Original Research: Long-Term Prognosis After ST-Elevation Myocardial Infarction in Patients with a Prior Cancer Diagnosis

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ABSTRACT

Introduction: It is unknown how long-term prognosis after ST-elevation myocardial infarction (STEMI) in patients with a prior cancer diagnosis is impacted by cancer-related factors as diagnosis, stage, and treatment. We aimed to assess long-term survival trends after STEMI in this population to evaluate both cardiovascular and cancer-related drivers of prognosis over a follow-up period of 5 years.

Methods: In this retrospective single-center cohort study, patients with a prior cancer diagnosis admitted with STEMI between 2004 and 2014 and treated with primary percutaneous coronary intervention (PCI) were recruited from the STEMI clinical registry of our institution.

Results: In the 211 included patients, the cumulative incidence of all-cause death after 5 years of follow-up was 38.1% ($N = 60$). The cause of death was predominantly malignancy-related ($N = 29$, 48.3% of deaths) and nine patients (15.0%) died of a cardiovascular cause. After correcting for age and sex, a recent cancer diagnosis (< 1 year relative to > 10 years, HR_{adj} 2.98 [95% CI: 1.39–6.41], $p = 0.005$) and distant metastasis at presentation (HR_{adj} 4.02 [1.70–9.53], $p = 0.002$) were significant predictors of long-term mortality. While maximum levels of cardiac troponin-T and creatinine kinase showed significant association with mortality (resp. HR_{adj} 1.34 [1.08–1.66], $p = 0.008$; HR_{adj} 1.36 [1.05–1.76], $p = 0.019$), other known determinants of prognosis after STEMI, e.g., hypertension and renal insufficiency, were not significantly associated with survival.

Conclusions: Patients with a prior cancer diagnosis admitted with STEMI have a poor survival rate. However, when the STEMI is optimally treated with primary PCI and medication, cardiac mortality is low, and prognosis is mainly determined by factors related to cancer stage.

Keywords: Cardio-oncology; STEMI; Prognosis; Cancer

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Key Summary Points

Why carry out the study?

It is unknown how long-term prognosis after ST-elevation myocardial infarction (STEMI) in patients with a prior cancer diagnosis is impacted by cancer-related factors as diagnosis, stage, and treatment.

What was learned from the study?

While long-term prognosis in patients with a prior cancer diagnosis who presented with STEMI and treated with primary PCI appears to be poor with cumulative incidence of all-cause mortality of 38.1% after 5 years of follow-up, cardiovascular mortality is infrequent when patients are optimally with PCI and medications.

The majority of deaths were due to malignancy-related causes and determinants related to cancer staging and treatment made a significant impact on survival.

The present study shows that a collaborative effort between the cardiology and oncology teams is warranted to optimize care for this vulnerable subgroup of STEMI patients.

INTRODUCTION

Coronary artery disease and cancer are two major causes of mortality worldwide. They share both modifiable (smoking, obesity, hypertension), as well as non-modifiable risk factors (age, sex) [1–3]. These diseases are related in regards to their interactions and etiology [2, 4]. Tumor cells can produce pro-inflammatory cytokines, initiating the inflammatory cascade, which contributes to the progression of both cancer and cardiovascular disease.

Furthermore, depending on tumor type and the presence of metastasis, active cancer leads to an increased risk of arterial and venous thromboembolism, due to enhanced aggregability and platelet activation [5]. A relevant concern in the treatment of myocardial infarction is increased risk of in-stent thrombosis [6]. Cancer treatment can also predispose to coronary artery disease. Several forms of anticancer therapeutics, in particular thoracic irradiation, enhance the risk of a variety of cardiotoxic complications (e.g., ischemic heart disease, heart failure, valvulopathy, and left ventricular dysfunction) [3, 7–9].

Prognosis after ST-elevation myocardial infarction (STEMI) depends on several procedure-related factors including infarction size and location, presence of collaterals, door-to-balloon time, occurrence of complications (major bleeding and stroke, stent thrombosis, arrythmia), and left ventricular function [10]. Also, various comorbidities, such as renal disease, diabetes, and hypertension, are related to a poor long-term prognosis [11]. Furthermore, prognosis is also contingent on lifestyle changes (smoking cessation, controlling blood pressure, weight loss or control and increasing physical activity), participating in a cardiac rehabilitation program and (therapeutic compliance to) secondary preventive medication.

