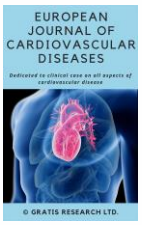


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Research Article

# Cardiovascular Vital Signs at Solid Tumor Diagnosis: Hypotension and Tachycardia Predict Shorter Overall Survival

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ABSTRACT

**Objective:** We examined whether cardiovascular vital signs (VS) were prognostic for overall survival (OS) in newly diagnosed adult cancer outpatients. **Methods:** Electronic medical records data for patients with a solid tumor diagnosis and ≥2 consecutive weight measurements were analysed. BP (mmHg) and RHR (beats/minute) were identified at diagnosis (T1) and final visit (T2; >=7 days after T1). Systolic blood pressure (SBP) categories: <120; 120-129; 130-139; 140-149; ≥150. RHR categories: <60; 60-69; 70-79; 80-89; 90-100; 101-109; ≥110. Proportional Hazards Models examined potential prognostic factors for OS. Kaplan-Meier analysis estimated OS using lower (<80), normal (80-119), higher (≥120) SBP, and RHR of normal (60-100), bradycardia (<60), tachycardia (>100) categories. **Results:** N=5819; 59% men; mean age 61 (±12) years; 77% Caucasians; 9% African Americans. The most common tumor sites: prostate (19%), lung (15%), breast (14%). 18% had metastatic disease. Median OS after diagnosis was 27 months (range 25-28). Tachycardia had 2 to 3-fold increase in mortality. Survival time decreased by 8-10 months with lower SBP. RHR and SBP remained independently prognostic after adjusting clinically relevant characteristics at both timepoints. **Conclusion:** Elevated RHR and lower SBP independently predicted greater mortality in newly diagnosed cancer outpatients. These associations remained statistically significant longitudinally, and the differences observed were clinically important.

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## 1. Introduction

Cancer and heart disease are the most common causes of death for adults and are responsible for 50% of all deaths in the US [1]. They significantly overlap with common risk factors like diabetes, hypertension (HTN), obesity, tobacco use, metabolic and inflammatory conditions [2]. Greater understanding of the interplay between cancer, heart disease, and other comorbidities may improve both cardiovascular disease (CVD) and cancer outcomes. HTN is a known poor prognostic indicator and a preventable cause of CVD in cancer and noncancer populations. New-onset HTN was present within three months post-diagnosis in one-third of 25,090 adults with solid tumors [3]. New-onset HTN could also be a marker of cancer treatment efficacy [4]. Blood pressure (BP) assessment is essential before, during, and after cancer treatment for this potentially modifiable risk factor for heart disease.

Hypotension and tachycardia are common clinical observations in advanced cancer and often attributed to dehydration or autonomic dysfunction (AD). Loss of normal heart rate variability (HRV), a marker of cardiovascular AD, is specifically associated with increased mortality risk in advanced cancer [5]. Higher mortality risk has been found in cancer patients with elevated resting heart rate (RHR) [6, 7]. RHR ≥75 beats/min has been associated with higher mortality in people with advanced colorectal, pancreatic, and non-small cell lung cancer [8]. Sinus tachycardia (RHR ≥100) predicted increased risk of adverse cardiovascular outcomes and mortality within one year of a cancer diagnosis [9]. Both studies [8, 9] were in advanced cancer cohorts - but had a limited range of primary cancer sites. They related mortality risk to the mean RHR category. The direction and strength of the relationship between RHR and mortality were unclear. There is a need to extend these associations to earlier disease stages and perform studies on a larger scale.

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Prior studies [8, 10] have demonstrated the prognostic value of elevated cardiovascular biomarkers (natriuretic peptides and troponins) in cancer patients without overt heart disease. A pilot study [11] showed that BP, cardiac output, and stroke volume were higher in advanced cancer than in healthy individuals or those with chronic heart failure. Another [12] showed that HRV and left ventricular ejection fraction were impaired in treatment-naïve colorectal cancer patients and deteriorated after chemotherapy. These observations suggested cardiovascular changes induced by the cancer itself rather than by chemotherapy.

Prognostication is essential for oncology decision-making but remains a clinical challenge. RHR is not recommended in American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for CVD risk assessment [13]. Dose-response data on the relation between RHR and cardiovascular mortality have been inconsistent [9, 14-16]. In addition, optimal thresholds for cardiovascular events may differ among populations due to different pathophysiological mechanisms [14]. Because of our clinical observations and these research findings, we examined whether cardiovascular vital signs (VS) were prognostic for overall survival (OS) in a large, real-world cohort of newly diagnosed cancer outpatients in a major cancer institute. The dataset was collected as part of a study [17] of weight changes noted at diagnosis in solid tumors in an attempt to explain the pathophysiology of cancer cachexia.

