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FULL RESEARCH PAPER
Cardiovascular disease

Association of myocardial injury with adverse long-term survival among cancer patients

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Aims

Over time, cardiovascular disease (CVD) deaths increasingly exceed those from malignancy among cancer survivors. However, the association of myocardial injury with long-term survival (beyond 3 years) in cancer patients has not been previously described.

Methods and results

The high-sensitivity cardiac troponin (hs-cTn) and morbidities databases from the National Health and Nutrition Examination Survey (1999–2004) were linked with the latest mortality dataset isolating records were respondents reported cancer diagnosis by a healthcare professional. Myocardial injury was then determined by elevated hs-cTn. A total of 16 225 560 weighted records (1058 unweighted) were included in this observational study, with myocardial injury identified in 14.2%. Those with myocardial injury had progressively worse survival at 5 (51.6 vs. 89.5%), 10 (28.3 vs. 76.0%), and 15 years (12.6 vs. 61.4%) compared with those without myocardial injury. After adjusting for baseline characteristics, those with myocardial injury had an adjusted hazard ratio (aHR) of 2.10 [95% confidence interval (CI) 2.09–2.10, $P < 0.001$] for all-cause mortality, 2.23 (2.22–2.24, $P < 0.001$) for cardiovascular mortality, and 1.59 (95% CI 1.59–1.60, $P < 0.001$) for cancer mortality compared with those without myocardial injury. Among patients with no pre-existing CVD, the hs-cTn I Ortho assay was a strong independent predictor of all-cause (aHR 6.29, 95% CI 6.25–6.33, $P < 0.001$), CVD (aHR 11.38, 95% CI 11.23–11.54, $P < 0.001$), and cancer (aHR 5.02, 95% CI 4.96–5.07, $P < 0.001$) mortalities.

Conclusion

As a marker for myocardial injury, hs-cTns were independently associated with worse long-term survival among cancer patients with a stronger relationship with all-cause, cardiovascular, and cancer mortalities using hs-cTn I Ortho assay.

Lay summary

We conducted an observational analysis using the US' National Health and Nutrition Examination Survey (NHANES) database to examine the association of myocardial injury, as defined by elevated cardiac biomarkers in the form of four different high-sensitivity cardiac troponins, with long-term outcome among cancer survivors.

- Cancer survivors with myocardial injury had progressively worse survival at 5 (51.6 vs. 89.5%), 10 (28.3 vs. 76.0%), and 15 years (12.6 vs. 61.4%) compared with those without myocardial injury.
- After adjusting for population characteristics including cancer type, the risk of death from any cause among cancer survivors with myocardial injury was more than double that of those without myocardial injury [adjusted hazard ratio of 2.10 (95% confidence interval 2.09–2.10, $P < 0.001$)].

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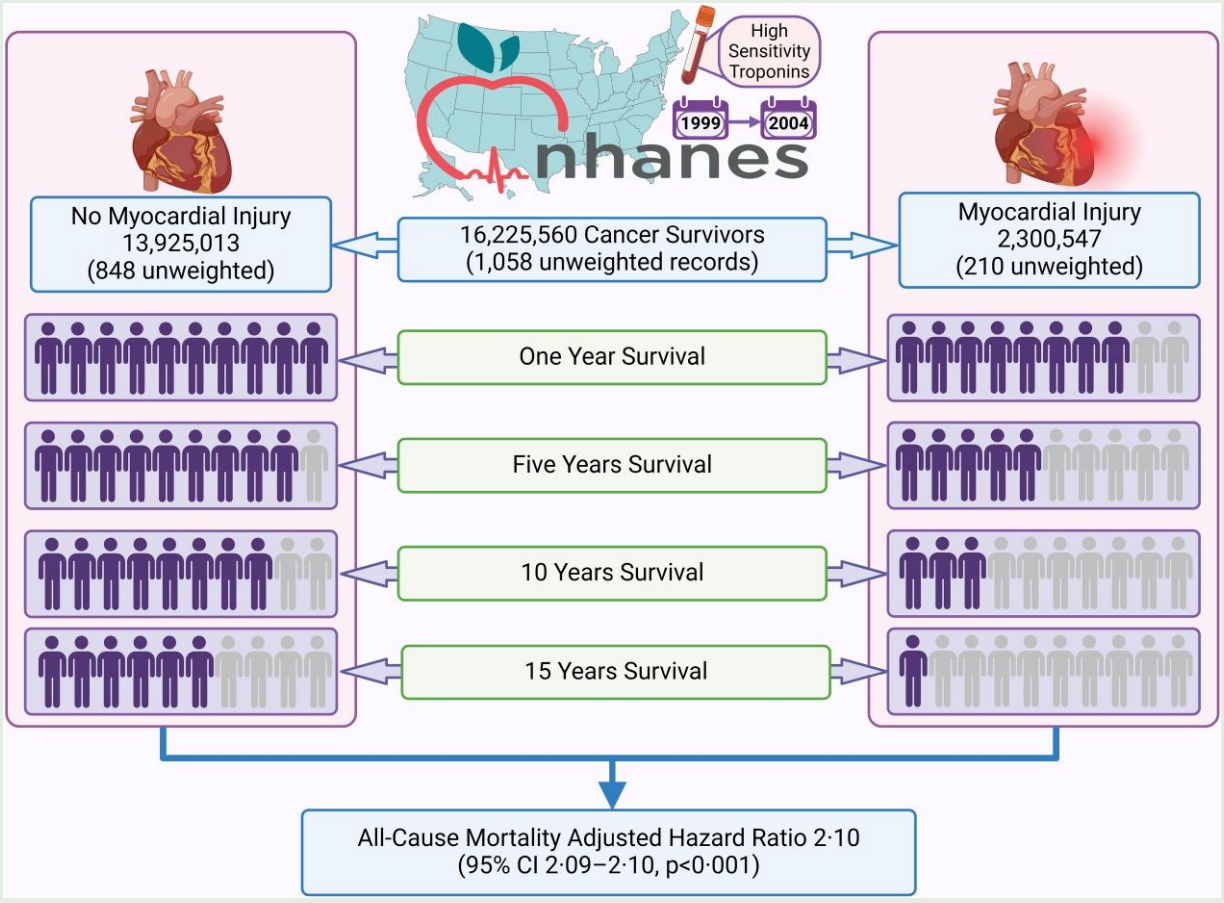
Graphical Abstract