However, for patients with a prior cancer diagnosis, short-term prognosis after STEMI is also influenced by the tumor location and stage as shown in several studies [3, 8, 12]. These results have shown that STEMI patients with a prior cancer diagnosis are susceptible to an increased risk of re-infarction, bleeding, and death within 1 year compared to STEMI patients without a prior cancer diagnosis [13]. To the best of our knowledge, no previous study has evaluated the long-term prognosis and cause-specific mortality in this group of patients.

The aim of this study is to assess survival trends after STEMI in patients with a prior cancer diagnosis and optimal treatment with successful primary percutaneous coronary intervention (PCI) during long-term follow-up of 5 years. In addition, drivers of prognosis were evaluated including both cancer-related and STEMI-related factors.

METHODS

Patient Population and Data Collection

Patients with a prior cancer diagnosis who presented to our hospital with STEMI between 2004 and 2014 were recruited from the prospective MISSION! acute coronary syndrome clinical registry [14]. The associated institutional protocol is a standardized prehospital, in-hospital, and outpatient clinical framework for STEMI care, and is based on European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on treatment of acute coronary syndrome [15, 16].

For the purpose of this investigation, patients who did not undergo successful primary PCI were excluded from analysis. Failure of PCI was defined as culprit artery Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or less at end of index procedure. Furthermore, patients who did not survive the index STEMI hospitalization were excluded. Also patients with a primary cancer diagnosis of non-melanoma skin cancer were excluded in this analysis, due to negligible prognostic implications.

The aim of the current study is to evaluate long-term survival trends and identify the main drivers of long-term prognosis in patients with a prior cancer diagnosis. Therefore the clinical registry was reviewed for information on demographic factors, traditional cardiovascular risk factors, lab results, procedural characteristics of catherization laboratory activation, medications at hospital admittance, and discharge/transfer. Hypertension and hypercholesteremia at admission were defined as a history or medical treatment for the respective conditions. Renal insufficiency at admission as defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2.

For the acquisition of information on cancer diagnosis, cancer stage by Union of International Cancer Control /American Joint Committee on Cancer (UICC/AJCC) classification, both active and prior anticancer treatment were collected by two independent investigators through chart review and were obtained from the Leiden University Medical Center (LUMC) cancer registry system (OncDoc), which is linked to the Netherlands Cancer Registry and frequently updated. Active cancer treatment included ongoing regimens of chemotherapy, radiotherapy, immunotherapy, and/or oncological surgery within 6 months prior to STEMI diagnosis.

Study Endpoints and Follow-Up

The main study endpoints were all-cause mortality and cause-specific mortality at 5 years after index hospitalization for STEMI. These data were acquired through municipal civil registries and the departmental information system (EPD-Vision, Leiden, The Netherlands). The cause of death was classified as malignancy-related death, cardiac death, or death by other causes, and was determined by consensus between the two investigators. In case the primary cause of death was not known, the last known treating physician or primary care doctor was contacted. The primary cause of death was defined as condition or injury (or circumstances of the injury) that initiated the train of morbid events leading directly to death. Specifically, pericarditis carcinomatosa was classified as cancer-related death.

Compliance with Ethics Guidelines

The local Medical Ethical Committee (METC Leiden-Den Haag-Delft) approved this study (reference number: G20.127). All patients gave informed consent to participate in the MISSION! study. This study complies with the Declaration of Helsinki 1964 and its later amendments.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, or median [25th–75th percentile] depending on variable distribution. Normality of distribution was assessed graphically. Categorical data are presented as frequencies and percentages.

Differences in baseline characteristics were compared using independent Student's t test or Chi-square test. The maximum serum level of cardiac troponin T ($cTn-T_{max}$) and creatinine kinase (CK_{max}) was log-transformed, due to right-skewness of data.

Cumulative incidence of cause-specific mortality was calculated to study survival trends over the 5-year follow-up period. Cox proportional hazards modeling was performed to assess the hazard ratios (HR) of demographic, cancer-related, and STEMI-related determinants of all-cause mortality at 5 years of follow-up. Both unadjusted and (age + sex)-adjusted HRs are presented. To assess confounding, Cox regression was used. The survival curves of the multivariable Cox regression models were plotted to demonstrate the impact of the determinants on event rates. The proportional hazards assumption was assessed using log-minus-log survival plots. Listwise deletion was utilized for missing data.

A p value of < 0.05 was considered to be statistically significant. All statistical analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

A total of 442 patients with a known cancer diagnosis in the Mission! clinical registry were evaluated. A STROBE diagram is provided in Fig. 1 to elaborate on the selection process. After exclusion of 231 patients who did not meet the inclusion/exclusion criteria, the study population consisted of 211 patients.

