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Diabetes and Obesity as Risk Amplifiers for Cancer in Heart Failure Patients: a retrospective study, using an electronic health record network

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Abstract

Background:

Evidence suggests a bidirectional relationship between heart failure (HF) and cancer. Type 2 diabetes mellitus (T2DM) and obesity are independently associated with increased cancer risk, yet their combined impact in HF patients remains incompletely characterized.

The objective of the present study is to evaluate the incidence and prevalence of neoplasms in patients with HF, and to determine whether the coexistence of T2DM and obesity further increases cancer risk in this population.

Methods:

Using the TriNetX Global Collaborative Network, we identified patients with HF; separate cohorts were constructed based on the presence or absence of T2DM and obesity. Outcomes were assessed over a ten-year follow-up using Kaplan–Meier survival analysis, Cox proportional hazards regression, and competing risk analysis accounting for mortality as a competing event.

Results:

The HF cohort showed a neoplasm prevalence of 30.6% and an incidence of 20.7% over 5 years. Cox regression confirmed age, obesity and nicotine dependence as independent risk factors. Competing risk analysis revealed a 10-year cumulative neoplasm incidence of 39.5%, exceeding mortality (34.4%).

Patients with T2DM had a significantly higher risk of developing neoplasms compared with patients without diabetes (32.20% versus 29.37%); similarly, patients with obesity showed an increased risk relative to those without obesity. (34.12% vs. 26.59%).

HF patients with both T2DM and obesity had the highest absolute cancer risk, approximately 7% higher in absolute terms compared to HF patients without either comorbidity.

Conclusions:

Patients with HF carry a substantial burden of neoplastic disease, with obesity emerging as a relevant modifiable driver of increased cancer risk in this population. The coexistence of T2DM further amplifies this risk.

Background

Heart failure (HF) is a highly prevalent condition in Western countries, affecting approximately 1–2% of the general population. HF is associated with substantial mortality, a high risk of hospitalization, and poor quality of life. Its clinical management is frequently complicated by the presence of multiple comorbidities, which may directly or indirectly influence disease progression and outcomes. The association between cancer and heart failure, two major global health burdens, has gained increasing attention in recent years. Historically, the relationship between cancer and heart failure was considered unidirectional, primarily focusing on the increased risk of HF in patients undergoing chemotherapy; at the same time a significant incidence of cardiovascular diseases (CVD) has also been demonstrated among cancer survivors, in whom cardiovascular diseases account from 27% to 49% of all deaths across different studies [1,2].

More recently, research has begun to explore the reverse association, namely, the risk of cancer in patients with chronic heart failure. Emerging evidence suggests a significant link between HF and an elevated risk of cancer. Large-scale epidemiological studies report adjusted hazard ratios (HRs) ranging from 1.05 to 2.16, with most estimates exceeding 1 [3–9]. Moreover, cancer has been independently associated with increased mortality in HF patients [3], with cancer-related deaths accounting for 6% to 14% of total mortality in randomized controlled trials involving patients with heart failure with reduced ejection fraction [10].

Increasing attention is being paid to the interplay between heart failure and other medical conditions that are also associated with an increased risk of cancer, particularly type 2 diabetes mellitus (T2DM) and obesity. A high body mass index (BMI) is a recognized risk factor for various types of cancer [11], while the presence of T2DM is associated with an approximately 10% increased risk of cancer development [13–14].

The aim of this study is to evaluate the incidence and prevalence of cancer in patients with chronic heart failure, and to determine whether the coexistence of diabetes and obesity further increases the risk of cancer in this population.

Methods

Data Source

TriNetX (www.trinetx.com) is a federated, cloud-based research network that provides access to electronic medical records from over 150 healthcare organizations (HCOs) in different countries worldwide [15], including hospitals, primary care providers, and specialty clinics.

Only when the data quality, technical infrastructure and data governance frameworks are adequate and robust is membership to TriNetX granted. The agreement is formalized in accordance with the European Union General Data Protection Regulation (GDPR) and the United States Health Insurance Portability and Accountability Act (HIPAA). TriNetX is certified to the ISO 27001:2022 standard.

Study Design and Cohorts Construction

The study was conducted using the TriNetX platform on Sep 01, 2025. We selected the Global Collaborative Network for this analysis. TriNetX's Global Collaborative Network spans numerous countries across different geographical areas of the world, including the US Network, the EMEA Network, the LATAM Network and the APAC Network.

Cohorts were constructed by applying specific inclusion and exclusion criteria based on diagnoses, temporal relationships between criteria were defined as needed. The primary cohort (C1) included patients with a diagnosis of heart failure (HF, 10-CM code: I50) and without a diagnosis of type 1 diabetes mellitus (ICD-10-CM code: E10). The index event was the first instance of HF. The incidence and prevalence of neoplasms were assessed within the primary cohort.

We subsequently identified a cohort of patients who had no diagnosis of type 1 diabetes mellitus and/or no prior diagnosis of neoplasms before the onset of decompensated heart failure (HFc), which was defined as the index event. This cohort was used to evaluate the impact of age, sex, type 2 diabetes mellitus (T2DM), obesity, and nicotine dependence (ICD-10-CM code F17) on the risk of developing neoplasms within a 10-year time window following the index event, using Cox proportional hazards models.

The same cohort was also used for competing risk analyses, as described below.

