Sex, Racial, Income, and Regional Disparities in PCI Among Cardio-Oncology Patients: Propensity Score and Machine Learning Augmented Nationally Representative Case-Control Study of Over 30 Million Hospitalizations

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Abstract

Background

Mortality disparities in sex, income, and race are unknown among patients with cancer who undergo percutaneous coronary intervention (PCI).

Methods

Propensity score adjusted multivariable regression for mortality was performed in this case-control study of the 2016 National Inpatient Sample. Regression models by PCI weighted by the complex survey design were adjusted for age, race, income, cancer metastases, NIS-calculated mortality risk by Diagnosis Related Group (DRG), acute coronary syndrome (ACS), and the likelihood of undergoing PCI. Model optimization was conducted with forward and backward stepwise regression, standard regression diagnostics, and performance comparison to backward propagation neural network machine learning (ML) according to root mean squared error (RMSE).

Results

Of 4,659,200 hospitalized adult cancer patients, females were less likely than males to have ACS (41.52% versus 58.48%), and less likely to undergo PCI during ACS (37.86% versus 62.14%). Multivariable regression in the subgroup of cancer patients who underwent PCI found significant disparities in mortality reduction according to sex, males (OR 0.56; 95%CI 0.50–0.62; p < 0.001) versus females (OR 0.61; 95%CI 0.53–0.69; p < 0.001), and race, whites (OR 0.50, 95%CI 0.46–0.55, p < 0.001) versus non-whites (OR 0.58, 95%CI 0.49–0.68, p < 0.001). However, there was no significant mortality disparity according to region, the interaction of income and region, nor the interaction of non-white race and region. There were significant regional disparities in PCI frequency among patients with cancer. RMSE confirmed comparable model performance to ML analysis.

Conclusion

Our nationally representative study suggests that females are less likely than males to undergo PCI and survive, among patients with cancer. Mortality disparities were observed according to race, but not income and region in PCI among patients with cancer.

1. Introduction

Disparities in mortality, healthcare access and resource utilization are major areas of interest in medical literature. Cardiology is no different, with social disparities being well documented in acute coronary syndrome (ACS). However, this has primarily been studied in non-oncologic patients. As more efforts are
directed towards establishing the standard of cardiovascular care in the cancer population, we must also address the socioeconomic inequalities that come into view.

Disparities in cardiac medical management result from differences in sex, race, income, and geography. In the general population, women presenting with chest pain are found to be less likely to have cardiac enzymes drawn or have clinicians act on positive stress testing. Rates of PCI, procedural complications, and cardiac rehabilitation referrals may also be different according to genders, race, and geography. Carrying a cancer diagnosis can drive and augment these disparities. Although the exact mechanisms by which these inequalities occur are unknown, we hope that recognizing the impact of these socioeconomic factors in a cancer patient population will trigger reflection and collective action towards providing equitable care.

### 2. Methods

#### 2.1. Data Source

The 2016 National Inpatient Sample (NIS) was selected for this study as the largest all-payer hospitalized data set in the United States. The NIS was first formed in 2004 from a collection of select hospitals and grew in 2012 to include data from all Healthcare Cost and Utilization Project (HCUP) participating hospitals. It is currently maintained within the HCUP and is sponsored by the US Department of Health and Human Services’ Agency for Healthcare Research and Quality. Currently, approximately 1 in 5 discharges from all community hospitals in the United States are included in this data set. NIS data coding adopted the International Classification of Disease, Tenth Revision, Clinical Modifications (ICD-10) in 2016. The current data set has modified its sampling strategy to minimize sampling bias and now allows more generalizable results for all inpatient discharges in the US.

#### 2.2. Study Design

This nationally representative multi-center analysis investigated inpatient mortality among all eligible hospitalized adults with and without PCI, by sex (male and female), race (white and non-white), geographic region (New England, Mid Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, Pacific), income quartiles (1st, 2nd, 3rd, and 4th) and cancer (yes/no, including overall and primary organ site). The 2016 dataset was selected as it provides the most recent demographic data and clinical outcomes after PCI. All 2016 NIS hospitalization of patients 18 years and older fell within the study’s inclusion criteria. The NIS is classified as a limited data set by the United States' Agency for Healthcare Research and Quality under the Department of Health and Human Services. As an HCUP limited data set, the NIS does not require institutional review board (IRB) approval under Healthcare Insurance Portability and Accountability Act (HIPAA). The study was performed under the ethical principles in the 1975 Declaration of Helsinki and related global bioethical standards.
Patients treated with PCI were identified by ICD-10 procedure codes 00.66 (percutaneous transluminal coronary angioplasty), 36.06 (insertion of non-drug-eluting coronary artery stent(s)), and 36.07 (insertion of drug-eluting coronary artery stent(s)). Additional characteristics such as demographics, comorbidities, outcomes were also identified by ICD-10 codes. Clinical Classification Software, although used by HCUP before the 2016 NIS, was not used to classify cancer in this study (e.g., primary type, current versus prior), as it is no longer reliable when applied to 2016 NIS ICD-10 data.

