

# Associations Between Sinus Tachycardia and Adverse Cardiovascular Outcomes and Mortality in Cancer Patients

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## Research

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# Abstract

## Background

Sinus tachycardia in cancer reflects significant multi-system organ stressor and disease, with sparse literature describing its clinical significance. We assessed cardiovascular (CV) and mortality prognostic implications of sinus tachycardia in cancer patients.

## Methods

We conducted a case-control study of 622 cancer patients at a U.S. urban medical center from 2008 to 2016. Cases had ECG-confirmed sinus tachycardia (heart rate [HR]  $\geq 100$  bpm) in  $\geq 3$  different clinic visits within 1 year of cancer diagnosis excluding history of pulmonary embolism, thyroid dysfunction, left ventricular ejection fraction  $< 50\%$ , atrial fibrillation/flutter, HR  $> 180$  bpm. Adverse CV outcomes (ACVO) were heart failure with preserved ejection fraction (HFpEF), HF with reduced EF (HFrEF), hospital admissions for HF exacerbation (AHFE), acute coronary syndrome (ACS). Regression analyses were conducted to examine the effect of sinus tachycardia on overall ACVO and survival.

## Results

There were 51 cases, age and sex-matched with 571 controls (mean age  $70 \pm 10$ , 60.5% women, 76.4% Caucasian). In multivariate analysis over a 10-year follow-up period, sinus tachycardia (HR  $\geq 100$  vs.  $< 100$  bpm) was an independent predictor of overall ACVO (OR 2.8, 95% CI: 1.4-5.5;  $p = 0.006$ ). There was increased incidence of HFrEF (OR 3.3, 95% CI: 1.6-6.5;  $P = 0.004$ ) and AHFE (OR 6.3, 95% CI: 1.6-28;  $P = 0.023$ ), but not HFpEF or ACS ( $p > 0.05$ ) compared with controls. Sinus tachycardia was a significant predictor of overall mortality after adjusting for significant covariates (HR 2.9, 95% CI 1.8-5;  $p < 0.001$ ).

## Conclusion

Independent of typical factors that affect cardiovascular disease, sinus tachycardia around the time of cancer treatment is associated with increased ACVO and mortality in cancer patients at 10 years of follow-up.

## Introduction

Numerous studies have examined elevated resting heart rate (RHR) as an independent risk factor for mortality [1, 2]. These studies have demonstrated that elevated RHR has significant associations with cardiovascular disease, diabetes mellitus, stroke, renal disease, and all-cause mortality [3, 4, 5, 6,]. More recently, there has been heightened interest in the possible contributions of cardiovascular disease to the elevated mortality observed in patients with various forms of advanced cancer. Prior studies have demonstrated increased stress on cardiac function in cancer patients due to higher cardiac output and maximal rate of pressure rise in isovolumic contraction compared to healthy subjects [7]. von Haelhing et al. [7] demonstrated that patients with cancer tended to have altered cardiac hemodynamics, including

elevated blood pressure, cardiac output, and stroke volume compared to controls and patients with chronic heart failure. Thus, researchers hypothesize that these alterations in cardiac hemodynamics lead to adverse cardiac events, such as blood pressure dysregulation, ischemia, arrhythmias, and heart failure. Recent studies have examined the prognostic value of elevated RHR in cancer patients [8], but none to our knowledge have investigated the prognostic value of ECG-confirmed sinus tachycardia defined as heart rate (HR)  $\geq 100$  beats per minute (bpm) in this patient population. Sinus tachycardia in cancer may reflect significant multi-system organ stressor and disease, with sparse literature describing its clinical significance.

The goal of this analysis is to determine associations between baseline sinus tachycardia and future risk of adverse cardiovascular outcomes (ACVO) and increased mortality in cancer patients.

## Methods

### Study Population and Patient Selection

This case-control study was conducted at Rush University Medical Center (RUMC), Chicago, USA. The study was reviewed and approved by the Institutional Review Board at RUMC. Patients presented to RUMC clinics with newly diagnosed malignancy between 2008 and 2016. Only patients with a histopathological confirmation of cancer diagnosis and a documented sinus tachycardia (HR  $\geq 100$ ) on  $\geq 3$  different clinic visits within 1 year of cancer diagnosis were included in the study. Exclusion criteria included: (i) age  $< 18$  years old; (ii) active treatment for venous thromboembolism (VTE); (iii) untreated thyroid disease; (iv) known heart failure with reduced ejection fraction ( $< 50\%$ ); (v) clinical signs of decompensated heart failure; (vi) documented history of atrial fibrillation or flutter; and (vii) patients with a heart rate (HR)  $> 180$  bpm. Individuals on active treatment for VTE (including pulmonary embolism) were excluded, as the presence of VTEs was viewed as a potential confounder for sinus tachycardia.