## 2. Methods

### 2.1. Study Design

The protocol was structured to evaluate the relationship of weight changes to cancer prognosis, including the potential importance of cardiovascular VS. Adult outpatients who attended a major cancer institute over a contiguous 36-month period with a solid tumor diagnosis and a minimum of two weight measurements ≥7 days apart were included. People with a primary diagnosis of hematological malignancies, those with a single recorded outpatient visit, those who attended for non-clinical encounters, or those without RHR, BP, or body mass index (BMI) measurements were excluded. The Institutional Review Board approved this protocol and waived the requirement for informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was used to guide this manuscript.

### 2.2. Data Collection

Data were extracted from the electronic medical records [(EMR) (EPIC Systems Corporation, Verona, WI)] and downloaded to a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA). Detailed data collection methods are reported elsewhere [17]. T1 was defined as the diagnosis date, and T2 the last encounter within the study period when weight was measured, ≥7 days after the diagnosis date. Percent weight change was calculated as follows: current weight (kg) – previous weight (kg) / previous weight (kg) × 100. BP readings were obtained and recorded by routine outpatient clinical practices and equipment. BMI (kg/m$^2$) was categorized as underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30) [18]. Comorbidities were assessed by the Charlson Comorbidity Index (CCI) [19], ranging from 0 to 37 based on their number and severity. The date of death was obtained from the EMR and verified by the Social Security Death Index database.

### 2.3. Statistical Analysis

Categorical variables were summarized as frequency counts and percentages and compared with the Chi-square test. Means were reported for continuous variables and compared with parametric and nonparametric tests as appropriate.

The primary endpoint was OS, defined as the number of months from T1 to the date of death. All patients were observed to time of death or censored at T2. Cox Proportional Hazards Models (PHM) examined potential prognostic factors for OS. Systolic blood pressure (SBP) was categorized into five levels; <120; 120-129; 130-139; 140-149; ≥150. RHR was categorized into seven levels; <60; 60-69; 70-79; 80-89; 90-100; 101-109; ≥110. For Kaplan-Meier analysis, we used lower (<80), normal (80-119), and higher (≥120) SBP [20], and RHR of normal (60-100), bradycardia (<60), and tachycardia (>100) [21] categories. Such 10-unit intervals are consistent with a recent meta-analysis that assessed the association between RHR and cancer mortality [7] and previous BP reduction trials [22].

We used Goodness-of-Fit and log [-log (survival)] plots to assess the proportional hazards assumption. We designed a Reduced Stratified Cox PHM to adjust for BMI and SBP and confirm the independent effects of cardiovascular VS on OS. Another Cox PHM further elucidated the direction and strength of the relationships between RHR, SBP, and mortality risk. There were no violations of the proportional hazards assumptions. Variables assessed as potential prognostic factors for OS included age, gender, race, metastatic disease, primary cancer site, CCI score, RHR, SBP, BMI at T1. In addition, percent weight change and cancer therapies received were assessed at T2.

We generated Kaplan-Meier survival plots and used the log-rank test to compare survival between the variables. We estimated median and percent survival with standard error (SE) at 6, 12, and >24 months after diagnosis. Results are shown as hazard ratios (HR) with 95% confidence intervals (CI). All statistical tests were two-sided; $p<0.05$ indicated statistical significance. Analyses were performed with SAS software (version 9.4; SAS Institute Inc, Cary, NC). All statistical analyses were based on participants with complete data. Percentages are rounded to the nearest whole number and numbers to one decimal throughout the text unless otherwise specified.

## 3. Results

### 3.1. Descriptive Summary of the Data

Records for 6801 consecutive outpatients were reviewed; 5819 (86%) met all inclusion criteria. The reasons for exclusion included unknown BP (n=564), weight measurements <7 days apart (n=297), unknown height and BMI (n=102), unknown RHR (n=9), non-cancer diagnosis (n=5), and unverified date of death (n=5). Table 1 contains the demographic and clinical characteristics of the study population. The population was predominantly male (59%). Seventy-seven percent were Caucasians, and 14% African Americans. Prostate, lung, and breast

cancers accounted for nearly half (48%) of all cases. Eighteen percent (n=1048) had known metastatic disease at diagnosis. At T2, chemotherapy (40%) and radiotherapy (39%) were the most common treatment modalities. Hormone therapy, biologic modifiers, and monoclonal antibodies were administered in 17%, 16%, and 6%, respectively.

