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ORIGINAL ARTICLE

Heart failure during acute coronary syndrome and the long-term cancer risk: the ABC-9† Study on heart disease

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Abstract

Aims A higher risk of cancer among patients with heart failure (HF) has been suggested in recent community-based studies. This study aimed to investigate the impact of HF during hospitalization with acute coronary syndrome (ACS) on the long-term cancer risk.

Methods and results The study included 572 patients admitted with ACS to three Italian hospitals, discharged cancer-free, and prospectively followed for 24 years or until death. All but three patients completed the follow-up, which represented 6440 person-years (mean age: 66 ± 12 years; 70% males). Baseline HF was diagnosed in 192 (34%) patients. A total of 129 (23%) patients developed cancer (103 without HF and 26 with HF), and 107 (19%) patients died due to it (81 without HF and 26 with HF). The incidence rates for cancer onset and cancer death were not different according to HF status. Cox regression analysis revealed no association between HF or left ventricular ejection fraction (LVEF) and cancer risk. In addition, no difference in cancer risk was observed among patients with HF with preserved ejection fraction, HF with mildly reduced ejection fraction, and HF with reduced ejection fraction. In competing risk regression analysis, the risk of cancer onset associated with HF was sub-hazard ratio (SHR) 0.47 [95% confidence interval (CI): 0.30–0.72; P = 0.001] and SHR 1.02 (95% CI: 1.01–1.04; P = 0.002) with LVEF. Results were the same in the adjusted model. Yet the fully adjusted model showed an attenuated association between cancer death and HF (SHR: 0.63; 95% CI: 0.37–1.05; P = 0.08) and LVEF (SHR: 1.02; 95% CI: 0.99–1.06; P = 0.08). Consistent results were obtained after using propensity score matching analysis that created 192 pairs. A negative interaction between age and HF and a positive interaction between age and LVEF for cancer risk have also been found.

Conclusions An inverse association between baseline HF and long-term cancer risk has been observed among the ABC Study on heart disease patients who were followed for 24 years after ACS.

Keywords Acute coronary syndrome; Heart failure; Incident cancer; Cancer mortality; Epidemiology; Follow-up studies

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Introduction

Heart failure (HF) is common among patients hospitalized for acute coronary syndrome (ACS) with an incidence ranging from 14% to 37%.[1,2] The prognostic significance of HF complicating myocardial infarction (MI) has been documented in many studies as an important predictor of all-cause and cardiovascular mortality risks.[3–5]

Recently, reports have suggested an increased risk of cancer and cancer-related mortality in patients who survived ACS.[6–10] Both pathologies are linked by inflammation and oxidative stress and share several modifiable risk factors such as smoking, sedentary lifestyle, unhealthy diet, and obesity, possibly reflecting a shared biology.[7,11–15] Yet it is not well understood which patients have this higher risk.

There is a paucity of reports considering the association between HF and cancer risk with conflicting results.[16–20] In the present prospective study, we investigated the impact of HF during hospitalization with ACS on the subsequent cancer risk in the ABC Study patients who were discharged free from malignancy and followed for 24 years.

Methods

Patients

The ABC Study on Heart Disease (www.abcheartdiseasestudy.org/en/) is an ongoing prospective study designed to represent, as closely as possible, an unbiased population of patients with ACS. Specifically, the study includes Caucasian patients who were admitted to intensive care units of three general hospitals in Italy's Veneto region between June 1995 and January 1998 with definite ACS, including ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), or unstable angina. The study originally aimed to monitor these patients concerning long-term natural history, both non-fatal and fatal events, and causes of death. An additional aim of the study was to investigate the prognostic value of multiple baseline clinical variables. The diagnosis of ACS was based on the presence of at least two of the following criteria: typical changes in serum enzymes [e.g. total creatine kinase (CK) and creatine kinase MB (CK-MB)], typical electrocardiogram changes (i.e. localized ST-T changes and/or pathological Q waves in at least two contiguous leads), and central chest pain lasting more than 30 min.[21]

Of the 741 consecutive unselected patients who were considered eligible upon admission, the study excluded 84 patients for having diseases other than ACS and 23 patients with missing baseline data. Forty-five patients died during the index hospitalization, and 17 patients had a pre-existing malignancy and were excluded from the present analysis. Hence, the post-discharge follow-up study included 572 patients free from neoplasia for whom the final analysis was conducted (*Figure 1*). Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. The study protocol followed the Declaration of Helsinki and was approved by the ethics committee of each hospital. All enrolled patients provided written informed consent.

Measurements and follow-up

A thorough medical history was collected from the patient's medical records and patient interviews at the time of enrolment. All of the analysed baseline clinical and laboratory data were obtained during the first 7 days of hospitalization in the intensive coronary care unit as previously described in detail.[22–24] The presence and degree of HF were assessed on the first, third, and seventh days after admission following the Killip classes.[25] Killip classification was recorded as follows: Class I, no signs of HF; Class II, pulmonary rales; Class III, pulmonary oedema; and Class IX, cardiogenic shock.[22] The highest class observed during the first 7 days of the hospital stay was used and analysed as a categorical variable: Killip Class I (no HF) vs. Killip Class >I (HF).