Keywords Troponin • Cardiac biomarkers • Myocardial damage • All-cause mortality • Long-term • Myocardial injury

Introduction

Cancer is one of the leading causes of mortality and morbidity in the developed world.[1] However, survival of cancer patients has been steadily increasing due to therapeutic advances in immunotherapies (checkpoint inhibitors, targeted gene-matching chemotherapies, antibody delivered cancer-purging toxins), adjuvant chemotherapies, radiation therapies, and surgeries.[2] Consequent to this improved survival from some cancers, cardiovascular diseases are now the leading cause of death in many malignancies.[3]

It is established that cancer survivors, especially those following chemotherapy, are at increased risk of CVD, to the point that these patients warrant specialized strategies for risk assessment and prevention.[4,5] Further, conventional models for predicting CVD events in the general population, such as the Framingham risk score, have been shown to underestimate this risk among those with cancer.[6] Cardiac biomarkers, such as troponins, can increase in cancer patients, and this offers a potential avenue for CVD prognostication.[7]

Previous literature has demonstrated that troponin elevation, even among healthy individuals, is associated with the risk of developing cardiovascular events.[8] Among cancer patients, myocardial injury has previously (i) been linked to very early mortality within 6 months of visiting emergency department and (ii) independently associated with early mortality within 2 years after cancer surgery.[9–11] Similarly, among cancer patients treated with chemotherapy, myocardial injury identified by cardiac troponin was associated with late cardiovascular events within 3 years of follow up.[12] However, the association between longer term survival (beyond 3 years) and markers of myocardial injury among cancer survivors has not been elucidated.

The aim of this study was to examine the association between myocardial injury, as determined using high-sensitivity troponin assays, and long-term survival including all-cause mortality, cardiovascular mortality, and cancer mortality in a large national database.

Methods

Ethical approval

This observational study was performed in accordance with the declaration of Helsinki, and the survey data used in this analysis were approved by the Institutional Review Board of the Centers for Disease Control and Prevention (CDC) through protocol #98–12.

Data sources

The National Center for Health Statistics, part of the CDC, produces the National Health and Nutrition Examination Survey (NHANES). The NHANES is major programme that generates a nationally representative sample of the US population from about 5000 individuals each year. These are generated through complex, multi-stage, probability sampling process (i.e. not a simple random sample) with oversampling of specific