The diagnosis of sinus tachycardia was confirmed by reviewing serial 12-lead electrocardiogram (ECG) data obtained following initial diagnosis of cancer and during visits to RUMC oncology clinics. The study variables (Table 1) were extracted from the RUMC electronic health records and stored in the REDCap database software. Data were collected and reviewed by two independent research coordinators; then exported to SPSS software for statistical analysis.

The primary outcomes of interest for ACVO were new onset heart failure of any sort, including heart failure with reduced ejection fraction (HFrEF;  $EF \leq 40\%$ ), new onset heart failure with preserved ejection fraction (HFpEF;  $EF \geq 50\%$ ), admissions for heart failure exacerbation (AHFE) and acute coronary syndromes (ACS). We also assessed the implications of sinus tachycardia on overall survival up to 10 years from the date of initial cancer diagnosis.

### Statistical Analyses

All calculations were performed using SPSS/PC statistical program (version 21, SPSS Inc., Chicago IL, USA). Continuous variables were reported as means  $\pm$  SD while categorical variables were expressed as numbers or ratios. Cases and controls were matched by age and sex. Groups were compared using unpaired Student's t-test for continuous variables while  $\chi^2$  was used to evaluate dichotomous variables.

Univariate analyses for predictors of ACVO were conducted. In addition, odds ratios were calculated using a multivariate logistic regression model which included sinus tachycardia in addition to significant covariates and clinically relevant predictors of ACVO (age, race, beta blocker use, chronic kidney disease, type of malignancy, albumin, hemoglobin, anticoagulation, anthracyclines and radiation).

Univariate Cox-proportional hazards analyses were conducted to identify predictors of survival in cancer patients. Multivariate survival analysis was performed to further investigate the impact of sinus tachycardia on overall survival over a 10-year follow-up period. In our first model, we included all statistically significant predictors of mortality plus covariates that were significantly different between the sinus tachycardia group and patients with HR < 100: sinus tachycardia, race, hemoglobin, albumin, beta-blocker use, chronic kidney disease, type of malignancy, and use of anticoagulation (model 1). In order to eliminate any possible confounders, our second model (model 2) included sinus tachycardia, age and gender in addition to clinically relevant predictors of mortality (smoking, history of coronary artery disease (CAD), diabetes, aspirin, beta-blockers, history of stroke, radiation and anthracyclines).

P value < 0.05 was considered statistically significant in all analyses.

## Results

### Study Population

We included 51 patients with ECG-identified baseline sinus tachycardia (HR  $\geq$  100 bpm), and 571 age and sex-matched controls with HR < 100 bpm (total 622 patients; mean age  $70 \pm 10$  years, 60.5% women, 76.4% Caucasian). Baseline characteristics were stratified according to heart rate and the total cohort are summarized in Table 1. Of the 622 patients, 44% had primary lung cancer, 21% had lymphoma, 11.6% had multiple myeloma, 17.4% had leukemia, and 6% had either breast, thyroid, neuroendocrine, colorectal or pancreatic malignancies. A total of 69.4% of patients were classified as stage 4 cancer according to the American Joint Committee on Cancer (AJCC). Cardiovascular risk factors including age, gender, body mass index (BMI), diabetes, hypertension, CAD and smoking status were not significantly different between study group and controls. Sinus tachycardia patients were noted to have overall lower levels of serum albumin (3 g/dL vs. 3.5 g/dL,  $p=0.043$ ) and hemoglobin (10.5 g/dL vs. 11.7 g/dL,  $p= 0.001$ ), compared with controls. Additionally, underlying renal dysfunction (GFR < 60 mL/min/1.73m<sup>2</sup>) was more prevalent in the sinus tachycardia group (46% vs, 17.1%,  $p<0.001$ ).