Left ventricular ejection fraction (LVEF) was assessed by two-dimensional echocardiography according to Simpson's method[26] within 7 days after admission. Four- and two-chamber apical views were recorded and examined by two physicians who had no knowledge of patients' clinical data.

Clinical check-ups were done for each patient 1, 3, 5, 7, 10, 12, 15, 17, 20, 22, and 24 years after enrolment. At each recruitment hospital, two cardiologists were responsible for monitoring the cohort of patients throughout the follow-up.

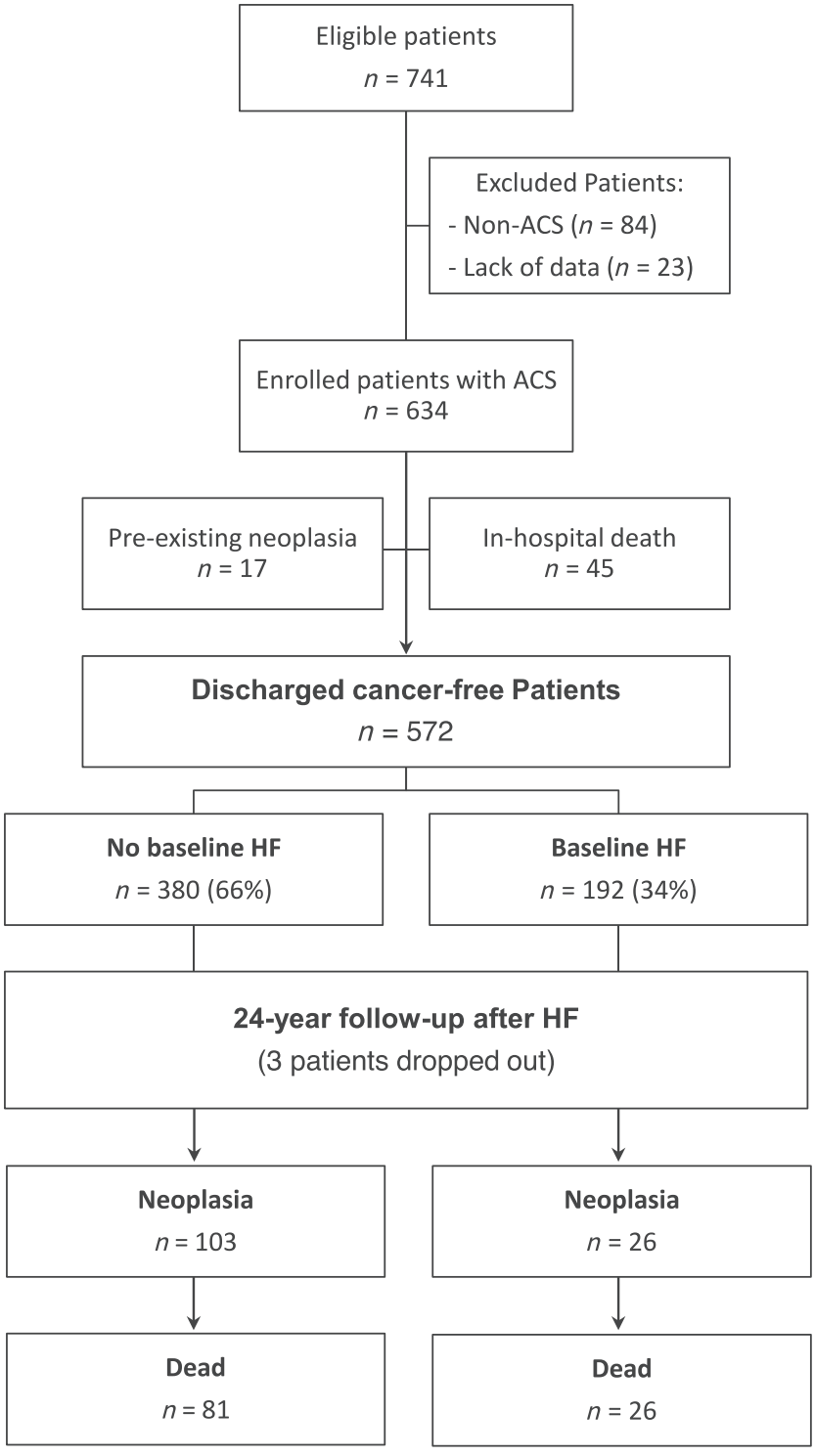
For the present analysis, the pre-specified primary endpoint was the occurrence of a new malignancy (i.e. the first documented malignancy). According to the ABC Study on Heart Disease protocol,[7] establishing the clinical diagnosis of cancer began with a thorough history and physical examination including laboratory tests and then substantiated by confirmatory pathology or cytology reports. Cancer mortality was the secondary endpoint. Data were obtained from scheduled examinations, public administrations, hospital records, family doctors, post-mortem examinations, and death certificates. The medications received during the index hospitalization and follow-up treatments were also recorded. All post-enrolment data were recorded prospectively according to the ABC Study on Heart Disease protocol.[23] Baseline data and follow-up data were recorded in two different datasheets that were merged after the completion of 24 years of follow-up.