The baseline characteristics of the study population are summarized in Table 1. The mean age was 69.3 ± 11.4 years and the majority of patients were male (N = 131, 62.1%). In these 211 patients, there were 245 known primary malignancies. Breast and prostate cancer were the most frequent diagnoses; see Table 2. No patients had more than two prior primary cancer diagnoses at time of STEMI. The median interval between the most recent cancer diagnosis and STEMI presentation

was 5.5 years (66.0 months) and 17.1% of patients had STEMI within 1 year of cancer diagnosis (N = 36). In five patients, the date of cancer diagnosis could not be determined. Twenty-five patients were on active cancer treatment, when they presented with STEMI (11.8%). Distant metastases were known in nine patients (4.3%). Both prevalent hypertension and active smoking at time of STEMI were frequent cardiovascular risk factors (respectively N = 99, 46.9%; N = 63, 29.9%).

Long-Term Survival Trends

The 5-year survival status was available in all patients and the median follow-up time was 42.0 [12.1–60.0] months. The estimated cumulative incidence of all-cause death after 5 years of follow-up was 38.1% (N = 60 deaths) and the primary cause of death was identified in 54 cases (90.0% of deaths); see Fig. 2. The cause of death was predominantly malignancy-related (N = 29, 48.3% of deaths) and only nine patients (15.0% of deaths) died of a cardiovascular cause. Of the 16 patients who died of a miscellaneous cause (26.6% of deaths), the most frequent causes of death were sepsis (N = 3, 5.0%), pulmonary disease (excluding pulmonary sepsis; N = 3, 5.0%), and stroke (N = 3, 5.0%). Of six patients, the primary cause of death could not be identified. The majority of these patients were of old age, had multiple comorbidities, and no attempt was undertaken by the treating physician to identify a primary cause of death.

The 5-year cumulative incidence of death by all causes, including unknown cause of death (N = 6), after STEMI is 38.1% (N = 60). Nearly half of deceased patients died of a malignancy-related cause (N = 29, 48.3% of deaths), follow by death by other causes (N = 16, 26.7%) and cardiac death (N = 9, 15.0%).

Drivers of Prognosis

Figure 3 shows HRs for the risk of incident all-cause deaths at 5 years of follow-up in an age- and sex-adjusted model (HR_{adj}). There were significantly increased risks of the study endpoint when patients were on active cancer
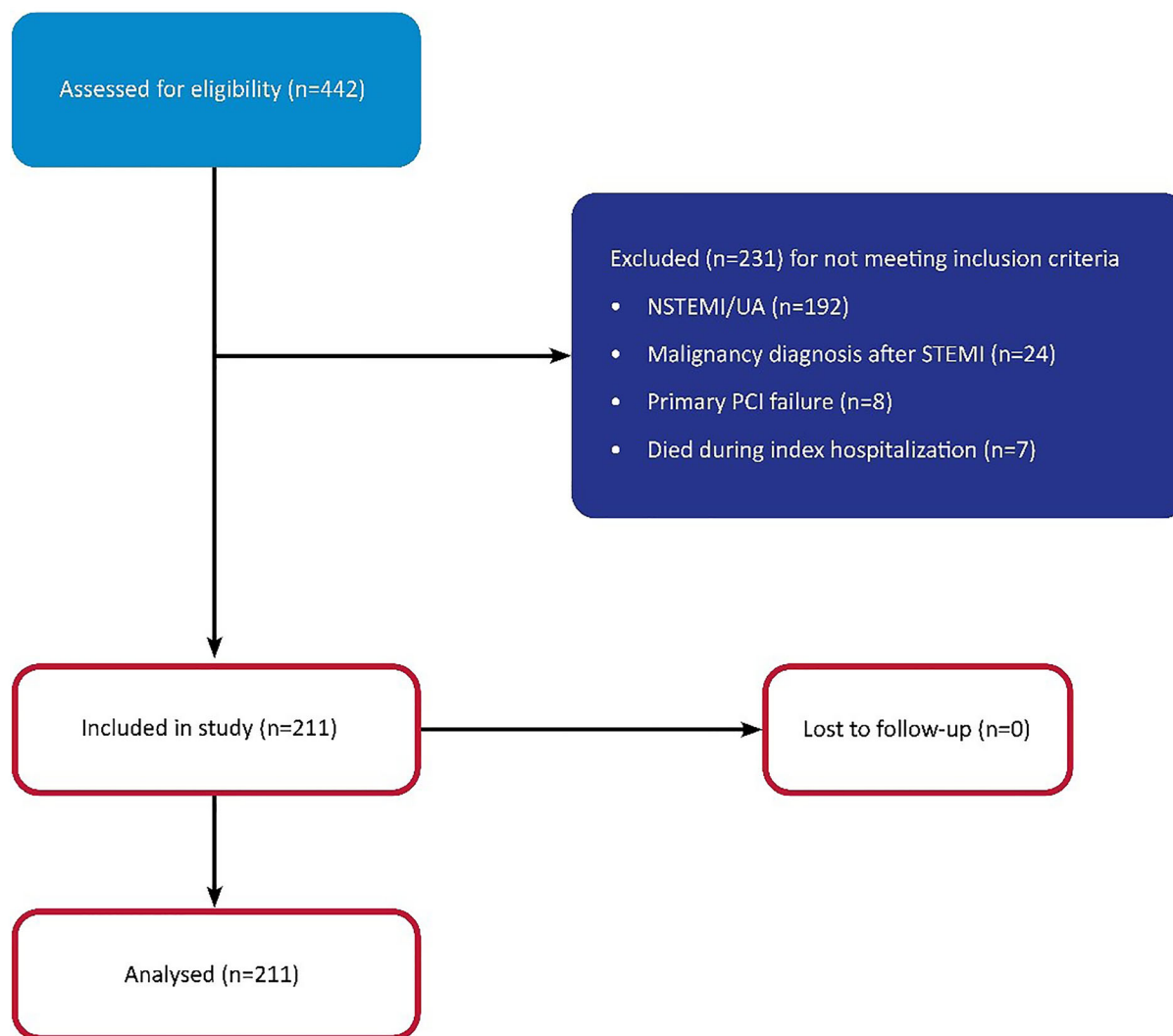
Fig. 1 STROBE diagram of the study patient selection procedure. *NSTEMI/UA* non ST-elevation myocardial infarction/ unstable angina, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction

treatment or had a known distant metastasis at STEMI presentation (respectively HR$_{adj}$1.93 [95% confidence interval 1.03–3.62], p value = 0.040; HR$_{adj}$ 4.01 [1.70–9.53], p = 0.002). Furthermore, there was an inverse relation between long-term prognosis and the duration between cancer diagnosis and STEMI presentation. Compared to patients with a cancer diagnosis more than 10 years before STEMI, patients with a cancer diagnosis within 12 months of STEMI were at 198% increased risk of all-cause death at 5 years of follow-up (HR$_{adj}$ 2.98 [1.03–3.62], p = 0.040).

To assess whether the effect of active cancer treatment was confounded by cancer diagnosis-STEMI interval, the latter variable was added to the age- and sex-adjusted model of active cancer treatment: significant association of active cancer treatment and all-cause mortality was no longer present (HR 1.45 [0.68–3.10], p = 0.340). When controlling for age, sex, and cancer diagnosis-STEMI interval, a significant effect of distant metastasis persisted (HR 3.98 [1.66–9.50], p = 0.002).

Furthermore, there was a relation between the natural logarithm of biochemical infarct size—represented by maximum level of Ln(cTn-

Table 1 Baseline characteristics of the study population

Age, years	69.3 ± 11.4
Male sex	131 (62.1%)
BMI, kg/m^2	25.5 ± 3.8
Traditional cardiovascular risk factors and medical history	
Hypertension	99 (46.9%)
Hypercholesteremia	43 (20.4%)
Diabetes mellitus type 2	20 (9.5%)
Active smoking	63 (29.9%)
Positive family history of heart disease	58 (27.5%)
Myocardial infarction	23 (10.9%)
PCI	19 (9.0%)
CABG	7 (3.3%)
Stroke/cerebrovascular accident	22 (10.4%)
STEMI hospitalization	
Culprit vessel LAD/LM	90 (42.7%)
Killip classification	
I	201 (95.3%)
II	9 (4.3%)
III	0 (0.0%)
IV	1 (0.5%)
Stent type	
BMS	43 (20.4%)
DES	160 (75.8%)
POBA	8 (3.8%)
Maximum cTn-T level, ng/ml	3.86 [1.53–7.50]
Maximum CK level, U/l	1165 [564–2209]
Complete revascularization	122 (57.8%)
Glucose level, mmol/l	8.3 ± 2.5
Hb level at admission, mmol/l	8.2 ± 1.1
Hb < 6.0 mmol/l	8 (3.8%)