### Predictors of Overall Adverse Cardiovascular Outcomes

In univariate analysis (Table 2), over a follow-up period of 10 years, sinus tachycardia was a predictor of overall ACVO (OR 3.8, 95% CI: 2.1-6.6; p=0.001). Race, albumin, hemoglobin, beta-blocker use, and chronic kidney disease were also identified as significant predictors of overall ACVO. In multivariate analysis, sinus tachycardia remained an independent predictor of ACVO (OR 3.1, 95% CI: 1.5 – 6.2; p = 0.002) even after adjusting for significant covariates (Table 2). In a separate multivariate logistic regression model, sinus tachycardia remained an independent predictor of ACVO after adjusting for clinically and statistically significant covariates (OR 2.8, 95% CI: 1.4 -5.5; p = 0.006) (Figure 1). As depicted in Figure 1, patients with sinus tachycardia had increased incidence of HFrEF (OR 3.3, 95% CI: 1.6- 6.5; P= 0.004) and acute heart failure exacerbation (AHFE) [OR 6.3, 95% CI: 1.6-28; P = 0.023]; but not HFpEF or ACS (p>0.05) as compared to controls.

### **Predictors of Overall Survival**

We used univariable Cox-proportional hazards analyses, which identified sinus tachycardia (HR 2.4, 95% CI 1.5-3.6; p <0.001) and serum hemoglobin  $\leq$  10 g/dL (HR 1.8, 95% CI 1.26 – 2.6) as significant predictors of mortality in cancer patients (data not shown). To further investigate the impact of sinus tachycardia on survival in cancer patients, we performed multivariable survival analyses with Kaplan Meier survival curves shown in Figures 2A and 2B. Sinus tachycardia remained an independent predictor of survival after adjusting for all covariates in model 1 which included serum hemoglobin (HR 2.9, 95% CI 1.8-5; p < 0.001) (Figure 2A). Additionally, sinus tachycardia remained an independent predictor of mortality in cancer patients even after adjusting for all covariates in model 2 (HR 2.5, 95% CI 1.5-4; p= 0.001) (Figure 2B).

## **Discussion**

We sought to address the clinical significance and prognostic value of sinus tachycardia in cancer patients. This study shows that sinus tachycardia around the time of cancer treatment, independent of typical risk factors that affect patients with cancer, was associated with the development of ACVO and higher risk of all-cause mortality at 10 years of follow-up. To our knowledge, this is the first study to determine the prognostic impact of sinus tachycardia on cardiovascular outcomes and mortality in cancer patients.

Many patients with cancer undergoing chemo- and/or chest radiation therapy are at increased risk cardiovascular disease [9, 12]. It has been well documented that certain types of chemotherapy such as anthracyclines, tyrosine kinase inhibitors, and monoclonal antibodies are associated with adverse effects on the cardiovascular system such as the development of heart failure or arrhythmias [9,10,11,12,13]. Additionally, radiation therapy is associated with increased incidence of myocardial fibrosis and valvular disease [14,15,16]. High cardiac output states are frequently noted in patients with underlying cancer [17]. The pathophysiology of high output states in this patient population is often related to underlying anemia, hyperthyroidism, shunting of blood through the tumors, or secretion of antidiuretic hormone [18]. In patients undergoing therapy with multiple chemotherapeutic agents and radiation, these negative

cardiovascular effects could be amplified [19,20]. As a result, identifying patients with higher risk for cardiotoxicity is a key strategy in reducing morbidity and mortality associated with cancer treatment.

The effects of elevated RHR at baseline on cardiovascular mortality and morbidity in cancer patients have been extensively studied and well documented in the literature [1,2,3,4,5,6]. Elevated RHR such as sinus tachycardia results in decreased diastolic filling, decreased myocardial perfusion, and increased left ventricular function. Over time, these effects may result in myocardial damage and congestive heart failure [21,22]. Similarly in the Framingham study, elevated RHR was directly associated with increased all-cause mortality in patients with baseline hypertension after 36 years of follow-up [23]. Additionally, the prognostic effects of RHR on patients with CAD and left ventricular systolic dysfunction were studied in the randomized BEAUTIFUL (Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction) trial. The authors reported that patients with RHR  $\geq$  70 bpm had more frequent cardiovascular events including increased number of admissions for heart failure, myocardial infarction and cardiovascular related mortality during 19-months of follow-up [24]. Given the substantial effects of HR on cardiovascular outcomes and survival, slowing the HR has been a target for management of patients with CAD and heart failure.