Statistical analysis

Unpaired Student's *t*-test and Pearson χ^2 test were used for measured and categorical variables, respectively. Log transformations were used to correct positive-skewed distributions, as appropriate. If a patient dropped out before 24 years of follow-up, his or her data were censored at that time.

In survival analysis, enrolment age and LVEF were analysed as terciles of increasing values. Survival curves were constructed using cumulative incidence as a function of incident cancer and cancer-related death.[27] Incident cancer and cancer-specific death rates with person-time denominators were calculated. Person-time at risk was accumulated from index admission for ACS until cancer onset, death, or end of follow-up, whichever came first. Cox proportional hazard regression analysis and competing risk regression analysis using the Fine–Gray method[28] were performed to estimate

Figure 1 Flow diagram of the study population and progress during follow-up. ACS, acute coronary syndrome; HF, heart failure.



the hazard ratios (HRs), sub-hazard ratios (SHRs), and 95% confidence intervals (CIs) for risk of cancer onset and cancer death associated with HF. Scaled Schoenfeld residuals were used to test the proportionality assumption with 95% CIs. Because age is a strong determinant of cancer risk, models were repeated using age as the timescale. To study the effect modification, survival regression models including a formal interaction term between different clinical variables were

used. Marginal post-estimation analysis was used to graphically show the predicted relative hazards.

To confirm the robustness of the results, we performed a subsequent propensity score matching (PSM)-based analysis. To construct the propensity score (PS), we built a multivariable logistic regression model with the following covariates: patient's age, gender, body mass index (BMI), smoking, education level, diabetes mellitus, hypertension, history of previous infarction, baseline heart rate, atrial fibrillation (AF), serum cholesterol, and presentation with STEMI to calculate the PS score of every subject. A 1:1 match was done by nearest neighbour matching based on PS. Equal distribution of the baseline characteristics was tested using standardized mean difference (SMD), with an overall SMD of <0.10 representing a good balance.

Results were reported as medians and inter-quartile ranges (IQRs) for continuous variables and numbers and percentages for categorical variables. Unless otherwise indicated, two-tailed P values <0.05 were deemed significant. The statistical analyses were performed using STATA 18 (College Station, TX, USA).

Results

Study population and baseline characteristics

Among the 572 enrolled patients, HF was diagnosed in 192 (34%) patients. *Table 1* summarizes patients' main clinical characteristics by HF status. Overall, patients who had HF were older, more likely to be women, with diabetes mellitus and a history of previous MI, and had STEMI and AF at presentation with higher values of biochemical markers of necrosis. They had lower education levels, were less likely to receive mechanical revascularization, and were less often

Table 1 Patients' baseline characteristics according to heart failure status

Variable	Overall population (n = 572)	No heart failure (n = 380)	Heart failure (n = 192)	P values
Demographics and clinical data				
Age (years)	67 (59–75)	64 (56–72)	72 (65–79)	<0.0001
Females	30	24	41	<0.0001
Body mass index (kg/m^2)[a]	26 (24–28)	26 (24–28)	25 (23–28)	0.06
Current smokers	38	42	30	0.008
Alcohol consumption	74	73	74	0.74
Education higher than primary school	26	29	19	0.01
Hypertension	47	47	47	0.99
Diabetes mellitus	23	18	33	<0.0001
Previous myocardial infarction	24	19	33	<0.0001
In-hospital characteristics				
Prehospital time delay (min)[a] (n = 474)	180 (120–540)	180 (120–420)	240 (120–660)	0.003
Systolic blood pressure (mmHg)	120 (110–130)	120 (110–133)	120 (110–130)	0.57
Diastolic blood pressure (mmHg)	80 (70–80)	80 (70–81)	75 (70–80)	0.12
Heart rate (b.p.m.)	71 (60–82)	70 (60–80)	80 (67–88)	<0.0001
ST-elevation myocardial infarction	62	58	69	0.01
Left ventricular ejection fraction (%) (n = 488)	52 (45–60)	58 (50–63)	46 (35–51)	<0.0001
Atrial fibrillation/flutter[b]	10	5	20	<0.0001
Thrombolysis[b]	35	37	31	0.12
Laboratory data				
Creatine kinase peak (U/L)[a]	828 (360–1621)	735 (322–1501)	1075 (466–1848)	0.0004
Creatine kinase-MB peak (U/L)[a]	103 (43–204)	96 (38–184)	118 (56–251)	0.0002
LDH peak (U/L)[a]	847 (515–1380)	732 (461–1200)	1117 (693–1659)	<0.0001
Haemoglobin (g/L)	14 (13–15)	14 (13–15)	13 (12–15)	0.05
Blood glucose (mg/dL)	120 (101–159)	116 (99–147)	142 (107–192)	<0.001
Total cholesterol (mg/dL)[a]	208 (179–243)	210 (182–242)	205 (172–246)	0.31
eGFR (mL/min/1.73m^2)[a]	72 (54–96)	76 (56–101)	61 (48–88)	<0.0001
Follow-up treatment[c]				
Thrombolytic therapy	35	37	31	0.12
PTCA/CABG	35	43	19	<0.0001
Anti-platelet	90	92	84	0.002
Beta-blockers	53	63	34	<0.0001
Statin	47	54	34	<0.0001

