Acute Myocardial Infarction treatments and outcomes in 6.5 million patients with current or a historical diagnosis of cancer in the United States

Running title: Outcomes of AMI in cancer patients

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Abbreviations:

AMI- Acute Myocardial Infarction

AHRQ- Agency for Healthcare Research and Quality

CABG- Coronary Artery Bypass Graft

CAD- Coronary Artery Disease

COPD- Chronic Obstructive Pulmonary Disease

CVD- Cardiovascular Disease

HCUP- Healthcare Cost and Utilisation project

MACCE- Major Adverse Cardiovascular and Cerebrovascular Events

NIS- National Inpatient Sample

PCI- Percutaneous Coronary Intervention

STEMI- ST segment Elevation Myocardial Infarction

Abstract

Aim:

The aim of this study is to evaluate temporal trends, treatment and clinical outcomes of patients who present with an acute myocardial infarction (AMI) and have a current or historical diagnosis of cancer, according to cancer type and presence of metastases.

Methods and Results:

Data from 6,563,255 patients presenting with an AMI between 2004-2014 from the US National Inpatient Sample (NIS) database were analysed. A total of 5,966,955 had no cancer, 186,604 had current cancer and 409,697 had a historical diagnosis of cancer. Prostate, breast, colon and lung cancer were the four most common types of cancer. Patients with cancer were older with more comorbidities. Differences in invasive treatment were noted, 43.9% received percutaneous coronary intervention (PCI) in patients without cancer whilst only 21.0% of patients with lung cancer received PCI. Lung cancer was associated with the highest in-hospital mortality (odds ratio (OR) 2.71 95% confidence interval (CI) 2.62,2.80), major adverse cardiovascular and cerebrovascular complications (OR 2.38 95% CI 2.31,2.45) and stroke (OR 1.91 95% CI 1.80,2.02), while colon cancer was associated with highest risk of bleeding (OR 2.82 95% CI 2.68,2.98). Irrespective of the type of cancer, presence of metastasis was associated with worse in-hospital outcomes, and historical cancer did not adversely impact on survival (OR 0.90, 95% CI 0.89,0.91).

Conclusions

A concomitant cancer diagnosis is associated with a conservative medical management strategy for AMI, and worse clinical outcomes, compared to patients without cancer. Survival and clinical outcomes in the context of AMI vary significantly according to the type of cancer and metastasis status. The management of this high-risk group is challenging and requires a multi-disciplinary and patient-centred approach to improve their outcomes.

Keywords: AMI; cancer; complications; mortality

Introduction

Cardiovascular disease and cancer together account for nearly 70% of disease-related mortality in developed countries.[1] Advances in therapies for cancer have resulted in a decline in mortality, thereby increasing life expectancy in cancer survivors. A significant number of patients with active malignancy or a history of it will present with cardiovascular disease, that has been shown to be the leading cause of death in cancer survivors [2]. The risk of cardiovascular disease varies depending on the type of cancer and therapy that the patient has been subjected to, ranging from two fold higher risk in testicular cancer survivors [3] to a seven fold higher risk in survivors of childhood malignancies [4]. Although cardiovascular disease and cancer are thought of as two distinct disease processes, there is considerable overlap in etiopathogenesis both at an epidemiologic and molecular level. Whilst shared epidemiologic risk factors such as age, smoking [5], diabetes [6] and obesity [7] are well known, the complex molecular mechanisms that are responsible for these diseases and the interplay between them remains less clearly understood.

Patients with a malignancy pose several challenges when presenting with an acute myocardial infarction (AMI). They are often older [8-10], with more comorbidities [10, 11] and have more extensive coronary artery disease (CAD) [8]. Their hematologic and coagulation abnormalities pose challenges to the use of anticoagulants, antiplatelet agents and percutaneous coronary intervention (PCI). There is limited evidence-based guidance in this cohort, further adding to the clinical dilemma. [12, 13] Patients with active malignancy have been excluded from randomised controlled trials that have been used to define best practice in AMI. Furthermore, there is omission of cancer from all contemporary risk stratification scores used to define ischemic and bleeding risk, despite the fact that cancer diagnosis has far greater implications than the comorbidities included in these scores. [14-17]

There are limited data on clinical outcomes following AMI in patients with a cancer diagnosis, as studies in the literature currently do not differentiate between current and prior cancer diagnoses, cancer type or the presence of metastases. We, therefore, sought to analyse the temporal trends, treatment patterns and clinical outcomes in a large contemporary cohort of over 6 million patients with AMI stratified by the type of cancer diagnosis and presence of metastasis over a 10-year period using the National Inpatient Sample (NIS) database a publicly available database in the Unites States containing weighted data from over 35 million hospital stays each year.

