	-
Others	7 (1.3)	4 (1.7)	3 (0.9)	0.42	-
Cancer treatment					
Platin	105 (19.1)	40 (17.2)	65 (20.4)	0.36	-
Taxane	157 (28.5)	55 (22.4)	105 (32.9)	**0.01**	0.01
Anthrazykline	147 (26.7)	56 (24.1)	91 (28.5)	0.25	-
Gemcitabine	24 (4.4)	19 (8.2)	5 (1.6)	**0.0002**	0.03
5-FU	46 (8.3)	20 (8.6)	26 (8.2)	0.84	-
Trastuzumab (Her2neu)	60 (10.9)	16 (6.9)	44 (13.8)	**0.01**	0.01
Tyrosine kinase inhibitors	21 (3.8)	16 (6.9)	5 (1.6)	**0.001**	0.02
Surgical treatment	304 (55.2)	110 (47.4)	194 (60.8)	**0.002**	0.02
Radiotherapy	213 (38.7)	79 (34.1)	134 (42.0)	0.06	-
Stem cell transplantation	26 (4.7)	13 (5.6)	13 (4.1)	0.40	-
History of transfusion	80 (14.5)	56 (24.1)	24 (7.5)	**<0.0001**	0.05
Treatment with ESA	12 (2.2)	8 (3.4)	4 (1.3)	0.08	-
Laboratory parameters					
Creatinine (mg/dl)	1.14±0.83	1.28±1.08	1.03±0.57	0.001	0.007
GFR (ml/min)	66.3±29.3	62.1±34.2	69.2±25.0	0.01	0.01
HbA1c (%)	6.1±1.4	6.0±1.3	6.2±1.5	0.33	-
Hb (g/dl)	11.6±2.1	9.4±1.5	13.2±1.4	**<0.0001**	0.22
TSH (U/l)	2.1±6.2	1.8±3.1	2.4±7.9	0.37	-
Vit. D (U/l)	25.3±16.5	20.5±12.7	27.4±17.6	**<0.05**	0.02
Concomitant diseases, n (%)					
Hypertension	324 (58.8)	143 (61.6)	181 (56.7)	0.25	-
Diabetes	96 (17.4)	43 (18.5)	53 (16.6)	0.56	-
Nicotine consumption	155 (28.1)	65 28.0)	90 (28.2)	0.96	-
CAD	100 (18.1)	49 (21.1)	51 (16.0)	0.12	-
Heart failure	82 (14.9)	38 (16.4)	44 (13.8)	0.40	-
CKD (GFR <60 ml/min)	205 (37.2)	105 (45.3)	100 (31.3)	**0.001**	0.01
Concomitant medication					
Betablocker	206 (37.4)	95 (40.9)	111 (34.8)	0.24	-
ACE inhibitor/ ARB	226 (41.0)	101 (43.5)	125 (39.2)	0.48	-
Anticoagulant	172 (31.2)	88 (37.9)	84 (26.3)	**0.01**	0.01
Platelet inhibiton	118 (21.4)	56 (24.1)	62 (19.4)	0.26	-
Vit. D	109 (19.8)	47 (20.3)	62 (19.4)	0.95	-
Diabetes medication	77 (14.0)	36 (15.5)	41 (12.9)	0.48	-

Data are presented as mean±SD or numbers (frequency). Spearman's correlation coefficient R^2. 5-FU: 5-Fluorouracil; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CKD: chronic kidney disease; CUP: cancer of unknown primary; ESA: erythropoiesis stimulating agent; GFR: glomerular filtration rate; Hb: hemoglobin; HPB: hepatopancreaticobiliary; m: male; n: number; ORL: otorhinolaryngological; TSH: thyroid stimulating hormone; Vit.: Vitamin. Bold values indicate statistical significance.

(63.8±14.4 *vs*. 59.9±15.4, p=0.003) and showed a slightly lower Karnofsky performance status (75±19 *vs*. 79±19, p=0.02). Patients with lower Hb were more likely to have advanced tumour disease (92 (39.7%) *vs*. 83 (26.0%), p=0.0007) and received more often palliative treatment (148 (63.8%) *vs*. 115 (36.1%), p<0.0001) (Table I).