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; LDH, lactate dehydrogenase-1 isoenzyme; PTCA, percutaneous transluminal coronary angioplasty.
Data are presented as median (inter-quartile range) or percentages.
[a]P values were calculated using log-transformed data.
[b]During the first 7 days of hospital stay.
[c]At enrolment and/or at any time during follow-up.

treated with anti-platelet, beta-blockers, and statins during follow-up (*Table 1*). All enrolled patients completed the follow-up unless pre-empted by death, except three patients for whom survival time was censored before 24 years: two withdrew consent, and one moved overseas.

Incident cancer risk

By the end of follow-up, which represented 6440 person-years, 129 (23%) patients developed cancer; of them, 103 had no HF (27% of patients without HF) and 26 had baseline HF (14% of patients with HF) (*Figure 1*).

The most frequent sites of malignancy were lung (31%), colorectal (18%), prostate (15%), breast (6%), and pancreatic cancer (6%).

Among patients who developed cancer, the median time from enrolment to first cancer diagnosis was 10.0 years (IQR: from 4.7 to 15.9 years) with no difference in time according to baseline HF status: median (IQR) = 6.6 (2.8–13.0) vs. 10.3 (5.3–16.6) years in patients with and without HF, respectively, $P = 0.12$.

The incidence rate (IR) of cancer diagnosis was 20 per 1000 person-years (*Table 2*), with no difference according to HF status [IRs were 18 vs. 21 for patients with and without HF, respectively ($P = 0.63$)] (*Figure 2* and Supporting Information, *Figure S1*).

Cox proportional hazard models showed no association between the risk of incident cancer and HF status (HR: 0.96; 95% CI: 0.62–1.48; $P = 0.86$). The analysis also demonstrated that cancer risk was not associated with LVEF (HR: 1.00 0.96; 95% CI: 0.98–1.01; $P = 0.82$). The association remained non-significant after adjusting for several covariates (Supporting Information, *Table S1*) and even after using age as the timescale in the Cox model.

Table 2 Incidence rate per 1000 person-years of incident cancer and cancer death

	Incident cancer	Cancer death
Analysis time (person-years)	6440	6913
Incidence rate		
Overall	20	15
Age terciles		
1st	14	9
2nd	23	20
3rd	33	30
Gender		
Male	21	16
Female	18	14
HF		
No	21	15
Yes	18	17
LVEF terciles		
1st	22	19
2nd	22	18
3rd	18	12

HF, heart failure; LVEF, left ventricular ejection fraction.

The unadjusted HRs for incident cancer were 0.48 (95% CI: 0.16–1.37; $P = 0.17$), 0.90 (95% CI: 0.40–2.06; $P = 0.81$), and 0.81 (95% CI: 0.42–2.68; $P = 0.73$) for patients with HF with preserved ejection fraction (HFpEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with reduced ejection fraction (HFrEF), respectively.

Although using competing risk regression analysis, where death was treated as a competing event, we observed a significantly lower risk of long-term incident cancer in patients with baseline HF (SHR: 0.47; 95% CI: 0.30–0.72; $P = 0.001$). Similar results were obtained using the adjusted model, as in *Table 3*. The table also shows a consistent result for LVEF (SHR: 1.02; 95% CI: 1.01–1.04; $P = 0.002$). The results kept the same even after using age as a time-varying covariate.

When a formal interaction term between the two indicators of HF and age was considered, we observed a negative interaction between HF and age and a positive interaction between LVEF and age for the long-term risk of incident cancer (*Table 3* and *Figure 3*).

Cancer death risk

One hundred seven (19%) patients had died due to cancer at the end of follow-up; of them, 81 had no HF (21% of patients without HF) and 26 had baseline HF (13% of patients with HF) (*Figure 1*).

The median (IQR) time to cancer death was 14.5 (7.0–21.6) years in patients who developed cancer. The median time was 11.6 (3.8–17.3) and 15.8 (8.6–22.8) years in patients with and without HF respectively, with $P = 0.04$. Of note, 22 cancer patients in the no HF group survived beyond the 24th year of follow-up, while none of the cancer patients in the HF group survived up to 24 years of follow-up.

The IR of cancer death was 15/1000 person-years (*Table 2*), with no difference according to HF status [IR was 17 vs. 15 for patients with and without HF, respectively ($P = 0.48$)] (*Figure 2* and Supporting Information, *Figure S1*).