**TABLE 1:** Demographic and clinical characteristics at solid tumor diagnosis (T1) and final visit (T2) (N=5819).

| Characteristic | T1† | T2†, ‡ | P-Value |
|---|---|---|---|
| Age (years) | 61 ± 12 | 62 ± 12 | **<0.0001** |
| Primary Cancer Site | | | |
| Prostate | 1134 (19) | | |
| Lung | 900 (15) | | |
| Breast | 803 (14) | | |
| Head & Neck | 420 (7) | | |
| Kidney & Urinary & Bladder | 419 (7) | | |
| Colorectal & Anal | 340 (6) | | |
| Hepatobiliary & Pancreas | 339 (6) | | |
| Upper Gastrointestinal | 335 (6) | | |
| Unknown Primary | 243 (5) | | |
| Melanoma | 190 (3) | | |
| Uterus & Cervix | 190 (3) | | |
| Brain | 139 (2) | | |
| Other | 367 (7) | | |
| BMI (kg/m$^2$) | 29 ± 6 | 28 ± 7 | **<0.0001** |
| Overweight (25.0-29.9) | 2063 (35) | 1967 (34) | **<0.0001** |
| Obese (≥30) | 1964 (34) | 1866 (32) | |
| Normal (18.5-24.9) | 1659 (29) | 1774 (30) | |
| Underweight (<18.5) | 133 (2) | 212 (4) | |
| SBP (mmHg) | 135 ±19 | 132 ± 19 | **<0.0001** |
| <120 | 1270 (22) | 1590 (27) | |
| 120-129 | 1048 (18) | 1074 (18) | |
| 130-139 | 1213 (21) | 1100 (19) | |
| 140-149 | 987 (17) | 965 (17) | |
| ≥150 | 1301 (22) | 1090 (19) | |
| RHR (beats/min) | 80 ± 15 | 82 ± 17 | **<0.0001** |
| <60 | 386 (7) | 397 (7) | |
| 60-69 | 1101 (19) | 1073 (18) | |
| 70-79 | 1492 (26) | 1368 (24) | |
| 80-89 | 1317 (23) | 1299 (22) | |
| 90-100 | 897 (15) | 877 (15) | |
| 101-109 | 386 (7) | 419 (7) | |
| ≥110 | 240 (4) | 386 (7) | |

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RHR: Resting Heart Rate.
†Mean ± standard deviation or count (%). ‡Final visit ≥7days after diagnosis.
All numbers and percentages are rounded to the nearest whole number.

RHR was normal in the majority (83%), and SBP ≥120 mmHg in over three-quarters (78%) at T1. The mean weight (kg) was 83 (± 21) at T1 and 82 (± 21) at T2 (p<0.0001). Most (69%) were either overweight or obese at both time points. At T2, 37% had lost weight, 25% gained weight, and 37% were unchanged. The median CCI score did not differ between T1 [5 (range 2-18)] and T2 [5 (range 2-16)]. The median follow-up from T1 to T2 was 6 months (range 0-36).

### 3.2. Cox Proportional Hazards Models

Age, gender, metastatic disease, primary cancer site, CCI score, RHR, SBP, and BMI were independent predictors of OS at T1 (Table 2) and T2 (Appendix 1). In addition, race, treatment modality, and weight change were independent predictors of OS at T2.

### Cardiovascular Vital Signs

Compared to an RHR of 60-69, the hazard of death was 5%, 26%, 49%, 72%, and 285% higher with RHR of 70-79, 80-89, 90-100, 101-109, and ≥110 at T1. Similarly, this was 22%, 46%, 220%, 272%, and 419% greater, respectively, at T2. The hazard of death increased progressively with each higher RHR category at T1 and T2.

Compared to an SBP of 120-129, the hazard of death was lower by 29%, 18%, 19%, with SBP of 130-139, 140-149, and ≥150 at T1. This was 20%, 27%, and 35% lower, respectively, at T2. The hazard of death decreased progressively with each higher SBP category.

Table 3 summarizes Cox PHM results using the patient group with RHR 60-69 and SBP 120-129 as a reference at T1. Compared to the reference group, the hazard of death was highest (530%) in those with RHR of ≥110 and SBP of <120 (p<0.0001).