In addition, a subgroup analysis was carried out, with Hb <9 g/dl and Hb >9 g/dl serving as cut-off. The subgroup analysis showed no relevant differences in baseline parameters (Table II).

Tumour entities. The most common tumour entities were breast cancer (24.7%), with significantly fewer diagnoses in patients with lower Hb [38 (16.4%) *vs*. 98 (30.7%], p<0.0001), 12% of patients had haematological neoplasia, which in turn showed a positive association with lower Hb [40 (17.2%) *vs*. 26 (8.2%), p=0.001] and gastrointestinal tumours (10.7%), which did not show a different distribution with regard to Hb [27 (11.6%) *vs*. 32 (10.0), p=0.55]. Lymphoma and malignant melanoma were found more often in patients with higher Hb values, whereas gynaecological tumours and HPB tumours were more frequent in patients with lower Hb (Table III).

Cancer treatment. Taxane-based chemotherapy and trastuzumab, which are used in the treatment of breast cancer, were prescribed more often in patients with higher Hb. Patients with higher Hb underwent more often surgical treatment, while gemcitabine or tyrosine kinase inhibitors were used more often in patients with lower Hb in a palliative setting.

Fifteen percent had a history of transfusion due to CRA, with significant more transfusions in patients with lower Hb [56 (24.1%) *vs*. 24 (7.5%), p<0.0001]. In comparison, the use of erythropoietin stimulating agents (ESA) was very low (2.2%), without differences between groups.

Laboratory parameters. Lower Hb values were associated with higher creatinine levels and lower GFR. There were no differences regarding HbA1c or TSH. Vit. D levels were significantly lower in patients with anaemia (20.5±12.7 *vs*. 27.4±17.6, p<0.05).

Concomitant diseases and medication. CV risk factors (hypertension, diabetes and nicotine consumption) were similar in the two groups. There were no differences regarding CAD or HF. Patients with lower Hb were more likely to have CKD. Concomitant medications were comparable, except of anticoagulants that were used more often in patients with lower Hb [88 (37.9%) *vs*. 84 (26.3%), p=0.01].

Echocardiographic parameters. Lower Hb values were observed in patients with a reduced LVEF (51.9±11.0% *vs*. 55.1±9.7%, p=0.003). There were discrete changes in both septal and lateral MAPSE, without reaching statistical significance. LV and LA dimensions and volumes were comparable. TAPSE, as a measure of the longitudinal RV function, was significantly reduced in patients with lower Hb values, but still within the normal range (21.1±4.0 mm *vs*. 22.5±3.7 mm, p=0.001).

Correlation analysis revealed a significant correlation of LVEF in dependence of Hb (R^2=0.07, p<0.0001) (Figure 2). Echocardiographic parameters are outlined in Table IV.

A subgroup analysis was performed for echocardiographic parameters (with Hb <9 g/dl and Hb >9 g/dl serving as cut-off). Both lateral (12.8±2.4 *vs*. 13.8±2.5, p=0.03) and septal (10.7±2.4 *vs*. 11.7±2.4, p=0.02) MAPSE were significantly decreased in patients with Hb below 9 g/dl, while in the main analysis (where Hb <11.4 g/dl and Hb >11.4 g/dl served as cut-off) only minor changes were apparent (Table V).

Follow-up. During the follow-up [median=41 (95%CI=40-43) months] 140 (25.4%) patients were deceased. Significantly more deaths occurred in patients with lower Hb [108 (46.6%) *vs*. 32 (10.0%), p<0.0001]. Table III provides an overview of these 140 patients, with mortality rates in different tumour entities and average Hb values. Mortality rates were highest in patients with HPB tumours, followed by gynaecological tumours (50.0%, excluding breast carcinoma) and sarcomas (44.4%). Average Hb values were lowest in patients with haematological diseases (8.3±2.0), followed by tumours of the urinary tract (8.8±1.5) and gastrointestinal tumours (8.8±2.7). One patient with teratoma and another with an undefined conglomerate tumour also died during follow-up. Hb values were also significantly reduced in these two cases (8.4±0.8). Hb levels of patients who died, grouped according to the main tumour are displayed in Figure 3.