Methods

Data source

Data was obtained from the US National Inpatient Sample (NIS) between 2004- 2014. The NIS is an all-payer database developed by the Agency for Healthcare Research and Quality (AHRQ), as part of the Healthcare Cost and Utilisation project (HCUP).[18] The NIS database is made up of hospital admission data, and represents approximately 20% of US hospital admissions each year. Unweighted, the NIS contains information from 7 to 8 million admissions each year. Discharge weights are provided to give national estimates. The NIS contains no individual patient identifier, therefore repeat admissions in the same year or across multiple years are unable to be identified. Since 2012, the NIS samples discharges from all hospitals participating in HUCP, approximating a 20% stratified sample of all discharges from US community hospitals. The sampling strategy has changed over time in order to produce more generalizable estimates by reducing sampling bias. Before 2012 the NIS retained all discharges, but only from a sample of hospitals.

Study design

The NIS was used to identify patients who were admitted to hospital with a primary diagnosis of AMI. Using the international classification of disease, ninth edition, clinical modification (ICD-9-CM) codes, primary admission with ST-segment elevated myocardial infarction (STEMI) was identified using codes 410.0x, 41.01x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x, 410.9x and non ST-segment elevated myocardial infarction (NSTEMI) using 410.7x. Only patients with a primary diagnosis of AMI were considered. Hospitalisations were excluded if the patient was under the age of 18.

Baseline patient characteristics included patient age, sex, median household income, primary expected payer and hospitalization admission day (weekday/weekend). We also included information about the hospital to which the patient was admitted including bed size and teaching/location status. Additional patient comorbidities were identified from the diagnosis codes using ICD-9-CM codes. These included known CAD, smoking status, prior MI or stroke, prior PCI and prior coronary artery bypass graft (CABG), chronic obstructive pulmonary disease (COPD). Finally, Elixhauser comorbidities were also considered.

For each patient who had been admitted with a primary diagnosis of AMI, patients with either a current cancer diagnosis or a historical diagnosis were identified. Current cancer

diagnoses were found using the clinical classifications software codes, with ICD-9-CM codes being used to identify the historical cancer diagnoses. The 30 most common types of cancer were in this population were considered (presented in Supplemental Table 1).

Patient treatments and complications

Supplemental Table 2 overviews ICD-9-CM codes used to identify patient characteristics, complications and procedures. Procedural ICD-9-CM codes were used to determine treatment received by the patient. These included coronary angiography (88.52 88.53 88.54 88.55 88.56 37.22 37.23), percutaneous coronary intervention (00.66 36.01 36.02 36.06 36.07 3609) or coronary artery bypass graft (36.1x 36.20 36.31 36.32 36.9x). If none were recorded it was assumed that the patient had been medically managed. The NIS does not capture pharmacological data. Other procedural characteristics that were considered include long-term or short-term ventricular assist device (VAD), intra-aortic balloon pump (IABP), and intubation or mechanical ventilation.

Clinical Outcomes

In-hospital clinical outcomes including mortality, major adverse cardiovascular or cerebrovascular events (MACCE) (a composite of all-cause mortality, cardiac complications and stroke), stroke and bleeding were identified. Cardiac complications included hemopericardium, cardiac tamponade, need for pericardiocentesis and occurrence of coronary dissection. Bleeding complications included gastrointestinal, retroperitoneal, intracranial, intracerebral haemorrhage, unspecified haemorrhage, and whether a blood transfusion was required. The ICD-9-CM codes used to identify the clinical outcomes are given in Supplemental Table 2. The length of stay on the discharge record and the total billed hospitalisation charge for each individual discharge were recorded. As the total billed charge is not representative of the hospital services cost, a charge to cost conversion ratio was used in order to covert the reported charges into the actual cost for the payer.