Similarly, our study demonstrated that baseline sinus tachycardia resulted in 3-fold increased incidence of HFrEF, 6-fold increase in AHFE, and almost 3-fold increase in mortality. This study, while uniquely focused on cancer patients, adds to the current evidence that elevated RHR is associated with increased mortality and morbidity. These findings raise the question of whether controlling a patient's HR with medication could improve mortality and decrease the risk of ACVO and mortality in this population. Beta-blockers and Ivabradine are two types of drugs that result in substantial decrease in HR and increased survival in patients with underlying cardiovascular disease [25,26]. However, no randomized control trials have been performed to evaluate potential benefits of these medications in treating cancer patients with sinus tachycardia. It is possible that the presence of sinus tachycardia in these patients is a compensatory mechanism (and therefore, a marker) reflecting their body's adjustment to a systemic and multi-organ inflammatory and hypermetabolic state in the setting of their underlying malignancy. This idea, however, raises another question as to whether medically controlling the HR could harm these patients by blunting their cardiovascular response to the underlying disease process. Additionally, there is no strong evidence to support treating isolated sinus tachycardia in the absence of underlying cardiovascular disease. Therapeutic considerations for these patients are largely focused on lifestyle modification including regular aerobic exercise, hydration, avoiding stimulants, and maintaining normal body weight.

Some limitations of our study include the retrospective nature of the study and the small number of patients in the study group. We compensated for the latter concern by using the 1:10 matched control group to increase the power of our study in order to detect differences between both groups. Furthermore, we could not determine if sinus tachycardia was present in these patients prior to their diagnoses of cancer because most of them were referred to our oncology clinic after cancer diagnosis. Additionally, we were not able to determine the exact cause of death in these patients. This is partly due to the fact that

the clinical picture in advanced cancer is rather complex and varies greatly between cancer types. We should note that the majority of the patients included in this study were elderly (70±10 years). Additional research is required to evaluate the risk of adverse cardiac outcomes and mortality on a younger patient population.

## Conclusion

Independent of typical factors that affect disease, baseline sinus tachycardia around the time of cancer treatment was associated with ACVO and increased mortality at 10 years of follow-up. Future studies are required to assess the presence of sinus tachycardia as a marker of systemic inflammation and overall disease prognosis, in the setting of cancer. Moreover, further research is needed to evaluate the impact of treating sinus tachycardia using agents such as beta-blockers or ivabradine on risk reduction of ACVO and improvement in overall mortality.

## Abbreviations

RHR = resting heart rate. Bpm = beats per minute. HR = heart rate. ACVO = adverse cardiovascular outcomes. HFrEF = heart failure with reduced ejection fraction. HFpEF = heart failure with preserved ejection fraction. ACS = acute coronary syndrome. AHFE = acute heart failure exacerbation. CAD = coronary artery disease. BMI = body mass index.

## Declarations

**Ethics approval and consent to participate:** This study was conducted at Rush University Medical Center (RUMC), Chicago, USA; and was reviewed and approved by the Institutional Review Board at RUMC.

**Consent for publication:** Under our institutional rules for retrospective chart review studies, a waiver of consent is applicable under certain conditions which include: the use of existing data and records that have been recorded prior to a certain date, information recorded by the researchers must not identify the subjects or any items that would enable identification of any of study subjects. Please note that our study is compliant with these requirements. The following statement is documented on our institution's IRB website: "Exempt review: The **human subjects' protection division** screens studies for exemptions from the requirement of **45 CFR 46**. Studies that are exempt involve a low risk to subjects and, in many cases, record data so that subjects cannot be identified directly or by an identifier linked to the subject" (<https://www.rushu.rush.edu/research/office-research-affairs/research-regulatory-operations/protection-human-subjects/institutional-review-boards>)

**Availability of data and materials:** Study data are available upon request

**Competing interests:** None

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## Authors Contributions

- Mohamad Hemu: primary author, participated in project design, data collection, conducted primary analysis and wrote major portions of the manuscript
- Caleb J Chiang, MD contributed significantly in conducting extensive chart review, collection of important covariates, and revision of the manuscript
- Parva K Bhatt and Aamir Ahmed: contributed to data collection and writing parts of the manuscript
- Talal Mourad, BA, Megan E Randall, MD, Andres P Palomo, MD, Jason B Kramer: these authors have contributed significantly in conducting extensive chart review and collecting the important covariates
- Louis Fogg: provided significant input on appropriate statistical analysis for this project. Assisted in developing multivariate analysis for this project
- Philip Bonomi and Ibtihaj Fughhi: participated in literature review, provided expert opinion, revised and provided expert input to the manuscript
- Tochukwu M Okwuosa: lead-investigator and expert in cardio-oncology. Designed the project and supervised each step of it with extensive revisions and input.