Table 1 Baseline cancer patients' characteristics

Characteristics[b]	Without myocardial injury (*n* = 13 925 013; 85.8%)	Myocardial injury (*n* = 2 300 547; 14.2%)	*P*-value
Unweighted records, *n*	848	210	
Age (years), median (IQR)	61 (49–71)	77 (69–84)	<0.001
Sex, %			<0.001
Female	59.9	57.0	
Male	40.1	43.0	
Race/Ethnicity, %			<0.001
Mexican American	1.7	0.7	
Non-Hispanic Black	5.1	6.3	
Non-Hispanic White	89.4	89.3	
Other Hispanic	2.2	0.7	
Other race/multi-racial	1.5	3.1	
Comorbidities, %			
Anaemia	4.7	13.1	<0.001
Asthma	14.7	14.4	<0.001
COPD	14.2	16.8	<0.001
Hypercholesterolaemia	39.1	40.3	<0.001
CVD	16.8	45.7	<0.001
CHF	4.5	23.9	<0.001
CAD	6.3	21.6	<0.001
Angina	6.6	14.5	<0.001
Heart attack	7.0	20.4	<0.001
Stroke	5.2	11.8	<0.001
Diabetes mellitus	10.5	26.3	<0.001
Family history of CAD	16.6	11.8	<0.001
Hypertension	43.5	71.1	<0.001
Liver disease	4.8	5.5	<0.001
Overweight	34.3	39.0	<0.001
Smoking history[a]	58.5	64.0	<0.001
Number of cancers			<0.001
One	91.1	90.4	
Two	8.6	9.0	
Three	0.3	0.6	
Cancer organ/type, %			
Bladder	2.3	2.2	<0.001
Blood	0.1	0.0	<0.001
Bone	1.1	1.4	<0.001
Brain	0.4	0.5	<0.001
Breast	13.8	16.5	<0.001
Cervical	9.3	2.6	<0.001
Colon	4.3	6.6	<0.001
Isolated non-melanoma skin cancers	18.2	17.4	<0.001
Oesophagus	0.6	0	<0.001
Kidney	1.1	3.0	<0.001
Larynx	0.7	0.7	<0.001
Leukaemia	1.0	1.8	<0.001
Liver	0.4	0	<0.001
Lung	2.3	5.9	<0.001
Lymphoma	2.9	0	<0.001
Melanoma	8.0	6.8	<0.001
Ovarian	3.6	0.7	<0.001

Continued

Table 1 *Continued*

Characteristics[b]	Without myocardial injury ($n = 13\,925\,013$; 85.8%)	Myocardial injury ($n = 2\,300\,547$; 14.2%)	*P*-value
Prostate	9.2	15.3	<0.001
Rectum	1.1	1.1	0.099
Stomach	0.6	1.3	<0.001
Testicular	1.5	1.3	<0.001
Thyroid	2.4	0.9	<0.001
Uterus	6.0	4.3	<0.001

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IQR, inter-quartile range.
[a]Smoked at least 100 cigarettes.
[b]All analyses and estimates are based on weighted records.

subgroups to improve the reliability and accuracy in these populations. In addition to demographics, socioeconomic, and health-related questions, the surveys also include medical, physiological, and laboratory measurements.

The NHANES survey partakers' vital status was assessed via a probabilistic record match to death certificate records from the National Death Index. Additional sources were used to determine mortality status, including those obtained via linkages with the US Social Security Administration and/or by active follow-up of survey partakers. Follow-up duration was calculated from the baseline survey interview date until the first of either death registration date or the study end date (31 December 2019).

Study sample

The NHANES programme released the high-sensitivity cardiac troponin (hs-cTn) dataset in September 2022.[13] This dataset included measurements of hs-cTn in all the 1999–2004 survey participants who had stored serum samples taken at the time of the survey and consented for their use in future research. The measurements took place on these stored samples between 2018 and 2020 at the University of Maryland School of Medicine, Baltimore, MD, USA, and included four assays: hs-cTn T (Roche, using the Cobas e601), hs-cTn I (Abbott, using the ARCHITECT i2000SR), hs-cTn I (Siemens, using the Centaur XP), and hs-cTn I (Ortho, using the Vitros 3600). The used assays were dictated by the published database and were not specifically selected for cancer patients. Survey responders who answered yes to the question 'Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?' were then identified as cancer patients and included in this analysis. Those with cancer were then asked, 'What kind of cancer?', and their answer was recorded to specify the type of malignancy. Cases with pregnancy and missing data weighting were excluded (326 records, 23.6%; see Supplementary material online, *Figure S1*).

Statistical analysis

The IBM SPSS software version 29.0.1 was used for all statistical analysis. Estimation of a representative US non-institutionalized civilian population sample was done through sample weights as advised by the NHANES to account for survey non-response, complex design, and post-stratification. The weighting variable was available for each survey cycle. Combined weights across the three survey cycles between 1999 and 2004 were produced according to the recommended NHANES formulae for combining weights across three survey cycles. Data weighting variable was then rounded to the nearest integer. Quantitative variables were presented as median with inter-quartile range (IQR), while qualitative variables were presented as percentages. Myocardial injury was defined as any of the four hs-cTn assays having a value above the sex and assay-specific 99th percentile upper reference limit (hs-cTn T > 22 and 14 ng/L, hs-cTn I Abbott >35 and 17 ng/L, hs-cTn I Siemens >58 and 39.6 ng/L, and hs-cTn I Ortho >12 and 9 ng/L, for males and females, respectively).[14] It has been assumed that the survey partakers did not have acute myocardial ischaemia at the time of their participation since they were at home, and as such the definition of myocardial injury used in this paper matches the definition used by the fourth Universal Definition of Myocardial Infarction (UDMI), for myocardial injury.[15] For this analysis, cardiovascular disease (CVD) was defined as any of congestive heart failure, coronary heart disease, angina, heart attack, or stroke. Patients with pre-existing CVD were excluded for the sensitivity analysis. The cause of death in this study is based on death certificates that use the International Classification of Diseases (ICD) codes. Specifically, cardiovascular mortality encompassed diseases of the heart (ICD codes: I00–I09, I11, I13, and I20–I51) as well as cerebrovascular diseases (ICD codes: I60–I69), while malignant neoplasm mortality was defined as ICD codes C00–C97.