Statistical analysis

Continuous variables are expressed as median and interquartile range between parentheses (IQR) due to skewed nature of the data. Categorical variables are expressed using percentages. Where missing data were less than 10% of the covariate data, the observations with missing data were removed. Data was assumed to be missing at random.

For calculation of national estimates and correct variances, sampling weights for each individual discharge that were provided by the AHRQ were used. In order to ensure that the analysis provided an accurate national representation, weighted estimates were produced using the survey analysis method (svy command in Stata). Individual weights were provided for each record, with a hospital variable to account for clustering within hospitals. Due to the redesign of the NIS data and the alternative sampling strategy used before 2012, these weights needed to be updated from the original sampling weights for 2004-2011 in order for the analysis to be conducted across all included years. All analyses were conducted using Stata 14.

Multivariable analyses were used to look at the impact of cancer diagnoses on the clinical outcomes. Logistic regression models were fitted to examine the association between current or historical cancer diagnoses and in-hospital outcomes (mortality, MACCE, stroke and bleeding), presented as odds ratios (OR) with corresponding 95% confidence interval (CI). In order to assess the impact of the cancer diagnosis, all models were adjusted for potential confounders. These included age, gender, median income, expected payer, elective admission, hospital bed size and location, diagnosis of shock, use of VAD or IABP, history of CAD, previous MI, previous CABG, previous stroke, previous PCI, STEMI diagnosis, treatment and year of hospitalisation, as well as the Elixhauser comorbidities. The models were adjusted for the patient, hospital and procedural characteristics listed in Table 1. Other models were fitted to examine the association between the following subgroups and aforementioned outcomes; 1) the most prevalent current cancers, 2) the presence of metastases, 3) patients with only STEMI diagnosis, and 4) patients admitted between 2010 and 2014. Further models were fitted to examine predictors of receipt of invasive management (coronary angiography, PCI and CABG). As a sensitivity analysis, a propensity score matching was used to calculate the average treatment effect, which was the difference between a cancer diagnosis or no cancer diagnosis.

Results

A total of 6,563,255 weighted records were identified with a primary diagnosis of AMI between 2004 and 2014 excluding records with missing information and/or patients under the age of 18, accounting for approximately 3% of records (Figure 1). Between 2004 and 2014 there was a small rise in the rate of patients admitted with a primary diagnosis of AMI with a current diagnosis of cancer (2004 to 2014: 2.5% to 3.0%), and an even greater rise in the rate of patients admitted with a historical cancer diagnosis (2004 to 2014: 4.8% to 7.7%).

The 10 most prevalent cancer types and the percentage of records that had either a current or historical diagnosis of these cancers are shown in Supplemental Figure 1. The most common current cancer diagnosis was lung cancer followed by prostate cancer and leukaemia. For historical cancers the most prevalent was prostate cancer followed by breast cancer.

1. Cancer diagnoses

The patient characteristics of each of the considered groups (no cancer, current cancer and historical cancer) are shown in Table 1. The prevalence of STEMI was 29.0% in the current cancer group, 28.7% in the historical cancer group and 36.0% in the no cancer group. Cancer patients were older (median ages of 75 (67,82) years and 77 (67,84) years compared to 67 (56,79) years). Female prevalence was highest in the historical cancer cohort (43%) and lowest in the current cancer group (35%). The prevalence of previous MI, PCI or CABG were similar across the groups. The rates of deficiency anaemia were higher in both the current and historical cancer diagnoses compared to the no cancer group, as were the rates of complicated diabetes mellitus and chronic renal failure. Patients with current cancer had a higher prevalence of COPD, coagulopathy, fluid and electrolyte disturbances and weight loss.