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## Tables

**Table 1. Baseline characteristics of patients according to baseline resting heart rate**

	All Patients	HR ≤ 100	HR > 100	P-value
N (%)	622	571	51	-
Age	70±10	71±9	67±13	0.674
Gender (Female %)	376 (60.5)	348 (60.8)	28 (56)	0.502
Race (white %)	475 (76.4)	445 (77.8)	30 (60)	0.005
BMI	27.7±7.1	27.7 ± 7	27.4 ± 7.4	0.963
AJCC (Stage 4)	297 (69.4)	279 (69.9)	18 (62.1)	0.375
Albumin	3.44±1.47	3.5 ± 1.5	3 ± 0.89	0.043
Hemoglobin	11.6 ±2.4	11.7 ±2.2	10.5 ±2.8	0.001
N/L	5.3 ± 7.43	5.21 ± 7.5	5.7 ±7.44	0.094
Diabetes	124 (19.9)	109 (19.1)	15 (30)	0.063
Hypertension	418 (67.2)	386 (67.5)	32 (64)	0.615
Hyperlipidemia	230 (37)	210 (36.8)	20 (40)	0.651
Coronary artery disease	91 (14.6)	83 (14.5)	8 (16)	0.775
Stroke/TIA	57 (9.2)	54 (9.4)	3 (6)	0.419
Chronic kidney disease	121 (19.5)	98 (17.1)	23 (46)	< 0.001
Leukocytosis	157 (25.2)	141 (24.7)	16 (32)	0.251
Smoking	298 (47.9)	273 (47.7)	25 (50)	0.758
Beta-blockers	204 (32.8)	180 (31.5)	24 (48)	0.017
Calcium channel blockers	124 (20)	115 (20.2)	9 (18)	0.712
ACE/ARB	197 (31.8)	184 (32.3)	13 (26)	0.356
Hydralazine	10 (1.6)	8 (1.4)	2 (4)	0.161
Aspirin	167 (26.8)	158 (27.6)	9 (18)	0.141

Anticoagulation	45 (7.2)	34 (5.9)	11 (22)	< 0.001	
Spirolactone	8 (1.3)	7 (1.2)	1 (2)	0.640	
Type of Malignancy	Primary Lung	272 (44)	257 (45)	15 (29)	0.001
	Lymphoma	130 (21)	120 (21)	10 (20)	
	Multiple myeloma	72 (11.6)	69 (12.1)	3 (6)	
	Leukemia (17.4)	10	88 (15.4)	20 (40)	
	Other	40 (6)	37 (6.5)	3 (6)	
Chemotherapy at time of visit	341 (56.4)	314 (56.6)	27 (54)	0.725	
Anthracyclines	118 (19)	107 (18.7)	11 (22)	0.573	
Radiation	267 (43)	249 (43.6)	18 (36)	0.297	

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables, BMI body mass index, AJCC American Joint Committee on Cancer, N/L neutrophil/lymphocyte ratio, ACE-I/ARB angiotensin converting enzyme inhibitors/angiotensin receptor blockers