**TABLE 2:** Cox predictive model for overall survival in solid tumors by demographic and clinical characteristics (T1).

| **Variable**† | | **DF** | **Estimate** | **SE** | $\chi 2$ | **P-Value** | **HR** | **95% CI** |
|---|---|---|---|---|---|---|---|---|
| Gender (Female) | Male | 1 | 0.2 | 0.1 | 10.6 | **0.00** | 1.22 | 1.1-1.4 |
| Race (White) | Black | 1 | 0.2 | 0.1 | 3.6 | 0.06 | 1.17 | 1.0-1.4 |
| | Other & Unknown | 1 | 0.0 | 0.1 | 0.1 | 0.72 | 1.03 | 0.9-1.2 |
| Age (per year) | | 1 | 0.0 | 0.0 | 60.3 | **<.0001** | 1.02 | 1.0-1.0 |
| Metastatic Disease (No) | Yes | 1 | 0.6 | 0.1 | 63.1 | **<.0001** | 1.73 | 1.5-2.0 |
| Primary Cancer Site (Prostate) | Brain | 1 | 2.2 | 0.2 | 140.3 | **<.0001** | 9.28 | 6.4-13.4 |
| | Colorectal & Anal | 1 | 1.2 | 0.2 | 49.8 | **<.0001** | 3.22 | 2.3-4.5 |
| | Breast | 1 | -0.1 | 0.2 | 0.2 | 0.68 | 0.92 | 0.6-1.4 |
| | Head & Neck | 1 | 0.6 | 0.2 | 10.6 | **0.00** | 1.78 | 1.3-2.5 |
| | KUB | 1 | 1.6 | 0.1 | 110.9 | **<.0001** | 4.73 | 3.5-6.3 |
| | Hepatobiliary & Pancreas | 1 | 2.3 | 0.1 | 257.9 | **<.0001** | 9.93 | 7.5-13.1 |
| | Lung | 1 | 1.7 | 0.1 | 163.0 | **<.0001** | 5.57 | 4.3-7.2 |
| | Melanoma | 1 | 1.3 | 0.2 | 37.8 | **<.0001** | 3.66 | 2.4-5.5 |
| | Other | 1 | 1.3 | 0.2 | 64.7 | **<.0001** | 3.78 | 2.7-5.2 |
| | Unknown Primary | 1 | 1.9 | 0.2 | 150.8 | **<.0001** | 6.82 | 5.0-9.3 |
| | Upper Gastrointestinal | 1 | 2.0 | 0.1 | 195.3 | **<.0001** | 7.70 | 5.8-10.3 |
| | Uterus & Cervix | 1 | 1.3 | 0.3 | 19.9 | **<.0001** | 3.56 | 2.0-6.2 |
| CCI score‡ | | 1 | 0.0 | 0.0 | 6.5 | **0.01** | 1.03 | 1.0-1.1 |
| BMI§ (Normal weight) | Underweight | 1 | 0.2 | 0.1 | 1.9 | 0.17 | 1.22 | 0.9-1.6 |
| | Overweight | 1 | -0.3 | 0.1 | 25.7 | **<.0001** | 0.72 | 0.6-0.8 |
| | Obese | 1 | -0.4 | 0.1 | 26.5 | **<.0001** | 0.69 | 0.6-0.8 |
| SBP (120-129) | <120 | 1 | 0.0 | 0.1 | 0.2 | 0.65 | 1.04 | 0.9-1.2 |
| | 130-139 | 1 | -0.2 | 0.1 | 7.6 | **0.01** | 0.79 | 0.7-0.9 |
| | 140-149 | 1 | -0.2 | 0.1 | 4.5 | **0.02** | 0.82 | 0.7-1.0 |
| | ≥150 | 1 | -0.2 | 0.1 | 5.5 | **0.02** | 0.81 | 0.7-1.0 |
| RHR (60-69) | <60 | 1 | 0.1 | 0.1 | 0.2 | 0.70 | 1.05 | 0.8-1.4 |
| | 70-79 | 1 | 0.1 | 0.1 | 0.3 | 0.57 | 1.05 | 0.9-1.3 |
| | 80-89 | 1 | 0.2 | 0.1 | 7.1 | **0.01** | 1.26 | 1.1-1.5 |
| | 90-100 | 1 | 0.4 | 0.1 | 18.5 | **<.0001** | 1.49 | 1.2-1.8 |
| | 101-109 | 1 | 0.5 | 0.1 | 24.5 | **<.0001** | 1.72 | 1.4-2.1 |
| | ≥110 | 1 | 1.1 | 0.1 | 79.4 | **<.0001** | 2.85 | 2.3-3.6 |

χ2: Chi-Square; SE: Standard Error; DF: Degrees of Freedom; HR: Hazard Ratio; CI: Confidence Interval; KUB: Kidney, Ureter, and Bladder; CCI: Charlson Comorbidity Index; BMI: Body Mass Index; SBP: Systolic Blood Pressure; RHR: Resting Heart Rate. Numbers are rounded to one decimal place.
†Reference values are in parenthesis. ‡Continuous variable. §Normal weight: 18.5-24.9; Underweight: <18.5; Overweight: 25-29.9; Obese: ≥30.
P-values and hazard ratios are rounded to two decimal places.

**TABLE 3:** Cox predictive model for overall survival in solid tumors by systolic blood pressure and resting heart rate (T1).

| | **Hazard Ratios: RHR (beats/min)** | | | | | | |
|---|---|---|---|---|---|---|---|
| SBP (mmHg) | <60 | 60-69 | 70-79 | 80-89 | 90-99 | 100-109 | ≥110 |
| <120 | 1.6 | 1.2 | 1.5* | 2.3*** | 2.3*** | 3.5*** | 5.3*** |
| 120-129 | 0.8 | R | 1.6* | 1.6* | 2.4*** | 2.9*** | 4.2*** |
| 130-139 | 1.0 | 1.0 | 1.1 | 1.1 | 1.6* | 2.3** | 2.7*** |
| 140-149 | 1.1 | 1.1 | 0.7 | 1.6* | 1.5 | 1.3 | 4.2*** |
| ≥150 | 0.9 | 0.9 | 0.9 | 1.0 | 1.4 | 1.7 | 2.1* |

RHR: Resting Heart Rate; SBP: Systolic Blood Pressure; R: Reference Group.
*<0.05; **<0.001; ***<0.0001
Confidence intervals for hazard ratios are not reported for brevity.