1.1 Management strategy

The crude rates of invasive procedures (coronary angiography, PCI and CABG) according to timing of cancer are presented in Figure 3. Patients with a current cancer diagnosis had the lowest rates of PCI and CABG, compared to those without cancer or with a history of cancer, and the highest rates of coronary angiography. These findings persisted in multivariate analysis where patients with current cancer were associated with significantly lower odds of all 3 procedures (OR coronary angiography: 0.54 95% CI 0.54, 0.55, PCI: 0.64 95% CI 0.63, 0.65 and CABG: 0.44 95% CI 0.43, 0.45) compared to those without cancer. (Supplemental Table 3) Patients admitted to larger bed size (vs. small bed size) and urban (vs. rural) hospitals were more likely to undergo invasive management, as were patients admitted to US regions other than the Northeast.

1.2 Clinical Outcomes

In-hospital mortality was almost twice as high in patients with a current cancer diagnosis than those with historical or no cancer, (11.1% vs 5.4% and 5.7% respectively). (Table 3) MACCE and stroke were also significantly higher in the current cancer group, compared to both the historical group and the no cancer group (MACCE: 13.3% vs. 7.2% and 7.7%, respectively, and stroke: 2.4% vs. 1.5% and 1.7%). Similar patterns were observed for

bleeding complications, where the current cancer group had twice the rates of bleeding than the historical cancer and no cancer groups (18.4% vs 9.7% and 8.8% respectively). Patients with a current cancer diagnosis had an increase in the odds of in-hospital mortality compared to those with no cancer (OR 1.68 (95% CI 1.65,1.71)). (Supplemental Table 5) In contrast, patients with a historical cancer diagnosis had decreased odds of mortality (OR 0.90 (95% CI 0.89,0.91)). Patients with a current cancer diagnoses had increased odds of MACCE (OR 1.53 (95% CI 1.51,1.55)) and stroke (OR 1.26 (95% CI 1.22,1.30)) whilst those with historical cancer had reduced odds of either event (MACCE: OR 0.88 (95% CI 0.87,0.89), stroke: OR 0.85 (95% CI 0.83,0.87)) compared to no cancer. The odds of bleeding complications were 2-fold higher in patients with current cancer compared to those without cancer, (OR 1.98 (95% CI 1.95,2.00)), with only a modest increase in odds in the historical cancer group (OR 1.04 (95% CI 1.03,1.06)). Similar findings were observed in patients admitted between 2010 and 2014 (Supplemental Table 4), and in the STEMI group (Supplemental Table 5) Finally, a propensity score matched analysis was conducted as a sensitivity analysis. (Supplemental Table 6). The results compared any cancer diagnosis to no cancer, and support the results seen in the main analysis.

2. *Four Most Prevalent Cancer Diagnoses*

The prevalence rates of the 10 most common cancer types are depicted in Supplemental Figure 1. In patients who were admitted with AMI, the four most common malignancies were prostate, breast, colon, and lung cancer. Approximately 98% of patients diagnosed with breast cancer were female, while diagnoses of colon and lung cancer had a broader sex distribution, although there were consistently less females than males across all diagnoses (ranges between 42.2% and 41.4%). The number of patients with prostate, breast and colon cancer remain fairly stable, however, over time there was a much larger variability in the number of patients with lung cancer (from 55 people per 10 000 records up to over 68 people per 10 000 records in 2007 and 60 per 10 000 records in 2014).

Patients across the 4 different cancer types were less likely to be admitted with a primary diagnosis of STEMI and were on average older than the patients admitted with no cancer. (Table 3) Patients with prostate cancer had the highest median age (79 (72,85) years). Patient with cancer diagnosis were less likely to receive invasive treatments. Patients with lung cancer were the least likely to receive any treatment, with only 21% of patients receiving a PCI compared to 43.8% of patients with no cancer.