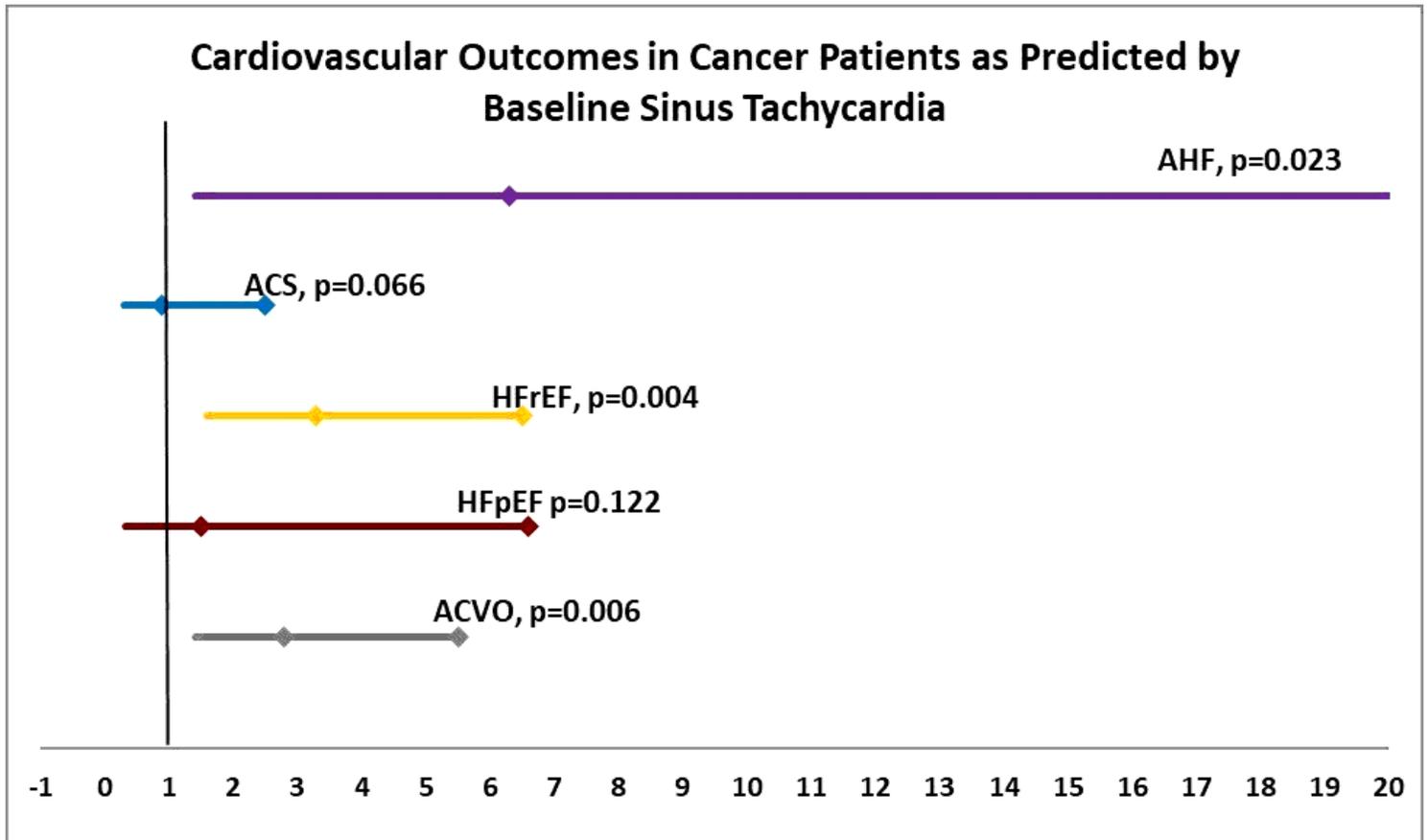
**Table 2. Univariate and Multivariate Logistics Regression Analysis for Predictors of Adverse Cardiovascular Outcomes**

Variables	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sinus Tachycardia	3.8 (2.1-6.6)	0.001	3.1 (1.5-6.2)	0.002
Race (white %)	1.9 (1.2-2.8)	0.003	1.8 (1.1-2.9)	0.017
Albumin	0.64 (0.48-0.86)	0.003	0.88 (6.3-1.2)	0.465
Hemoglobin	0.85 (0.81-0.93)	0.001	0.94 (0.83-1.01)	0.095
Beta-Blockers	0.31 (0.21-0.45)	0.001	0.246 (0.25-0.62)	0.001
Renal disease ( <i>GFR</i> < 60 mL/min/1.73m <sup>2</sup> )	1.4 (1.36-2.7)	0.010	0.730 (0.43-1.24)	0.246

Covariates with  $P < 0.05$  in Table 1 (race, albumin, hemoglobin, beta-blocker use, chronic kidney disease), anticoagulation, type of malignancy) were included in multivariate analysis.