We adjusted for BMI categories in a reduced model of age, gender, SBP, and RHR. SBP and RHR independently predicted OS at T1 and T2 (Appendix 2). Similarly, we adjusted for SBP categories in a reduced model of age, gender, BMI, and RHR. BMI and RHR independently predicted OS at T1 and T2 (Appendix 3).

### 3.3. Kaplan-Meier Survival Estimates for RHR, SBP, and BMI (Table 4)

Twenty-five percent (n=1466) had died by the end of study from any cause. For the entire cohort (N=5819), the median OS after diagnosis was 27 months (range 25-28); 6-month survival 88%, 12 months 75%, and >24 months 54%.

**TABLE 4:** Kaplan-Meier estimates of survival (months) for resting heart rate, systolic blood pressure, and body mass index at T1 and T2.

| | T1 | | | | | | T2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Median†** | **95% CI** | **6 months** | **12 months** | **>24 months** | | **Median†** | **95% CI** | **6 months** | **12 months** | **>24 months** |
| RHR (beats/min)§ | | | **%‡** | **%‡** | **%‡** | | | | **%‡** | **%‡** | **%‡** |
| Bradycardia | 29 | (23 – -) | 92 | 82 | 53 | | – | (31.2 – -) | 96 | 87 | 69 |
| Normal | 28 | (27 – 30) | 90 | 77 | 57 | | 30 | (28 – 31) | 91 | 80 | 59 |
| Tachycardia | 17 | (15 – 19) | 74 | 60 | 35 | | 12 | (11 – 13) | 72 | 49 | 23 |
| SBP (mmHg)¶ | | | | | | | | | | | |
| Low | 11 | (- – 6) | 84 | 62 | 34 | | 10 | (7 – 14) | 79 | 56 | 31 |
| Normal | 21 | (19 – 24) | 85 | 69 | 45 | | 18 | (16 – 20) | 83 | 67 | 37 |
| High | 28 | (26 – 30) | 90 | 78 | 57 | | 31 | (30 – 33) | 91 | 80 | 63 |
| BMI (kg/m$^2$)¥ | | | | | | | | | | | |
| Underweight | 14 | (10 – 20) | 76 | 54 | 20 | | 13 | (10 –17) | 78 | 50 | 22 |
| Normal | 22 | (19 – 25) | 85 | 69 | 46 | | 19 | (18 – 21) | 84 | 66 | 42 |
| Overweight | 27 | (24 – 32) | 89 | 77 | 54 | | 29 | (26 – 31) | 90 | 79 | 57 |
| Obese | 31 | (29 – 33) | 91 | 81 | 63 | | 33 | (31 – 37) | 92 | 84 | 69 |

BMI: Body Mass Index; CI: Confidence Interval; RHR: Resting Heart Rate; SBP: Systolic Blood Pressure.
†Estimate of survival in months. ‡Estimate percentage of survival. §Bradycardia: <60; normal: 60-100; tachycardia: >100. ¶Low: <80; Normal: 80-119; High: ≥120. ¥Underweight: <18.5; Normal Weight: 18.5-24.9; Overweight: 25-29.9; Obese: ≥30
Numbers and percentages are rounded to the whole number.

#### 3.3.1. T1

Those with any tachycardia had a median OS of 17 months, compared to 28 months with normal RHR. Seventy-four percent of those with tachycardia survived 6 months and 35% 24 months, whereas OS was 90% and 57% respectively at those time points with normal RHR.

People with high SBP as a group had a median OS of 28 months longer than normal SBP (21 months). In the high and normal SBP groups, 90% and 85% respectively survived 6 months while 57% and 45% survived 24 months. Those who were obese had a median OS of 31 months, versus 22 months for the normal BMI group. In obese and normal BMI groups, OS was 91% and 85% respectively at 6 months, 63%, and 46% at 24 months.

