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RESEARCH ARTICLE

Increased resting heart rate and prognosis in treatment-naïve unselected cancer patients: results from a prospective observational study

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Aims Cancer patients suffer from impaired cardiovascular function. Elevated resting heart rate (RHR) has been identified as a marker for increased long-term mortality in cancer patients prior to the receipt of anticancer treatment. We aimed to establish whether RHR is associated with survival in treatment-naïve cancer patients.

Methods and results This prospective study enrolled 548 unselected treatment-naïve cancer patients between 2011 and 2013. The median age of the cohort was 62 years; 40.9% were male and 32.7% had metastatic disease. Median RHR was 72 b.p.m. Most patients were in sinus rhythm ($n = 507$, 92.5%). Clinical heart failure was noted in 37 (6.8%) patients. RHR was not related to cancer stage ($P = 0.504$). Patients in the highest RHR tertile had higher levels of high-sensitivity troponin ($P = 0.003$) and N-terminal pro-B-type natriuretic peptide ($P = 0.039$). During a median follow-up of 25 months (interquartile range: 16–32 months; range: 0–40 months), 185 (33.8%) patients died from any cause [1-year-mortality: 17%, 95% confidence interval (CI) 13–20%]. In univariate survival analysis, RHR predicted all-cause mortality [crude hazard ratio (HR) for a 5 b.p.m. increase in RHR: 1.09, 95% CI 1.04–1.15; $P < 0.001$], and remained significantly associated with outcome after adjustment for age, gender, tumour entity, tumour stage, cardiac status and haemoglobin (adjusted HR for a 5 b.p.m. increase in RHR: 1.10, 95% CI 1.04–1.16; $P < 0.001$). There was no significant impact of metastatic/non-metastatic disease state on the predictive value of RHR ($P = 0.433$ for interaction). In subgroup analyses, the strongest associations for RHR with mortality were observed in lung (crude HR 1.14; $P = 0.007$) and gastrointestinal (crude HR 1.31; $P < 0.001$) cancer.

Conclusions Treatment-naïve cancer patients with higher RHRs display higher levels of cardiovascular biomarkers. RHR was independently associated with all-cause mortality, especially in lung and gastrointestinal cancers. Elevated RHR and cardiovascular biomarkers may represent early signs of incipient cardiac dysfunction.

Keywords Treatment-naïve cancer patients • Survival • Resting heart rate • Electrocardiogram

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Introduction

Each year, 14 million new cancer diagnoses are made worldwide and 8 million cancer-associated deaths occur.[1] In total, 33 million people currently suffer from cancer worldwide (5-year prevalence).[1] In the industrialized nations the most common causes of death are cancer and cardiovascular (CV) disease.[2] These diseases are associated on many different levels[3] and patients frequently exhibit similar symptoms, such as dyspnoea, oedema, fatigue, weight loss and muscle wasting.[4–6] They also share similar risk factors, such as tobacco smoking, diabetes, obesity and hypertension.[7] Research in cardio-oncology mainly focuses on cancer patients in receipt of anticancer therapies, which can cause cardiotoxicity.[8] Although the cardiotoxic effects of anticancer therapies have been studied frequently,[9,10] few studies have looked at the effects of cancer itself on the heart by investigating treatment-naïve cancer patients. Karlstaedt *et al.*[11] demonstrated that oncometabolites (D-2-hydroxyglutarate) can cause cardiac dysfunction in rodent models. In preclinical models[12] and humans[13] advanced cancer has been shown to be associated with cardiac wasting. We have reported that cardiac hormones are elevated in cancer patients prior to anticancer therapy and that they are strongly related to outcome.[13] In a previous study, we found that CV function markers, such as left ventricular ejection fraction (LVEF), heart rate variability and exercise capacity, are impaired in colorectal cancer patients, independent of the administration of chemotherapy.[14] Following this study, we investigated the prognostic impact of resting electrocardiographic (ECG) data in a real-world cohort of unselected cancer patients who had previously received chemotherapy (73%).[15] We found that resting heart rate (RHR) was increased in cancer patients in comparison with healthy control subjects and that it represented a strong and independent predictor of long-term mortality. Whether the alteration in RHR was attributable to the anticancer therapy or a phenomenon of cancer itself could not be deduced from these data. We therefore hypothesized that RHR is influenced by cancer itself and that an elevation of RHR will be associated with poor prognosis in a cohort of treatment-naïve cancer patients.

