Association of cancer with heart failure, and the prognostic value of NT-proBNP in cancer patients: findings from the NHANES (1999-2018).

Cancer and heart failure in NHANES.

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Tweet: In the large NHANES population, HF was significantly associated with cancer. NT-proBNP was higher in cancer patients, with significant prognostic value in cancer patients.

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ABSTRACT

Background: Cancer and heart failure (HF) are two common and serious diseases, and there is a growing recognition of their association.
Objective: This study aims to investigate the association between HF and cancer from the NHANES database from 1999 to 2018, and further explore the prognostic value of NT-proBNP in cancer patients.
Methods: We included all participants with valid answer to qustion of self-reported cancer and HF from the National Health and Nutrition Examination Survey (NHANES). Propensity Score Matching (PSM) method and weighted logistic regression models were conducted.
Results: We analyzed 54,847 participants from 1999 to 2018, which revealed significant association between HF and cancer. HF was associated with an increased occurrence of cancer (OR=1.31, 95% CI: 1.11-1.55, p=0.002), which remained significant after PSM (OR=1.46, 95% CI: 1.17-1.82, p<0.001). Cancer was associated with a higher occurrence of HF (OR=1.33, 95% CI: 1.11-1.59, p=0.002). Moreover, Kaplan-Meier survival analysis over 10 years revealed shortest survival in patients with both HF and cancer compared to those with either disease alone, while patients with HF but no cancer showed significantly shorter survival than patients with cancer but no HF (log-rank p < 0.0001). Importantly, NT-proBNP was significantly higher in cancer patients, no matter whether with known HF (p<0.01). In cancer patients without HF, NT-proBNP higher than 51.51 pg/ml was associated with shorter survival (log-rank p < 0.0001).
Conclusion: In the large NHANES population, HF was significantly associated with cancer. NT-proBNP was higher in cancer patients, with significant prognostic value in cancer patients.

Keywords: cardiac failure, cancer, survival probabilities, NT-proBNP, nationwide health and dietary assessment survey.

Abbreviations list:
VEGF= vascular endothelial growth factor
NHANES= National Health and Nutrition Examination Survey
PSM= Preference Score Matching
MEC= Mobile Exploration Centers
CI= confidence interval
OR= odds ratio
HF= heart failure
non-HF= non-heart failure
CA= cancer

INTRODUCTION

The number of newly diagnosed cancer has soared from 18.7 million in 2010 to 23.6 million in 2019, with an increase of 26.3%. At the same time, the global death from cancer rose from 8.29 million to 10 million, an increase of 20.9% in the last decade[1]. Compared to these cancer statistics, the global burden of HF ranges from 1-3% in the general adult population, from 1 to 20 cases per 1,000 people, with a five-year mortality rate of 50 to 75%[2]. In clinical practice, we observed that cancer patients are prone to suffer from HF.In 2013, Tal Hasin and his team conducted the first in-depth study of the association between HF and cancer, showing that HF patients with tumors had an increased risk of death[3]. Recent research has shown that HF patients are more likely to develop cancer, but there is insufficient research evidence to prove that whether there is an association between the two diseases and whether having both diseases results in an increase in mortality.

Cancer patients are prone to develop HF[4],which can be observed after a variety of treatments including chemotherapy, radiotherapy, targeted therapy and immunotherapy. Chemotherapy is widely considered an effective anti-cancer treatment. However, some medication, e.g. anthracycline, can cause damage to cardiomyocytes, leading to a decline in heart function and, ultimately, heart failure[4]. Radiotherapy is used to treat some types of cancer but can cause problems such as cardiomyopathy, pericarditis[5].In addition, the heart can be adversely affected by radiation, which impairs heart function and increases the risk of heart failure. Certain targeted therapies can also have harmful effects on the heart, causing damage to the myocardium and reduce heart function. Inhibitors of vascular endothelial growth factor (VEGF), for example, may increase the risk of HF through a variety of mechanisms, including endothelial damage, vasoconstriction and remodeling, and inflammatory responses. Immunotherapy (for example, PD-1 inhibitors and CTLA-4 inhibitors) may also cause the immune system to attack heart tissue sometimes, which leads to myocarditis and compromised heart function. At the same time, cancer itself has the potential to affect heart function in a number of ways, such as cancerous cardiomyopathy and cancerous pericarditis.

Heart failure may increase the risk of cancer, which may be attributed to factors such as weakened immune system and HF medication. HF patients are more likely to be attacked by tumour cells due to their dysfunctional immune system, leading to increased incidence of cancer[6]. Some HF medication are thought to be associated with the development and progression of cancer, especially in patients who take certain medications for long periods of time. In a national insurance cohort study in South Korea, which investigated the cancer risk in HF patients, found that valsartan, which is used in HF patients, increased the risk of liver and kidney cancer compared to other ARBs[7]. In addition, there are many common risk factors between cardiovascular disease and cancer, such as age, smoking, overweight, diabetes and hyperlipidemia[8]. But a clear association between the two diseases has yet to be established. In addition, markers for early screening of HF in cancer patients have not been determined[9]. Therefore, the purpose of this study was to determine whether there is an association between HF and cancer, as well as its impact on survival, and to further explore whether NT-proBNP level in cancer patients are predictive of HF in NHANES database between 1999 and 2018.

METHODS

Ethics approval

Since the study used only secondary data analysis and did not identify the personal information of any of the participants by extracting statistics from the NHANES website, further ethical approval is not required to conduct the study (for more information, visit http://www.ethicsguidebook.ac.uk/Secondary-analysis-106.

Study population

As noted elsewhere, the National Health and Nutrition Examination Survey (NHANES) is a nationwide, population-based, multiyear cross-sectional study. The study sample is a representative sample of the U.S. civilian population that is not institutionalized. Demographic information (for more information, visit http://wwwn.cdc.gov/nchs/nhanes/), as well as self-reported health status with or without cancer (MCQ220) and heart failure (MCQ160B), were obtained through home interviews using questionnaires whose data were well preserved and shipped to relevant health research centers for analysis. Detailed data processing and analysis methods can be found on the NHANES website (for more information, visit https://wwwn.cdc.gov/nchs/nhanes/2017-2018/MCQ_J.htm). For the current analysis, a 1999-2018 cohort was selected to study the relationship between cancer and heart failure. NHANES researchers received informed consent from participants.

Data collection

The present study collected data from participants between the age of 20 and 85. Before statistical analysis,we excluded participants who had missing data in either MCQ220 or MCQ160B from the analysis.For data missing from variables other than MCQ220 and MCQ160B, we treated the missing data separately depending on whether the variable is categorical or continuous. For categorical variables, individuals with missing data are categorized as a separate group. For continuous variables, we deleted the variable when the missing rate is > 40%, we use mean values to fill missing data when the missing rate is less than 5%, and we use multiple insertions to fill missing data when the missing rate is between 5% and 40%.

NT-proBNP Measurement

We used serum NT-proBNP data from the 1999-2004 NHANES cycle with a range of 5 pg/ml to 35,000 pg/ml. In addition, we explored significant differences in NT-proBNP levels between different HF and cancer groups using ANOVA and Tukey multiplex comparison assays.

Statistical Analyses

In this study, we first performed a detailed descriptive statistical analysis of baseline characteristics of included participants. These characteristics include important demographic variables such as age, gender, race and education.For categorical variables, we displayed percentage (95%CI). For continuous variables following a normal distribution, we calculated the mean and standard deviation (mean ± SD). However, due to the significant skewness of NT-proBNP in the NHANES data, we used the mean and standard error of the mean (mean ± SEM) for its representation.

Preference Score Matching (PSM)

To further analyze the association between heart failure and cancer, we performed a bias score matching (PSM) application. PSM is a statistical method used to reduce the impact of potentially confounding variables in observational studies by matching participants from different groups (e.g., with or without heart failure, cancer, etc.) to ensure similarity in key covariates. Before and after PSM, we performed a balancing test to ensure the validity and accuracy of PSM. The specific operations of the match include the use of the nearest neighbor method and standardized calibration value settings, as well as careful balancing assessment of the match results. Comparing baseline features, we evaluated significant differences between groups using the Kruskal Wallis rank sum test and / or Fisher precision probability test.

Logical regression model

To comprehensively assess the association between self-reported cancer and heart failure in adults, we used a survey-weighted logistic regression model based on NHANES data. For our regression analysis, we used weighted variables designed by NHANES, considering our study included hematology variables, we chose Mobile Exploration Centers (MEC) weights. The weight calculation formula for 1999–2000 and 2001–2002 was 2/10 × wtmec4yr, and the weight calculation formula for 2003–2018 was 1/10 × wtmec2yr. We constructed multiple models to explore the relationship between heart failure and cancer. For example, we present three weighted logistic regression models before and after PSM in Table 2. Model 1 analyzed the coefficient of cancer on HF, model 2 added covariates such as gender, age, race and education to model 1. Model 3 further added variables such as diabetes, systolic blood pressure, diastolic blood pressure and BMI to model 2. Overall, the results of these weighted logistic regression models provide odds ratio (OR) and 95% confidence interval (CI) and P values for each variable, further enhancing the interpretation of the results. In this way, we were able to effectively assess and quantify the association between cancer and heart failure, taking into account multiple possible confounding factors.