Multivariable analysis. Variables provided to have a R^2 >0.02 in univariate analysis were included in multivariable analysis. The following variables showed a strong correlation with Hb in univariate analysis: advanced tumour stage, palliative treatment, age at first diagnosis, breast cancer, haematological diseases, HPB tumours, vitamin D, surgical treatment and cancer treatment with gemcitabine or tyrosine kinase inhibitors. Lower Hb values were identified as independent predictor of mortality (with OR=5.3, CI=0.41-0.89, p<0.0001), while the other parameters showed no statistical significance.

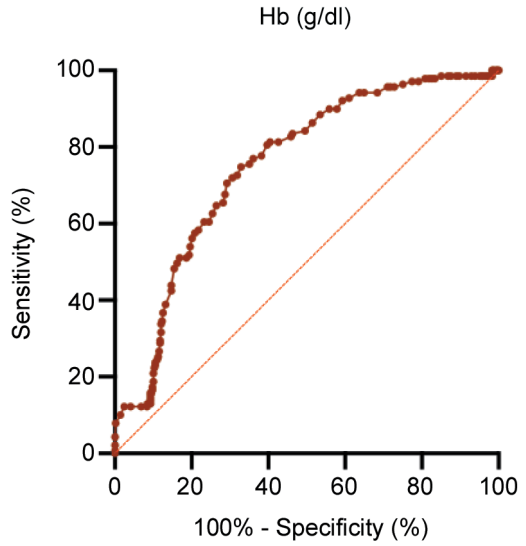
Discussion

In the present study, we investigated the role of Hb in a cohort of patients with cancer receiving anti-cancer treatment under cardiological surveillance. There was a strong association of

Table II. *Subgroup analysis with comparative analysis for Hb <9 g/dl and Hb >9 g/dl, similar to Table I.*

	Hb <9 g/dl (n=86, 15.6%)	Hb >9 g/dl (n=465, 84.4%)	*p*-Value (univariate)
Gender, m (%)	35 (40.7)	238 (51.2)	0.07
Age at first diagnosis	65.0±14.1	60.9±15.2	**0.02**
Advanced tumor disease (metastasized)	37 (43.0)	138 (29.7)	**0.0007**
Relapse	10 (11.6)	34 (7.3)	0.30
Secondary tumor	14 (16.3)	77 (16.6)	0.95
Palliative treatment	67 (77.9)	196 (42.2)	**<0.0001**
Karnofsky-Index	73.5±19.3	78.0±18.8	**0.04**
Tumour entities, n (%)			
Breast cancer	7 (8.1)	129 (27.7)	**0.0001**
Haematological	19 (22.1)	47 (10.1)	**0.002**
Gastrointestinal	14 (16.3)	45 (9.7)	0.07
Lung	12 (14.0)	39 (8.4)	0.10
Kidney/ Urothelium	7 (8.1)	31 (6.7)	0.62
Dermatological	0 (0)	32 (6.9)	**0.01**
Prostate	4 (4.7)	27 (5.8)	0.67
Lymphoma	3 (3.5)	27 (5.8)	0.39
Melanoma	1 (1.2)	20 (4.3)	0.16
Sarcoma	3 (3.5)	15 (3.2)	0.90
Gynaecological	3 (3.5)	15 (3.2)	0.90
ORL	1 (1.2)	16 (3.4)	0.26
HPB	7 (8.1)	8 (1.7)	**0.001**
Cerebral	2 (2.3)	7 (1.5)	0.58
CUP	1 (1.2)	2 (0.4)	0.40
Others	2 (2.3)	5 (1.1)	0.34
Cancer treatment			
Platin	14 (16.3)	91 (19.6)	0.48
Taxane	15 (17.4)	142 (30.5)	**0.01**
Anthrazykline	17 (19.8)	130 (28.0)	0.12
Gemcitabine	6 (7.0)	18 (3.9)	0.20
5-FU	10 (11.6)	36 (7.7)	0.23
Trastuzumab (Her2neu)	6 (7.0)	54 (11.6)	0.21
Tyrosine kinase inhibitors	8 (9.3)	13 (2.8)	**0.003**
Surgical treatment	34 (39.5)	270 (58.1)	**0.001**
Radiotherapy	30 (34.9)	183 (39.4)	0.44
Stem cell transplantation	9 (10.5)	17 (3.7)	**0.01**
History of transfusion	19 (22.1)	61 (13.1)	**0.03**
Treatment with ESA	1 (1.2)	11 (2.4)	0.48
Laboratory parameters			
Creatinine (mg/dl)	1.23±0.87	1.12±0.83	0.25
GFR (ml/min)	61.9±33.9	67.0±28.4	0.19
HbA1c (%)	6.3±1.7	6.1±1.3	0.40
Hb (g/dl)	7.9±1.0	12.3±1.8	**<0.0001**
TSH (U/l)	1.8±1.8	2.2±6.8	0.57
Vit. D (U/l)	15.9±10.7	26.1±16.7	0.09
Concomitant diseases, n (%)			
Hypertension	143 (61.6)	181 (56.7)	0.25
Diabetes	43 (18.5)	53 (16.6)	0.56
Nicotine consumption	65 28.0)	90 (28.2)	0.96
CAD	49 (21.1)	51 (16.0)	0.12
Heart failure	38 (16.4)	44 (13.8)	0.40
CKD (GFR <60 ml/min)	105 (45.3)	100 (31.3)	**0.001**
Concomitant medication			
Betablocker	38 (44.2)	168 (36.1)	0.23
ACE inhibitor/ ARB	37 (43.0)	189 (40.6)	0.86
Anticoagulant	39 (45.3)	133 (28.6)	**0.004**
Platelet inhibiton	21 (24.4)	97 (20.9)	0.56
Vit. D	15 (17.4)	94 (20.2)	0.47
Diabetes medication	11 (12.8)	66 (14.2)	0.70