Methods

Study population

Consecutive patients with a primary diagnosis of cancer were enrolled between April 2011 and June 2013 at the Vienna General Hospital, a university-affiliated tertiary care centre. Eligible patients were those presenting with a suspected or confirmed diagnosis of cancer. Exclusion criteria included a history of prior anticancer therapy, clinical signs of infection or an unconfirmed diagnosis of cancer subsequent to the initial work-up. Patients were classified according to tumour entity and tumour stage. Comorbidities such as arterial hypertension, diabetes mellitus, smoking status and medical therapy were recorded. RHR was determined using 12-lead ECG after 5 min of supine rest. All ECGs were recorded on a GE MAC 2000 (Soma Technology, Inc., GE Healthcare, Bloomfield, CT, USA) and automatically analysed by the equipment's software (Marquette 12SL). Each reading was validated by a cardiologist. Cardiac abnormalities were assessed in order to adjust for underlying heart disease. Cardiac status was considered to be normal when there was no history of cardiac disease, no ECG abnormalities and plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were found to be <400 pg/mL.

If cardiac status was not considered to be normal, echocardiography was performed to confirm the presence of cardiac disease. Significant echocardiographic findings were defined as: a mild, moderate or severe reduction in left or right ventricular function; moderate or severe valvular disease, or diastolic dysfunction with pseudonormal or restrictive filling patterns. Abnormal cardiac status was finally defined as a history of cardiac disease or abnormal ECG findings, regardless of echocardiographic findings, or a significant echocardiographic finding in patients with NT-proBNP levels of ≥400 pg/mL.

Written informed consent was obtained from all study participants. The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee of the Medical University of Vienna.

Laboratory analysis

Venous blood samples were drawn at first hospital presentation. Laboratory parameters were analysed according to local laboratory standard procedures. Additionally, high-sensitivity troponin T (hsTnT) and NT-proBNP were determined in heparin plasma using the Elecsys System (Roche Diagnostics GmbH, Mannheim, Germany).

Study endpoint

All-cause mortality was chosen as the primary study endpoint. Data were obtained from the Central Office of Civil Registration Austria.

Statistical analysis

Continuous data are presented as the median and interquartile range (IQR) and categorical data as counts and percentages. For the baseline characteristics table, RHR was divided into tertiles and parameters were presented for the total cohort, as well as for RHR tertiles, respectively. For continuous variables, groups were compared using the Mann–Whitney U-test or Kruskal–Wallis test. Distributions of categorical variables were compared using the chi-squared test. Spearman's rho correlation coefficient was calculated for RHR and other variables. Cox proportional hazard analysis was used to evaluate the relationship between RHR and all-cause mortality in the total cohort and in subgroups of cancer patients. To account for potential confounding effects, multivariable Cox regression analyses were performed, including age, gender, tumour entity, tumour stage, cardiac status and haemoglobin. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Interaction term analysis was performed to determine the influence of metastatic/non-metastatic disease state on the association of RHR with overall survival. To assess the association of RHR levels with the primary endpoint graphically, the total population was divided into tertiles and overall survival illustrated using Kaplan–Meier graphs. Groups were compared using the log-rank test. For all tests, two-sided *P*-values of <0.05 were considered to indicate differences of statistical significance. The analyses were carried out using SPSS Version 22.0 (IBM Corp., Armonk, NY, USA).

Table 1 Baseline characteristics of treatment-naïve patients diagnosed with cancer ($n = 548$) stratified for resting heart rate by tertile