Pearson's χ^2 or Mann–Whitney *U* test was used to compare the variables as appropriate. Survival was plotted using the Kaplan–Meier survival curves and compared using the Log rank test. Cox regression model survival curves were used to produce hazard ratios [HRs, with 95% confidence interval (CI)] adjusted for the following available variables: age, sex, chronic obstructive lung disease, asthma, anaemia, congestive heart failure, coronary artery disease (CAD), angina, heart attack, stroke, diabetes mellitus, family history of CAD, liver disease, overweight, hypertension, hypercholesterolemia, smoking history (at least 100 cigarettes smoked in life), number of malignancies, and cancer type. These variables were defined based on answering yes to the question 'Has a doctor or other health professional ever told you that you had the respective clinical condition?'. The primary outcome of this analysis was the association of myocardial injury among cancer survivors with long term all-cause mortality, while its association with long-term cardiovascular and malignant neoplasm mortality was included as secondary outcomes.

Results

A total of 16 225 560 weighted records (1058 unweighted) with a history of cancer were included in the analysis, all of them were adults, with a minimum age of 21 year, and no missing vital status. Those with myocardial injury, based on at least a single hs-cTn assay, accounted for 14.2% (2 300 547 records, 210 unweighted) of the cases. The distribution of the hs-cTn values in both arms of the study is available in Supplementary material online, *Table S1*.

Baseline characteristics

Patients with myocardial injury were older (77 vs. 61 years, $P < 0.001$), more likely to be male (43 vs. 40.1, $P < 0.001$), and Black race (6.3 vs. 5.1%, $P < 0.001$). Survey responders with cancer and myocardial injury also had a higher prevalence of comorbidities and cardiovascular risk factors such as anaemia (13.1 vs. 4.7%, $P < 0.001$), chronic obstructive pulmonary disease (COPD, 16.8 vs. 14.2%, $P < 0.001$), CVD (45.7 vs. 16.8%, $P < 0.001$), diabetes mellitus (26.3 vs. 10.5%, $P < 0.001$), hypercholesterolaemia (40.3 vs. 39.1%, $P < 0.001$), hypertension (71.1 vs. 43.5%, $P < 0.001$), liver disease (5.5 vs. 4.8%, $P < 0.001$), overweight

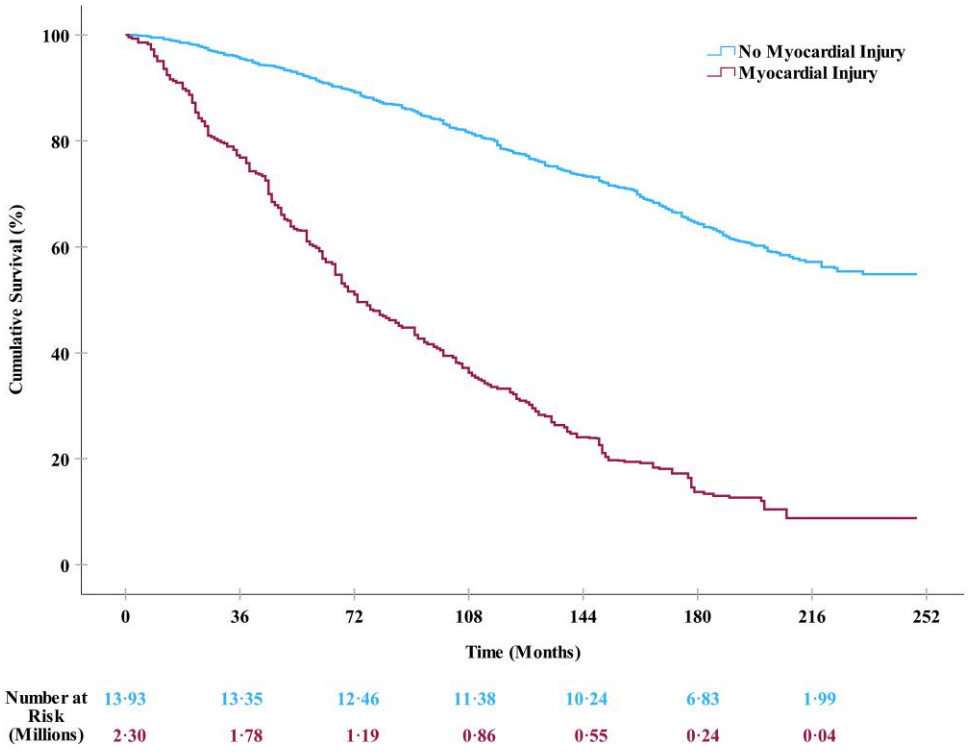


Figure 1 Kaplan–Meier survival curve for cancer patients using any high-sensitivity cardiac troponin assay to define myocardial injury (log-rank $P < 0.001$, all analyses and estimates are based on weighted records).