We use R software (version 4.3.1) and Empower 6.0 for all statistical analysis.

RESULTS

We first compared weighted baseline characteristics based on the presence or absence of heart failure（Table1）. Before Propensity Score Matching (PSM), marked differences were observed between heart failure (HF) and non-heart failure (non-HF) groups in terms of age (P<0.0001), poverty income ratio (P<0.0001), body mass index (BMI) (P<0.0001), cancer (P<0.0001), gender (P=0.0065), race (P<0.0001), education years (P<0.0001), marital status (P<0.0001), diabetes (P<0.0001), smoking (P<0.0001), exercise habits (P<0.0001), hepatitis C virus status (P=0.004), and hepatitis B virus status (P=0.8222). After PSM, disparities were resolved between the HF and non-HF groups. The majority of baseline characteristics between the HF and non-HF groups no longer showed significant differences, including age (P=0.107), poverty income ratio (P=0.734), gender (P=0.624), race (P=0.898), education years (P=0.743), marital status (P=0.684), diabetes (P=0.556), smoking habits (P=0.966), exercise habits (P=0.066), hepatitis C virus (P=0.361), and hepatitis B virus (P=0.289). However, BMI continued to show a significant difference (P<0.001). The statistical analyses involved survey-weighted linear regression for continuous variables and survey-weighted Chi-square test for categorical variables.

Secondly, we compared weighted baseline characteristics based on the presence or absence of cancer（Table2）. Before PSM, significant differences between the cancer and non-cancer groups were found in heart failure prevalence (P<0.0001), age (P<0.0001), poverty income ratio (P<0.0001), systolic and diastolic blood pressure (P<0.0001), waist circumference (P<0.0001), gender (P<0.0001), race (P<0.0001), education level (P<0.0001), marital status (P<0.0001), diabetes (P<0.0001), and smoking (P<0.0001). After PSM, disparities in all variables were adjusted. Survey-weighted linear regression for continuous variables and survey-weighted Chi-square test for categorical variables were applied.

Furthermore, we constructed 3 logical regression models using heart failure as an outcome variable and cancer as a covariate before and after PSM (Table 3). In the pre-PSM analysis, model 1 demonstrated that cancer was a significant factor associated with an increased likelihood of heart failure (OR = 3.23, 95% CI = 2.77-3.77, p<0.001). Model 2 adjusted for additional variables including gender, age, race, education, poverty income ratio, and marital status, yielding a lower odds ratio for the association between cancer and heart failure (OR = 1.41, 95% CI = 1.18-1.67, p<0.001). Model 3 made further adjustments including diabetes, blood pressure, smoking, body mass index, and waist circumference, which slightly altered the odds ratio again (OR = 1.33, 95% CI = 1.11-1.59, p=0.002).

Following propensity score matching, model 1 found that the association between cancer and heart failure was not statistically significant (OR = 1.12, 95% CI = 0.93-1.34, p=0.2). Model 2 , maintaining the adjustments from Model 2 Pre-PSM, also showed a non-significant association (OR = 1.12, 95% CI = 0.93-1.36, p=0.2). Finally, model 3, which included all the adjustments from Model 3 Pre-PSM, confirmed the non-significant association (OR = 1.16, 95% CI = 0.95-1.41, p=0.2) using heart failure as outcome and cancer as covariate.

We next constructed 3 logical regression models using cancer as an outcome variable and heart failure as a covariate before and after PSM (Table 4). In the pre-PSM analysis, model 1 demonstrated that HF was a significant factor associated with an increased likelihood of cancer (OR = 3.23, 95% CI = 2.77-3.77, p<0.001). Model 2 adjusted for additional variables including gender, age, race, education, poverty income ratio, and marital status, yielding a lower but significant odds ratio for the association (OR = 1.39, 95% CI = 1.18-1.64, p<0.001). Model 3 made further adjustments including diabetes, smoking, moderate activity, hepatitis C RNA, and hepatitis B surface antigen, which showed significant odds ratio for the association (OR = 1.31, 95% CI = 1.11-1.55, p=0.002).

Following propensity score matching, model 1 indicated that the association between heart failure and cancer was still present (OR = 1.41, 95% CI = 1.14-1.74, p=0.002). Model 2, which retained the adjustments from Model 2 Pre-PSM, showed an odds ratio of (OR = 1.48, 95% CI = 1.19-1.84, p<0.001). Model 3 with all the additional adjustments from Model 3 Pre-PSM, maintained the significant association (OR = 1.46, 95% CI = 1.17-1.82, p<0.001).

Based on the available data, we have made the following statistics. The prevalence of heart failure was 3.0% in participants without cancer and 7.9% in people with cancer (Figure 2). The prevalence of cancer in participants without heart failure was 8.9%, and in people with heart failure it was 21.4% (Figure 3).

As can be seen from the Figure 4, different cancer types were associated with different HF prevalence, esophagus and blood cancer was associated with higher HF prevalence.

In the analysis of participants without known heart failure, those with cancer diagnosis exhibited significant higher ($P < 0.01$) average levels of NT-proBNP (316.33 pg/mL) than those without cancer (151.90 pg/mL)（Figure 5）. In patients with known heart failure, those with concurrent cancer demonstrated significantly ($P < 0.01$) elevated NT-proBNP levels, with an average of 1597.50 pg/mL compared to 1114.89 pg/mL without cancer. Patients with cancer (412.36 pg/mL) had a significantly higher mean NT-proBNP level of compared to those without cancer (178.40 pg/mL)（$P < 0.01$）（Figure 7）. As shown in Figure 8, participants with both heart failure and cancer (HF/CA) displayed the highest average NT-proBNP level, while the group with neither condition (No HF/No CA) had the lowest average NT-proBNP level. The ANOVA results revealed significant differences between four groups ($F = 145.5$, $p < 0.01$), while Tukey's post hoc tests confirmed significant disparities between each two groups (all $p < 0.01$).

In order to explore the prognostic value of NT-proBNP in cancer patients, Kaplan-Meier survival analysis was performed in cancer participants without known heart failure（Figure 9）. Patients were divided into two groups according to median NT-proBNP level: those with NT-proBNP≤ 51.51 pg/mL (low NT-proBNP group) and those with NT-proBNP > 51.51 pg/mL (high NT-proBNP group). High NT-proBNP group showed significant poorer survival compared with low NT-proBNP group. The log-rank test confirmed significant difference ($p<0.0001$). We further categorized patients into four distinct groups based on the presence or absence of heart failure (HF) and cancer (CA). The Kaplan-Meier survival analysis （Figure 11）compared survival between the four groups over a course of 120 months. Participants with no heart failure and no cancer (No HF/No CA) exhibited highest survival. Conversely, participants with both heart failure and cancer (HF/CA) exhibited lowest survival, log-rank test showed significant difference among four groups ($p < 0.0001$).

DISCUSSION

This study included 54,847 participants in the NHANES cohort from 1999 to 2018. Based on the presence or absence of heart failure and cancer, we employed weighted logistic regression models to analyze the association between cancer and heart failure. The results showed significant association using cancer as an outcome variable and heart failure as a covariate after adjusting for known risk factors of heart failure and cancer, while no significant association persisted using heart failure as outcome and cancer as covariate after adjusting for known risk factors of heart failure and cancer. Our results confirmed significant association between heart failure and cancer in a representative population. Moreover, through a two-way interaction analysis, this association may be attributed by the occurrence of cancer in heart failure patients. Our in-depth study of the association between different types of cancer and heart failure found that esophageal and blood cancers were associated with higher risk of heart failure compared with other types of cancer. Secondly, this study found the longest median survival time in participants without heart failure or cancer, the shortest median survival time in participants with heart failure and cancer. Interestingly, participants with heart failure but without cancer showed significant longer median survival time than participants with cancer but without heart failure. The poor prognosis in participants with heart failure and cancer may be attributed to several factors. Cancer patients with combined heart failure may not be able to tolerate invasive treatments such as surgery due to factors such as reduced heart function, which may influence the treatment effect of cancer and lead to poor prognosis. Moreover, certain cancer treatments such as chemotherapy, immunotherapy or

radiotherapy, may aggravate or cause heart failure, and result in adverse outcome. Patients with heart failure had reduced heart function and increased heart burden, which may promote the growth and metastasis of cancer cells, which may potentially compromise survival time. Thirdly, in order to distinguish cancer patients with poor prognosis, we compared NT-proBNP level in different participant groups. This study found significantly higher level of NT-proBNP in participants with cancer than those without cancer, no matter they have known heart failure or not. In cancer participants without known heart failure whose NT-proBNP level was higher than 51.51 pg/mL exhibited significant shorter survival time. These results suggest that NT-proBNP could act as a prognostic marker in cancer patients. However, the cut-off value of NT-proBNP needs systematical evaluation in cancer population for prognosis, with or without heart failure.