	All patients ($n = 548$)	RHR, tertile 1 ($n = 197$)	RHR, tertile 2 ($n = 188$)	RHR, tertile 3 ($n = 163$)	*P*-value
RHR, b.p.m., median (IQR)	72 (64–81)	62 (57–65)	73 (70–75)	89 (82–96)	—
Age, years, median (IQR)	62 (52–71)	62 (52–71)	62 (52–71)	64 (54–72)	0.366
Male sex, *n* (%)	224 (41%)	99 (50%)	65 (35%)	60 (37%)	**0.007**
BMI kg/m^2, median (IQR)	25.0 (22.6–28.6)	25.0 (22.7–28.1)	24.9 (22.6–28.2)	25.6 (22.5–29.8)	0.572
Systolic BP, mmHg, median (IQR)	138 (126–151)	138 (126–154)	136 (126–146)	140 (128–155)††	**0.034**
Comorbidities					
Known CAD, *n* (%)	28 (5%)	14 (7%)	6 (3%)	8 (5%)	0.307
Heart failure, *n* (%)	37 (7%)	15 (8%)	10 (5%)	12 (7%)	0.882
Diabetes mellitus, *n* (%)	42 (8%)	13 (7%)	11 (6%)	18 (11%)	0.131
Arterial hypertension, *n* (%)	248 (45%)	99 (50%)	75 (40%)	74 (45%)	0.308
CKD, *n* (%)	31 (6%)	11 (6%)	5 (3%)	15 (9%)	0.179
COPD, *n* (%)	113 (21%)	32 (16%)	37 (20%)	44 (27%)	**0.011**
Cancer disease stage[a]					
Stage I, *n* (%)	94 (17%)	39 (26%)	32 (22%)	23 (17%)	0.126
Stage II, *n* (%)	49 (9%)	16 (11%)	21 (15%)	12 (9%)	
Stage III, *n* (%)	107 (20%)	34 (22%)	35 (24%)	38 (29%)	
Stage IV, *n* (%)	179 (33%)	63 (41%)	56 (39%)	60 (45%)	
Cardiac biomarkers, median (IQR)					
hsTnT, ng/L	6 (3–11)	5 (3–10)	5 (3–10)	7 (3–13)**††	**0.003**
NT-proBNP pg/mL	129 (64–284)	123 (58–249)	116 (57–297)	153 (77–334)*†	**0.039**
Laboratory parameters, median (IQR)					
GFR, mL/min/1.73 m^2	74.2 (63.7–85.8)	73.0 (63.4–85.8)	74.6 (64.0–85.7)	73.7 (62.7–86.2)	0.752
BUN, mg/dL	15 (12–19)	16 (13–20)	15 (12–18)*	15 (12–20)	0.061
Haemoglobin, g/dL	13.3 (12.0–14.3)	13.4 (12.3–14.3)	13.2 (12.0–14.1)	13.3 (11.6–14.6)	0.468
BChE, kU/L	7.30 (6.10–8.40)	7.29 (6.28–8.51)	7.47 (6.39–8.53)	6.97 (5.67–8.13)*†	**0.029**
AST (SGOT), U/L	24 (19–32)	25 (20–33)	22 (18–28)**	24 (20–34)††	**0.010**
ALT (SGPT), U/L	22 (16–33)	24 (18–37)	21 (15–28)**	22 (16–35)	**0.027**
GGT, U/L	32 (21–63)	33 (24–61)	29 (18–53)*	38 (23–82)††	**0.007**
Bilirubin, mg/dL	0.58 (0.44–0.78)	0.60 (0.47–0.80)	0.58 (0.42–0.78)	0.57 (0.40–0.78)	0.191
Albumin, g/L	43.0 (40.0–45.5)	43.4 (40.8–45.8)	42.8 (40.3–45.4)	42.6 (38.7–44.6)*	**0.044**
CRP, mg/dL	0 (0–1)	0 (0–0)	0 (0–1)	1 (0–2)***†††	**<0.001**
SAA, µg/mL	8 (4–26)	6 (3–21)	7 (4–18)	14 (6–51)***†††	**<0.001**
IL-6, pg/mL	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.913

Continuous variables are given as medians (IQR). Counts are given as n (%). Continuous variables were compared using the Kruskal–Wallis test and Mann–Whitney U-test. Counts were compared using the chi-squared test; P-values for a linear association are indicated.

ALT, alanine transaminase; AST, aspartate transaminase; BChE, butyryl-cholinesterase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GFR, glomerular filtration rate; GGT, γ-glutamyltransferase; hsTnT, high-sensitivity troponin T; IL-6, interleukin-6; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RHR, resting heart rate; SAA, serum amyloid A.

Statistical significance: * or †, respectively, for comparisons of the tertile 3 vs. tertile 1 or tertile 2: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$.

[a]Tumour stage was assessed by the respective treating oncologist and was indicated for all patients excluding those with myeloproliferative neoplasias.

Results

Baseline characteristics

A total of 548 consecutive patients were included in the study. The detailed baseline characteristics of the study population are displayed in *Table 1*. A complete description of tumour entities is presented in supplementary material online *Table S1*. The median age of the cohort was 62 years (IQR 52–71 years) and 40.9% of the patients were male. Overall, 32.7% of patients presented with a stage IV tumour. Of the 548 patients, 410 (74.8%) had a generally unobtrusive cardiac status. Median RHR was 72 b.p.m. (IQR 64–81 b.p.m.) and 507 (92.5%) patients were in sinus rhythm. A total of 228 (41.6%) patients had an RHR of ≥75 b.p.m. and 76 (13.9%) had an RHR of ≥90 b.p.m.