2.1 Clinical outcomes

The incidence of in-hospital mortality, MACCE, bleeding and stroke were all higher in the different cancer types than patients with no cancer. (Table 4) The highest in-hospital mortality rates occurred in patients with lung cancer, which was nearly 3 times greater compared to patients with no cancer (15.7% vs 5.7%). Patients who were medically managed had mortality outcomes consistently worse than those observed in patients that were managed invasively, with in-hospital mortality rates varying between 13.3% to 19.3% compared to 11.1% in patients that were managed medically that did not have an active cancer diagnosis. (Figure 4) Supplemental Figure 2 shows the crude in-hospital mortality of the 4 considered cancer types and whether metastases were present, with the percentage of records that received each of the different treatment types, medically managed, angiography, PCI or CABG. We also report the percentage of records with each unadjusted outcome stratified by the receipt of radiotherapy. (Supplemental Table 7)

Patients with any of the four types of cancer had an increased risk of MACCE, mortality and stroke compare to patients with no cancer. (Table 5) The odds of MACCE and mortality were highest (2-fold) in the lung cancer group compared to those without cancer (OR 2.38 (95% CI 2.31,2.45) and OR 2.71 (95% CI 2.65,2.80), respectively), followed by colon cancer (OR 1.49 (95% CI 1.39,1.59 and OR 1.68 (95% CI 1.56,1.81). (Figure 5) The odds of bleeding were highest in the colon cancer group (OR 2.82 (95% CI 2.68,2.98), compared to those without cancer, followed by lung cancer (OR 2.06 (95% CI 2.00-2.12). The odds of stroke were only significantly raised in patients with lung cancer (OR 2.31 (95% CI 2.12,2.52) but no difference was observed between other cancer groups and those without cancer. Similar findings were observed in patients admitted between 2010 and 2014 (Supplemental Table 8), and in the STEMI subgroup (Supplemental Table 9). Several factors other than cancer diagnosis were associated with increased in-hospital mortality, including STEMI, peripheral vascular disease, female sex, renal failure and coagulopathies, and advanced age. (Supplemental Table 10).

Mortality was higher when metastases were present for all types of cancer. (Supplemental Table 11) When the different cancer types are stratified into the whether or not metastases were present, the outcomes of patients with metastases were significantly worse than in patients without metastases and patients without a cancer diagnosis. In the no metastases group, once differences in baseline covariates were adjusted for, only patients with lung cancer

had an increase in the odds of in-hospital mortality, (OR 1.73 (95% CI 1.44, 2.08), Figure 5) compared to patients without cancer.

Overall, the adjusted odds of adverse events (MACCE, mortality and bleeding) were significantly higher in patients with metastases than those without, however, there were exceptions according to the type of cancer and metastases status. (Supplemental Table 12) There was no difference in MACCE and mortality between patients with non-metastatic breast and prostate cancers and those without cancer (OR 0.92, 95% CI 0.82, 1.02 and OR 1.02, 95% CI 0.96, 1.08, respectively), and no difference in bleeding in patients with non-metastatic breast cancer (OR 1.07, 95% CI 0.99, 1.17). Furthermore, there was no difference in stroke between patients with breast and colon cancers and those without cancer regardless of metastases status.

Discussion

The present study of over 6.5 million patients is the largest to report the prevalence and outcomes of patients with cancer in a national cohort of AMI hospitalisations, and shows that close to 1 in 10 patients had either a current or historical diagnosis of cancer, with lung, breast, colon and prostate cancers being the four most prevalent cancers. We observe a rise in the prevalence of cancer in patients presenting with AMI, mainly driven by an increase in patients with a historical diagnosis of cancer. This could be explained by the improvement in cancer therapies leading to an rise in the number of cancer survivors.[19] In our study patients in the cancer group who presented with AMI were older and had more comorbidities, consistent with the findings of previous studies. [10, 11, 20] We demonstrate that patients with a current diagnosis of cancer are less likely to receive invasive management (coronary angiography, PCI or CABG), compared to patients without cancer, despite invasive management being consistently associated with lower in-hospital mortality rates irrespective of the type of cancer diagnosis. We also observe a disparity in outcomes depending on the subtype of cancer and metastases status, with outcomes generally worse in patients with metastases. Once baseline risk profile was adjusted for, in the absence of metastases, lung cancer and colon cancers were associated a higher risk of in-hospital mortality whereas prostate and breast cancers were not. In the presence of metastases, all common cancer subtypes (breast, prostate, colon and lung) were at a higher risk of mortality, bleeding and stroke, compared to those without cancer.