To investigate the impact of T2DM (ICD-10-CM code: E11) and obesity (ICD-10-CM code: E66) on the risk of developing neoplasms (ICD-10-CM code: C00 – D49) during ten-year time window, separate cohorts were created for:

- HF patients with and without T2DM (HF/T2DM and HF/no T2DM, respectively)
- HF patients with and without obesity (HF/Obesity and HF/no Obesity, respectively)
- HF patients without T2DM and with and without obesity (HF/no T2DM/Obesity and HF/no T2DM/ no Obesity, respectively)
- HF patients with T2DM and with and without obesity (HF/T2DM/Obesity and HF/T2DM/ no Obesity, respectively)

We excluded patients with a diagnosis of neoplasm prior to the index event (HF) and all the patients with a diagnosis of type 1 diabetes mellitus.

To evaluate the impact of T2DM and obesity on the risk of developing neoplasms during ten-year time window, the separated cohorts mentioned above where compared in pair using the “Compare outcomes” feature. Further information on the inclusion and exclusion criteria for the cohorts is provided in the **supplementary materials.**

Incidence and Prevalence

Incident and prevalent cases over a five-year period (2015–2020) were identified in cohort C1 using the ‘Incidence and Prevalence’ TriNetX function (**see Supplement**). The look-back period could start at any time up to one day before the start of each time window. Patients diagnosed with a neoplasm only during the time window were considered incident cases. Patients diagnosed with a neoplasm between the start of the look-back period and the end of the time window were considered prevalent cases.

Competing risk

When studying risk of cancer, death from non-oncological causes represents a competing risk. So, a competing risk analysis has been performed for an unbiased evaluation of the cumulative risk of cancer. The incorporation of competing risk methodology ensures that survival analyses accurately reflect the complex reality of clinical outcomes, where multiple endpoints may compete for occurrence within the same patient population. Further information on the Competing Risk TriNetX function can be found in the **supplementary materials.**

Matching and Statistical Comparison

To compare cohorts, we used the “Compare Outcome” function (**see Supplement**). After defining the index event (HF), the outcome (neoplasm) and an observation period of ten years, cohorts were matched using Propensity Score Matching (PSM) based on the following covariates: age, sex and nicotine dependence. In particular, it was used the built-in TriNetX PSM algorithm for 1:1 matching, a greedy nearest neighbor approach with a caliper of 0.1 pooled standard deviation of the logit of the propensity score. Any characteristic with a standardized mean difference between cohorts lower than 0.1 was considered well matched.

Sensitivity Analyses

To minimize potential bias and confounding, several sensitivity analyses were conducted. We computed the risk of neoplasm across the different cohorts excluding outcome events occurring immediately after the index event to reduce the likelihood of including pre-existing conditions. Analyses were repeated at 1 day, 90 days, and 365 days post-index event to evaluate the temporal effect.

Additionally, we narrowed the pre-index event window to 3 years to better capture conditions potentially related to the index event while excluding distant, unrelated factors.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), or as median and interquartile range (IQR) when the distribution is non-normal. Categorical variables are presented as percentages. Initial unadjusted analyses included all patients meeting the inclusion criteria. To evaluate the independent risk of neoplasm in HF patients with diabetes and obesity, Cox regression analysis was performed, adjusting for age (stratified for ten years), sex, and nicotine dependence.

Adjusted analyses were performed using propensity score-matched cohorts. Kaplan–Meier survival curves were compared using the log-rank test. The assumption of proportional hazards was verified by the test proposed by Gramsch and T herneau [16] incorporated in the TriNetX platform.

Result

Incidence and Prevalence of Neoplasms in Patients with Heart Failure.

The cohort C1 consisted of 4,859,920 patients diagnosed with heart failure and without type 1 diabetes mellitus, as defined in the Methods section.

During the five-year time window, the incidence and prevalence of neoplasms were respectively 20.7% and 30.6%. Age and sex strata were implemented, results are reported in Table 1. The highest incidence of neoplasms was observed in the 65–69 and 70–74 age groups.

Table 1
Incidence and Prevalence of Neoplasms in Patients with Heart Failure in time window 2015-01-01–2020-12-31, with age and sex strata.

Strata	Incidence Proportion	Prevalence	Incidence Rate (cases/person-day)	Incidence Rate (cases/1000 person-day)
40–44	0,138	0,193	0,000099	0,099
45–49	0,157	0,219	0,000115	0,115
50–54	0,175	0,249	0,000129	0,129
55–59	0,197	0,280	0,000147	0,147
60–64	0,228	0,317	0,000175	0,175
65–69	0,244	0,344	0,000189	0,189
70–74	0,247	0,357	0,000195	0,195
75–79	0,235	0,354	0,000191	0,191
80–84	0,219	0,343	0,000186	0,186
85 and older	0,189	0,329	0,000173	0,173
Female	0,202	0,310	0,000154	0,154
Male	0,204	0,299	0,000161	0,161
Unknown Gender	0,354	0,382	0,000308	0,308

Cox Proportional Hazards Analysis.

The HFc cohort consisted of 3,647,425 individuals. Due to infrastructural limitations, as there were too many patients for a model with more than three covariates, two separate models were built. One model considered the age and sex covariates, and the other considered the T2DM, obesity, and nicotine dependence covariates. A higher HR was found for the obesity and nicotine dependence covariates (HR = 1.128 or HR = 1.134, $p < 0.000$), indicating a 12.8% and a 13.4% higher risk, respectively. Furthermore, the results showed that the older the age group (60–70 years or 70–85 years), the higher the HR (HR = 1.331 or HR = 1.415, $p < 0.000$), representing an increased risk of 33.1% or 41.5% respectively. Meanwhile, male sex was linked to a 1.8% increased risk (HR = 1.018, $p < 0.000$). Complete results are reported in Table 2.