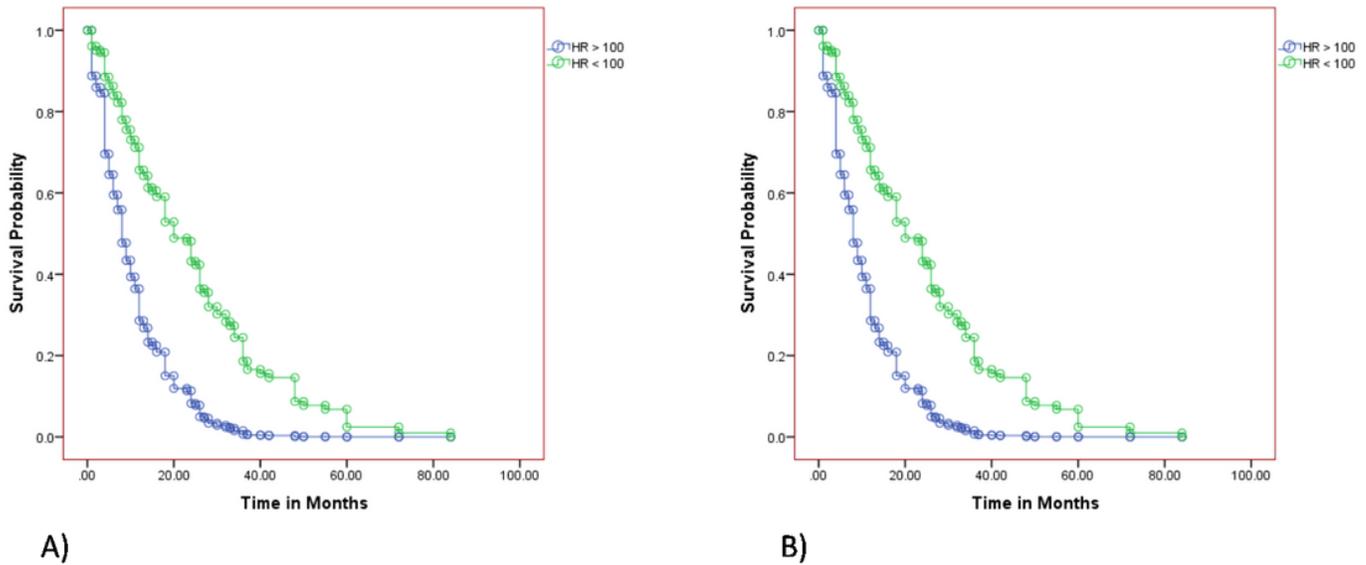
OR, Odds ratio; CI, confidence interval. GFR, glomerulus filtration rate.

## Figures



**Figure 1**

Cardiovascular Outcomes as Predicted by Baseline Sinus Tachycardia. Legend: Odds Ratio (OR), 95% Confidence Intervals; for heart rates  $\geq 100$  vs.  $< 100$  bpm. Sinus tachycardia was associated with increased incidence of AHFE and HFrEF, but not HFpEF or ACS. ACS=Acute Coronary Syndromes; AHFE=Acute Heart Failure Exacerbation; HFpEF=Heart Failure with preserved Ejection Fraction; HFrEF=Heart Failure with reduced Ejection Fraction; CVO=Cardiovascular Outcomes \* Model adjusted for age, race, beta blocker use, renal disease (GFR  $< 60$  mL/min/1.73m<sup>2</sup>), type of malignancy, albumin, hemoglobin, anticoagulation, anthracyclines and radiation



**Figure 2**

Kaplan-Meier Survival Curves in Cancer Patients as Predicted by Resting Heart Rate. Legend: A) Sinus tachycardia was a significant predictor of mortality (HR 2.9, 95% CI 1.8-5;  $p < 0.001$ ) after adjusting for variables in model 1 (race, albumin, hemoglobin, beta-blockers, chronic kidney disease (GFR < 60 mL/min), anticoagulation and type of malignancy). B) Sinus tachycardia remained an independent predictor of mortality (HR 2.5, 95% CI 1.5-4;  $p < 0.001$ ) even after adjusting for all covariates in model 2 (smoking, history of coronary artery disease (CAD), diabetes, aspirin, beta-blockers, history of stroke, radiation and anthracyclines).