Data are presented as mean±SD or numbers (frequency). Spearman's correlation coefficient R^2. 5-FU: 5-fluorouracil; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CKD: chronic kidney disease; CUP: cancer of unknown primary; ESA: erythropoiesis stimulating agent; GFR: glomerular filtration rate; Hb: hemoglobin; HPB: hepatopancreaticobiliary; m: male; n: number; ORL: otorhinolaryngological; TSH: thyroid stimulating hormone; Vit.: Vitamin. Bold values indicate statistical significance.



AUC: 0.75
95% CI: 0.71-0.80
***p*-Value:** <0.0001

Cut-off: <11.4 mg/dl
Sensitivity: 79%
Specificity: 61%

Figure 1. *ROC analysis and determination of a cut-off value for Hb. AUC: Area under the curve; CI: confidence interval.*

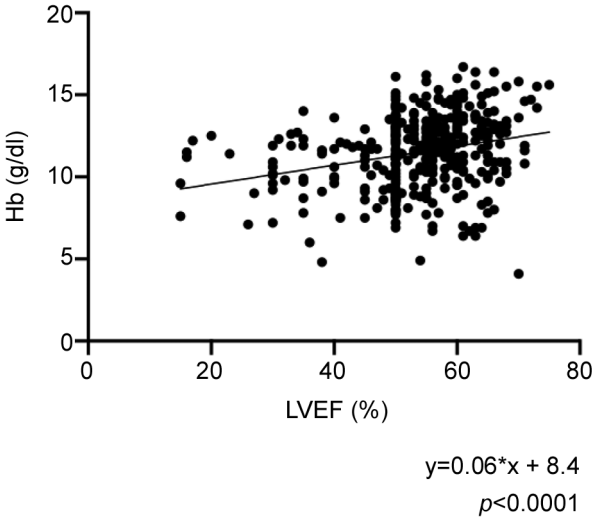


Figure 2. *Correlation analysis of LVEF in dependence of Hb. Hb: Hemoglobin; LVEF: left ventricular ejection fraction.*