The aim of this study was to comprehensively assess the association of cancer with heart failure and consequent risk of death in the U.S. population, and explore the prognostic value of NT-proBNP in cancer patients. This study followed a rigorous research program and quality control process, with a large representative sample of data, and successfully captured multiple key covariates through the integration of NHANES data. In addition, there are many confounding factors for cancer and heart failure, including gender, age, race, BMI et al. We used standardized methods and three different models to adjust for various possible confounding factors in order to control important possible confounding factors.

Study limitation

However, our study has some limitations. Firstly, due to limitations of current cross-sectional data, we cannot draw definitive cause-and-effect conclusions. Secondly, heart failure is identified by self-report, not every participant has NT-proBNP data, thus a definitive diagnosis of heart failure is limited. Thirdly, the NHANES database does not collect echocardiographic data, the study did not specify the type of heart failure (such as heart failure with reduced ejection fraction or heart failure with preserved ejection fraction), it is impossible to establish association between cancer and different types of heart failure.

Taken together, the current study revealed significant association between cancer and heart failure in a representative Health and Nutrition Examination Survey cohort, co-morbidity of cancer and heart failure leads to an increased risk of death. Significantly higher level of NT-proBNP was found in participants with cancer than those without cancer, no matter they have known heart failure or not. In cancer participants without known heart failure higher NT-proBNP levels may indicate poor prognosis. This study supports the literature on the relationship between cancer and heart failure, which highlights the importance of early diagnosis and treatment of heart failure in cancer patients, as well as the need to emphasise cancer risk in patients with heart failure.

Central Illustration: This study revealed significant association between HF and cancer. HF was associated with an increased occurrence of cancer, and cancer was associated with a higher occurrence of HF. Moreover, Kaplan-Meier survival analysis revealed shortest survival in patients with both HF and cancer compared to those with either disease alone, while patients with HF but no cancer showed significantly shorter survival than patients with cancer but no HF. In cancer patients without HF, NT-proBNP higher than 51.51 pg/ml was associated with shorter survival.

Clinical Perspectives: In cancer patients with or without known heart failure, NT-proBNP was higher in cancer patients, NT-proBNP could be used as prognostic marker in cancer patients.

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Figure legends

Figure 1. Flowchart of participants inclusion.

Figure 2. Incidence rate of heart failure among all participants with/without cancer.

Figure 3. Incidence rate of cancer among all participants with/without heart failure.

Figure 4. Incidence rate of heart failure among all participants with different types of cancer.

Figure 5. Comparision of NT-proBNP level in participants without known heart failure, stratified by cancer status.

Figure 6. Comparision of NT-proBNP level in participants with heart failure, stratified by cancer status.

Figure 7. Comparision of NT-proBNP level in participants no matter wheter they have known heart failure or not, stratified by cancer status.

Figure 8. Comparision of NT-proBNP level across four patient groups categorized by the presence or absence of heart failure (HF) and cancer (CA).

Figure 9. Kaplan-Meier survival analysis in cancer participants without known heart failure according to NT-proBNP level.

Figure 10. Kaplan-Meier survival analysis across four patient groups categorized by the presence or absence of heart failure (HF) and cancer (CA).

Table-1 Baseline Characteristics of Heart Failure Groups Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Non-HF (52949)	HF (1898)	P-value	Non-HF (1898)	HF (1898)	P-value
Age(years)	46.5 (46.2 ,46.9)	66.4 (65.6 ,67.3)	<0.0001	69.0 ± 12.7	68.4 ± 12.5	0.107
Poverty income ratio	3.0 (2.9 ,3.0)	2.3 (2.2 ,2.4)	<0.0001	2.1 ± 1.3	2.1 ± 1.3	0.734
Body Mass Index (kg/m^2)	28.7 (28.6 ,28.8)	31.5 (31.0 ,32.1)	<0.0001	29.3 ± 6.5	31.2 ± 8.0	<0.001
Cancer			<0.0001			0.029
No	90.8 (90.5 ,91.2)	75.4 (72.6 ,78.0)		1545 (81.4%)	1491 (78.6%)	
Yes	9.2 (8.8 ,9.5)	24.6 (22.0 ,27.4)		353 (18.6%)	407 (21.4%)	
Sex			0.0065			0.624
female	52.1 (51.6 ,52.5)	48.1 (45.3 ,50.9)		842 (44.4%)	857 (45.2%)	
male	47.9 (47.5 ,48.4)	51.9 (49.1 ,54.7)		1056 (55.6%)	1041 (54.8%)	
Race			<0.0001			0.898
Mexican American	8.3 (7.3 ,9.4)	4.1 (3.1 ,5.4)		219 (11.5%)	206 (10.9%)	
Other Hispanic	5.7 (4.9 ,6.6)	4.3 (2.9 ,6.3)		112 (5.9%)	117 (6.2%)	
Non-Hispanic White	67.9 (65.8 ,69.9)	72.2 (69.2 ,75.0)		1021 (53.8%)	1022 (53.8%)	
Non-Hispanic Black	11.2 (10.1 ,12.4)	14.5 (12.4 ,16.8)		442 (23.3%)	457 (24.1%)	

Other Race - Including Multi-Racial	7.0 (6.4 ,7.7)	4.9 (3.6 ,6.7)		104 (5.5%)	96 (5.1%)	
Education(years)			<0.0001			0.743
Less Than 9th Grade	5.9 (5.5 ,6.3)	14.1 (12.4 ,16.1)		408 (21.5%)	390 (20.5%)	
9-11th Grade (Includes 12th grade with no diploma	11.3 (10.7 ,11.9)	18.3 (16.0 ,20.9)		383 (20.2%)	385 (20.3%)	
High School Grad/GED or Equivalent	24.0 (23.2 ,24.8)	27.2 (24.7 ,29.9)		430 (22.7%)	460 (24.2%)	
Some College or AA degree	30.8 (30.1 ,31.5)	27.5 (25.0 ,30.1)		460 (24.2%)	461 (24.3%)	
College Graduate or above	28.0 (26.7 ,29.5)	12.8 (10.5 ,15.6)		217 (11.4%)	202 (10.6%)	
Marriage			<0.0001			0.684
Married	56.1 (55.1 ,57.1)	50.8 (47.4 ,54.3)		911 (48.0%)	882 (46.5%)	
Widowed	5.8 (5.5 ,6.0)	23.6 (21.1 ,26.3)		514 (27.1%)	500 (26.3%)	
Divorced	9.9 (9.5 ,10.3)	12.7 (11.0 ,14.7)		225 (11.9%)	255 (13.4%)	
Separated	2.5 (2.3 ,2.7)	2.8 (2.0 ,3.8)		63 (3.3%)	66 (3.5%)	
Never married	18.1 (17.3 ,19.0)	6.9 (5.5 ,8.7)		136 (7.2%)	139 (7.3%)	
Living with partner	7.6 (7.2 ,8.1)	3.1 (2.2 ,4.5)		49 (2.6%)	56 (3.0%)	
Diabetes			<0.0001			0.556
No	90.0 (89.6 ,90.4)	59.9 (57.2 ,62.7)		1075 (56.6%)	1087 (57.3%)	
Yes	8.2 (7.8 ,8.5)	37.3 (34.5 ,40.2)		752 (39.6%)	752 (39.6%)	

	Borderline	1.8 (1.6 ,2.0)	2.7 (2.0 ,3.7)		71 (3.7%)	59 (3.1%)	
	Missing	0.0 (0.0 ,0.1)	0.0 (0.0 ,0.0)				0.966
Smoking				<0.0001	790 (41.6%)	798 (42.0%)	
	Not at all	24.2 (23.5 ,24.9)	42.0 (38.8 ,45.4)		53 (2.8%)	51 (2.7%)	
	Some days, or	3.8 (3.5 ,4.0)	2.8 (1.9 ,4.1)		286 (15.1%)	276 (14.5%)	
	Every day,	17.8 (17.1 ,18.5)	16.2 (14.1 ,18.5)		769 (40.5%)	773 (40.7%)	
	Missing	54.3 (53.3 ,55.2)	39.0 (36.0 ,42.1)				0.066
Exercise				<0.0001	937 (49.4%)	896 (47.2%)	
	No	42.8 (42.0 ,43.6)	46.6 (43.6 ,49.6)		561 (29.6%)	542 (28.6%)	
	Yes	47.9 (47.0 ,48.9)	29.2 (26.7 ,31.9)		400 (21.1%)	460 (24.2%)	
	Missing	9.2 (8.7 ,9.8)	24.2 (21.3 ,27.3)				
Hepatitis C virus				0.004			0.361
	Negative	0.8 (0.7 ,0.9)	1.3 (0.8 ,2.0)		25 (1.3%)	25 (1.3%)	
	Positive	0.9 (0.8 ,1.1)	1.7 (1.0 ,2.9)		42 (2.2%)	30 (1.6%)	
	Missing	98.3 (98.2 ,98.5)	97.0 (95.7 ,97.9)		1831 (96.5%)	1843 (97.1%)	
Hepatitis B virus				0.8222			0.289
	Negative	75.0 (73.7 ,76.2)	74.6 (71.2 ,77.8)		1319 (69.5%)	1274 (67.1%)	
	Positive	0.3 (0.3 ,0.4)	0.4 (0.1 ,1.5)		6 (0.3%)	7 (0.4%)	
	Missing	24.7 (23.4 ,26.0)	24.9 (21.8 ,28.3)		573 (30.2%)	617 (32.5%)	

The study compared the baseline characteristics of patients with heart failure (HF, n=1898) to those without (Non-HF, n=52949) using propensity score matching. Before matching, continuous variables were assessed using weighted linear regression, while categorical ones were evaluated through weighted chi-square tests. The analysis provided weighted means and their 95% confidence intervals (CI) for continuous variables, and weighted percentages with 95% CI for categorical variables. However, post-matching, effective analysis of weighted baseline characteristics was hindered due to certain strata containing only one primary sampling unit (PSU). Hence, continuous variables were represented by mean±standard deviation (Mean±SD), and categorical variables by count and percentage (N(%)). For continuous variables, the Kruskal Wallis rank-sum test was used to calculate P-values. For count variables with theoretical counts less than 10, Fisher's exact test determined P-values.