Association of resting heart rate with baseline demographic parameters

Resting heart rate was not associated with baseline demographic parameters such as age ($r = 0.27$, $P = 0.54$), systolic blood pressure ($r = 0.02$, $P = 0.73$) or body mass index ($r = 0.04$, $P = 0.41$). RHR was higher in female than in male patients [74 b.p.m. (IQR

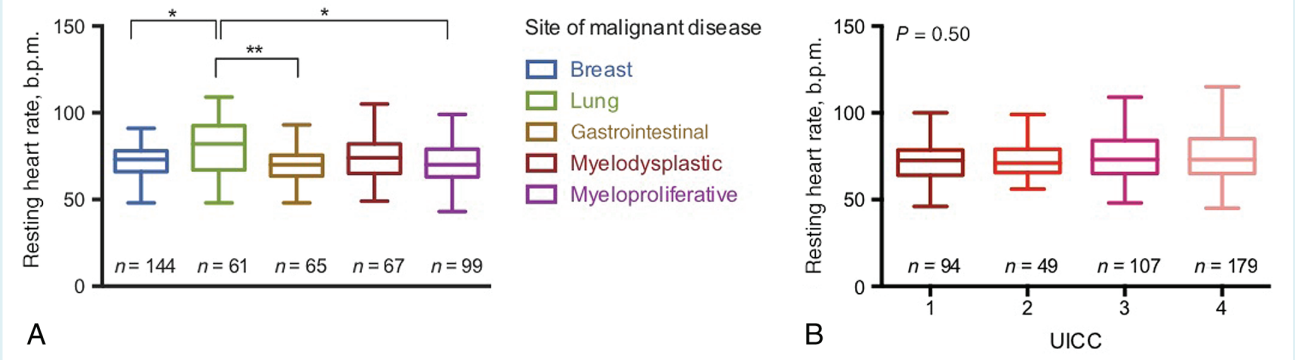

Figure 1 Tukey boxplots for resting heart rate in (*A*) the most common tumour entities (i.e. breast cancer, lung cancer, gastrointestinal cancer and myelodysplastic and myeloproliferative disease) and (*B*) by tumour stage. Medians were compared using the Mann–Whitney U-test; *P*-values were adjusted for multiple comparisons in (*A*). *$P < 0.05$, **$P < 0.01$. UICC, Union Internationale contre le Cancer.

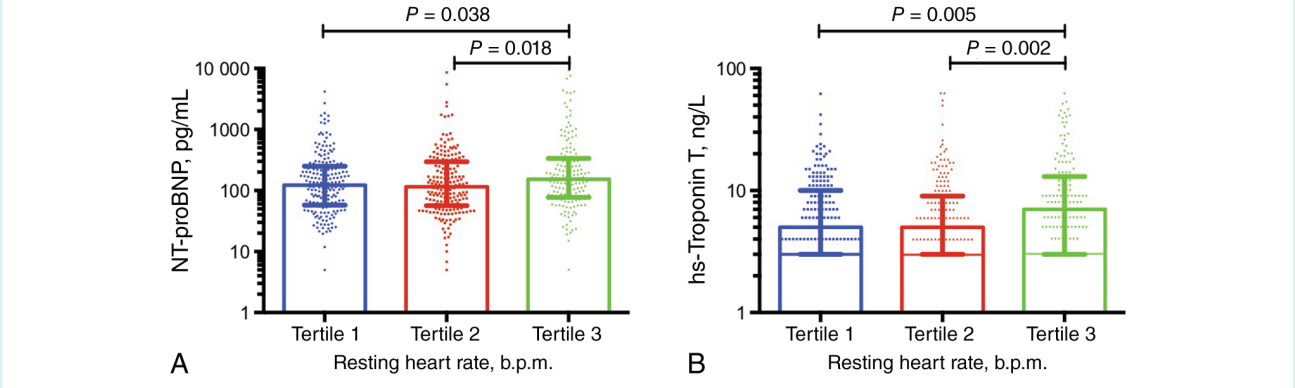

Figure 2 Association of resting heart rate (RHR) with cardiac biomarkers. Medians and interquartile ranges are shown for (*A*) N-terminal pro-B-type natriuretic peptide (NT-proBNP) and (*B*) high-sensitivity troponin T according to RHR tertiles. Parameters were compared using the Mann–Whitney U-test; statistical significance is indicated.