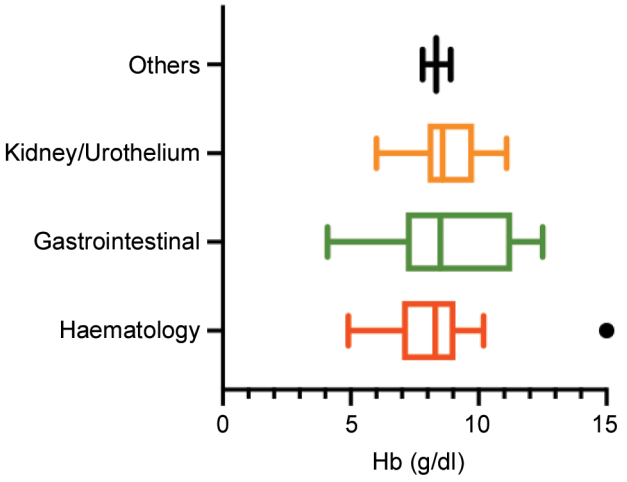


Figure 3. *Box-Whisker-Plots for Hb levels of patients who died, grouped according to the main tumour entities. Hb: Hemoglobin.*

Table III. *Deaths during follow-up and median Hb values in different tumour entities.*

Death during follow-up (n=140)	n (absolute mortality rate)	Hb (g/dl), median [IQR]
Breast cancer	26 (19.1)	10.6 [9.8, 11.4]
Haematology	24 (36.4)	8.3 [7.1, 9.0]
Gastrointestinal	13 (22.0)	8.5 [7.2, 11.2]
Lung	16 (31.4)	9.0 [8.7, 11.6]
Kidney/ Urothelium	8 (21.1)	8.6 [8.4, 9.7]
Dermatological	2 (6.3)	11.3 [10.7, 11.8]
Prostate	8 (25.8)	10.9 [9.2, 11.7]
Lymphoma	5 (16.7)	9.4 [8.9, 9.5]
Melanoma	6 (28.6)	11.9 [11.4, 12.1]
Sarcoma	9 (50.0)	9.2 [9.0, 10.4]
Gynaecological	8 (44.4)	10.3 [9.5, 10.6]
ORL	3 (17.6)	11.2 [9.5, 12.3]
HPB	8 (53.3)	10.2 [8.8, 11.1]
Cerebral	2 (22.2)	8.9 [8.1, 9.7]
Others	2 (20.0)	8.4 [8.1, 8.6]

Data are presented as median [interquartile range] or numbers (frequency). Hb: Hemoglobin; HPB: hepatopancreaticobiliary; n: number; ORL: otorhinolaryngological.

lower Hb values and increased mortality during follow-up. Patients with lower Hb values were diagnosed more often at an advanced tumour disease stage and received more often palliative treatment. In addition, there was a significant correlation of Hb with cardiac function (LVEF).

Anaemia is a common finding in patients with cancer and depends both on the type of cancer and the choice of treatment (14). Anaemia can be caused by hemolysis, blood loss or impaired red blood cell production (15). In our cohort, lower Hb values were found in patients with haematological diseases

Table IV. *Echocardiographic parameters of included patients, with a comparative analysis according to a threshold of Hb <11.4 g/dl and Hb >11.4 g/dl.*

	All patients (n=551)	Hb <11.4 g/dl (n=232, 42.1%)	Hb >11.4 g/dl (n=319, 57.9%)	*p*-Value (univariate)	R^2
LVEF (%)	53.7±10.4	51.9±11.0	55.1±9.7	**0.003**	0.02
LVEDV (ml)	78.0±26.6	77.7±24.9	78.1±27.7	0.90	-
LVESV (ml)	35.2±17.5	36.3±16.3	34.5±18.2	0.43	-
LVEDD (mm)	46.1±7.1	46.1±7.1	46.0±7.2	0.86	-
MAPSE (sep.)	11.6±2.4	11.2±2.5	11.8±2.3	0.58	-
MAPSE (lat.)	13.7±2.5	13.4±2.4	13.9±2.6	0.12	-
TAPSE (mm)	21.9±4.0	21.1±4.2	22.5±3.7	**0.001**	0.03
LA (M-Mode) (mm)	37.2±8.2	37.1±8.4	37.3±8.0	0.84	-
LAVI (ml/m^2)	26.6±13.0	26.1±10.2	26.9±14.1	0.75	-