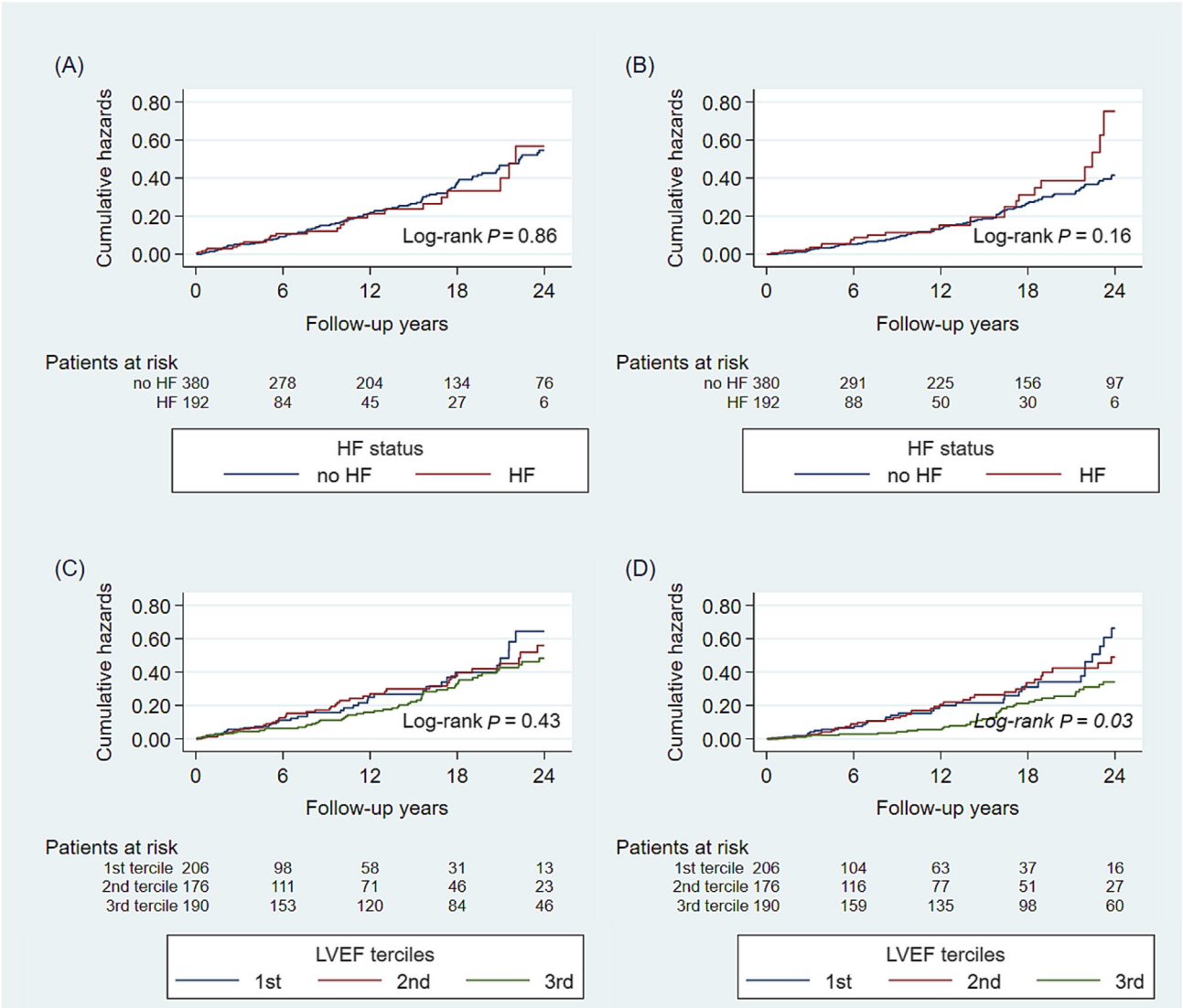
The unadjusted Cox regression model showed that the risk of cancer death was not associated with HF (HR: 1.38; 95% CI: 0.88–2.15; $P = 0.16$) or with LVEF (HR: 0.98; 95% CI: 0.96–1.00; $P = 0.07$).

The association remained non-significant after adjusting for several covariates (Supporting Information, *Table S1*) and even after using age as the timescale in the Cox model.

The unadjusted HRs for cancer death were 0.52 (95% CI: 0.18–1.52; $P = 0.23$), 1.37 (95% CI: 0.57–3.30; $P = 0.47$), and 1.01 (95% CI: 0.30–3.38; $P = 0.89$) for patients with HFpEF, HFmrEF, and HFrEF respectively.

The fully adjusted competing risk regression model, where non-cancer-related death was treated as a competing event, also shows no association between long-term cancer death risk and baseline HF (SHR: 0.63; 95% CI: 0.37–1.05;

Figure 2 Cumulative hazards of (A, C) incident cancer and (B, D) cancer death 24 years after acute coronary syndrome according to baseline heart failure (HF) and left ventricular ejection fraction (LVEF).