66–81 b.p.m.) vs. 69 b.p.m. (IQR 62–81 b.p.m.); $P < 0.001$], but, importantly, was comparable between patients with normal cardiac status and patients with any cardiac abnormality [(72 b.p.m. (IQR 64–82 b.p.m.) vs. 71 b.p.m. (IQR 65–82 b.p.m.); $P = 0.713$]. Further details on RHR according to distinct tumour entities and disease stage are shown in *Figure 1*. RHR differed significantly between tumour entities ($P = 0.008$ for the comparison between all groups), and was highest in patients with lung cancer [82 b.p.m. (IQR 67–92 b.p.m.)] and myelodysplastic disease [74 b.p.m. (IQR 65–82 b.p.m.)] among the most common malignancies. Notably, there was no significant difference in RHR among the Union Internationale contre le Cancer (UICC) cancer stages ($P = 0.504$ for the comparison between all groups) (*Figure 1B*). Similarly, there was no difference with regard to planned anticancer therapy including surgery, chemotherapy and radiation. There was also no difference in RHR between metastatic disease (i.e. stage IV) and non-metastatic disease (i.e. stages I–III) ($P = 0.484$). Patients in the highest RHR group had higher levels of hsTnT and NT-proBNP (*Figure 2*).

Associations of resting heart rate with routine laboratory parameters

No significant or statistically relevant correlation emerged between RHR and any of the laboratory parameters of sodium and potassium levels, the kidney function markers creatinine and urea, and the liver function parameters aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), butyrylcholinesterase (BChE), bilirubin, albumin and haemoglobin ($r = -0.15$, $P = 0.001$ for creatinine; $r = -0.09$, $P = 0.047$ for albumin; $r = -0.10$, $P = 0.020$ for sodium; P = non-significant for all others).

Survival analyses

A total of 185 (33.8%) patients died during a median follow-up of 25 months (IQR 16–32 months). *Table 2* shows the association of RHR as a continuous variable with outcome in the total cohort, as well as the most common tumour entity subgroups. RHR was a significant risk factor for all-cause mortality in univariate

Table 2 Association of resting heart rate with all-cause mortality in unselected treatment-naïve cancer patients according to tumour site ($n = 548$)

	Crude HR	*P*-value	Adjusted HR	*P*-value
Total cohort ($n = 548$)	1.09 (1.04–1.15)	**<0.001**	1.10 (1.04–1.16)[b]	**<0.001**
Breast cancer ($n = 144$)	1.09 (0.90–1.32)	0.398	1.07 (0.90–1.27)[a]	0.456
Lung cancer ($n = 61$)	1.14 (1.04–1.25)	**0.007**	1.13 (1.02–1.24)[a]	**0.015**
Gastrointestinal cancer ($n = 65$)	1.31 (1.15–1.50)	**<0.001**	1.31 (1.13–1.51)[a]	**<0.001**
Myelodysplastic neoplasia ($n = 67$)	1.17 (0.99–1.38)	0.072	1.21 (1.01–1.46)[a]	**0.037**
Myeloproliferative disease ($n = 99$)	0.97 (0.77–1.22)	0.789	0.98 (0.78–1.22)[a]	0.850

Univariate and multivariate Cox regression analyses were performed; hazard ratios (HRs) refer to an increase in heart rate of 5 b.p.m.
Bold type indicates statistical significance ($P < 0.05$).
[a]Adjusted for age, gender and haemoglobin.
[b]Adjusted for age, gender, haemoglobin, tumour entity and stage.