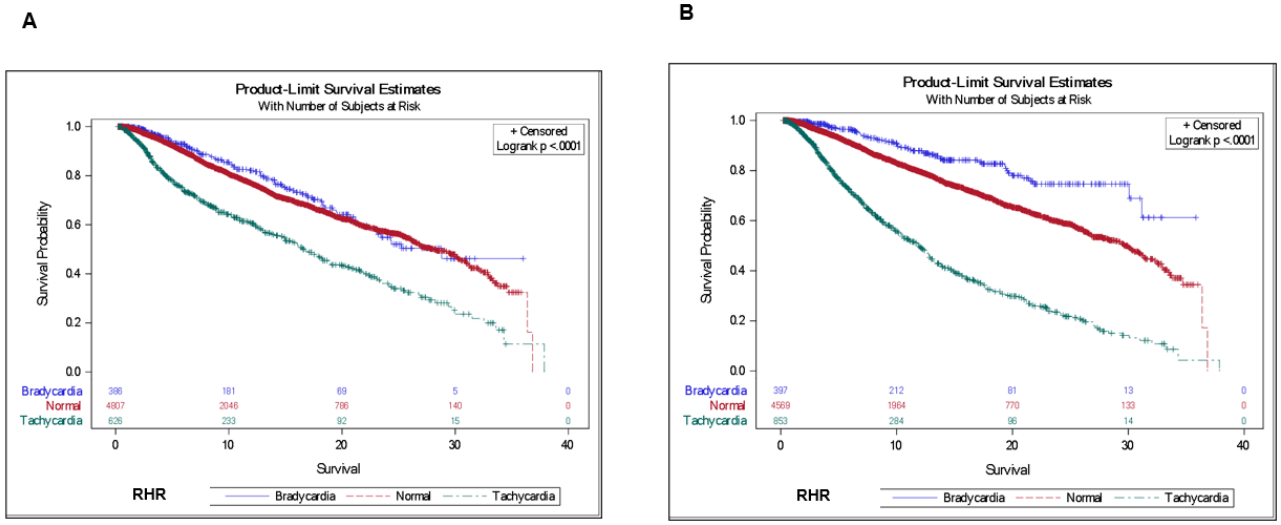


**FIGURE 1:** Kaplan-Meier plot of overall survival (months) by resting heart rate category at **A)** diagnosis (T1) and **B)** final visit (T2).
RHR: Resting Heart Rate; Bradycardia: <60; Normal: 60-100; Tachycardia: >100.

### 3.3.2. T2

Those with tachycardia as a group had a median OS of 12 months versus 30 months with normal RHR. In those with tachycardia, and normal RHR, 72% and 91% respectively survived 6 months; at 24 months, OS was 23% and 59%. People with high SBP had a median OS of 31 months, longer than normal SBP (18 months). In high and normal SBP, 91% and 83% respectively survived 6 months; at 24 months, OS was 63% and 37%.

Those who were obese had a median OS of 33 months, versus 19 months for normal BMI. In those with obese and normal BMI, 92% and 84% survived 6 months; at 24 months, OS was 69% and 42%, respectively. Kaplan-Meier survival plots were generated for RHR (Figure 1), SBP (Figure 2), BMI (Appendix 4), and diastolic BP (Appendix 5) categories at T1 and T2.

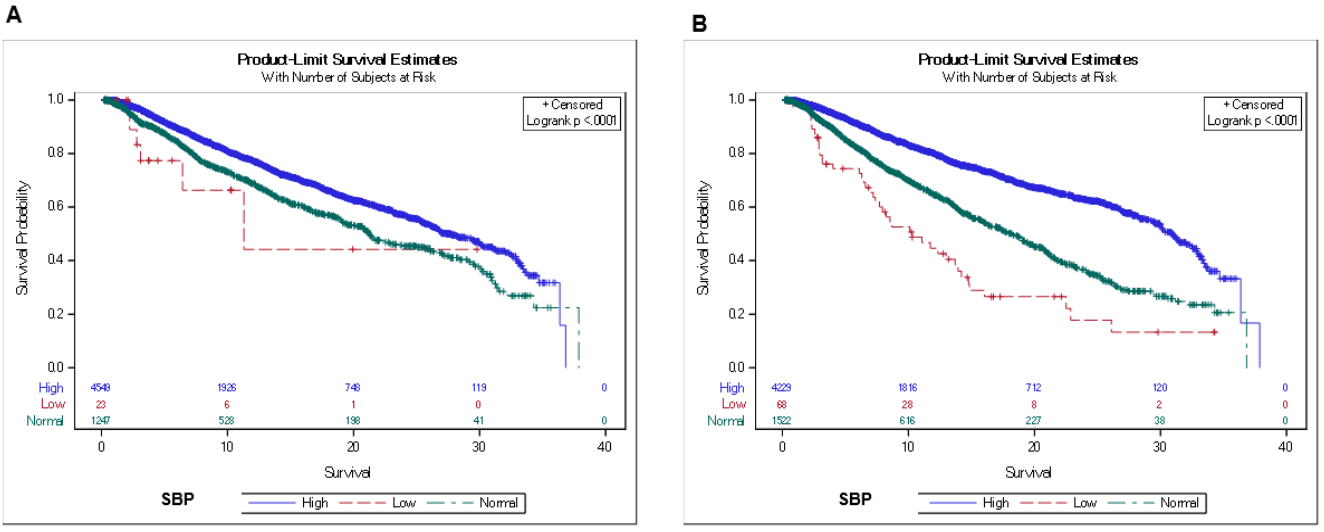


**FIGURE 2:** Kaplan-Meier plot of overall survival (months) by systolic blood pressure category at **A)** diagnosis (T1) and **B)** final visit (T2).
SBP: Systolic Blood Pressure; Low <80; Normal: 80-119; High ≥120.