Data are presented as mean±SD. EDD: End-diastolic diameter; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LA: left atrium; lat.: lateral; LAVI: left atrial volume index; LV: left ventricular; MAPSE: mitral annular plane systolic excursion; sep.: septal; TAPSE: tricuspid annular plane systolic excursion.

and tumours of the gastrointestinal or urogenital system, where bleeding and insufficient erythropoiesis are common. Until the 1990s, CRA was treated by RBC transfusions, which carry a potential risk of infection and transfusion incidents. The use of ESA initially offered a promising therapeutic approach, which was also adopted into the guidelines from 2006 from the European Organisation for Research and Treatment of Cancer (EORTC) (16). Accordingly, treatment with ESA is recommended in patients with Hb levels of 9-11 g/dl, while RBC transfusions should only be considered in patients with severe anaemia (16, 17). A large meta-analysis indicates that ESA therapy in cancer patients is associated with an increased risk of thromboembolic events and mortality (18). Thereafter, the use has decreased and is ultimately limited to a few indications, such as myelodysplastic syndrome (19). This was also observed in the present cohort, where only 2.2% received ESA. In contrast, almost 15% of patients had a history of transfusions, which were significantly more frequently used in patients with lower Hb. Patients with heart failure (HF) also showed a higher prevalence of anaemia, which was associated with a poor outcome (20). Since cancer and HF often coincide, the question arises whether this is a simple association or if there is actually a causal link (21, 22). On the one hand, an increased rate of CV diseases can be observed in long-term cancer survivors, presumably due to the toxicity of tumour-reducing therapies and consequent susceptibility (23, 24). However, the opposite scenario was also observed, namely that patients with CV diseases develop more malignancies (25, 26). Due to inflammatory processes and oxidative stress, both diseases activate a reciprocal cascade that might lead to a deterioration of both entities (21). This can even be seen in patients with a transient deterioration of the cardiac function, as in Takotsubo cardiomyopathy, for which a frequent occurrence of cancer has also been described (27). In our cohort, both lower LVEF (still within the normal range), and slightly decreased TAPSE were observed in patients with lower Hb. For patients with even lower Hb values (Hb <9 g/dl), MAPSE was also significantly reduced. Furthermore, a significant positive correlation of LVEF and Hb was identified, which might indicate on the one hand that HF also contributes to anaemia, or on the other hand that low Hb is a surrogate for the extent of cancerous damage. There are several mechanisms that are responsible for this finding. A distinction must be made between direct triggers of anaemia in HF and secondary causes. Secondary causes include relative anaemia due to volume

Table V. *Subgroup analysis of echocardiographic parameters of included patients, with a comparative analysis according to a threshold of Hb <9.0 g/dl and Hb >9.0 g/dl.*

	Hb <9 g/dl (n=86, 15.6%)	Hb >9 g/dl (n=465, 84.4%)	*p*-Value (univariate)
LVEF (%)	50.9±10.4	54.2±10.3	**0.02**
LVEDV (ml)	71.9±28.0	78.7±26.4	0.19
LVESV (ml)	36.9±20.8	35.0±17.1	0.59
LVEDD (mm)	44.8±7.8	46.3±7.0	0.15
MAPSE (sep.)	10.7±2.4	11.7±2.4	**0.02**
MAPSE (lat.)	12.8±2.4	13.8±2.5	**0.03**
TAPSE (mm)	21.2±4.5	22.0±3.9	0.18
LA (M-Mode) (mm)	37.6±8.5	37.1±8.1	0.74
LAVI (ml/m^2)	25.6±11.4	26.7±13.2	0.75

Data are presented as mean±SD. EDD: End-diastolic diameter; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LA: left atrium; lat.: lateral; LAVI: left atrial volume index; LV: left ventricular; MAPSE: mitral annular plane systolic excursion; sep.: septal; TAPSE: tricuspid annular plane systolic excursion. Bold values indicate statistical significance.