Table 2
Cox proportional hazards model results. Cox regression analysis identified obesity and nicotine dependence as the main independent risk factors for neoplasm development. Advanced age showed an even greater impact, with a 33.1% increased risk in patients aged 60–70 years, rising to 41.5% in the 70–85 age group. Male sex was associated with a marginal 1.8% increase in risk.

covariates	hazard ratio	coefficient	standard error	z	P > |z|	95% CI Lower	95% CI Upper
Type 2 diabetes mellitus	1,049	0,05	0,003	14,45	0,00	1,042	1,056
Overweight and obesity	1,128	0,12	0,004	30,14	0,00	1,119	1,137
Nicotine dependence	1,340	0,13	0,005	27,41	0,00	1,124	1,144
Male	1,018	0,018	0,002	7,283	0,000	1,013	1,023
Age at Index							
40–50 Years	0,851	-0,162	0,006	-27,080	0,000	0,841	0,861
50–60 Years	1,041	0,040	0,004	8,952	0,000	1,032	1,049
60–70 Years	1,331	0,286	0,004	74,454	0,000	1,321	1,341
70–85 Years	1,415	0,347	0,004	98,169	0,000	1,405	1,425

Competing risk.

Competing risk analysis was performed, considering two competitive outcomes: death and neoplasm. At ten years, the cumulative incidence of neoplasms reached 39.50%, slightly higher than that of death, which was 34.356%. These findings indicate that while both outcomes contribute significantly to the clinical burden in the studied population, the occurrence of neoplasms is more frequent and represents the dominant competing risk. Complete results are reported in Table 3. Aalen-Johansen cumulative incidence curve is shown in Fig. 1.

Table 3
Competing risk results. At ten years, the cumulative incidence of neoplasms reached 39.505%, slightly higher than that of death, which was 34.4%.

Outcome Name	Patient Count	Percentage of Cohort	Cumulative Incidence at End of Time Window
Deceased	796441	0,175	0,344
Neoplasms	1076603	0,237	0,395

Comparison Between Patients with and without Type II Diabetes Mellitus.

To assess whether the coexistence of T2DM increases the risk of cancer in patients with chronic heart failure, HF/T2DM and HF/no T2DM cohorts were matched. Following matching, both cohorts comprised 1,170,016 individuals, with median follow-up periods of 629 days for patients with heart failure and T2DM, and 457 days for those with heart failure but no T2DM.

There was a statistically significant difference in neoplasm-free survival, with a higher survival probability in patients without T2DM (67.90% and 70.63%, $p < 0.0000$). A Hazard ratio (HR) of 1.04 indicated a 4% higher risk of developing a neoplasm in patients with heart failure and T2DM, even though this HR was not constant throughout the study period (Table 4). Kaplan-Meier curves (Fig. 2) shows an increasing difference between the two cohorts starting from 5 years.

Table 4
comparison of patients with and without diabetes mellitus(A), and with and without obesity (B) (after propensity score matching)

Cohort	Patients in cohort	Age	Male	Nicotine dependence	Patients with outcome	Median follow up	Hazard ratio	95% CI	p	Survival probability at the end fo time window
A										
HF/T2DM	1,170,016	69 ± 13	53.5%	6.8%	142,136	629	1.041	(1.033, 1.049)	0.000	67.90%
HF/no T2DM	1,170,016	69 ± 13	53.5%	6.8%	122,991	457				70.63%
B										
HF/Obesity	813,362	64 ± 14	49.7%	9.0%	113,873	835	1.190	(1.179, 1.201)	0.000	65.88%
HF/no Obesity	813,362	64 ± 14	50.0%	8.8%	79,269	469				73.41%

Comparison Between Patients with and without Obesity.

To assess whether the coexistence of obesity increases the risk of cancer in patients with chronic heart failure, HF/Obesity and HF/no Obesity cohorts were matched. Following matching, both cohorts comprised 813,362 individuals, with median follow-up periods of 835 days for patients with heart failure and obesity, and 469 days for those with heart failure but no obesity.

There was a statistically significant difference in neoplasm-free survival, with a higher survival probability in patients without obesity (65.88% and 73.41%, $p < 0.0000$). A HR of 1.19 indicated a 19% higher risk of developing a neoplasm in patients with heart failure and obesity, even though this HR was not constant throughout the study period (Table 4). Kaplan-Meier curves (Fig. 3) shows an increasing difference between the two cohorts starting from 2 years.

Comparison Between Patients with and without Diabetes or Obesity

To evaluate the impact of obesity on cancer risk among patients with HF, analyses were conducted separately in cohorts stratified by the presence or absence of T2DM, with matched comparisons between obese and non-obese individuals.

In patients without T2DM, the matched HF/no T2DM/Obesity and HF/no T2DM/no Obesity cohorts each included 347,091 individuals. Median follow-up was longer in the obese group (770 days) compared to the non-obese group (515 days). A statistically significant difference in neoplasm-free survival was observed, with higher survival probabilities in non-obese patients (72.55% vs 66.73%, $p < 0.0000$). The hazard ratio (HR) of 1.17 indicated a 17% increased risk of neoplasm development in obese patients, although this effect was not constant over time.