(39 vs. 34.3%, $P < 0.001$), and smoking (64 vs. 58.5%, $P < 0.001$) compared with those without myocardial injury. The distribution of cancer types between the two groups is detailed in *Table 1*.

Outcomes

The median follow-up period for this analysis was 17.3 years (IQR 15.7–18.9). At 1 year, those with myocardial injury had worse survival compared with those without myocardial injury (84.3 vs. 97.8%) which progressively became worse at 5 (51.6 vs. 89.5%), 10 (28.3 vs. 76.0%), and 15 years (12.6 vs. 61.4%; *Figure 1*). The survival figures stratified by the type of hs-cTn assay used to define myocardial injury are detailed in *Table 2* and represented in the Kaplan–Meir curves (see Supplementary material online, *Figures S2–S5*).

After adjustment for baseline characteristics and comorbidities using Cox regression model, those with myocardial injury had an adjusted HR (aHR) of 2.10 (95% CI 2.09–2.10, $P < 0.001$) for all-cause mortality and 2.23 (95% CI 2.22–2.24, $P < 0.001$) for cardiovascular mortality compared with those without myocardial injury (*Table 3*). The aHR for cancer mortality was 1.59 (95% CI 1.59–1.60, $P < 0.001$). When stratifying the adjusted outcomes according to the type hs-cTn assay used to define myocardial injury, a wide variation was found (*Table 3*), and the hs-cTn I Ortho assay demonstrated the greatest independent association with all-cause mortality (aHR 3.59, 95% CI 3.58–3.60, $P < 0.001$), CVD mortality (aHR 4.56, 95% CI 4.53–4.59, $P < 0.001$), and cancer-specific mortality (aHR 2.29, 95% CI 2.27–2.30, $P < 0.001$).

Sensitivity analysis excluding records with pre-existing cardiovascular disease

After excluding records with known CVD, a total of 12 837 967 survey responders (790 unweighted records) were included in this sensitivity analysis. Those without myocardial injury accounted for most of the records (90.3%, 675 unweighted records). The distribution of demographics, comorbidities, cancer types, and cardiovascular risk factors between those with and without myocardial injury was generally similar to that of the overall analysis (see Supplementary material online, *Table S2*). Compared with those without myocardial injury, the 1-year survival in those with myocardial injury was less favourable (88.7 vs. 98.2%), and this was shown to be increasingly worse at 5 (64.1 vs. 91.1%), 10 (37.8 vs. 79.3%), and 15 years (19.1 vs. 66.2%; *Figure 2*). The survival outcomes stratified by the type of hs-cTn assay used to define myocardial injury are detailed in Supplementary material online, *Table S3* and demonstrated in the Supplementary material online, *Figures S6–S9*.

In comparison with those without myocardial injury using Cox regression to adjust for baseline characteristics, those with myocardial injury had aHR of 1.84 (95% CI 1.84–1.84, $P < 0.001$) for all-cause mortality (*Table 4*), aHR of 2.09 (95% CI 2.08–2.10, $P < 0.001$) for cardiovascular mortality, and aHR of 1.02 (95% CI 1.01–1.02, $P < 0.001$) for cancer mortality. Consistently, myocardial injury defined by the hs-cTn I Ortho assay displayed the highest correlation with all-cause mortality (aHR 6.29, 95% CI 6.25–6.33, $P < 0.001$), CVD mortality (aHR 11.38, 95% CI 11.23–11.54, $P < 0.001$), and cancer mortality (aHR 5.02, 95% CI 4.96–5.07, $P < 0.001$) when compared with those without myocardial injury, all of which were greater than when those with pre-existing CVD were included in the analysis.

Discussion

This large, national, observational study of long-term mortality in non-hospitalized cancer patients has produced several important findings. First, myocardial injury is common (14.2%) in this population and is independently associated with adverse survival regardless of which

Table 2 Unadjusted cumulative survival of cancer patients stratified by type of high-sensitivity cardiac troponin assay used to define myocardial injury at 1, 5, 10, and 15 years

hs-cTn assay/time point[a]	Without myocardial injury	Myocardial injury
Any hs-cTn assay, *n* (unweighted)	13 925 013 (848)	2 300 547 (210)
1 year, %	97.8	84.3
5 years, %	89.5	51.6
10 years, %	76.0	28.3
15 years, %	61.4	12.6
hs-cTn T, *n* (unweighted)	13 954 941 (851)	2 104 096 (194)
1 year, %	97.8	83.3
5 years, %	89.3	49.1
10 years, %	75.7	25.2
15 years, %	61.4	09.0
hs-cTn I Abbott, *n* (unweighted)	15 682 488 (1020)	319 399 (27)
1 year, %	96.4	76.2
5 years, %	85.0	46.7
10 years, %	70.2	26.1
15 years, %	55.2	18.2
hs-cTn I Siemens, *n* (unweighted)	15 383 123 (992)	389 745 (33)
1 year, %	96.2	85.1
5 years, %	85.2	50.4
10 years, %	70.3	27.5
15 years, %	55.5	20.6
hs-cTn I Ortho, *n* (unweighted)	15 665 859 (1009)	385 719 (38)
1 year, %	96.7	62.4
5 years, %	85.4	29.0
10 years, %	70.5	07.2
15 years, %	55.8	00.0

[a]All analyses and estimates are based on weighted records.