overload and consequent hemodilution, as well as common concomitant circumstances such as malnutrition due to cardiac cachexia or CKD, which were found in 45% of patients with lower Hb. On the other hand, patients with HF may often suffer from iron deficiency (28, 29). This may result from low iron intake, malabsorption and may be aggravated by gastrointestinal blood loss, *e.g.* due to prophylactic treatment with anticoagulants or platelet aggregation inhibitors (30). This is also consistent with our observations, where patients with lower Hb received more frequently anticoagulants, which are used especially in the prevention or recurrence prophylaxis of thromboembolic events. ACE inhibitors, which were used frequently in our CV risk cohort, can disturb the haemotopoiesis and may also lead to a lower Hb (31). Furthermore, HF is associated with chronic inflammation, characterized by increased levels of cytokines, which also lead to bone marrow suppression (32). Each of these causes contribute to a low Hb level in patients with HF.

Lower Hb was also identified as an independent predictor of mortality in patients with HF (33). Current studies aim to investigate whether additional use of iron will improve the outcome of patients with HF and iron deficiency (34). The 2016 ESC guidelines on heart failure recommend to treat patients with symptomatic HF with ferrocarboxymaltose to compensate the iron deficiency (35). Both, in patients with HF as well as in patients with cancer, anaemia is considered as anaemia of chronic disease. This is caused by a functional iron deficiency, which means that although the iron stores are not completely depleted, the disposable iron cannot be utilized (36). There is now growing evidence that intravenous iron administration may be beneficial in terms of quality of life for patients with cancer and absolute or functional iron deficiency (37). Due to impaired gastrointestinal absorption in patients with cancer, and chronic inflammation, malignant diseases are unsuitable for oral iron supplementation (38). However, up to now there are no clear recommendations on iron supplementation in patients with cancer.

RBC transfusions are associated with a variety of side-effects, including an increased risk of morbidity and mortality and should therefore be used diligently (39). This applies to both patients with CV diseases and patients with cancer. However, while there is a tendency to become more restrictive, the cut-off for the indication for a RBC transfusion is a little higher in patients with cancer and anaemia, depending on clinical symptoms, with a cut-off value for Hb <9 g/dl (40). Herein, patients with HF form a special group. A large national analysis of discharge data from California indicates that transfusions lead to an increase of mortality in patients with HF and CKD (41). However, higher transfusion thresholds do not consistently improve mortality rates (42). This reflects the difficulty and emphasizes the importance of balancing benefits and risks carefully, which must be assessed individually for each patient.

Strengths and weaknesses of the study. In the course of this study a broad cardio-oncological collective was examined in order to approximately reflect real life circumstances. For this reason, we have tried to choose a representative cohort size and a sufficiently long follow-up period. Given the mixed collective with relevant concomitant diseases, the aetiology of lower Hb values in the present cohort cannot be determined with certainty. Dosages of the individual drugs (chemotherapeutics, antibodies) were not completely recorded. Due to the observational and exploratory nature of the investigation, we can only speculate on the underlying mechanisms, in particular on the interrelation between Hb and cardiac function. The possible clinical implications will need to be further assessed in clinical studies.

Conclusion

Anaemia in patients with cancer could be identified as an independent prognostic factor. Furthermore, lower Hb levels were significantly correlated with lower LVEF. This suggests that lower Hb levels are not only a surrogate of anaemia, but rather of the severity of cancer, which then leads to reduced cardiac function. Hb levels can be used as a prognostic marker in the setting of cardiooncology for prognosis and as a predictor for an increased mortality in cancer patients.

Conflicts of Interest

All Authors of this manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Authors' Contributions

All Authors have made substantial contributions to the origin of the manuscript. M.B, A.H. and R.H. conceived the study. R.H., J.H. and S.G. provided data on tumour stages and cancer treatment and performed follow-up visits. S.R. and T.S. performed the echocardiographic examinations. A.H. and J.H. collected the data and performed statistical analysis. A.H. and S.G. wrote the manuscript. I.A. and M.B. provided essential scientific input. All Authors discussed the results and contributed to the final version of the manuscript.

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