There was considerable disparity in invasive management strategies depending on the presence and type of cancer in the present study. Patients with a current cancer diagnosis were at least 36% less likely to receive an invasive management strategy, even after adjustment for

other baseline differences. Amongst the most prevalent cancer groups, lung cancer patients were the least likely to receive coronary angiography and PCI compared to those without cancer. Interestingly, patients managed medically amongst all types of cancer diagnosis had consistently higher inpatient mortality rates compared to those patients managed by an invasive strategy by a factor between two to three. Whilst there may be an element of selection bias, where the lower risk "healthier" cancer patients are more likely to be invasively managed, our data provide supporting data for invasive management of such patients. To date, no randomised trial has evaluated the risks and benefits of conservative versus invasive strategies for treatment of AMI in cancer patients, who are frequently excluded from major randomized AMI trials.[13]

Abnormalities in hematologic parameters such as anaemia and thrombocytopenia and procoagulant states associated with certain types of cancer pose challenges for treatment. [21-23] The presence of malignancy was shown to be an independent predictor of stent thrombosis in the Dutch Stent Thrombosis Registry. [24] In an observational study of STEMI patients by Velders et al a diagnosis of cancer in the 6 months before primary PCI was strongly associated with early cardiac mortality. [11] In an analysis by Tabata et al malignancy was found to be an independent predictor of target lesion revascularization (TLR) following PCI. They also reported that time since completion of cancer treatment had an impact on the rate of TLR, which was the most among those with a current or recent cancer history. [9] The Society of Coronary Angiography and Interventions (SCAI) has put forth an expert consensus statement with emphasis on special considerations regarding coronary angiography and interventions in cancer patients.[12] It includes a recommended revascularization approach that takes into account the platelet count, TIMI risk score and the early involvement of a cardio-oncology team.

Our analysis also reveals that patients with AMI and current cancer were associated with at least 50% increased risk of MACCE, bleeding complications and in-hospital mortality as compared to those without no cancer, whereas patients with historical cancer were at no increased risk of adverse outcomes other than bleeding. Even when data was limited to the last 4 years of our study (2010-2014) for a more contemporary assessment of risk, similar findings were recorded. Although these findings are consistent with some previous studies, the majority of published outcomes data in this population are limited to PCI registries [8, 10, 11, 25, 26] with obvious exclusion of patients who were medically treated. Furthermore, prior studies considered cancer as a single condition, despite prognostic differences between cancer types and stages, and choice of revascularization (or lack thereof), as demonstrated in the present study. Subgroup analysis of the BleeMACS registry revealed that at one-year follow-up, patients with cancer more often experienced the composite endpoint of death and re-infarction

(15.2% vs. 5.3%, P<0.001) and bleeding (6.5% vs. 3%, P<0.001) as compared to those without cancer. [10] In a retrospective analysis from Israel, cancer survivors (mean cancer diagnosis-to-PCI interval was 3.6±3.4 years) had a 40% increased risk of a composite end point of death, nonfatal MI, target vessel revascularization, and coronary bypass surgery, over a mean follow-up period of 6.4±5.9 years. [25] In contrast, analysis of outcomes following PCI in cancer patients from the Duke [8] and Mayo [26] registries have, reported disparate findings. In the Duke study, the different subgroups of patients that were studied included 'pre-PCI cancer' (any cancer treatment before PCI), 'post-PCI cancer' (patients who received cancer treatment after the index PCI) and 'recent cancer' (cancer treatment within 1 year pre-PCI). In this database the majority of patients received PCI for acute coronary syndrome. The adjusted risk of long-term cardiovascular mortality was not significantly different in pre-PCI cancer versus non-cancer patients. However, for patients with post-PCI cancer, some of whom may have had occult cancer at the time of PCI, adjusted risk of cardiovascular mortality was significantly greater than for controls. [8] Analysis of data from the Mayo Clinic PCI registry, which included STEMI patients, revealed that patients with cancer had a higher in-hospital non-cardiac mortality but similar cardiac mortality as matched controls. Even at 6.2 years of median follow up the higher mortality seen in the cancer group was due to non-cardiac causes. [26].