P = 0.08) or LVEF (SHR: 1.02; 95% CI: 0.99–1.06; *P* = 0.08) in ACS patients (*Table 3*). The same results were obtained after using age as a time-varying covariate.

After considering the interaction terms between the two indicators of HF and age, we observed a negative interaction between HF and age and a positive interaction between LVEF and age for the long-term risk of cancer (*Table 3* and *Figure 3*).

Propensity score analysis

The subsequent 1:1 PSM revealed 192 matched pairs of patients with and without HF, and both groups were well balanced. *Table 4* and Supporting Information, *Table S2* show consistent results for the risk of incident cancer and cancer-related death according to HF status after PSM.

Discussion

In contrast to recent studies suggesting a higher risk of cancer in patients with HF,[16,17,19,29] this long-term prospective study did not show an association between HF and cancer risk in patients who survived ACS using the basic Cox survival analysis. A more profound competing regression analysis even demonstrated an inverse association where neoplastic risk

Table 3 Competing risk regression analysis for incident cancer and cancer death 24 years after acute coronary syndrome (n = 572)

	Unadjusted model			Adjusted model[a]		
	SHR	95% CI	*P* value	SHR	95% CI	*P* value
Incident cancer						
HF	0.47	(0.30–0.73)	0.001	0.55	(0.33–0.89)	0.02
LVEF	1.02	(1.01–1.04)	0.002	1.02	(1.00–1.03)	0.009
Age	0.85	(0.69–1.04)	0.12	1.00	(0.77–1.31)	0.99
Interaction						
HF × Age	0.57	(0.35–0.91)	0.02	0.57	(0.35–0.92)	0.02
LVEF × Age	1.35	(1.05–1.73)	0.02	1.35	(1.04–1.75)	0.03
Cancer death						
HF	0.61	(0.39–0.95)	0.03	0.63	(0.37–1.05)	0.08
LVEF	1.01	(0.99–1.03)	0.07	1.02	(0.99–1.06)	0.08
Age	1.05	(0.85–1.31)	0.66	1.23	(0.92–1.63)	0.15
Interaction						
HF × Age	0.43	(0.27–0.70)	0.001	0.43	(0.27–0.71)	0.001
LVEF × Age	1.51	(1.16–1.97)	0.002	1.50	(1.14–1.97)	0.003

BMI, body mass index; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; SHR, sub-hazard ratio; STEMI, ST-elevation myocardial infarction.
[a]Adjusted for age, gender, BMI, smoking, diabetes mellitus, total cholesterol level, and STEMI at admission.

Figure 3 Graphical representation of the interaction between age and heart failure (HF) as well as left ventricular ejection fraction (LVEF) for the risk of incident cancer (upper row) and cancer death (lower row) 24 years after acute coronary syndrome. Adjusted for age, gender, body mass index, smoking, diabetes mellitus, total cholesterol level, and ST-elevation myocardial infarction at admission.