Table-2 Baseline Characteristics of Cancer Groups Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Non-Cancer (49709)	Cancer (5138)	P-value	Non-Cancer (5138)	Cancer (5138)	P-value
Heart Failure			<0.0001			0.2232
No	98.0 (97.8 ,98.1)	93.8 (92.9 ,94.6)		94.4 (93.6 ,95.1)	93.8 (92.9 ,94.6)	
Yes	2.0 (1.9 ,2.2)	6.2 (5.4 ,7.1)		5.6 (4.9 ,6.4)	6.2 (5.4 ,7.1)	
Age(years)	45.4 (45.0 ,45.7)	62.5 (61.9 ,63.1)	<0.0001	62.0 (61.3 ,62.8)	62.5 (61.9 ,63.1)	0.3011
Poverty income ratio	2.9 (2.9 ,3.0)	3.2 (3.1 ,3.2)	<0.0001	3.2 (3.1 ,3.2)	3.2 (3.1 ,3.2)	0.962
Systolic: Blood pressure (first reading) mm Hg	122.1 (121.8 ,122.4)	128.4 (127.6 ,129.1)	<0.0001	128.1 (127.3 ,128.9)	128.4 (127.6 ,129.1)	0.5784
Diastolic: Blood pressure (first reading) mm Hg	71.1 (70.8 ,71.4)	69.1 (68.6 ,69.6)	<0.0001	69.0 (68.4 ,69.6)	69.1 (68.6 ,69.6)	0.7533

Body Mass Index (kg/m**2)	28.8 (28.6 ,28.9)	28.8 (28.5 ,29.0)	0.9909	28.9 (28.7 ,29.2)	28.8 (28.5 ,29.0)	0.3482
Waist Circumference (cm)	98.2 (97.8 ,98.5)	101.0 (100.4 ,101.5)	<0.0001	101.1 (100.5 ,101.8)	101.0 (100.4 ,101.5)	0.7202
Sex			<0.0001			0.7395
female	51.4 (51.0 ,51.8)	57.5 (55.8 ,59.2)		57.1 (55.3 ,58.8)	57.5 (55.8 ,59.2)	
male	48.6 (48.2 ,49.0)	42.5 (40.8 ,44.2)		42.9 (41.2 ,44.7)	42.5 (40.8 ,44.2)	
Race			<0.0001			0.6624
Mexican American	8.8 (7.7 ,10.0)	2.3 (1.9 ,2.9)		2.1 (1.7 ,2.6)	2.3 (1.9 ,2.9)	
Other Hispanic	6.0 (5.1 ,7.0)	2.4 (1.8 ,3.3)		2.5 (2.0 ,3.1)	2.4 (1.8 ,3.3)	
Non-Hispanic White	66.0 (63.9 ,68.1)	86.3 (84.7 ,87.7)		86.3 (84.8 ,87.7)	86.3 (84.7 ,87.7)	
Non-Hispanic Black	11.9 (10.8 ,13.1)	5.6 (4.8 ,6.4)		6.0 (5.2 ,7.0)	5.6 (4.8 ,6.4)	
Other Race - Including Multi-Racial	7.3 (6.7 ,8.0)	3.4 (2.7 ,4.3)		3.1 (2.5 ,3.7)	3.4 (2.7 ,4.3)	
Education(years)			<0.0001			0.9979
Less Than 9th Grade	6.2 (5.7 ,6.6)	5.3 (4.7 ,6.0)		5.2 (4.5 ,5.9)	5.3 (4.7 ,6.0)	
9-11th Grade (Includes 12th	11.6 (11.0 ,12.3)	9.6 (8.5 ,10.8)		9.5 (8.5 ,10.6)	9.6 (8.5 ,10.8)	

grade with no diploma						
High School Grad/GED or Equivalent	24.2 (23.4 ,25.0)	22.5 (20.8 ,24.2)		22.5 (20.9 ,24.1)	22.5 (20.8 ,24.2)	
Some College or AA degree	30.7 (30.0 ,31.5)	30.8 (29.0 ,32.6)		31.1 (29.0 ,33.2)	30.8 (29.0 ,32.6)	
College Graduate or above	27.2 (25.9 ,28.6)	31.8 (29.4 ,34.3)		31.7 (29.6 ,34.0)	31.8 (29.4 ,34.3)	
Marriage			<0.0001			0.3397
Married	55.3 (54.2 ,56.3)	62.4 (60.5 ,64.3)		61.0 (59.1 ,62.9)	62.4 (60.5 ,64.3)	
Widowed	5.3 (5.0 ,5.6)	14.4 (13.3 ,15.6)		13.9 (12.7 ,15.1)	14.4 (13.3 ,15.6)	
Divorced	9.8 (9.4 ,10.2)	11.9 (10.8 ,13.2)		13.1 (11.8 ,14.6)	11.9 (10.8 ,13.2)	
Separated	2.6 (2.4 ,2.8)	2.1 (1.6 ,2.6)		2.7 (2.1 ,3.3)	2.1 (1.6 ,2.6)	
Never married	19.1 (18.2 ,20.0)	5.7 (4.8 ,6.6)		5.4 (4.6 ,6.3)	5.7 (4.8 ,6.6)	
Living with partner	7.9 (7.5 ,8.4)	3.5 (2.9 ,4.1)		3.9 (3.2 ,4.8)	3.5 (2.9 ,4.1)	
Diabetes			<0.0001			0.6562
No	90.1 (89.7 ,90.5)	81.5 (80.2 ,82.8)		81.4 (80.0 ,82.8)	81.5 (80.2 ,82.8)	
Yes	8.2 (7.8 ,8.5)	15.2 (14.1 ,16.4)		15.7 (14.4 ,17.1)	15.2 (14.1 ,16.4)	
Borderline	1.7 (1.5 ,1.8)	3.2 (2.6 ,4.0)		2.8 (2.2 ,3.4)	3.2 (2.6 ,4.0)	
Missing	0.0 (0.0 ,0.1)	0.0 (0.0 ,0.2)		0.1 (0.0 ,0.4)	0.0 (0.0 ,0.2)	

Smoking			<0.0001			0.8497
Not at all	23.2 (22.5 ,23.8)	38.4 (36.6 ,40.2)		38.5 (36.6 ,40.5)	38.4 (36.6 ,40.2)	
Some days, or	3.9 (3.7 ,4.1)	2.2 (1.7 ,2.8)		2.3 (1.8 ,2.9)	2.2 (1.7 ,2.8)	
Every day,	18.1 (17.4 ,18.9)	14.4 (13.0 ,15.9)		13.6 (12.4 ,14.9)	14.4 (13.0 ,15.9)	
Missing	54.8 (53.9 ,55.8)	45.0 (43.2 ,46.9)		45.6 (43.6 ,47.6)	45.0 (43.2 ,46.9)	

This study utilized propensity score matching to compare baseline characteristics between patients with cancer (n=5138) and those without (n=49709). Continuous variables were analyzed using survey-weighted linear regression, while categorical variables were evaluated by survey-weighted Chi-square tests. The analysis provided survey-weighted means with 95% confidence intervals (CIs) for continuous variables and survey-weighted percentages with 95% CIs for categorical variables.