Table 3 Adjusted hazard ratio for cancer patients with myocardial injury stratified by type of high-sensitivity cardiac troponin assay used to define myocardial injury (Cox regression)

Outcome	hs-cTn assay	Myocardial injury aHR (95% CI)[a]	*P*-value
All-cause mortality	Any hs-cTn assay	2.10 (2.09–2.10)	<0.001
	hs-cTn T	2.19 (2.18–2.19)	<0.001
	hs-cTn I Abbott	2.69 (2.67–2.70)	<0.001
	hs-cTn I Siemens	2.36 (2.35–2.37)	<0.001
	hs-cTn I Ortho	3.59 (3.58–3.60)	<0.001
Cardiovascular mortality	Any hs-cTn assay	2.23 (2.22–2.24)	<0.001
	hs-cTn T	2.30 (2.29–2.31)	<0.001
	hs-cTn I Abbott	4.51 (4.48–4.54)	<0.001
	hs-cTn I Siemens	3.79 (3.77–3.82)	<0.001
	hs-cTn I Ortho	4.56 (4.53–4.59)	<0.001
Malignant neoplasms mortality	Any hs-cTn assay	1.59 (1.59–1.60)	<0.001
	hs-cTn T	1.63 (1.62–1.64)	<0.001
	hs-cTn I Abbott	1.25 (1.24–1.27)	<0.001
	hs-cTn I Siemens	0.99 (0.98–1.00)	0.031
	hs-cTn I Ortho	2.29 (2.27–2.30)	<0.001

Multivariable analysis—all analyses and estimates are based on weighted records. The following variables were adjusted: age, anaemia, angina, asthma, cancer type, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes mellitus, family history of coronary artery disease, heart attack, hypercholesterolaemia, hypertension, liver disease, number of cancers, overweight, sex, smoking history, and stroke.
aHR, adjusted hazard ratio.
[a]Reference group: cancer patients without myocardial injury.

hs-cTn assay was used to determine such injury for both cardiovascular and overall mortality. Second, while all assays showed consistent results, hs-cTn I assays were stronger independent predictors of overall long-term survival in this population than the hs-cTn T examined in this analysis. Third, these demonstrated associations were independent of the type of the malignancy.

The temporal relationship between myocardial injury and cancer can be described into three phases. First, myocardial injury can occur in association with a malignancy diagnosis before the initiation of any cancer treatment. The mechanism for this association is uncertain. CVD and cancer both share similar risk factors such as diabetes mellitus, dyslipidemia, obesity, age, impaired immune response, and common biological pathways, and several of these chronic conditions have been associated with elevation of troponin.[16,17] Myocardial injury is well described in some advanced forms of cancer, e.g. in the form of the clinical syndrome known as cancer cachexia.[18] In common with contemporary concepts about the significance of detecting any troponin in the blood, the 'Never Means Nothing' hypothesis,[19] previous studies have shown that raised cardiac troponin prior to cancer treatment has been associated with 21% increase in mortality (HR 1.2, 95% CI 1.13–1.32, $P < 0.001$) during a median follow-up of around 2 years.[20] Furthermore, myocardial injury has been shown to predict patients at increased risk of developing cardiotoxicity from planned tumour treatments.[21] The clinical impact of detecting elevated troponin prior to initiation of cancer therapy remains to be elucidated but clearly offers potential value.

The second phase in this relationship is myocardial injury associated with cancer therapies. Anti-cancer treatments can induce myocardial damage, which can either be permanent or transient and therefore can impact the survival, as well as the quality of life of those who survive.[22] While the current standard for diagnosing chemotherapy-induced cardiomyopathy is serial echocardiography, this modality is less sensitive to detect subclinical myocardial damage compared with cardiac troponins.[23] Indeed, there is growing support for the use of serial troponin measurements to monitor cardiovascular toxicity during cancer treatment with the initiation of heart failure therapies in selected patients with myocardial injury even if they are asymptomatic.[21]

The third phase includes cancer survivors who subsequently develop myocardial injury. This is particularly important since cancer survivors have a high burden of CVD.[24] Specifically, the risk of cardiovascular mortality for this population has been reported to be higher than cancer-related death, especially among those previously treated with chemotherapy.[25] Some of the mechanisms through which this elevated risk of CVD occurs include induction of endothelial dysfunction and accelerated atherosclerosis.[5] It has been previously reported that those with a history of malignancy were 26% more likely to have myocardial injury than those without this diagnosis (odds ratio 1.26, 95% CI 1.03–1.53).[26] Furthermore, chronic myocardial injury identified by persistently elevated cardiac troponin after cancer treatment has been associated with both a greater degree of cardiac impairment and higher