## 4. Discussion

Elevated RHR and lower SBP independently predicted greater mortality in newly diagnosed cancer outpatients. Overall, those with elevated RHR or lower BP had shorter survival, whereas overweight or obese BMI was associated with a better prognosis. These associations remained statistically significant longitudinally, and the differences observed were clinically important. The mortality risk increased progressively with each RHR, BP, and BMI category. This dose-response relationship provided further biological plausibility to the overall findings. Our findings support the original hypothesis that cardiovascular VS can provide valuable prognostic information in solid tumors before any cancer therapy.

The distribution of gender and race reflected the wider US population [23]. The study population also represented cancer mortality in the US by tumor site prevalence [23]. Sixty-nine percent were overweight or obese by BMI, like other studies in heterogeneous cancer cohorts [24, 25] and those who participated in clinical trials [26]. Based on data from the National Health and Nutrition Examination Survey (2011-2014), nearly two-thirds (70%) of adults in the US were overweight or obese, and 46% had HTN defined as a BP of 130/80 mmHg [27]. In our study, SBP was ≥120 mmHg in over three-quarters (78%), consistent with a nationally representative cross-sectional study [28] that applied the latest ACC/AHA BP guideline goals [29]. Overall, these suggest that our findings are generalizable to US cancer patients.

Consistent with other studies [8, 9, 30], elevated RHR independently predicted greater mortality. The association of RHR with subsequent mortality was continuous and progressive. Compared with 60-69, increased mortality risk was observed at 80-89 (T1, HR: 1.26; T2, HR: 1.46), which falls below the traditionally defined tachycardia threshold of 100. Two dose-response meta-analyses [6, 7] of observational studies showed the protective role of lower RHR against cancer mortality with similar relative risk estimates. It is noteworthy that this was the same cut-off point identified in our study as a valid independent predictor of mortality.

Tachycardia (RHR >100) was associated with an almost 2-fold and 3-fold greater mortality at T1 and T2, respectively, similar to a much smaller study [9] among outpatients with both solid and hematological malignancies. However, in that report, RHR was measured by an electrocardiogram at ≥3 different clinical visits within one year of a cancer diagnosis. Nearly 60% of the subjects had chemotherapy by the baseline visit. Those with sinus tachycardia (n=51) had 6-fold hospital admissions for heart failure exacerbation than controls (n=571). In that case-control study, solid tumors were less common (50%), most people had advanced disease (70%), and participants were older (mean age 70 years) than in our report. Additionally, the duration of follow-up from the initial cancer diagnosis date was longer (10 years).

The greatest prognostic impact of RHR was consistently observed in the highest RHR group (≥110) at both T1 and T2 (HR 2.85 vs. 4.19). Of all parameters we assessed, tachycardia had the strongest relationship to

survival, with a median 11 months and 18 months longer among persons with normal RHR, at T1 at T2, respectively. Overall, the magnitude of the relationship with survival was greatest at T2, perhaps due to the beneficial effects of cancer treatments.

Elevated RHR may reflect an increased sympathetic activation, consequently, an autonomic imbalance that indicates early (possibly reversible) cancer-induced cardiac dysfunction. These alterations in cardiac hemodynamics might be induced by the compensatory response to systemic inflammatory states in cancer [9]. In a rodent hepatoma model, elevated B-type natriuretic peptide (BNP) levels were attributed to the direct effects of cancer on the heart, including fibrotic remodeling and cardiac cachexia that leads to left ventricular dysfunction [31]. Elevated levels of NT-proBNP and high sensitivity Troponin T before chemotherapy predicted increased risk of all-cause mortality independent of manifest cardiac disease in a cohort of 555 participants with various cancers [10]. These biomarkers were also correlated with Interleukin-6 and C-reactive protein levels, which supports the role of systemic inflammation [32]. On the other hand, the positive association between elevated RHR and all-cause mortality persisted after adjusting for inflammatory markers, suggesting an independent association [33].

Anker *et al.* [8] showed that RHR ≥75 was associated with increased mortality (HR: 1.67) than those with RHR <75 in a cohort with advanced colorectal, pancreatic, and lung cancers. BMI, primary cancer site, and treatment modalities were important prognostic factors. Those with elevated RHR had elevated serum natriuretic peptides and troponins even without significant cardiovascular disease. These three studies [8, 10, 30] support the hypothesis that the cardiovascular system may be impacted by underlying cancer pathophysiology independent of any cancer treatments. RHR has been associated with increased mortality of GI [8, 34, 35], lung [8, 9, 34], and kidney cancers [34]. Some studies [16, 34] have shown a relationship between elevated RHR and breast cancer-specific mortality, while one [30] disagreed. In our analysis, those with brain, pancreas, and upper GI cancers had the shortest OS compared to those with prostate cancer. In contrast, the survival length did not differ between breast cancer and prostate cancer (p=0.68). When breast cancer was removed from the analysis, risk estimates were not significantly modified in magnitude or direction.