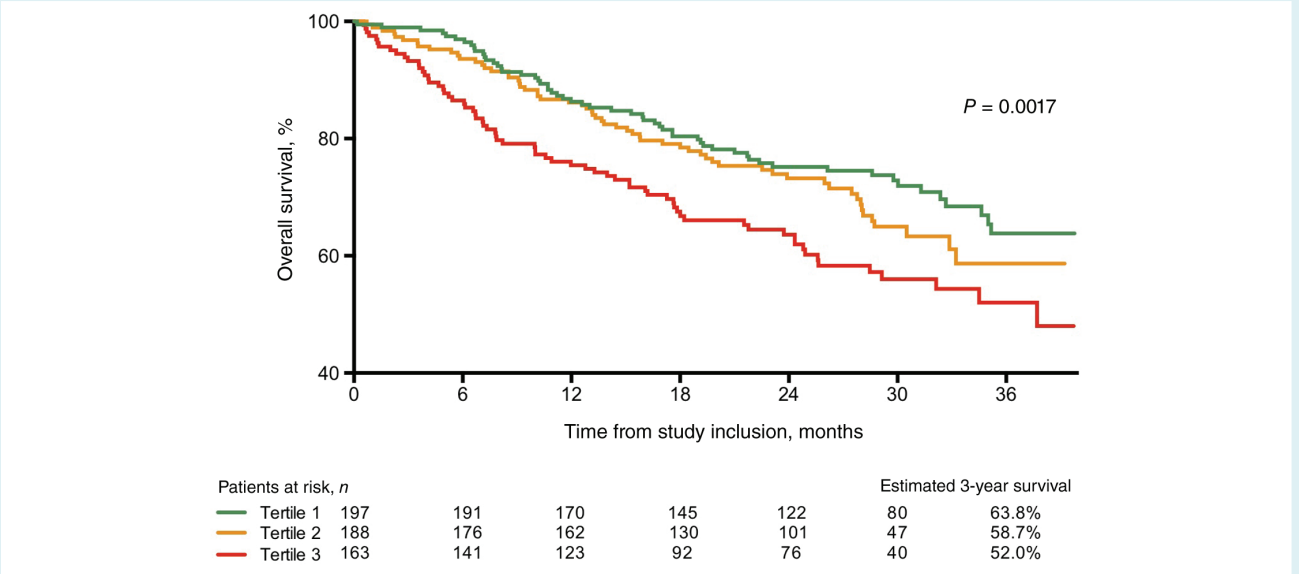

Figure 3 Association of resting heart rate with all-cause mortality. Overall survival rates in treatment-naïve cancer patients ($n = 548$) according to tertiles of resting heart rate shown in a Kaplan–Meier analysis. Groups were compared using the log-rank test ($P = 0.0017$ for trend).

analysis [crude HR for a 5-b.p.m. increase in RHR: 1.09 (95% CI 1.04–1.15); $P < 0.001$], after adjusting for age, gender, tumour entity and tumour stage [adjusted HR for a 5-b.p.m. increase in RHR: 1.09 (95% CI 1.04–1.15); $P < 0.001$], as well as after adjusting for age, gender, tumour entity, tumour stage, cardiac status and haemoglobin (adjusted HR for a 5-b.p.m. increase in RHR: 1.10 (95% CI 1.04–1.16); $P < 0.001$]. The corresponding analysis for patients with, respectively, RHRs of ≥75 b.p.m. and ≥90 b.p.m. as a dichotomous variable showed that RHR was a risk factor for all-cause mortality in the univariate analysis [crude HRs, respectively, 1.62 (95% CI 1.22–2.17; $P = 0.001$) and 2.00 (95% CI 1.40–2.86; $P < 0.001$] and remained significant after adjusting for age, gender, tumour entity and tumour stage, as well as cardiac status [adjusted HRs, respectively, 1.61 (95% CI 1.18–2.19; $P = 0.003$) and 1.66 (95% CI 1.15–2.41; $P = 0.007$)]. There was no significant interaction of metastatic/non-metastatic disease state with regard to the predictive value of RHR ($P = 0.433$ for interaction). Moreover, there was no significant interaction for the use of cardioprotective or heart rate-modulating therapies at baseline [$P > 0.280$ for concomitant beta-blocker therapy, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use and therapy with aldosterone antagonists or digitalis]. In the subgroup analysis including the most common malignancies, RHR was significantly associated with outcomes in lung cancer and gastrointestinal cancer and tended towards a significant association in myelodysplastic neoplasia, but not in breast cancer or myeloproliferative disease (*Table 2*).

Kaplan–Meier curves

Kaplan–Meier curves and log-rank analyses for the total cohort are shown in *Figure 3*. Estimates for survival at 12, 24 and 36 months

were, respectively, 86.3%, 75.2% and 63.8% in the first tertile, 86.2%, 73.2% and 58.7% in the second tertile and 75.5%, 63.6% and 52.0% in the third tertile, which confirms the discriminatory power of RHR for overall survival in treatment-naïve cancer patients ($P = 0.0017$ for trend across all groups, log-rank analysis).