Similarly, in patients with T2DM, the matched HF/T2DM/Obesity and HF/T2DM/no Obesity cohorts each comprised 427,650 individuals. Median follow-up durations were 858 days for obese patients and 533 days for non-obese patients. Neoplasm-free survival was again significantly higher in the non-obese group (71.39% vs 64.60%, $p < 0.0000$). The HR of 1.15 corresponded to a 15% increased risk of neoplasm in obese individuals, with variability in risk observed over the study period. Complete results are reported in Table 5. Kaplan-Meier curves comparing HF/no T2DM/Obesity and HF/no T2DM/ no Obesity patients are show in Fig. 4, while Kaplan-Meier curves comparing patients with diabetes and with and without obesity are show in Fig. 5

Table 5
comparison of patients with and without diabetes mellitus, and with and without obesity (after propensity score matching)

Cohort	Patients in cohort	age	Male	Nicotine dependence	Patient s with outcome	Median follow up	Hazard ratio	95% IC	p	Survival probability at the end of time window
HF/no T2DM/no Obesity	347,091	63 ± 16	48.5%	9.0%	35,247	515	1.173	(1.157, 1.190)	0.000	72.55%
HF/no T2DM/ Obesity	347,091	63 ± 16	48.5%	9.0%	46,807	770				66.73%
HF/T2DM/no Obesity	427,650	66 ± 12	53.0%	7.4%	45,714	533	1.152	(1.138, 1.166)	0.000	71.39%
HF/T2DM/Obesity	427,650	66 ± 12	51.8%	7.8%	61,918	858				64.60%

Sensitivity analysis.

To minimize potential bias and confounding, each analysis was repeated at 1 day, 90 days, and 365 days post-index event to evaluate the temporal effect. As expected, survival probabilities were consistently higher across all cohorts in the sensitivity analyses excluding events occurring within the first day, 90 days, and 365 days after the index event. However, the relative differences between groups remained unchanged. Patients with diabetes and/or obesity consistently showed lower survival rates than those without these comorbidities. This confirms the robustness of the main findings and indicates that early events did not materially influence the observed associations. Complete results are reported in Table 6

Table 6
Sensitivity analysis results in analyse outcomes. The sensitivity analysis confirmed the robustness and reliability of the

Cohort	Patients in cohort	Patients, 1 day	Patients, 90 day	Patients, 365 days	Survival probability, 1 day	Survival probability, 90 day	Survival probability, 365 days	HR, 1 day	HR, 90 days	HR, 365 days	95% IC, 1 day	95 IC da
HF/T2DM	1,170,016	142,136	119,671	95,691	67.90%	69.25%	71.00%	1.041	1.068	1.083	(1.033, 1.049)	(1 1.
HF/no T2DM	1,170,016	122,991	99,593	77,828	70.63%	72.10%	73.86%					
HF/Obesity	813,362	113,873	100,608	83,036	65.88%	66.96%	68.62%	1.190	1.277	1.326	(1.179, 1.201)	(1 1.
HF/no Obesity	813,362	79,269	63,787	49,917	73.41%	74.86%	76.50%					
HF/no T2DM/no Obesity	347,091	35,247	28,867	22,802	72.55%	73.92%	75.51%	1.173	1.233	1.266	(1.157, 1.190)	(1 1.
HF/no T2DM/Obesity	347,091	46,807	40,888	33,422	66.73%	67.88%	69.56%					
HF/T2DM/no Obesity	427,654	45,714	37,364	29,357	71.39%	72.73%	74.49%	1.152	1.228	1.273	(1.138, 1.166)	(1 1.
HF/T2DM/Obesity	427,654	61,918	54,966	45,476	64.60%	65.66%	67.32%					

Discussion

The main findings of our study highlight the significant prevalence and incidence of neoplasms among patients with HF. Patients with HF exhibit an elevated risk of developing neoplasia, with an observed incidence of over 20%. The risk of neoplasia increases with age, whereas no significant differences have been observed between sexes.

If patients have a diagnosis of T2DB, the risk increases by approximately 4%.

Even more than diabetes, the coexistence of obesity contributes to a greater increase in neoplasm risk. Patients with both HF and obesity showed a cumulative incidence of neoplasia that was 6.8% higher compared to patients with HF without obesity, with a 19% increased risk of developing neoplasia within the time window.

When comparing patients with diabetes with and without obesity, and patients without diabetes with and without obesity, we found that the group with both diabetes and obesity had the highest absolute risk of developing neoplasia. The risk of developing neoplasms in patients with obesity and diabetes increases proportionally over time, as demonstrated by Kaplan–Meier curves that progressively diverge. The divergence occurs earlier and more prominently in the presence of obesity.

Our data suggest that obesity is a primary factor driving the increased cancer risk in patients with heart failure and may partly explain the additional risk attributed to the presence of diabetes.

To address potential sources of bias, we conducted a sensitivity analysis, which confirmed the results of our primary analysis.

Furthermore, to overcome limitations related to competing events, we performed a competing risk analysis. This revealed that, when adjusting the neoplasia-free survival analysis for mortality, it is possible to estimate an even higher risk of developing neoplastic disease.

The cancer incidence observed in our study is consistent with findings from previous research. In the Olmsted County epidemiological study, the incidence of cancer among patients with heart failure was reported to be 22% [3]. Similarly, in a retrospective community-based cohort study, the incidence reached 25.1% [7], and similar data extracted from the Disease Analyzer database showed a cancer incidence of 25% among heart failure patients [9].

The association between these two comorbidities is driven by overlapping risk factors and by likely shared pathophysiological mechanisms [12]. Common risk factors include age, smoking, physical inactivity, unhealthy dietary habits, and environmental pollution. Moreover, ethnic and social determinants may also act as shared causal contributors.

The biological mechanisms linking the two diseases are still the subject of extensive research and growing scientific interest. In both patients with heart failure and those with cancer [17–18], chronic inflammation plays a role in the pathogenesis and progression of the disease, particularly when combined with aging, a condition known as inflammaging [19].