Table-3 Weighted Logistic Regression Results for Cancer Status on Heart Failure Pre and Post PSM

	Model 1 Pre-PSM			Model 2 Pre-PSM			Model 3 Pre-PSM			Model 1 Post-PSM			Model 2 Post-PSM			Model 3 Post-PSM		
Characteristic	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**
Cancer																		
No	—	—		—	—		—	—		—	—		—	—		—	—	

Yes	3.23	2.77, 3.77	<0.001	1.41	1.18, 1.67	<0.001	1.33	1.11, 1.59	0.002	1.12	0.93, 1.34	0.2	1.12	0.93, 1.36	0.2	1.16	0.95, 1.41	0.2
Sex																		
female				—	—		—	—					—	—		—	—	
male				1.59	1.40, 1.81	<0.001	1.42	1.22, 1.66	<0.001				1.59	1.29, 1.94	<0.001	1.47	1.14, 1.89	0.004
Age(years)				1.07	1.06, 1.08	<0.001	1.07	1.07, 1.08	<0.001				1.05	1.04, 1.06	<0.001	1.06	1.05, 1.07	<0.001
Race																		
Mexican American				—	—		—	—					—	—		—	—	
Other Hispanic				1.37	0.99, 1.90	0.056	1.53	1.09, 2.15	0.015				1.34	0.69, 2.58	0.4	1.59	0.80, 3.15	0.2

Non-Hispanic White	1.63	1.25, 2.13	<0.001	1.72	1.31, 2.26	<0.001	1.96	1.11, 3.45	0.021	2.23	1.26, 3.95	0.006
Non-Hispanic Black	2.2	1.65, 2.94	<0.001	2.08	1.54, 2.79	<0.001	2.29	1.25, 4.17	0.007	2.29	1.25, 4.17	0.007
Other Race - Including Multi-Racial	1.5	1.00, 2.24	0.052	1.62	1.07, 2.45	0.022	1.88	0.79, 4.45	0.2	2.15	0.94, 4.92	0.07
Education(years)												
Less Than 9th Grade	—	—		—	—		—	—		—	—	
9-11th Grade (Includes 12th grade with no diploma)	1.02	0.84, 1.24	0.8	0.97	0.79, 1.19	0.7	1.02	0.75, 1.38	>0.9	0.92	0.67, 1.28	0.6
High School Grad/GED or Equivalent	0.81	0.66, 0.99	0.039	0.8	0.65, 0.99	0.037	0.81	0.60, 1.10	0.2	0.8	0.58, 1.09	0.2

Some College or AA degree	0.83	0.68, 1.02	0.073	0.79	0.64, 0.97	0.026	0.77	0.57, 1.05	0.1	0.73	0.54, 1.00	0.049
College Graduate or above	0.49	0.38, 0.64	<0.001	0.54	0.41, 0.71	<0.001	0.39	0.26, 0.59	<0.001	0.43	0.28, 0.67	<0.001
Poverty income ratio (PIR)	0.77	0.73, 0.82	<0.001	0.78	0.74, 0.83	<0.001	0.84	0.77, 0.91	<0.001	0.86	0.79, 0.93	<0.001
Marital status												
Married	—	—		—	—		—	—		—	—	
Widowed	1.17	0.98, 1.39	0.079	1.27	1.06, 1.52	0.01	1.25	0.98, 1.60	0.071	1.31	1.02, 1.68	0.035
Divorced	1.16	0.96, 1.41	0.13	1.07	0.87, 1.32	0.5	1.16	0.88, 1.53	0.3	1.1	0.82, 1.48	0.5
Separated	1.28	0.89, 1.85	0.2	1.24	0.85, 1.82	0.3	1.08	0.55, 2.13	0.8	1.14	0.55, 2.33	0.7

Never married	1.01	0.76, 1.33	>0.9	1.07	0.81, 1.41	0.6	0.98	0.61, 1.57	>0.9	1.05	0.65, 1.72	0.8
Living with partner	0.9	0.61, 1.33	0.6	0.92	0.63, 1.36	0.7	1.11	0.52, 2.37	0.8	1.08	0.53, 2.20	0.8
Diabetes												
No				—	—					—	—	
Yes				2.69	2.31, 3.13	<0.001				2.23	1.78, 2.80	<0.001
Borderline				1.08	0.78, 1.50	0.6				0.69	0.42, 1.13	0.14
Missing				0	0.00, 0.00	<0.001				0	0.00, 0.00	<0.001
Systolic blood pressure				0.99	0.99, 1.00	<0.001				0.99	0.99, 1.00	0.055

Diastolic blood pressure	1	1.0, 1.00	0.8	1	0.99, 1.01	0.6
Smoking						
No	—	—		—	—	
Some days, or	1.36	0.88, 2.09	0.2	1.15	0.51, 2.62	0.7
Every day,	1.21	0.97, 1.50	0.085	1.3	0.90, 1.88	0.2
Missing	0.74	0.63, 0.87	<0.001	0.71	0.56, 0.91	0.007
Body Mass Index	1.03	1.01, 1.06	0.001	1.06	1.02, 1.10	0.001
Waist Circumference (cm)	1.01	1.00, 1.02	0.055	1	0.98, 1.01	0.8

We applied weighted logistic regression models to estimate the odds ratios (ORs)、95%CI、P value for heart failure associated with cancer status, alongside other demographic and clinical variables. Three models were assessed both pre- and post-PSM: Model 1 was unadjusted; Model 2 adjusted for sex, age, race, education， poverty income ratio, and marital status,Model 3 included additional adjustments for marital status, diabetes, blood pressure, smoking, body mass index (BMI), and waist circumference.

Table-4 Weighted Logistic Regression Results for Heart Failure Status on Cancer Pre and Post PSM

	Model 1 Pre-PSM			Model 2 Pre-PSM			Model 3 Pre-PSM			Model 1 Post-PSM			Model 2 Post-PSM			Model 3 Post-PSM		
Characteristic	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**	**OR**[1]	**95 % CI**[1]	**p-value**
Heart Failure																		
No	—	—		—	—		—	—		—	—		—	—		—	—	

Yes	3.23	2.77, 3.77	<0.001	1.39	1.18, 1.64	<0.001	1.31	1.11, 1.55	0.002	1.41	1.14, 1.74	0.002	1.48	1.19, 1.84	<0.001	1.46	1.17, 1.82	<0.001
Sex																		
female				—	—		—	—					—	—		—	—	
male				0.81	0.74, 0.88	<0.001	0.76	0.69, 0.83	<0.001				1	0.80, 1.26	>0.9	0.93	0.74, 1.16	0.5
Age(years)				1.06	1.06, 1.07	<0.001	1.06	1.06, 1.07	<0.001				1.05	1.04, 1.06	<0.001	1.05	1.04, 1.07	<0.001
Race																		
Mexican American				—	—		—	—					—	—		—	—	
Other Hispanic				1.19	0.92, 1.54	0.2	1.2	0.93, 1.55	0.2				1.74	0.81, 3.72	0.2	1.85	0.86, 3.99	0.11
Non-Hispanic White				2.45	2.09, 2.87	<0.001	2.41	2.06, 2.83	<0.001				3.96	2.30, 6.80	<0.001	4.12	2.38, 7.13	<0.001
Non-Hispanic Black				1.17	0.97, 1.40	0.094	1.15	0.96, 1.37	0.14				2.05	1.17, 3.60	0.013	2.03	1.15, 3.58	0.015
Other Race - Including Multi-Racial				1.13	0.86, 1.49	0.4	1.11	0.85, 1.46	0.4				1.67	0.73, 3.80	0.2	1.71	0.74, 3.96	0.2

Education(years)													
Less Than 9th Grade	—	—		—	—		—	—		—	—		
9-11th Grade (Includes 12th grade with no diploma)	1.19	1.01, 1.40	0.034	1.13	0.97, 1.32	0.13	1.21	0.86, 1.70	0.3	1.17	0.83, 1.65	0.4	
High School Grad/GED or Equivalent	1.22	1.05, 1.41	0.009	1.17	1.01, 1.35	0.035	1.11	0.81, 1.52	0.5	1.11	0.81, 1.53	0.5	
Some College or AA degree	1.56	1.35, 1.82	<0.001	1.51	1.30, 1.75	<0.001	1.31	0.94, 1.82	0.1	1.32	0.94, 1.86	0.11	
College Graduate or above	1.72	1.45, 2.04	<0.001	1.74	1.46, 2.06	<0.001	1.54	1.00, 2.36	0.049	1.59	1.03, 2.43	0.035	
Poverty income ratio (PIR)	1.02	0.99, 1.05	0.2	1.03	1.00, 1.06	0.078	1.1	1.01, 1.19	0.03	1.1	1.01, 1.20	0.023	
Marital status													
Married	—	—		—	—		—	—		—	—		
Widowed	0.77	0.68, 0.87	<0.001	0.78	0.69, 0.88	<0.001	0.83	0.63, 1.10	0.2	0.85	0.64, 1.12	0.2	

Divorced	1.04	0.91, 1.19	0.5	0.99	0.86, 1.13	0.8	0.97	0.66, 1.43	0.9	0.94	0.64, 1.38	0.8
Separated	1.39	1.07, 1.81	0.014	1.31	1.00, 1.72	0.047	1.91	0.98, 3.73	0.059	1.87	0.94, 3.72	0.075
Never married	0.82	0.69, 0.97	0.02	0.8	0.67, 0.95	0.01	0.91	0.50, 1.64	0.7	0.9	0.49, 1.66	0.7
Living with partner	1	0.82, 1.20	>0.9	0.91	0.75, 1.11	0.4	1.08	0.50, 2.31	0.8	1.1	0.50, 2.41	0.8
Diabetes												
No				—	—					—	—	
Yes				1.18	1.05, 1.32	0.005				1.29	1.04, 1.61	0.024
Borderline				1.39	1.07, 1.81	0.013				0.84	0.45, 1.54	0.6
Missing				0.81	0.19, 3.48	0.8						
Smoking												
No				—	—					—	—	