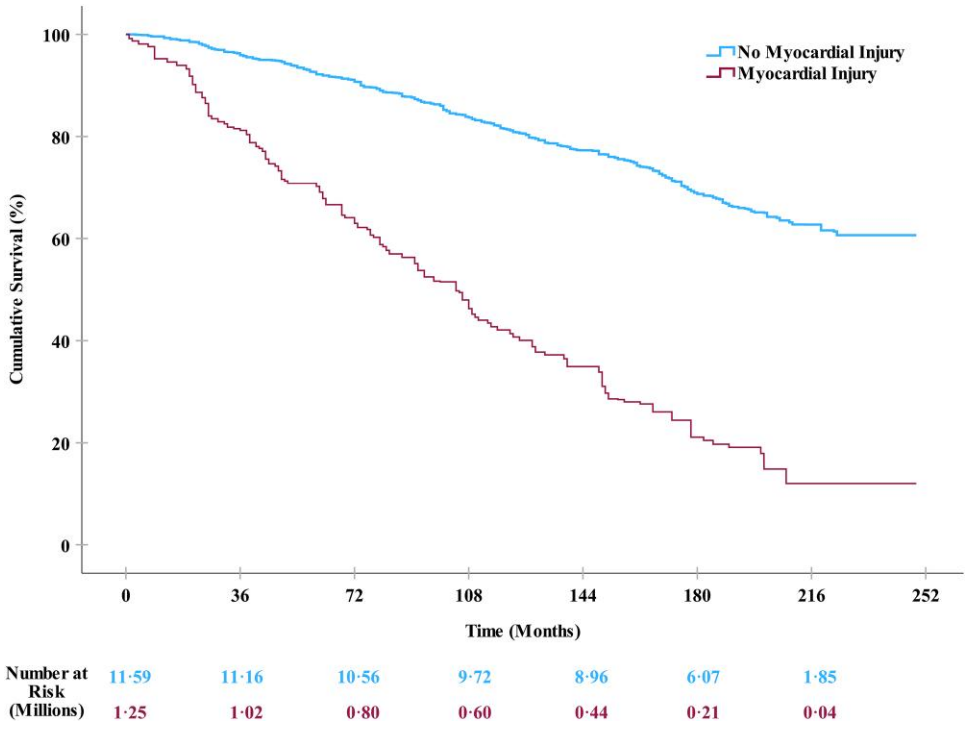


Figure 2 Kaplan–Meier survival curve for cancer patients with no known cardiovascular disease using any high-sensitivity cardiac troponin assay to define myocardial injury (log-rank $P < 0.001$, all analyses and estimates are based on weighted records).

incidence of acute CV events after 3 years of follow-up when compared with those with only transient myocardial damage (84 vs. 37%; $P < 0.001$).[12] Hence, there is a drive to exploit these findings to identify high-risk subgroups among cancer survivors who might benefit from intensive cardiovascular assessment, prevention, and treatment measures.[27] Currently, however, the evidence is inadequate to justify routine screening for myocardial injury (using cardiac troponin) among cancer survivors in order to detect early adverse cardiovascular outcomes and nor are there post-treatment care evidence-based guidelines for cancer survivors.[2,21]

Unfortunately, the current analysis cannot define in which of these three temporal phases the troponin measurements were undertaken due to the lack of information on cancer treatment, which is also an important confounder for the cancer mortality outcome. It is worth pointing out that previous literature did consider cancer diagnosis in the NHANES database as a previous malignancy.[28]

Our data demonstrate that myocardial injury independently predicts long-term survival and thus potentially provides additional support for the notion that there may be value in a strategy of long-term surveillance programmes for cancer survivors based on investigating for myocardial injury especially given that early markers of atherosclerotic disease have been shown to increase significantly after 7 years of cancer treatment.[29] This potential value needs first to be proven based upon evidence of clinical outcome benefit by intervention in the high-risk subgroup with aggressive cardiovascular risk factors modification. This pre-emptive approach to CVD treatment has been previously demonstrated to be effective especially in reducing adverse cardiac remodelling and cardiovascular events among cancer patients receiving chemotherapy.[30]

Furthermore, the current results also showed that myocardial injury is associated with cancer-specific mortality. This could serve as basis for future studies investigating whether there is clinical value in triggering screening for new malignancy or cancer recurrence in the long-term follow up of patients with evidence of troponin elevation. Cardiac troponins have been shown to be expressed in certain cancer tissues, such as non–small-cell lung cancer, and thus can be potentially used as diagnostic marker. Further, the reverse cardio-oncology concept, with evidence suggesting that CVD can potentiate neoplasm, highlights the potential two-way relationship between CVD and malignancy.[31,32] However, the interpretation of cause specific mortality in this analysis has its limitations at least due to the competing risk from cardiovascular and cancer mortality.