Other shared molecular pathways include disrupted immune signaling, oxidative stress, and epigenetic modifications [12].

More recently, clonal hematopoiesis has been identified as a potential common risk factor linking solid tumors and cardiovascular diseases [20].

Additionally, a detection bias may be present: patients with heart failure undergo more frequent medical evaluations, which may lead to earlier or increased identification of neoplastic diseases. It is conceivable that HF patients have more comorbidities and are therefore subject to more screening, with a higher probability of an early cancer diagnosis.

In the study by Hasin et al.[3], analysis of the Kaplan-Meier curves shows that the increased risk of cancer diagnosis in HF patients compared to controls is not constant over time. The curves diverge starting 2 years after HF diagnosis, with the maximum divergence of around 4 years, and overlapping again around 7 years, suggesting an earlier diagnosis of cancer in HF patients.

Certain heart failure–associated comorbidities are known to increase cancer risk, including diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, obesity, and metabolic syndrome. Notably, some of these conditions, particularly diabetes mellitus and obesity also share well-established etiopathogenetic links with HF. T2DM is a well-established risk factor for incident heart failure and increases the risk of morbidity and mortality in patients with pre-existing disease. The association between T2DM and HF may be mediated by ischemic heart disease, of which diabetes is a major risk factor, as well as by direct myocardial injury leading to the development of diabetic cardiomyopathy [21–22].

Diabetes also increases the risk of several cancers, particularly liver, pancreatic, colorectal, bladder, and endometrial malignancies. This association is supported by large epidemiological studies, although the underlying mechanisms are still under investigation and are thought to involve hyperinsulinemia, insulin resistance, and chronic inflammation. [13,14,23,24].

Obesity represents a major and modifiable determinant of HF, particularly HF with preserved ejection fraction (HFpEF), and constitutes a clinically relevant and therapeutically actionable condition.

Central adiposity, especially the accumulation of visceral and epicardial fat, plays a mechanistic role in HF pathophysiology through inflammatory pathways and hemodynamic loading [25]. Several pathophysiological mechanisms trigger a vicious cycle in patients with heart failure and obesity, leading to disease progression and worsening clinical outcomes [26].

Obesity too has been linked to an increased incidence of cancer and increased cancer related mortality[27].

A meta-analysis of 203 studies with more than 6.3 million participants found that obesity was associated with increased overall and cancer-specific mortality, especially among patients with breast, colon, and uterine cancer whereas patients with lung cancer, renal cell carcinoma, and melanoma exhibited a lower risk of death compared with patients with the same cancers who were not obese [28].

Recent evidence indicates that chronic inflammation is a central mediator linking obesity to cancer, [29]. Obesity and overweight cause adipose tissue dysfunction, promoting cancer through excess fatty acids, oxidative stress, inflammation, and hormonal imbalance. Elevated cytokines and estrogens stimulate tumor growth, while immune suppression favors cancer progression. Obesity-related gut microbiota alterations further enhance inflammation and oxidative stress, contributing to carcinogenesis [30].

Our finding confirms the results of a metanalysis of two European prospective cohorts in which the joint association of obesity and cardiovascular disease with neoplasm risk was higher than the sum of the separate associations of the two exposure [31].

However, when examining the complex association between HF, obesity, and cancer, a precise characterization of the obesity phenotype particularly adipose tissue distribution, is of paramount importance. Liu et al [32] reported that while obesity status and higher BMI were associated with a lower risk of lung cancer, further investigation into obesity-related phenotypes revealed that greater visceral and pericardial adipose tissue depots, along with elevated circulating C-reactive protein levels, were independently associated with an increased risk of overall and site-specific cancers, including lung cancer and melanoma.

The findings emerging from our study and from previous investigations carry relevant therapeutic implications. On one hand, there is a clear need for a comprehensive prevention strategy targeting both heart failure and cancer by addressing shared risk factors, including biosocial determinants, within a framework that has been defined as “syndemic” [33]. Furthermore, it will be important to evaluate whether novel therapeutic approaches to metabolic diseases, particularly type 2 diabetes and obesity, most notably GLP-1 receptor agonists, which have demonstrated significant body weight reduction, improvement of functional capacity, and reduction of C-reactive protein levels in patients with heart failure [34 –35], may also be associated with a reduced risk of cancer development.

Conclusion

Patients with chronic heart failure carry a substantial burden of neoplastic disease, with obesity emerging as a primary modifiable driver of increased cancer risk in this population. The coexistence of T2DM further amplifies this risk, suggesting a negative synergy and potential multiplication of the underlying biological pathways involved. These findings underscore the importance of proactive cancer surveillance and aggressive management of metabolic comorbidities in patients with HF with the ultimate goal of improving long-term outcomes in this high-risk population.

Study limitation

One of the limitations of the study is that approximately 50% of the patients are of white ethnicity; therefore, the conclusions of the study should be applied with caution to underrepresented populations, such as Asian communities.

The E66 code used for the diagnosis of obesity is a generic code applied to define “overweight and obesity.” The sensitivity of the E66 code for diagnosing obesity is low [36–37], whereas its specificity exceeds 90%.

Lastly, despite propensity score matching with appropriate covariates, residual confounding factors, particularly socioeconomic determinants, may still be present, as these were not assessed in the current analysis and could potentially influence the observed outcomes.