Table 1 continued

Age, years	69.3 ± 11.4
Anemia according to WHO definition*	57 (27.0%)
Renal insufficiency at admission	28 (13.3%)
LVEF at baseline < 45%	32 (15.2%)
Medication at discharge or transfer to other hospital	
Antiplatelet therapy	211 (100.0%)
ACE inhibitor/ARB	201 (95.3%)
Beta-blocker	187 (88.6%)
Statins	205 (97.2%)
Cancer diagnosis at STEMI admission	
Time between most recent cancer diagnosis and STEMI, months	66.0 [19.3–148.7]
< 1 years	36 (17.1%)
1–10 years	105 (49.8%)
> 10 years	67 (31.8%)
Active cancer treatment	25 (11.8%)
Chemotherapy	13 (6.2%)
Radiotherapy	7 (3.3%)
Chemoradiotherapy	3 (1.4%)
Surgery 6 months prior within to STEMI	10 (4.7%)
Prior cancer treatment	177 (83.9%)
More than one primary malignancy	34 (16.1%)
Distant metastasis	9 (4.3%)
UICC/AJCC stage (N = 113)	
Stage 0 (carcinoma in situ)	9 (4.2%)
Stage I	32 (14.9%)
Stage II	35 (16.3%)
Stage III	25 (11.6%)

Table 1 continued

Age, years	69.3 ± 11.4
Stage IV	12 (5.6%)

Values are in mean ± SD, or median [Q1−Q3]. Categorical values are in count (percentage of total population) *ACE/ARB* angiotensin converting enzyme/angiotensin II receptor blocker, *BMI* body mass index, *BMS* bare metal stent, *CABG* coronary artery bypass grafting, *CK* creatinine kinase, *cTn-T* cardiac troponin-T, *DES* drug-eluting stent, *HB* hemoglobin, *LAD/LM* left anterior descending artery or left main, *PCI* percutaneous coronary intervention, *POBA* plain old balloon angioplasty, *STEMI* ST-elevation myocardial infarction, *UICC/AJCC* Union of International Cancer Control/American Joint Committee on Cancer
*For men: Hb < 8.1 mmol/l; for women: Hb < 7.4 mmol/l

T_{max}) and maximum level of $Ln(CK_{max})$—and all-cause mortality: respectively HR_{adj} 1.34 [1.08–1.66], $p = 0.008$; HR_{adj} 1.36 [1.05–1.76], $p = 0.019$. There was no significant association between reduced left ventricular ejection fraction (< 45%) at baseline and the study endpoint.

Of the known clinical cardiovascular drivers of long-term survival in STEMI patients—prevalent hypertension, type 2 diabetes mellitus, and renal insufficiency—none showed a significant prognostic implication in this cohort of patients with a prior cancer diagnosis.

After inclusion, ten patients underwent coronary artery bypass grafting (CABG) (4.7%). None of these patients experienced the study outcome or was censored at the end of the 60-month follow-up period.

DISCUSSION

The present study reports the long-term prognosis of patients with a prior cancer diagnosis after STEMI who are optimally treated with primary PCI. The key findings are [1] the cumulative incidence of all-cause death at

Table 2 Distribution of primary tumors

Tumor location	Total population (%) N = 245	Men (%) N = 152	Female (%) N = 93
Bladder and ureter	25 (10.2)	25 (16.4)	–
Brain	7 (2.9)	2 (1.3)	5 (5.4)
Breast	46 (18.8)	–	46 (49.5)
Colorectal	32 (13.1)	19 (12.5)	13 (14.0)
ENT	9 (3.7)	7 (4.26)	2 (2.2)
Kidney	19 (7.8)	12 (7.9)	7 (7.5)
Lung and mesothelioma	9 (3.2)	6 (3.9)	3 (3.2)
Melanoma	12 (4.9)	9 (5.9)	3 (3.2)
Hematological malignancy*	23 (9.4)	21 (13.8)	2 (2.2)
Prostate	35 (14.3)	35 (23.0)	–
Uterus/ endometrium	5 (2.0)	–	5 (5.4)
Other[a]	23 (9.4)	16 (10.5)	7 (7.5)