Some days, or	1.02	0.75, 1.38	>0.9	1.44	0.59, 3.52	0.4
Every day,	1.1	0.96, 1.24	0.2	1.03	0.73, 1.45	0.9
Missing	0.72	0.65, 0.79	<0.001	0.71	0.55, 0.92	0.011
Moderate activity						
No	—	—		—	—	
Yes	1.01	0.93, 1.10	0.8	1.02	0.79, 1.31	0.9
Unable to do activity	1.09	0.95, 1.26	0.2	0.94	0.70, 1.26	0.7
Hepatitis C RNA (HCV-RNA)						
Negative	—	—		—	—	
Positive	0.77	0.43, 1.41	0.4	1.86	0.53, 6.54	0.3

Missing	0.82	0.52, 1.29	0.4	1.62	0.60, 4.41	0.3
Hepatitis B surface antigen						
Negative	—	—		—	—	
Positive	0.69	0.29, 1.62	0.4	2.76	0.61, 12.5	0.2
Missing	1.27	1.17, 1.39	<0.001	1.11	0.84, 1.46	0.4

This study conducted weighted logistic regression to evaluate the relationship between heart failure and cancer occurrence. Three models were applied both pre- and post-propensity score matching (PSM). Model 1 provided unadjusted odds ratios (ORs). Model 2 adjusted for sex, age, race, education, poverty income ratio (PIR), and marital status. Model 3 further adjusted for diabetes, smoking, moderate activity, and hepatitis B and C status.

Figure1

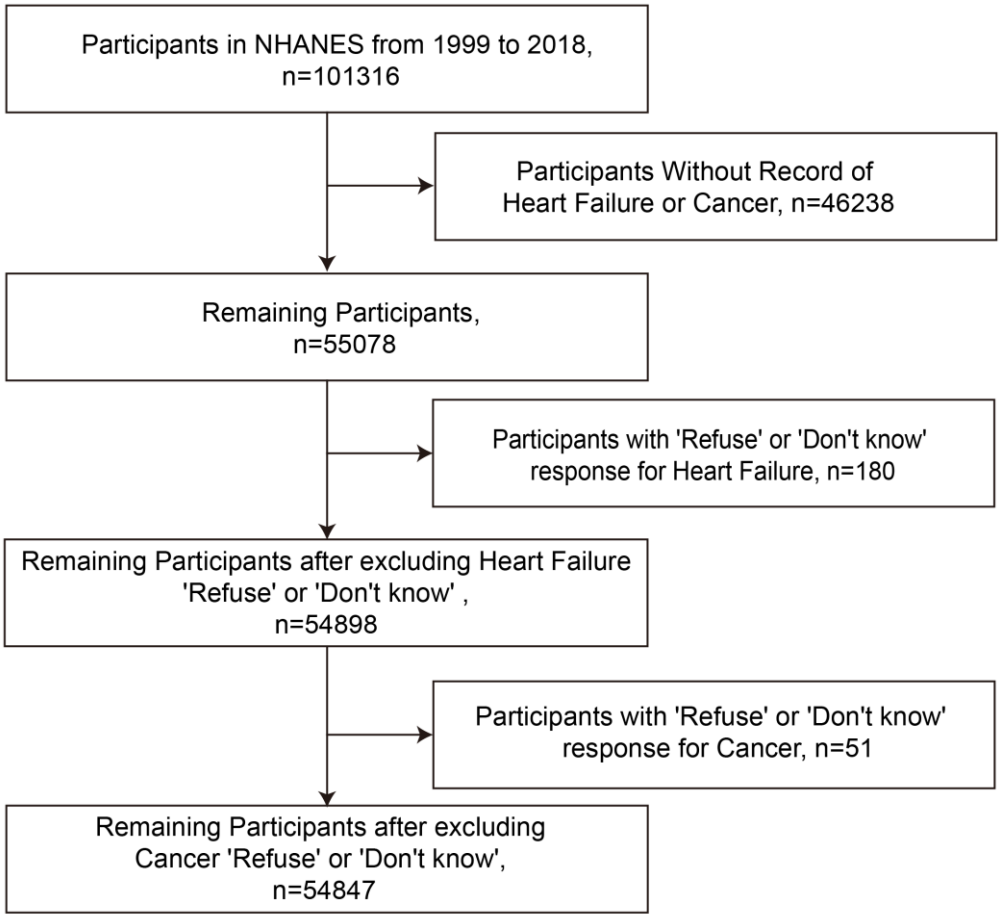

Participants in NHANES from 1999 to 2018, n=101316
Participants Without Record of Heart Failure or Cancer, n=46238
Remaining Participants, n=55078
Participants with 'Refuse' or 'Don't know' response for Heart Failure, n=180
Remaining Participants after excluding Heart Failure 'Refuse' or 'Don't know' , n=54898
Participants with 'Refuse' or 'Don't know' response for Cancer, n=51
Remaining Participants after excluding Cancer 'Refuse' or 'Don't know', n=54847

Figure2

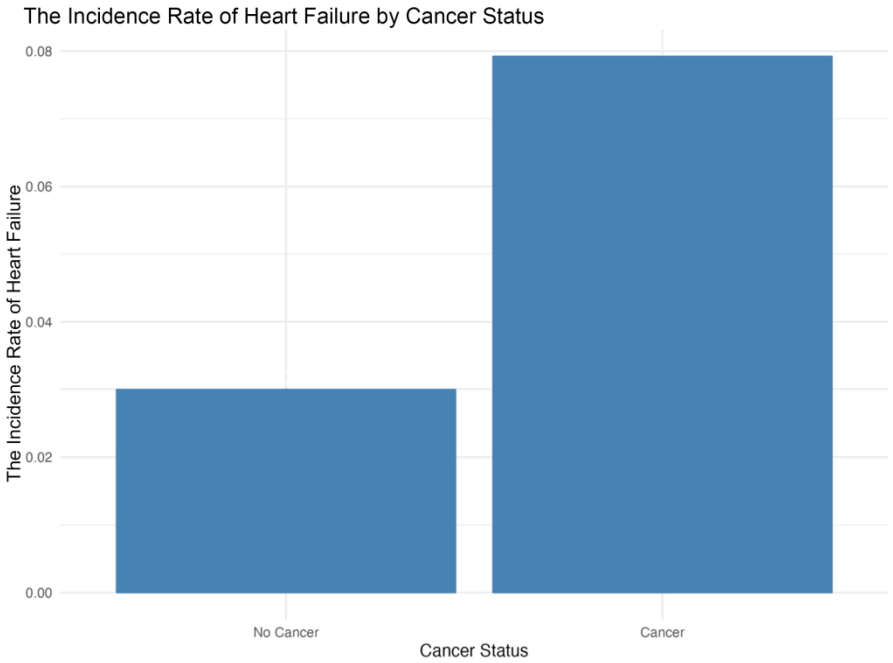

The Incidence Rate of Heart Failure by Cancer Status
0.08
0.06
0.04
0.02
0.00
The Incidence Rate of Heart Failure
No Cancer
Cancer
Cancer Status