Discussion

The present report represents the largest prospective observational study to be performed to date in treatment-naïve cancer patients, correlating resting ECG parameters with all-cause mortality. In this cohort, patients with the highest RHR had higher levels of hsTnT and NT-proBNP. RHR was independently associated with all-cause mortality. The associations were strongest in patients with lung cancer and gastrointestinal cancer, followed by myelodysplastic neoplasia. These results are very important because they emphasize that the autonomic regulation of the heart is affected in cancer patients in the absence of chemotherapy, immunotherapy, targeted or radiation therapy. We hypothesize that cancer patients with increased RHRs, who show increased CV biomarkers even before the commencement of anticancer therapy, are those in most need of attention from a CV perspective. Elevated RHR and CV biomarkers may be the first signs of incipient cardiac dysfunction. These data are in line with the results of other research that has shown tachycardia to be associated with the development of cardiomyopathies and heart failure (HF),[16] but further studies are needed to investigate the underlying mechanisms in cancer patients.

Many large-scale studies, such as the Malattie Cardiovascolari Aterosclerotiche, Istituto Superiore di Sanità (MATISS) Project[17] and the Framingham Study[18] have looked at RHR in the general population and found higher all-cause, CV and non-CV mortality rates in patients with higher RHR. By contrast, it is not entirely clear whether RHR can also predict the later occurrence of cancer in the general population. In 1981, three jointly published Chicago-based studies examined whether RHR could predict the occurrence of cancer. Whereas two of the studies, involving with 5784 and 1233 men, respectively, showed significantly higher probabilities for occurrences of lung and colon cancer, a third study, conducted in 1899 men, found no such associations.[19] Since then many studies have investigated this issue, but not all of them have found significant associations. Whereas the Paris Prospective Study I,[20] conducted in 6101 healthy men, showed a relative risk of 2.4 (95% CI 1.9–2.9) for highest vs. lowest quartile of RHR, other studies, such as the Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) Study,[21] carried out in 3527 men, showed only a weak trend towards higher cancer mortality with higher heart rate (adjusted relative risk 1.1, 95% CI 0.8–1.5). RHR has also been assessed as a possible marker for outcome in many other chronic diseases. It is known that elevated RHR in HF with reduced or preserved ejection fraction is associated with higher mortality and morbidity.[22,23] In addition to HF, an elevated RHR has been found in coronary artery disease, renal disease, pulmonary disease, stroke and multi-organ dysfunction syndrome, but whether lowering the heart rate in such patients will result in a better outcome has not so far been investigated.[24]

In 2016, we demonstrated that RHR was increased in cancer patients with colorectal, pancreatic and non-small cell lung cancers, without significant CV disease, in comparison with healthy controls. RHR in subjects without prior chemotherapy use was independently associated with all-cause mortality.[15] In this initial study, we prospectively included unselected cancer patients and followed them for up to 8 years. Of the cohort, 73% had previously received any chemotherapy and 28% had received cardiotoxic chemotherapy. In a large multivariate model, RHR of ≥75 b.p.m. was associated with increased mortality (HR 1.67, $P = 0.04$). Two studies have confirmed these initial observations in retrospective analyses. Lee *et al.*[25] followed 4786 breast cancer patients (stage I–III) for 5 years and found that those with RHR in the highest quintile (≥85 b.p.m.) had highest all-cause mortality (HR 1.57) compared with patients in the lowest quintile (RHR ≤67 b.p.m.). Park *et al.*[26] retrospectively analysed data for 300 cancer survivors who had initially been diagnosed with colorectal adenoma. The patients were followed for up to 8 years. Patients in the highest RHR quartile (≥81 b.p.m.) had a higher recurrence of advanced adenoma (HR 6.18) than those in the lowest RHR quartile (≤66 b.p.m.).

Many different factors can influence heart rate in cancer patients, such as chemotherapy,[27] chest radiation therapy,[28] depression[29] and tobacco smoking.[30] Furthermore, an elevated heart rate in cancer patients is supposedly a biomarker for neurohumoral activation along with stimulation of the sympathetic nervous system. Indeed, cancer patients show elevated levels of a set of cardiac neurohormones prior to anticancer therapy, which probably indicates a cancer-induced incipient cardiac dysfunction.[13] Likewise, arterial hypertension and elevated blood pressure are risk factors for the development of some cancer entities and represent markers for a worse prognosis.[31,32] Moreover, in a cancer mouse model, a higher sympathetic nervous system activation was associated with a 38-times greater metastasis growth rate, and this growth rate could be reduced with beta-blocker treatment.[33] The autonomic nervous system has already been identified as a therapeutic target in patients with HF,[34] but it may also represent a target for treatment in cancer patients.