The study group consisted of 211 patients in total, of which 34 patients had two primary tumors
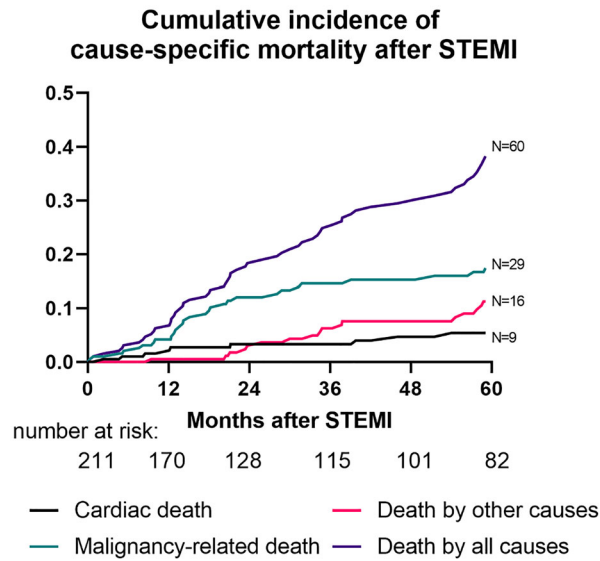*ENT* ear, nose, and throat
*Leukemia, (non-)Hodgkin lymphoma, multiple myeloma
[a] Esophagus, maxillofacial, myeloproliferative neoplasm, neuro-endocrine, ovary, pancreas and bile ducts, stomach, sarcoma, testes

5 years of follow-up was 38.1%, and [2] nearly half of the deaths were due to cancer-related causes. Furthermore, [3] a recent cancer diagnosis, active cancer treatment, or distant metastasis at presentation were the main cancer-related drivers of prognosis, while of the conventional cardiovascular predictors of long-term prognosis did not show an association with all-cause mortality at 5 years.

To our knowledge, this is the first study to show long-term cause-specific mortality in a

**Cumulative incidence of
cause-specific mortality after STEMI**

number at risk:
211   170   128   115   101   82

— Cardiac death
— Malignancy-related death
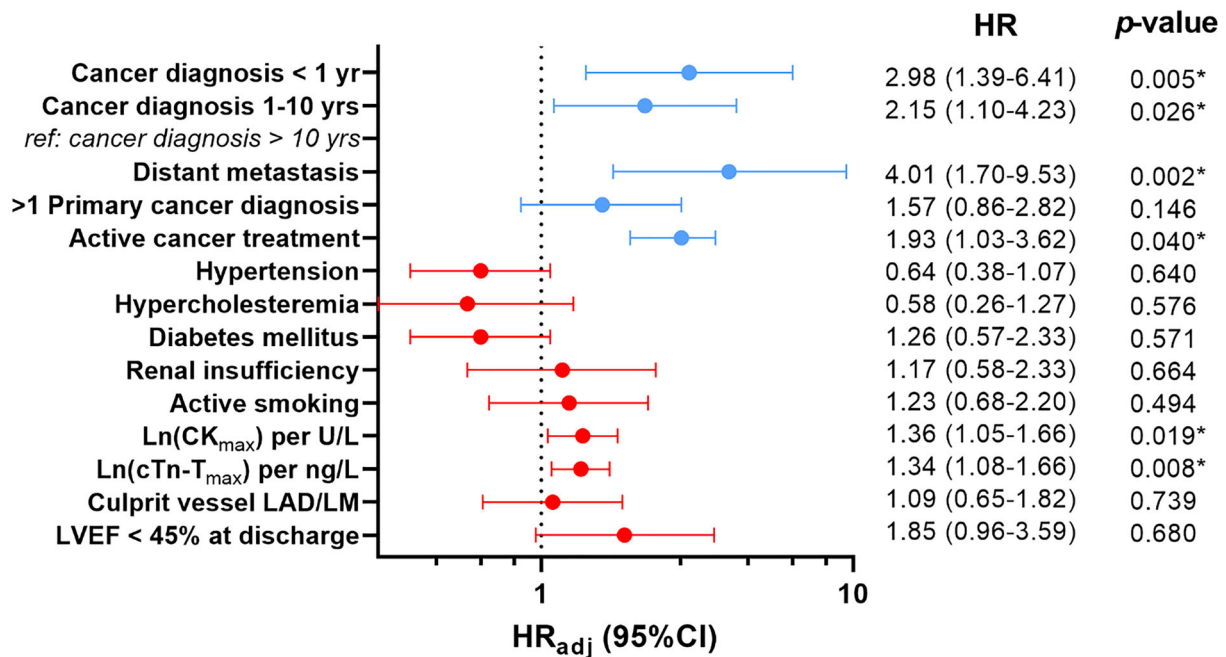— Death by other causes
— Death by all causes

Fig. 2 Cumulative incidence of cause-specific mortality at 5 years after STEMI

cohort of patients with a prior cancer diagnosis admitted with STEMI.

Long-Term Survival Trends

Our study confirms high mortality rates in patients with a prior cancer diagnosis after STEMI found in earlier studies [3, 8], but additionally demonstrates that when optimally treated with primary PCI and medication, cardiac mortality at the long term is low compared to malignancy-related mortality.