Abbreviations

HF: Heart failure

CVD: cardiovascular diseases

HRs: hazard ratios

T2DM: Type 2 diabetes mellitus

BMI: body mass index

HCOs: Healthcare organizations

GDPR: European Union General Data Protection Regulation

HIPAA: United States Health Insurance Portability and Accountability Act

ICD-10 international classification of disease version 10

US: United States

EMEA: Europe, Middle East, and Africa

LATA: Latin America

APAC: Asia-Pacific region

HER: Health Equity Research

PSM: Propensity Score Matching

IQR: Interquartile range

HFpEF: HF with preserved ejection fraction

Declarations

Ethics approval and consent to participate:

The data provided by TriNetX, used in the research reported in the paper are aggregated; therefore, our institution did not require approval from the Ethics Committee.

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Author Contribution

A P: conception and design of the work; acquisition data, analysis of data, interpretation of data; draft of the work; approved the submitted version G R: conception and design of the work; acquisition data, analysis of data, interpretation of data; draft of the work; approved the submitted version M B: conception and design of the work; interpretation of data; draft of the work; approved the submitted version M T L: conception and design of the work; interpretation of data; draft of the work; approved the submitted version MP: conception and design of the work; interpretation of data; draft of the work; approved the submitted version F G: conception and design of the work; interpretation of data; draft of the work; approved the submitted version M P: conception and design of the work; interpretation of data; draft of the work; approved the submitted version CR: conception and design of the work; acquisition data, analysis of data, interpretation of data; draft of the work; approved the submitted version D S : conception and design of the work; interpretation of data; draft of the work; approved the submitted version E Z: conception and design of the work; interpretation of data; draft of the work; approved the submitted version V T : conception and design of the work; acquisition data, analysis of data,interpretation of data; draft of the work; approved the submitted version R B : conception and design of the work; acquisition data, analysis of data, interpretation of data; draft of the work; approved the submitted version ll authors reviewed the manuscript

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none

Available data

include demographics, coded diagnoses (International Classification of Diseases (ICD)- version 10), procedures (ICD-10- Procedure Coding System or Current Procedural Terminology), medications (National Library of Medicine and the Department of Veterans Affairs), and measurements (laboratory tests and BMI, Logical Observation Identifiers Names and Codes). Within the TriNetX platform, electronic health records (EHRs) can be accessed and analyzed through five distinct Collaborative Networks (https://doi.org/10.3389/fphar.2025.1516126): The Global Collaborative Network (128 HCOs), the US Collaborative Network (66 HCOs), the Latin America (LATAM) Collaborative Network (32 HCOs), the Europe, Middle East, and Africa (EMEA) Collaborative Network (26 HCOs), and the Asian Pacific (APAC) Collaborative Network (14 HCOs).

The data provided by TriNetX are aggregated; therefore, our institution did not require approval from the Ethics Committee.

More details on the TriNetX Network and data analysis are presented in **Supplementary materials.**

Availability of data and materials:

data were obtained on TriNetX platform on Sep 01, 2025.

Competing interests

there are no competing interest

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Figures

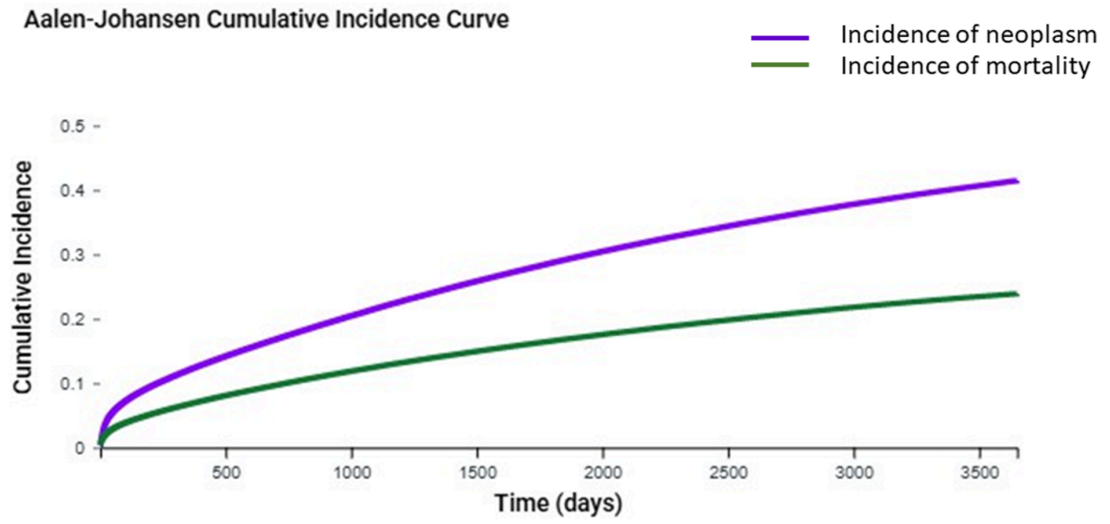
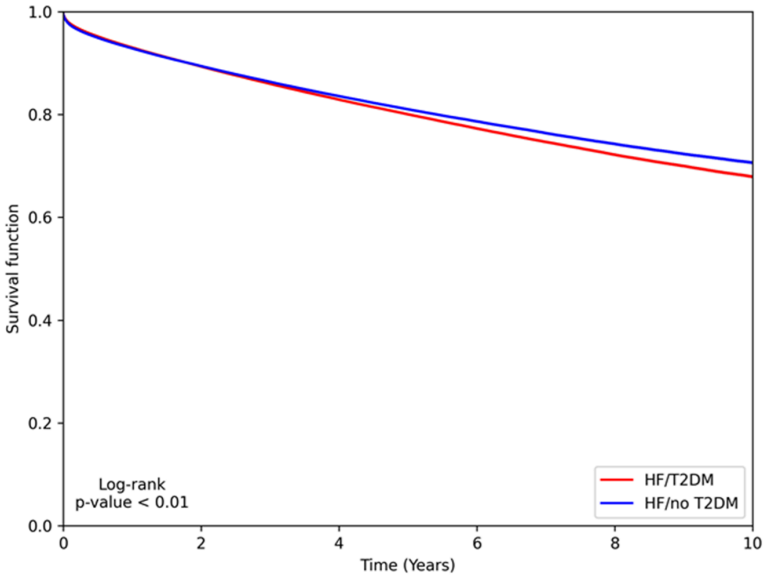