It is important to acknowledge the difference between selected and unselected cancer patients for research in the field of cardio-oncology because the probability of finding CV abnormalities may depend substantially on the study inclusion criteria. Commonly used strategies to identify possible CV dysfunction prior to cardiotoxic therapy, as well as during treatment, include echocardiography (with strain analysis), cardiac magnetic resonance imaging, and nuclear cardiac imaging.[8,35] The choice of modality depends on local expertise and availability; however, echocardiography is recommended prior to the initiation of potentially cardiotoxic agents in all patients.[8] Global longitudinal strain is a very sensitive and accurate marker of early cardiac damage[36] and has superior prognostic value to LVEF.[37] During anticancer treatment, a reduction of LVEF by 10 percentage points below the lower limit of normality suggests cardiotoxicity, whereas a reduction in global longitudinal strain by >15% from baseline may suggest a risk

for cardiotoxicity.[8] Although nuclear cardiac imaging is no longer often used, mainly as a result of the radiation exposure it involves, another high-resolution imaging technique that is available is cardiac magnetic resonance imaging.[8] The proportions of patients with incipient or overt cardiac dysfunction strongly depend on the time of their inclusion in the study (i.e. prior to or post-anticancer treatment), other comorbidities and tumour entity.[8] Oncologists often refer those patients with an elevated risk for CV abnormalities to a cardiologist for a complete CV examination. Common reasons for such CV investigations include the prior receipt of cardiotoxic anticancer therapies, palpitations, syncope, dyspnoea and chest pain. Therefore, retrospective analyses of these data often include patients with a high risk for CV disease. By contrast, this study, because of its prospective and unselected sample of treatment-naïve cancer patients, included many patients with a low level of risk. Hence, our patient cohort had a wide range of pre-test probability for CV abnormalities, representing a general cancer population.

There are two classes of drug that significantly reduce heart rate: beta-blockers (e.g. metoprolol succinate,[38] carvedilol,[39] bisoprolol[40] and nebivolol[41]) and I_f-inhibitors (ivabradine[42]). These drugs have been shown to reduce hospitalization and mortality rates in HF patients.[43] Of note, the degree to which RHR is lowered predicts subsequent mortality, but not the absolute beta-blocker dose required.[44] The extent to which increased RHR is not an innocent bystander that mirrors an underlying risk, but an independent risk factor for outcome or cardiotoxicity requires to be investigated in prospective studies.

In the CECCY trial, Avila *et al.*[45] tested the use of carvedilol vs. placebo in a randomized, prospective trial in 200 breast cancer patients. The primary endpoint was cardiotoxicity (defined by the authors as a drop of LVEF by 10%) during 6 months of low-dose anthracycline therapy. There was no difference between the treatment groups with respect to the primary endpoint (14.5% in the carvedilol group vs. 13.5% in the placebo group; $P = 1.0$). However, this does not contradict our proposal of RHR as a potential treatment target. The CECCY trial[45] had major shortcomings: (i) RHR was neglected as an inclusion or exclusion criterion, whereas the current study suggests that RHR might serve as an appropriate treatment target if a change in prognosis is the aim of the therapy, and (ii) breast cancer patients may not be an ideal target population as RHR was not associated with outcome in this subgroup in the present study.

Limitations

Laboratory measurements were performed only at a single time-point at baseline prior to the initiation of anticancer therapy, but studies that make serial measurements throughout the progression of disease and treatment may provide additional insights. Future studies should also assess whether pain and anxiety can influence heart rate in cancer patients and might use longer ECG recording periods to assess 24-h average heart rate and heart rate variability rather than RHR. In addition to all-cause mortality, more detailed information on the cause of death in patients would be of substantial clinical interest, but this is notoriously difficult to obtain in cancer patients under regular care because patients often die at home or in hospices, and are only rarely submitted to autopsy.

Conclusions

In a cohort of 548 unselected, prospectively included, treatment-naïve cancer patients, those with higher RHRs had higher levels of CV biomarkers. In this cohort, RHR was independently associated with all-cause mortality, especially in lung and gastrointestinal cancers.

Supplementary Information

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

Table S1. Tumour entities in treatment-naïve cancer patients ($n = 548$).

Figure S1. Distribution of disease in treatment-naïve cancer patients ($n = 548$). (*A*) Distinct cancer type according to tumour stage. (*B*) Tumour stage according to cancer type.

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