An important aspect of our study is that there is considerable variation in clinical outcomes following AMI depending on the type of cancer and the presence of metastases. Most previous studies [8, 10, 11, 25, 26], which have evaluated outcomes of AMI in cancer patients, lack granularity in terms of the type of cancer or presence of metastases. Given the different types of cancer and variations in their therapy and prognosis, this raises concerns about using a single pooled diagnosis of cancer for analysis. We show that patients with metastases were generally associated with worse adverse outcomes after AMI, except for stroke in patients with breast and colon cancer that was insignificant regardless of metastasis status. Patients with a diagnosis of lung cancer had the highest incidence of mortality, MACCE and stroke, which was further increased in the presence of metastases. A previous study which included only STEMI patients from the National Inpatient Sample database revealed that in-hospital mortality was 57.1% in patients with lung cancer, which was more than double that of the group without cancer (25.7%).[20] In our study the odds of having a bleeding complication were close to 3-fold higher in patients with colon cancer, and we and others have shown that the presence of colon cancer to be an independent predictor of bleeding following PCI.[27, 28] A 10-year observation study of 49,515 patients with metastatic cancer and ACS suggested that even PCI did not provide mortality benefits compared to conservative medical therapy in this cohort. [29]

The strength of our study lies in the large sample size, which is representative of a real-world population. Ours is the first study to present a comparison of data regarding co-morbidities, variations in treatment and clinical outcomes based on the type of cancer, which is lacking in most previous studies. Most of the previous studies relating to AMI in cancer patients are derived from PCI registries [8, 10, 11, 25, 26] thereby omitting a significant subgroup of patients who were medically managed. We acknowledge several limitations of our study, which are inherent to the database. The NIS does not capture data regarding the timing of cancer diagnosis, status of cancer therapy with relation to the AMI, which may in fact be a major prognostic factor as has been shown previously, [11] or cause of death, and lacks data regarding long term outcomes thereby limiting us to just in-hospital events. Furthermore, we were unable to stratify bleeding based on standardized definitions used in cardiovascular trials (major vs. minor).[30] The NIS also does not capture information on antithrombotic regimes, which may contribute to outcomes, particularly if patients with cancer are prescribed less potent anti-platelet agents or dual antiplatelet therapy due to concerns around major bleeding complications, or chemotherapy regimens. The latter may predispose to complications such as re-infarction or major bleeding, and absence of information on whether chemotherapy is ongoing or completed can represent a source of bias when evaluating the true outcomes in the oncologic setting. Furthermore, the NIS also does not capture haematological information such as anaemia or thrombocytopenia that will serve to impact both treatment decisions and clinical outcomes (e.g. bleeding complications). Finally, as with most administrative databases, coding errors and underreporting of secondary diagnoses are always a potential source of bias.

Conclusion

In conclusion patients with current or historical diagnosis of cancer who present with AMI have more comorbidities as compared to those without cancer. The majority of these patients are treated conservatively without PCI and outcomes such as in-hospital mortality and MACCE are greater. Furthermore, there is considerable variation in clinical outcomes noted among different types of cancer with lung cancer being associated with worse mortality outcomes with the risk of bleeding significantly higher in patients with a diagnosis of colon cancer. Additionally, the presence of metastasis is associated with worse clinical outcomes irrespective of the type of cancer. With an abject lack of data from randomized trials, the clinician is often faced with numerous clinical and therapeutic conundrums when treating cancer patients who present with AMI. These patients should be approached from a

multidisciplinary standpoint involving cardiology and oncology positioning the current AMI in the context of the expected prognosis and tailoring the treatment accordingly.

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Figure Legends

Figure 1. Flow diagram of study population selection

Caption: AMI: acute myocardial infarction

Figure 2: Changes in number of records with either a current of historical cancer diagnosis over time.

Figure 3: Distribution of treatments among current, historical and no cancer diagnoses

Caption: CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

Figure 4: Crude mortality for patients with a current diagnosis of the 4 considered cancers stratified by treatment received

**Caption: ***No CABG cases; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

Figure 5: Adjusted odds ratios for adverse events according to cancer type and presence of metastases.

Caption: MACCE: composite of all-cause mortality, cardiac complications and stroke