HTN is one of the most common comorbidities in cancer populations. Some studies [36-39] have shown the adverse effects of pre-existing HTN on cancer survival, but not all [40]. In the present analyses, we found an independent inverse relationship between elevated BP and mortality (highest mortality in the lowest BP group) after adjusting clinically relevant characteristics. People with SBP <80 had a median OS of 17-21 months shorter than those with SBP ≥120. In addition, the relationship between lower BP and mortality was progressive, strong, and consistent over time, suggesting our data have predictive validity. We also found that persons with both elevated RHR and lower SBP had a greater mortality risk. The most pronounced difference was observed in the group with the highest RHR (≥110) and lowest SBP (<120) (HR: 5.3, p<0.0001). The American Society of Clinical Oncology has defined the magnitude of the therapeutic benefit considered clinically meaningful in advanced cancer [41]. An improvement in median OS of 2.5 to 6 months (HR ≤0.8) was considered clinically important, comparable to many new cancer treatments [42]. Our striking findings indicate a large predictive power of VS and point to the clinical importance of tachycardia and hypotension as a risk factor for shorter survival.

A notable observation in our cohort was that those who were overweight or obese were more likely to have longer survival than those underweight. We have previously shown that those who gained weight at diagnosis or later had a better prognosis than those who lost weight [17]. Controversy exists whether excess body weight confers a survival advantage in cancer ("obesity paradox") as weight gain and loss have both been linked with disease progression. Nonetheless, we believe our observations and conclusions are robust. The identification of high BMI as an independent prognostic factor in our previous and current work lends clinical relevance and credibility to the prognostic effect of VS.

A major strength of this study is that it was based on a large and nationally representative sample, making our results generalizable to the US adult population. The prominent feature of our analysis was the evaluation of RHR and SBP at diagnosis before any cancer treatment. Our findings are important given that detailed data about pre-treatment VS assessment in hospital-based tumor registries are lacking [43]. The present cancer classification system does not consider comorbid health problems, including tachycardia and hypotension, as prognostic factors. Pre-existing VS abnormalities were not documented in most oncology trials, and persons with uncontrolled BP have been excluded from studies of new cancer treatments [44]. Available data on hypotension stem from clinical trials of heart failure drugs which often excluded patients with symptomatic hypotension. Consequently, optimal BP values in cancer populations remain unknown.

Due to the retrospective nature of this study, data on the cause of death was not available. The database did not record potential confounding factors such as comorbidities, medications, smoking status, and pre-diagnosis cardiovascular problems. The short study duration might have affected survival analysis. Finally, the results are derived from an observational study, thus, causation cannot be inferred. VS measurements were recorded at two timepoints, but studies that make serial measurements throughout disease may provide additional insights.

This data has important clinical and research implications. The use of cardiovascular VS as a predictor is a unique approach to exploring non-invasive ways for more accurate prognostication. The major premise of this approach in oncology is to help identify those most at risk for poor outcomes. Further research is warranted to confirm these observations and consider whether hypotension and tachycardia should represent therapeutic targets in the management of solid tumors. Interactions between VS and BMI should also be assessed (e.g., whether they affect prognosis synergistically) to inform oncology decision making.

## 5. Conclusion

At diagnosis, cardiovascular VS had clinically and statistically important relationships with OS in newly diagnosed outpatients with solid tumors. Tachycardia and hypotension predicted shorter survival, whereas overweight and obese BMI were associated with a better prognosis. These associations remained evident over time. Tachycardia had 2 to 3-fold increase in mortality at two time points. People with hypotension

survived 8-10 months shorter than those with normal SBP. These estimates were robust and independent from other covariates. The magnitude of associations between these VS and OS also increased progressively, with survival more pronounced with higher RHR and lower BP cohorts. These observations suggest that cardiovascular VS may help predict cancer survival and warrant further research.

### Author Contributions

Aynur Aktas: Conceptualization, data curation, investigation, methodology, validation, visualization, writing – original draft, and writing – review and editing; Declan Walsh: Conceptualization, data curation, investigation, methodology, validation, visualization, and writing – review and editing; Wael Lasheen: Formal analysis, investigation, methodology, software, and writing – review and editing; Bernadette Brady: Writing – review, and editing; Michelle Barrett: Writing – review, and editing; Bassam Estfan: Writing – review and editing.

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### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Ethical Approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study met the criteria for waiver of informed consent. The Cleveland Clinic Institutional Review Board (IRB) approved this study (Ethics approval number: 2011-12-28 / IRB 11-938).

### Informed Consent

This study met the criteria for waiver of informed consent as no protected health information was collected.

### Conflicts of Interest

None.

### Funding

None.

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