Figure3

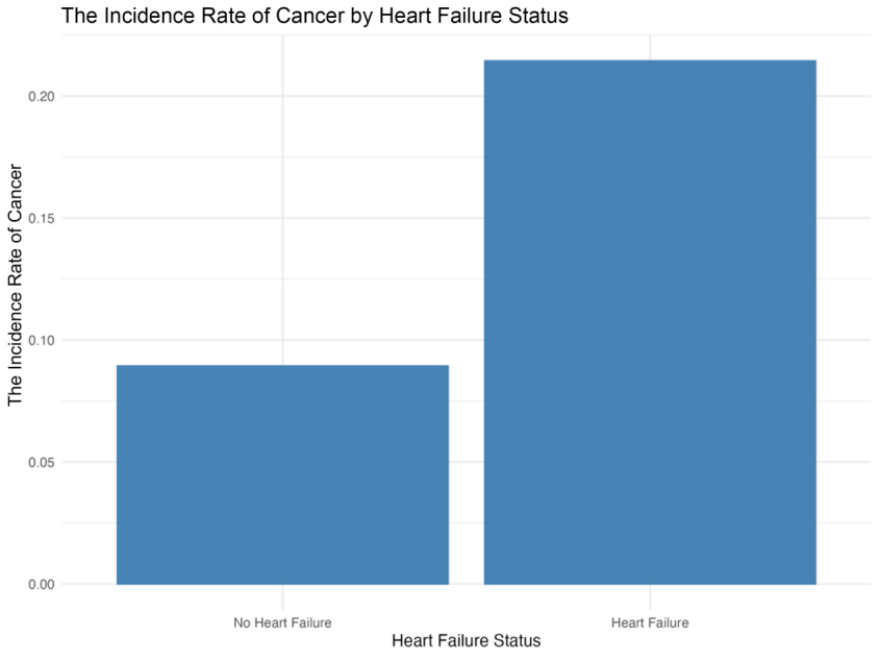


Figure4

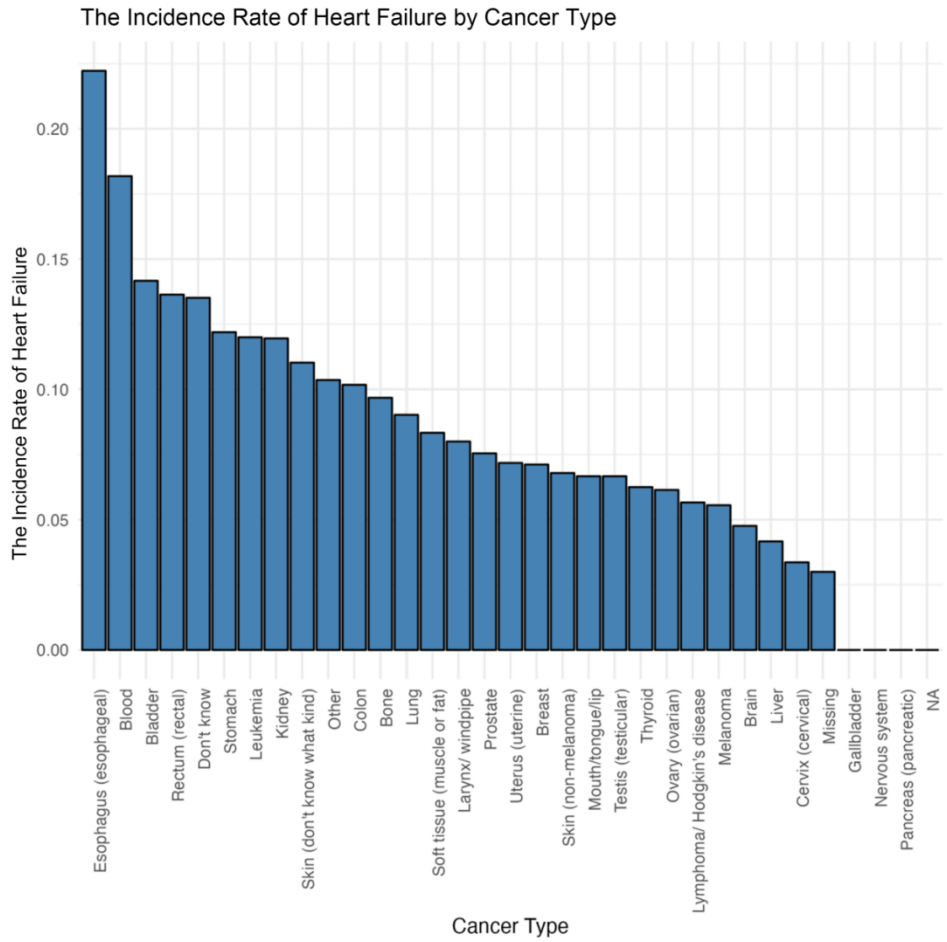


Figure5

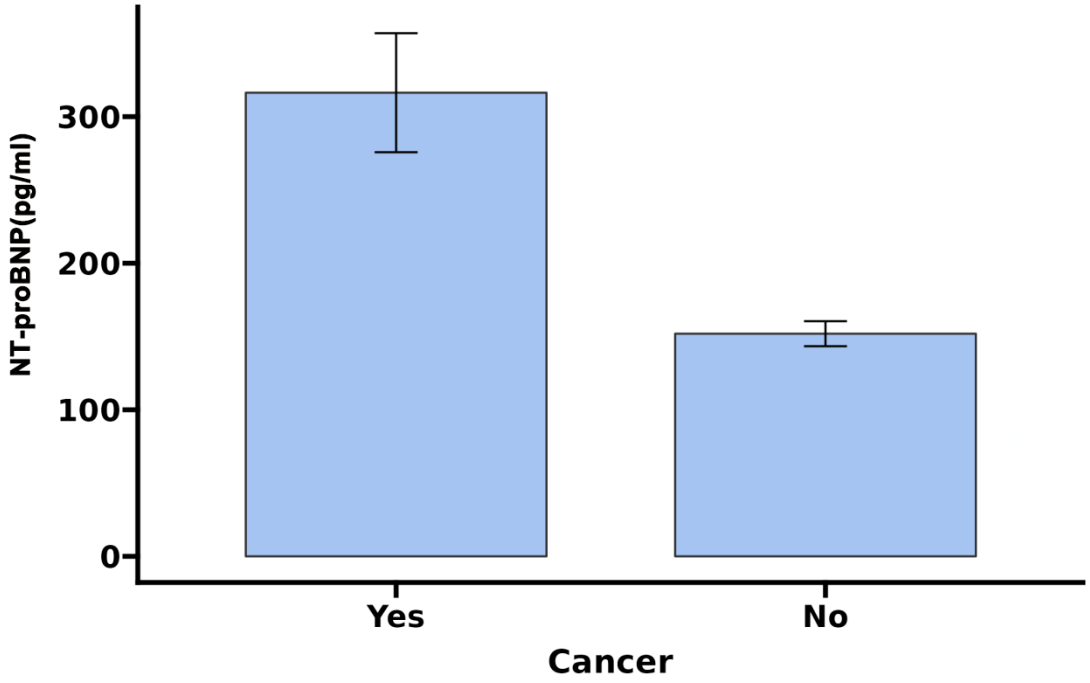


Figure6

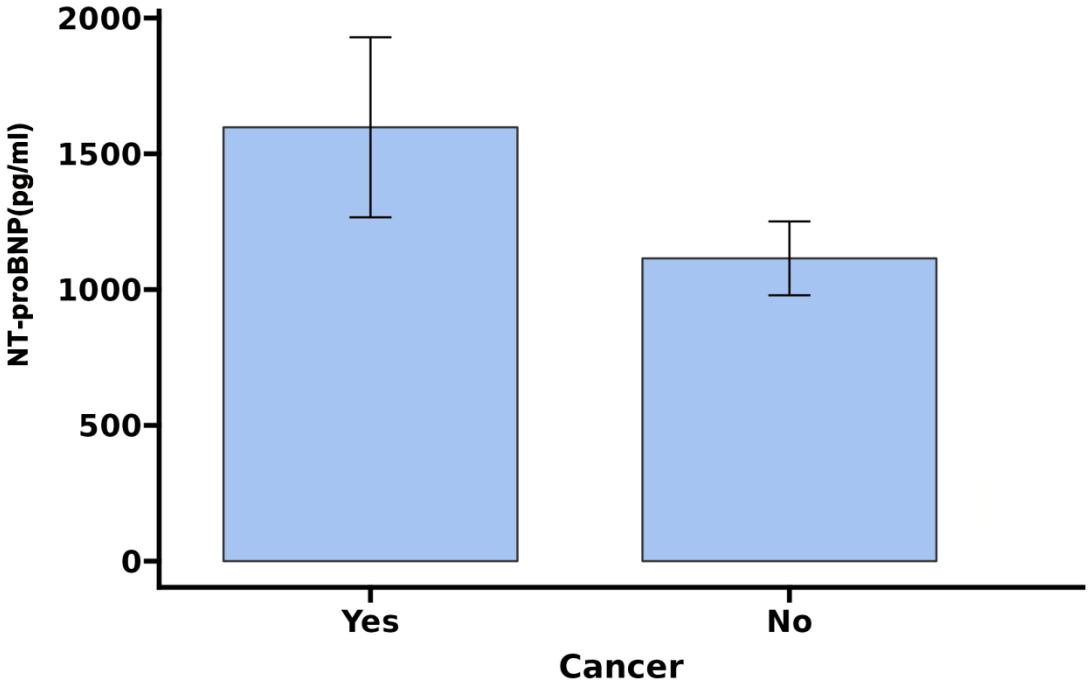


Figure7

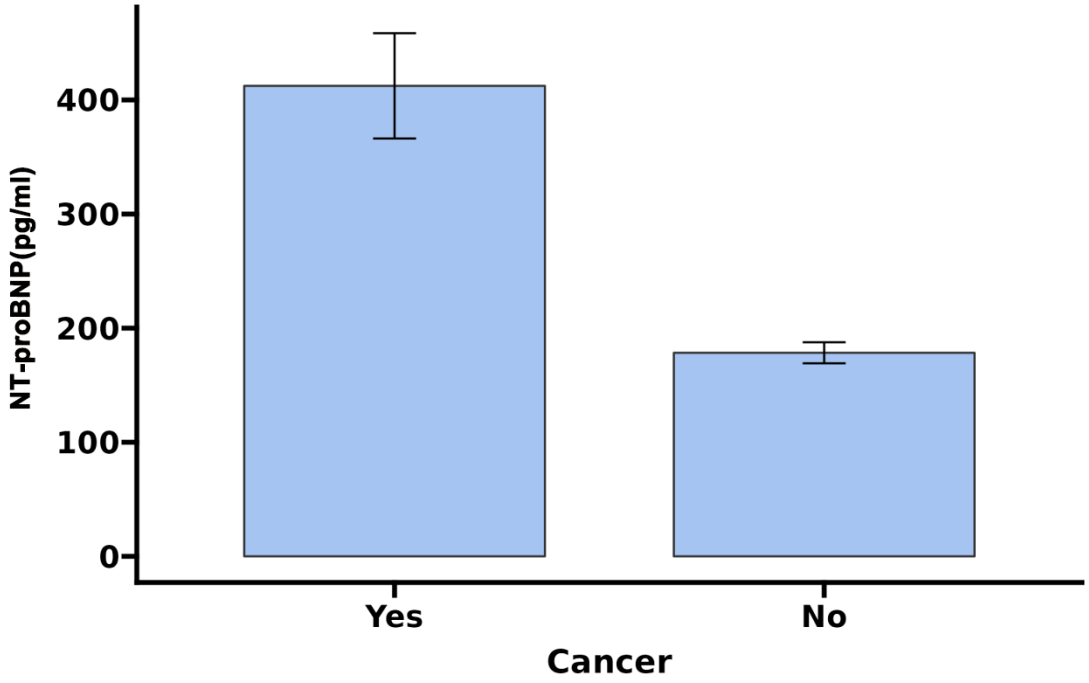


Figure8

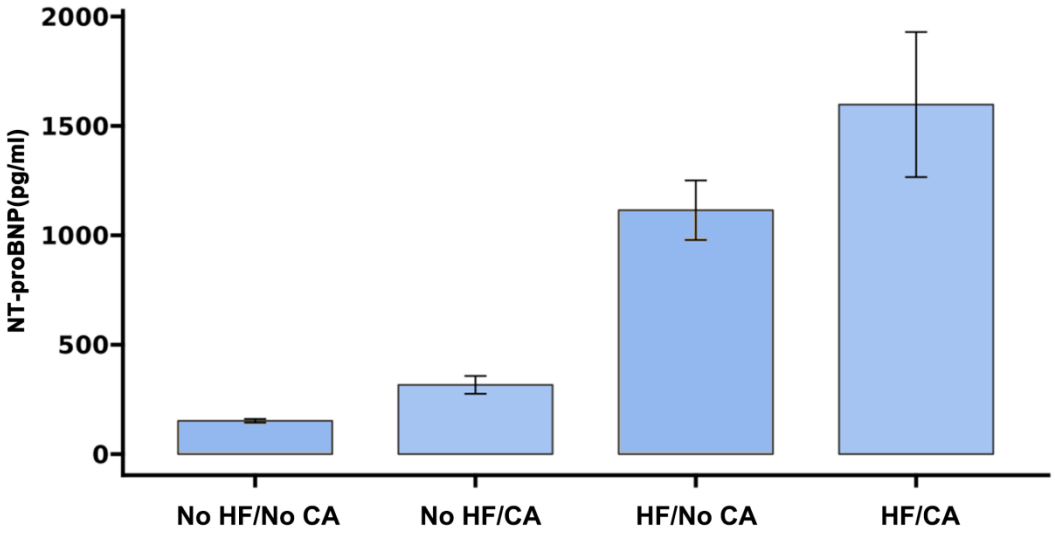


Figure9

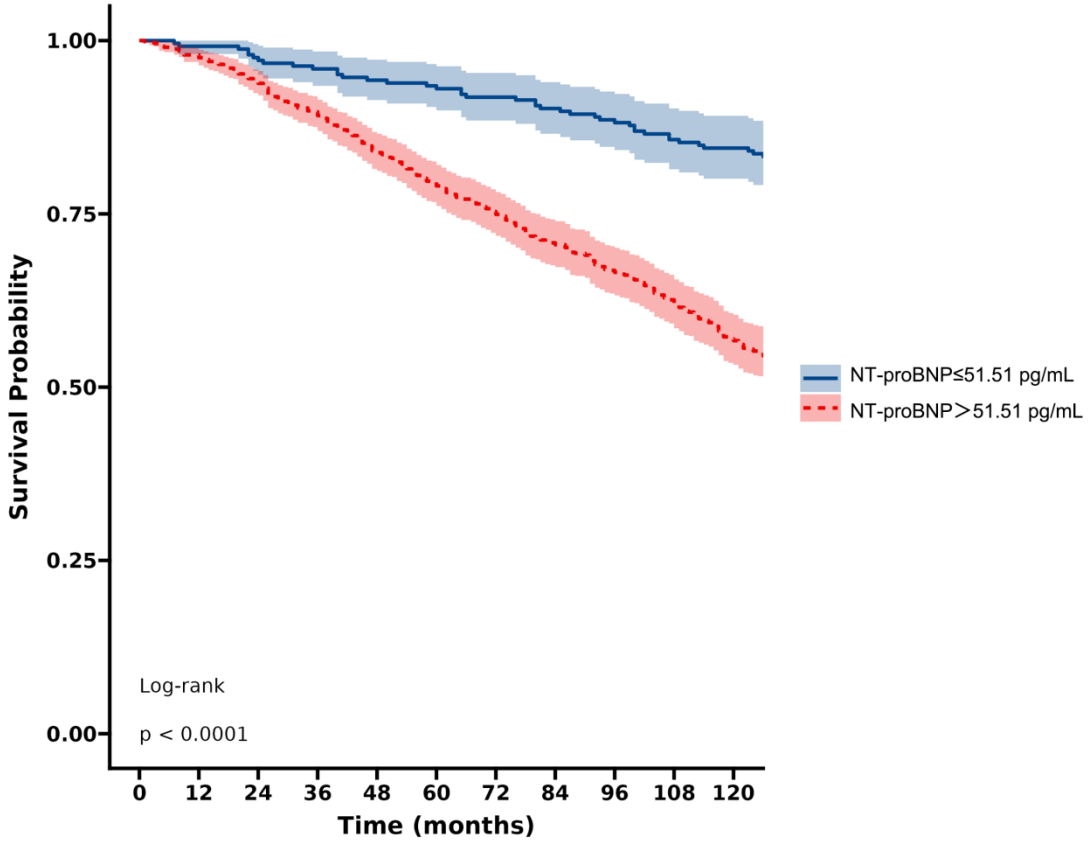