Hosseiny et al. [11] previously showed in an unselected group of consecutively enrolled STEMI patients that cardiac mortality is high in the first week after STEMI due to complications such as cardiogenic shock, and all-cause mortality at 1 year of follow-up was 7.3%. After this period, mortality rates stabilized at 2% per year,

	HR	p-value
Cancer diagnosis < 1 yr	2.98 (1.39–6.41)	0.005*
Cancer diagnosis 1–10 yrs	2.15 (1.10–4.23)	0.026*
ref: cancer diagnosis > 10 yrs		
Distant metastasis	4.01 (1.70–9.53)	0.002*
>1 Primary cancer diagnosis	1.57 (0.86–2.82)	0.146
Active cancer treatment	1.93 (1.03–3.62)	0.040*
Hypertension	0.64 (0.38–1.07)	0.640
Hypercholesteremia	0.58 (0.26–1.27)	0.576
Diabetes mellitus	1.26 (0.57–2.33)	0.571
Renal insufficiency	1.17 (0.58–2.33)	0.664
Active smoking	1.23 (0.68–2.20)	0.494
$Ln(CK_{max})$ per U/L	1.36 (1.05–1.66)	0.019*
$Ln(cTn\text{-}T_{max})$ per ng/L	1.34 (1.08–1.66)	0.008*
Culprit vessel LAD/LM	1.09 (0.65–1.82)	0.739
LVEF < 45% at discharge	1.85 (0.96–3.59)	0.680

HR_{adj} (95%CI)

Fig. 3 Forest plot of age- and sex-adjusted HR for the risk of incident all-cause deaths at 5 years of follow-up. Malignancy-related determinants (*blue*) made a significant impact on prognosis, while, besides biochemical infarction size, the majority of the conventional cardiovascular predictors of long-term prognosis (*red*) did not show a significant association with the outcome.

Ln(CKmax) natural logarithm of maximum creatinine kinase level, *Ln(cTn−Tmax)* natural logarithm of maximum cardiac troponin-T level, *LAD/LM* left anterior descending artery/left main artery, *LVEF* left ventricular ejection fraction

and the predominant causes of death were non-cardiac with 22–29% attributable to cancer after 1 and beyond 1 year of follow-up respectively. Our results shown in Fig. 2 reaffirm these findings as cardiac death stabilizes after 12 months whilst cancer-related mortality increases steadily up to 40 months of follow-up.

Drivers of Prognosis in Patients with a Prior Cancer Diagnosis

In view of the fact that in this population of STEMI patients treated with primary PCI cancer-related deaths were more prevalent than cardiac deaths, it was plausible that mortality is driven mainly by malignancy-related factors. For instance, the presence of distant metastasis is a well-known predictor of poor survival [17]. A novel finding was the association between active cancer treatment and worse survival. This relation could be confounded by the circumstance that patients with a recent cancer diagnosis—another previously reported determinant of worse prognosis after STEMI [3, 8, 12]—are more likely to be on active cancer treatment than patients with a past cancer diagnosis. However, it is conceivable to see increased death rates in these patients: the occurrence of major adverse cardiac events (MACE) during cancer treatment—such as STEMI—could be a reason to adjust or discontinue cancer treatment, which is known to have a negative impact on prognosis [18, 19].

As shown in previous studies, we also found an inverse relation between the duration between cancer diagnosis and STEMI and mortality [8, 12]. Both Velders et al., and Ueki et al., hypothesized—in cohort studies with up to 1 year of follow-up—that an explanation could be worse clinical condition in the subgroup of patients with a recent cancer diagnosis.

The present study demonstrates that the negative prognostic impact of a recent cancer diagnosis may be in part the result of a skewed distribution of malignancies with a poor prognosis. Table 3 displays the distribution of six tumor locations with the worst prognosis according to the most recent cancer survival rates per malignancy type [20]. Recent cancer

Table 3 Counts of the six malignancies with worst 5-year survival (the displayed malignancies are selected based on English Cancer Survival Statistics 20) within our cohort stratified by interval between cancer diagnosis and STEMI

	> 10 years prior to STEMI (N = 88)[a]	1–10 years prior to STEMI (N = 115)	< 1 year prior to STEMI (N = 37)
Lung and mesothelioma	–	4 (3.5%)	5 (13.5%)
Pancreas and bile ducts	–	–	2 (5.4%)
Brain	4 (4.5%)	2 (1.7%)	1 (2.7%)
Esophagus	–	2 (1.7%)	–
Stomach	2 (2.3%)	–	1 (2.7%)
Ovary	–	–	1 (2.7%)
Total	6 (6.8%)	8 (7.0%)	10 (27.0%)