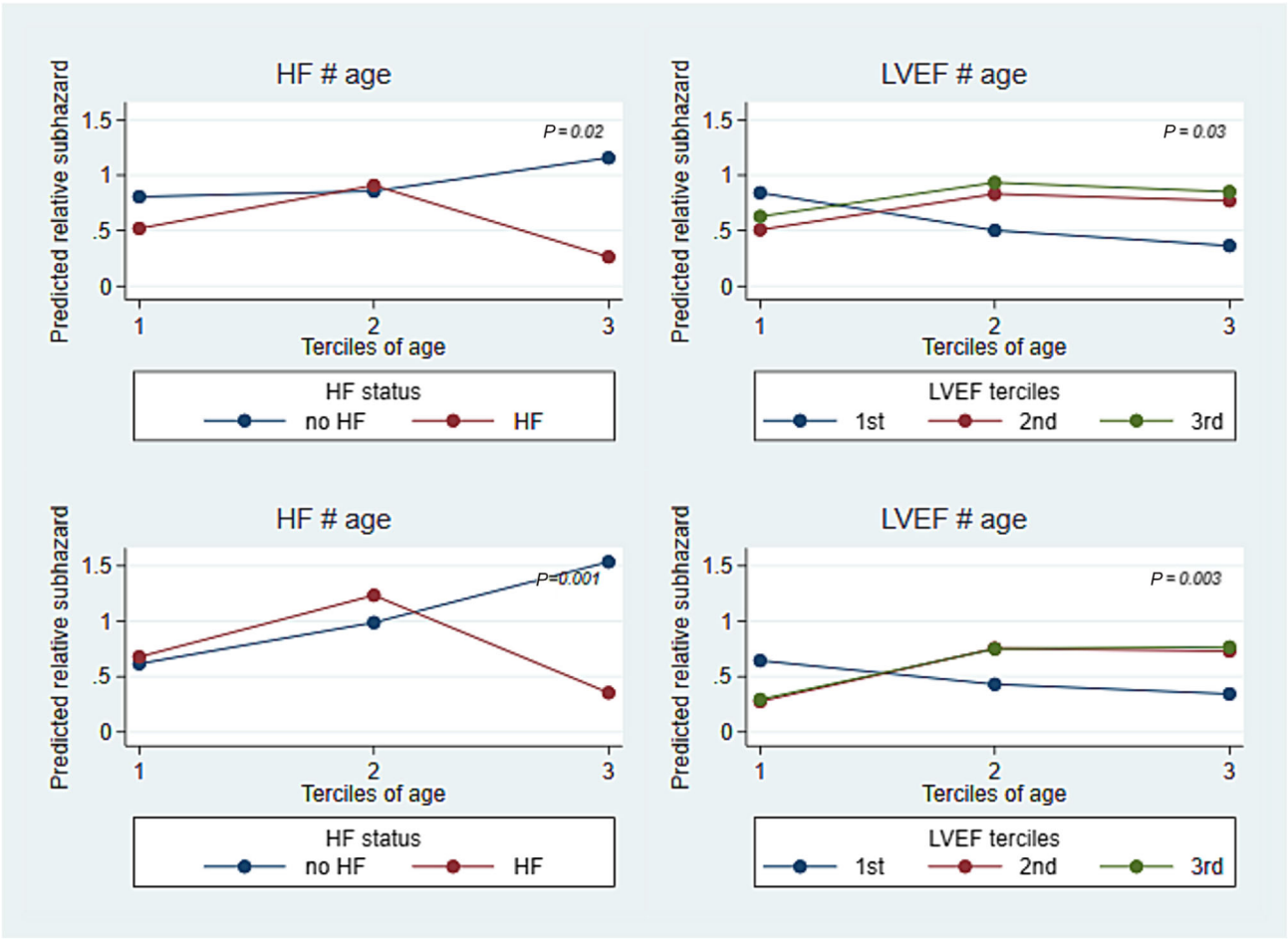


Table 4 Competing risk regression analysis for incident cancer and cancer death 24 years after acute coronary syndrome after propensity score matching (n = 384)

	Unadjusted model			Adjusted model[a]		
	SHR	95% CI	*P* value	SHR	95% CI	*P* value
Incident cancer						
HF	0.52	(0.32–0.85)	0.008	0.58	(0.35–0.95)	0.03
LVEF	1.23	(0.93–1.61)	0.14	1.18	(0.88–1.58)	0.27
Cancer death						
HF	0.62	(0.38–1.02)	0.06	0.67	(0.40–1.13)	0.13
LVEF	1.07	(0.81–1.42)	0.62	1.06	(0.78–1.44)	0.73

BMI, body mass index; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; SHR, sub-hazard ratio; STEMI, ST-elevation myocardial infarction.
[a]Adjusted for age, gender, BMI, smoking, diabetes mellitus, total cholesterol level, and STEMI at admission.

is higher among patients without HF at index hospitalization for ACS as compared with those with signs of HF. Moreover, no association between HF and cancer death using either method was found. The robustness of these results was confirmed after performing PSM analysis in comparison between HF and non-HF patients.

The issue is complex and under strong debate as cardiovascular disease and cancer intersect at multiple levels, which has raised the question of whether this is a simple association or a causal relationship.[30] Studies suggested shared common risk factors and, possibly, pathways of disease development between HF and cancer.[31,32] Yet mechanisms that underpin any potential causal relationship between HF and cancer are not well established. The problem of malignancies in patients with pre-existing HF has been far less discussed, and the results were conflicting.[31]

A lack of association between HF and malignancy was reported by Selvaraj *et al.*[18] among 28 341 Physicians' Health Study participants who were followed for 20 years. Another Danish nationwide study suggested that the association between HF and the risk of incident cancer might be explained by associated comorbidities and medications, rather than being independent. The multivariable-adjusted HR was 0.93 (95% CI: 0.91–0.96) for all-cause cancer in the general population and 1.05 (95% CI: 1.02–1.08) in 166 437 ischaemic heart disease (IHD) patients.[20]

In contrast, other studies showed an increased risk of cancer among HF patients with adjusted HRs ranging from 1.68 to 2.16[16,17] and another study with an IR ratio of 1.24 (95% CI: 1.05–1.24) after adjusted Poisson regression.[19] These studies, however, may have been limited by the relatively shorter follow-up duration (ranges from 5 to 7 years) and unadjudicated outcomes as cancer diagnosis was obtained from administrative databases[19] or from pre-existing population-based clinical registries[16,17] with the exclusion of non-melanoma skin cancer. The lack of data on LVEF in HF patients[16,17] and on shared risk factors, such as smoking[27] and alcohol,[16,17] as well as on the ongoing medical treatment,[16,17] is a further potential limitation of these studies. In addition, in these previous studies, detection bias may have played a non-negligible role because active follow-up of HF patients with regular visits may result in the detection of cancer at an early stage, which is missed in the general population. Yet this is unlikely in our cohort in which HF was diagnosed at enrolment and cancer detection was driven by a pre-specified protocol in which all patients were submitted to a timely pre-scheduled close clinical follow-up. Nevertheless, we highlight the crucial role that censoring plays in a common method for regression analysis of survival data, used in these earlier studies, in the presence of competing risks such as death, as patients who die were censored, which may overestimate the cumulative incidence of cancer. Instead, we implemented the Fine and Gray proportional subdistribution hazard models that use an estimate of the censoring distribution in calculating the weighted contribution to the risk set made by individuals that experience the competing event, which removes the need to treat the competing event as censored.[28,33]