Figure 1

Aalen-Johansen cumulative incidence curve for competing risk analysis

While both outcomes (death and neoplasm) contribute significantly to the clinical burden in the studied population, the occurrence of neoplasms is more frequent and represents the dominant competing risk.

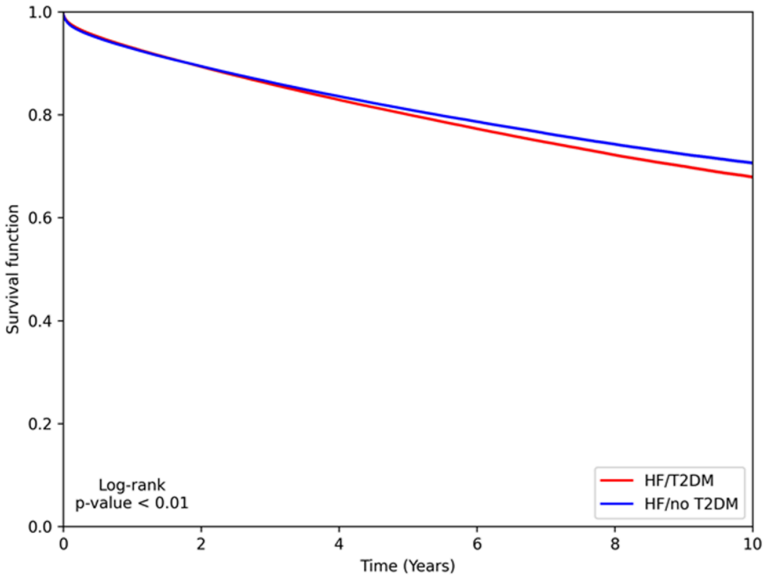


Time (Days)	1	500	1000	1500	2000	2500	3000	3500	3650
HF/T2DM	1170016	599606	403254	272162	183553	118471	75200	47028	40901
HF/no T2DM	1170015	529260	351473	236728	160430	105103	68034	43559	37858

Figure 2

Kaplan - Meier survival analysis comparing survival from neoplasm in HF with and with out diabetes.

The difference in neoplasm-free survival was statistically significant and higher in patients without diabetes mellitus (p < 0.0000).

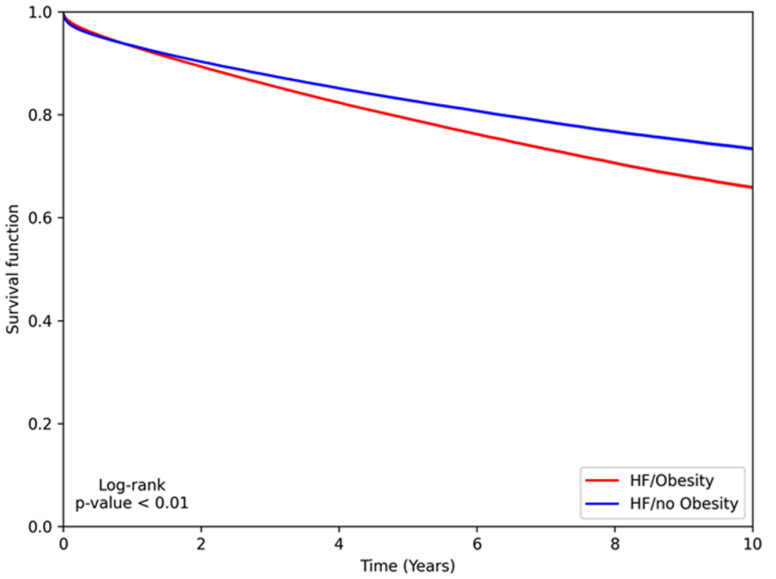


Time (Days)	1	500	1000	1500	2000	2500	3000	3500	3650
HF/T2DM	1170016	599606	403254	272162	183553	118471	75200	47028	40901
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Figure 2

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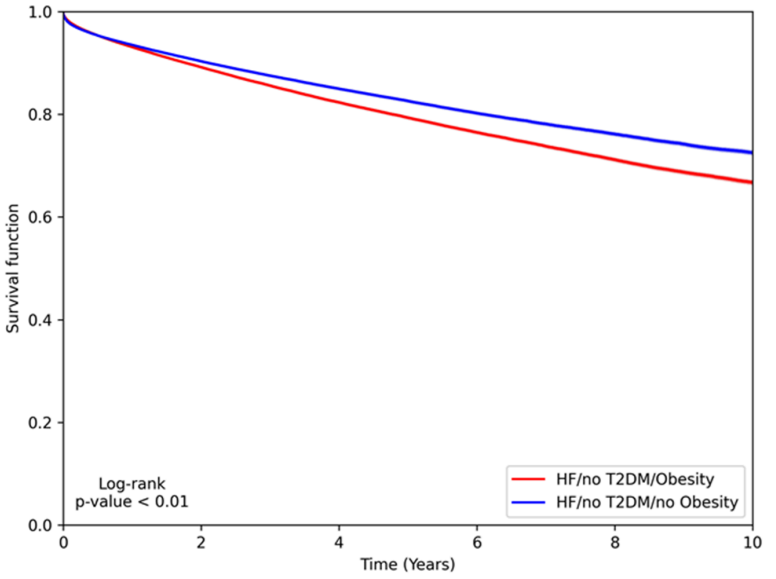
The difference in neoplasm-free survival was statistically significant and higher in patients without diabetes mellitus (p < 0.0000).