These findings also highlight the much greater impact of elevated troponin among cancer survivors with no pre-existing CVD. Using the hs-cTn I Ortho assay for example, myocardial injury was associated with all-cause mortality aHR of 6.29 among those without known CVD compared with all-cause mortality aHR of 3.59 in the overall study cohort. This may reflect the protective benefit of secondary prevention measures that cancer patients with known CVD are likely to be taking.

The underlying mechanisms for the association of myocardial injury with long-term mortality among cancer survivors are not elucidated. Possible hypothesis for this association could include the following: an underlying subclinical CVD among those with not known CVD, a more severe form of CVD among those with known CVD, and a direct insult that triggers biological cascades resulting in the development of CVD. Exploring these hypotheses would be an interesting area for future research.

This study has several important limitations, largely because of its observational design and the database shortcomings in cancer-specific research. First, the morbidities, including cancer diagnosis, are collected from survey participants. However, these diagnoses are conditioned by a doctor or healthcare professional informing them that they have the condition. Second, differentiation between those with active vs. historic malignancy was not possible. Third, comorbidities such as atrial

Table 4 Adjusted hazard ratio for cancer patients with myocardial injury and no known cardiovascular disease stratified by type of high-sensitivity cardiac troponin assay used to define myocardial injury (Cox regression)

Outcome	hs-cTn assay	Myocardial injury aHR (95% CI)[a]	*P*-value
All-cause mortality	Any hs-cTn assay	1.84 (1.84–1.84)	<0.001
	hs-cTn T	1.81 (1.81–1.82)	<0.001
	hs-cTn I Abbott	3.48 (3.45–3.50)	<0.001
	hs-cTn I Siemens	2.90 (2.89–2.91)	<0.001
	hs-cTn I Ortho	6.29 (6.25–6.33)	<0.001
Cardiovascular mortality	Any hs-cTn assay	2.09 (2.08–2.10)	<0.001
	hs-cTn T	2.12 (2.11–2.13)	<0.001
	hs-cTn I Abbott	0.53 (0.52–0.55)	<0.001
	hs-cTn I Siemens	2.99 (2.95–3.02)	<0.001
	hs-cTn I Ortho	11.38 (11.23–11.54)	<0.001
Malignant neoplasms mortality	Any hs-cTn assay	1.02 (1.01–1.02)	<0.001
	hs-cTn T	1.01 (1.00–1.01)	0.014
	hs-cTn I Abbott	2.59 (2.56–2.63)	<0.001
	hs-cTn I Siemens	1.32 (1.31–1.33)	<0.001
	hs-cTn I Ortho	5.02 (4.96–5.07)	<0.001

Multivariable analysis—all analyses and estimates are based on weighted records. The following variables were adjusted: age, anaemia, asthma, cancer type, chronic obstructive pulmonary disease, diabetes mellitus, family history of coronary artery disease, hypercholesterolaemia, hypertension, liver disease, number of cancers, overweight, sex, and smoking history.
aHR, adjusted hazard ratio.
[a]Reference group: cancer patients without myocardial injury.

fibrillation, chronic kidney disease, pulmonary embolism, and social determinants of health were not accounted for, which could have influenced the results. Fourth, the stage of the cancer at the time of diagnosis and the treatment received if any were not available on the database for adjustment. Fifth, the troponin measurements were performed at single point in time (i.e. no trend) and on stored frozen blood samples from many years although recent data did demonstrate that these assays appear to be less affected by inaccuracies in the very long-term.[33] Sixth, since survey partakers were at their own homes, this analysis assumed that they did not have acute myocardial ischaemia at the time of their participation, to meet UDMI definition for myocardial injury. Finally, other relevant non-mortality outcomes like non-fatal myocardial infarction, revascularization, and new heart failure were not available and therefore could not be analysed.

Conclusions

Myocardial injury, defined as an elevated hs-cTn, in patients who have survived cancer, was independently associated with adverse long-term overall survival as well as cardiovascular and cancer-specific mortality. These relationships were stronger in cancer survivors with no previous history of CVD. These data support the concept that screening for myocardial injury in this population may provide important prognostic information and identify a high-risk group of patients.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

H.B.: methodology, formal analysis, visualization, writing—original draft preparation, writing—reviewing and editing, and data interpretation; O.K.: methodology, formal analysis, validation, writing—reviewing and editing, and data interpretation; N.C.: supervision, resources, writing—reviewing and editing, and data interpretation; M.A.M.: supervision, conceptualization, resources, project administration, validation, writing—reviewing and editing, and data interpretation.

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Data availability

The datasets used in the current study are publicly available through the National Health and Nutrition Examination Survey (NHANES) website: https://www.cdc.gov/nchs/nhanes/index.htm.

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