The role of pharmacological treatment is to be considered as medications used to treat HF may have anti-inflammatory and anti-proliferative effects and thus prevent or delay cancer. Yet results from previous reports were inconsistent. For instance, a lower risk of cancer associated with angiotensin-converting enzyme inhibitors (ACEIs) was initially reported,[34] but subsequent meta-analyses found no effect on carcinogenesis in randomized controlled trials for ACEIs or angiotensin receptor blocker (ARB) usage.[35,36]

Earlier, our group reported a higher risk of cancer among ACS patients in the Veneto region of Italy, approximately three times higher than that observed in the general population.[7] Based on these data and data from other reports,[6–10] it is arguable that coronary artery disease (CAD) is associated with a higher neoplastic risk while HF *per se* does not seem to promote an increased risk for neoplasia onset and death in ACS patients considering that the median times of HF to cancer diagnosis in most of the prior studies were <3 years,[16–18] which may be too short of a period to explain a causal relationship.[18]

Limitations

One of the main strengths of the present study likely lies in the very long duration of follow-up almost with no dropouts. To the best of our knowledge, our study is the first to examine the prognostic information provided by baseline HF for as long as 24 years after ACS.

In contrast to, for example, *post hoc* analyses of randomized clinical trials of HF patients, where patients with a history of cancer (or other major comorbidities) are often excluded, our study included an unselected cohort of ACS patients, in which comparison of those with and without HF is advantageous due to the shared common disease mechanism (atherosclerosis), risk factor profile, treatment modalities, and follow-up regimens. Additionally, the availability of baseline characteristics, ongoing medical treatment, with comprehensive validated data on HF, ejection fraction, cancer diagnosis, and mortality, and the usage of advanced statistical methods are all important strengths of the present study.

However, our study inherits some limitations: a major limitation of the ABC Study was that the diagnosis of MI did not account for troponin measurement, as it was not in use at that time; therefore, we used the rise and gradual decline of CK and CK-MB as biochemical markers of necrosis. Nevertheless, these markers of necrosis are still recommended in the absence of troponin measurement.[37] Another limitation of the study is that baseline HF was assessed by clinical examination using the Killip classification. No biomarkers (e.g. B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide) or diastolic parameters by echocardiography were used routinely to confirm the diagnosis of HF at the beginning of the study. However, although studies of HF among patients hospitalized for an acute MI (AMI) have used different definitions of HF, most have at least collected Killip class, with Class II and Class III representing HF. The Killip classification is a relatively crude descriptor of HF, yet it is a powerful predictor of death that underscores the gravity of HF complicating AMI.[1,38] Additionally, at the time of patient enrolment, percutaneous transluminal coronary angioplasty (PTCA) was not yet used to reopen coronary arteries in patients with STEMI. Thus, whether the results may have been altered by early mechanical reperfusion remains uncertain. The lack of data about certain individual and environmental risk factors related to cancer development and mortality is another limitation. Nevertheless, most major risk factors were recorded and included in the fully adjusted models. Detection biases are possible yet; this is quite unlikely in our cohort in which HF was diagnosed at enrolment and cancer detection was driven by a pre-specified protocol in which all patients with and without baseline HF were submitted to a timely pre-scheduled close clinical follow-up by physicians who had no knowledge of patients' baseline clinical data. Finally, because the patients in this study were all Caucasians, we cannot generalize the present findings to other populations and ethnic groups.

Conclusions

Among the ABC Study on heart disease patients who were prospectively followed for 24 years after ACS, baseline HF was not associated with long-term incident cancer onset after adjusting for several potentially confounding variables. A more profound analysis even demonstrated an inverse higher risk of cancer among patients without HF. No association was found between baseline HF and cancer-specific death using either method. A negative interaction between HF and age and a positive interaction between LVEF and age for the long-term risk of cancer and cancer death have also been found.

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Conflict of interest

None declared.

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Supporting information

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

Table S1. Cox regression analysis for incident cancer and neoplastic death 24 years after acute coronary syndrome (n = 572).

Table S2. Cox regression analysis for incident cancer and neoplastic death 24 years after acute coronary syndrome after propensity score matching (n = 384).

Figure S1. Cumulative hazards of incident cancer (upper row) and cancer death (lower row) 24 years after ACS according to enrolment age and gender.

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