The fraction of malignancies with a poor prognosis is substantially larger in patients with a recent cancer diagnosis compared to patients with a cancer diagnosis more than 10 years before STEMI (27.0 vs. 6.8%). This could in part explain the cancer diagnosis-STEMI interval on overall survival; *STEMI* ST-elevation myocardial infarction

[a]Percentages are derived of total of malignancies (N = 240) per category of cancer diagnosis to STEMI interval. In five patients, the interval between cancer diagnosis and STEMI could not be determined

diagnoses were composed for 27.0% of malignancies with a poor prognosis, compared to 6.8% of malignancies diagnosed more than 10 years ago. Most notably, lung cancer, one of the most prevalent malignancies with a poor prognosis among males, was not represented in the > 10 years between diagnosis and the STEMI group [21]. In essence, this suggests that malignancies with a poor prognosis have relatively larger odds of being in the recent cancer diagnosis group, and therefore this negatively impacts overall survival in this subgroup. Unfortunately, the sample size did not allow additional analysis for tumor-specific mortality risk estimates.

When the analysis on drivers of prognosis was stratified on sex, an interesting finding was that active smoking only showed a significant association with survival in females (HR_{female} 3.05 [1.04–8.97], $p = 0.042$ vs. HR_{male} 0.93 [0.47–1.86], $p = 0.841$); see Supplementary Table 1 (S1). Previous publications have elaborated on this topic. An ecological cohort study in a primary prevention setting from the United Kingdom concluded that sex was an effect modifier for the effect of smoking and risk of subsequent acute myocardial infarction [22]. Not only was the peak STEMI rate for females later than for males (70–79 vs. 50–59), but active smoking was also associated with a significantly greater increase in STEMI rate for women than for men (incidence rate ratio 6.6). A study from the Korea-AMI registry reveals that, after STEMI, females had higher incidence rates of major adverse cardiac events (including cardiac death) compared to males at 1-year follow-up [23].

In earlier studies, several cardiovascular risk factors, most notably prevalent diabetes mellitus, hypertension, and renal disease, have been associated with worse long-term outcome in the overall STEMI population [11, 24–26]. The explanation that none of the aforementioned risk factors were significantly related with mortality can be a result of cohort selection: the patients in our study population underwent a successful primary PCI and received optimal medical treatment before discharge or transfer to another hospital according to international guidelines. This underlines that in patients with a prior cancer diagnosis, these traditional cardiovascular risk factors should not be neglected because overall cardiac prognosis in these patients is favorable when treated optimally.

Study Limitations

As mentioned previously, the sample size of the current study was not sufficient to determine accurate risk estimates per specific primary malignancy.

Furthermore, because the focus of the study was to study long-term prognosis of patients with a prior cancer diagnosis and STEMI, patients who died in the hospital were excluded from analysis. As shown by Hosseiny et al., cardiovascular mortality within 7 days of admission accounted for three-quarters of all deaths and therefore the reported survival trends in our cohort are only applicable to patients who survived the initial hospitalization [11].

In addition, it was only possible to determine UICC/AJCC stage in about half of patients due to missing staging information of especially patients with a long time between the cancer diagnosis and STEMI presentation. Therefore, the distribution of cancer stages does not reflect the entire study population, but mostly patients with a more recent cancer diagnosis.

CONCLUSIONS

In this first evaluation of long-term survival trends after optimally treated STEMI in patients with a prior history of cancer, it appears that overall survival is poor, with a cumulative incidence of all-cause death of 38.3% at 5 years of follow-up. The majority of deaths were caused by cancer and factors related to staging and cancer treatment made significant impact on prognosis. Oppositely, cardiovascular death is infrequent after successful primary PCI and optimal medical treatment in line with international guidelines. A comprehensive collaboration effort between the cardiac and oncology treatment teams is warranted to optimize care for this growing population.

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the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. JH and LA designed research; JH and EP collected data; JH and BM analyzed the data; JH and EP drafted the manuscript; BM, WJ, MS, and LA revised the manuscript; LA had primary responsibility for the final content. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Compliance with Ethics Guidelines. The local Medical Ethical Committee (METC Leiden-Den Haag-Delft) approved this study (reference number: G20.127). All patients gave informed consent to participate in the MISSION! study. This study complies with the Declaration of Helsinki 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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