Time (Days)	1	500	1000	1500	2000	2500	3000	3650
HF/Obesity	813361	470489	325743	222624	151510	98132	61570	33569
HF/no Obesity	813361	373598	252295	174079	120929	81665	54500	31564

Figure 3

Kaplan - Meier survival analysis comparing survival from neoplasm in HF with and with out obesity 2. The difference in neoplasm-free survival was statistically significant and higher in patients without a diagnosis of obesity ($p < 0.0000$).

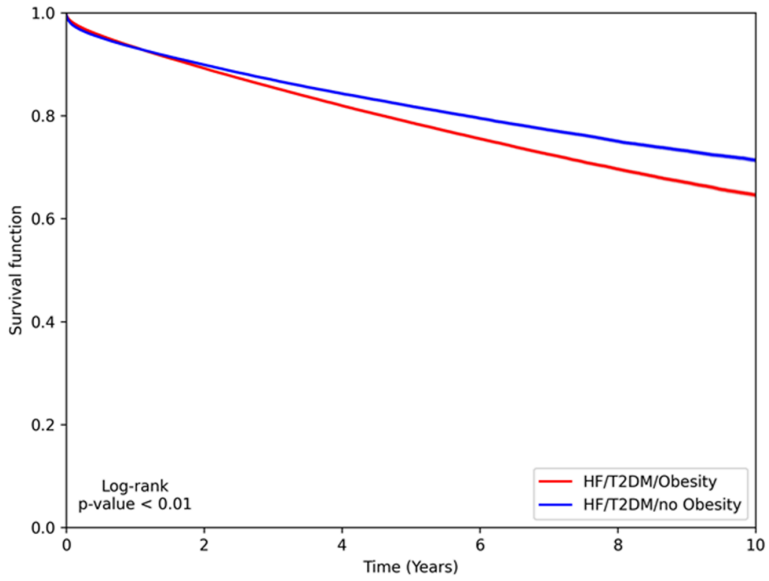


Time (Days)	1	500	1000	1500	2000	2500	3000	3650
HF/without T2DM/Obesity	347091	193273	132333	89833	61127	39776	25171	14009
HF/no T2DM/ no Obesity	347091	165019	112110	77217	53612	36012	24047	13910

Figure 4

Kaplan - Meier survival analysis comparing survival from neoplasm in HF without diabetes with and without obesity.

Obesity significantly increases the risk of developing neoplasms in patients with heart failure, without of diabetes

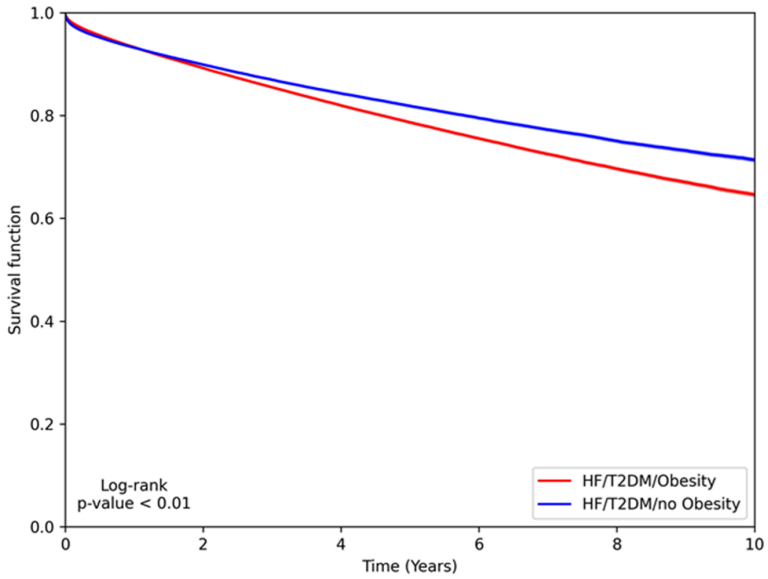


Time (Days)	1	500	1000	1500	2000	2500	3000	3650
HF/T2DM/ Obesity	427649	251006	173675	118255	79701	50822	31224	16425
HF/T2DM/ no Obesity	427649	205709	138256	94656	65284	43498	28781	16366

Figure 5

Kaplan - Meier survival analysis comparing survival from neoplasm in HF with diabetes with and without obesity.

Obesity significantly increases the risk of developing neoplasms in patients with heart failure, and diabetes



Time (Days)	1	500	1000	1500	2000	2500	3000	3650
HF/T2DM/ Obesity	427649	251006	173675	118255	79701	50822	31224	16425
HF/T2DM/ no Obesity	427649	205709	138256	94656	65284	43498	28781	16366

Figure 5

Kaplan - Meier survival analysis comparing survival from neoplasm in HF with diabetes with and without obesity.

Obesity significantly increases the risk of developing neoplasms in patients with heart failure, and diabetes

Supplementary Files

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