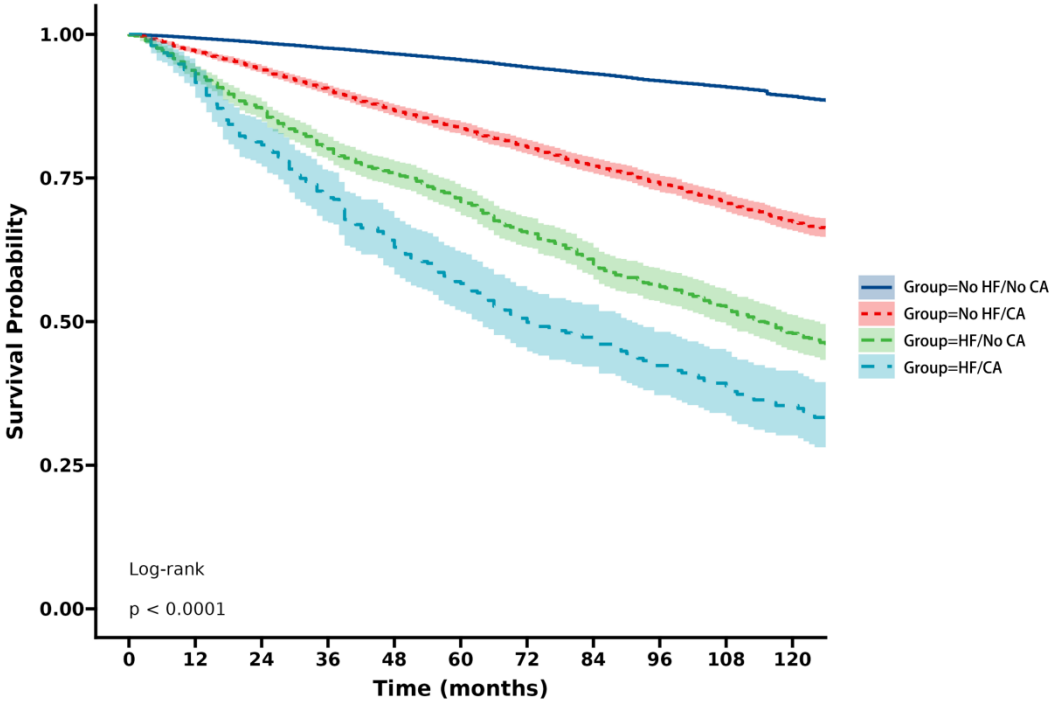

1.00
0.75
0.50
0.25
0.00
Survival Probability
Log-rank
p < 0.0001
0
12
24
36
48
60
72
84
96
108
120
Time (months)
NT-proBNP≤51.51 pg/mL
NT-proBNP>51.51 pg/mL

Figure10


1.00
0.75
0.50
0.25
0.00
Survival Probability
Log-rank
p < 0.0001
0
12
24
36
48
60
72
84
96
108
120
Time (months)
Group=No HF/No CA
Group=No HF/CA
Group=HF/No CA
Group=HF/CA