2.3. Descriptive and Bivariable Statistical Analysis

Descriptive statistics for comorbidities and demographics (i.e., age, sex, race, region, income) were collected for the whole sample. Comorbidities were chosen (and identified by their ICD-10 code) based on their clinical and/or statistical significance as reflected in the current literature. The comorbidities selected for analysis were hypertension, hyperlipidemia, diabetes, smoking, peripheral vascular disease, stroke, congestive heart failure, cardiac arrest, myocardial infarction, cardiogenic shock, valvular disease, anemia, chronic obstructive pulmonary disease, coagulopathy, cirrhosis, chronic kidney disease, obesity, poor diet, HIV, alcohol abuse, opioid abuse, depression, and malignancy (overall and by primary malignancy type). Bivariable analysis was conducted according to cancer (yes/no). Fisher exact tests or Pearson chi square tests were used to analyze categorical variables and compare proportions. Wilcoxon rank sum tests were used to analyze medians and independent sample t tests to compare means for continuous variables.

2.4. Regression Statistical Analysis, Machine Learning Analysis, and Model Optimization

The primary outcome was mortality (yes/no). To maximize the likelihood of valid (externally and internally) and replicable results, regression model performance was optimized according to the following sequential process. First, variables that were clinically or statistically significant were identified in the existing literature, clinic practice, and bivariable analysis to be considered in the final regression models. Second, those variables were included in forward and backward stepwise regression to augment decision-making on the variables that were ultimately included in the final regression models. Third, the regression results were compared to those generated by backward propagation neural network machine learning to ensure comparability by root mean squared error and accuracy. Fourth, regression model performance was additionally assessed with correlation matrix, area under the curve, Hosmer-Lemeshow goodness-of-fit test, Akaike and Schwarz Bayesian information criterion, variance inflation factor, and tolerance, multicollinearity, and specification error. Fifth, the models were re-run continually with fine tuning the final models and final variables until the above process confirmed optimal performance was reached. Based on the above process, all regression models were ultimately adjusted for age, sex, race, income, region, metastases, ACS mortality risk as calculated by the NIS according to DRG. Other variables were excluded based upon the machine learning analysis and diagnostic testing to produce the most clinically and statistically justifiable models.
2.5. Machine Learning-Augmented Propensity Score Adjusted Multivariable Regression (ML-PSr)

The ML-PSr method was then utilized. We first created the propensity score for the likelihood of undergoing inpatient PCI (the treatment, utilizing the same above variables used in the final regression model given the double propensity score adjustment method) [1, 5, 6]. Balance was confirmed among blocks, and then the propensity score was included in the final regression models as an adjusted variable. This causal inference approach (propensity score adjustment) was selected because it is a widely accepted methodology to reduce but not eliminate selection bias and the effect of confounding variables. Such competing causal inference approaches such as fixed, random, and mixed effects were not appropriate. Although these have the added advantage of reducing unobserved variable bias, since the dataset lacked adequate repeated hospitalizations from the same subjects. Propensity score adjustment was used rather than covariate adjustment without the propensity score to enable a more complicated propensity score model (i.e., able to test interactions and higher order terms to produce the best estimated probability of treatment assignment). This avoids risking over-parameterizing while still permitting diagnostic analysis of the final models to be done to confirm superior performance to simple covariate adjustment without the propensity score. Finally, propensity score adjustment rather than competing propensity score techniques was used because of its superior performance in the appropriate context (confirmed by current statistical theory and adequate diagnostic quantitative testing of the final models in cardiovascular studies [5, 6]), and because its inclusion in the final regression models had sufficient performance confirmation in the above specified optimization process.

The utility of this above hybrid analytic approach, which integrates the traditional statistical method of frequentist-based multivariable regression (supported by propensity score-based causal inference analysis) and supervised learning-based machine learning, has been previously demonstrated. The causal inference results, which are more familiar to medical science audiences, can be confirmed and replicated automatically through machine learning (and thus may accelerate real-time findings on larger high-dimensional datasets as they already increasingly do for other economic sectors outside of medicine), while producing more rapid and accurate results compared to traditional statistics [1, 2, 4, 7–9].

2.6 Stratification and Sub-Group Analysis

Regression models were stratified by cancer (yes/no). Sub-group analysis was conducted among patients with cancer additionally stratified by non-white race (yes/no), and then additionally among patients with cancer and PCI.

2.7. Model Validation, Reporting, and Analytic Software

An academic physician-data scientist and biostatistician (DJM) confirmed that the final regression models were sufficiently supported by the existing literature and clinical and statistical theory. Mean values are reported with standard deviation (SDs). Fully adjusted regression results were reported with
95% confidence intervals (CIs) with statistical significance set at a 2-tailed p-value of < 0.05. Statistical analysis was performed with STATA 14.2 (STATACorp, College Station, Texas, USA), and machine learning analysis was performed with Java 9 (Oracle, Redwood Chores, California, USA).

3. Results

3.1. Descriptive Statistics of Adult and Adult Cancer Hospitalizations

Our study consisted of 30,195,722 adult hospitalizations, of which 4,660,593 (15.43%) had cancer. In the subgroup of patients with cancer, the mean age was 68.70 years, 2,353,133 (50.49%) were female, 76.40% were white, and 135,147 (2.9%) had a myocardial infarction including 22,837 (0.49%) with a ST-elevation myocardial infarction (STEMI). The most common comorbidities amongst patients with cancer was hypertension (65.57%), hyperlipidemia (39.37%), and anemia (30.72%), all of which occurred at higher frequency compared to patients overall and those without cancer (p < 0.001).

3.2. Bivariable Analysis by Cancer

Patients with versus without cancer were significantly more likely to be male (49.51% versus 40.46%), white (76.40% versus 66.22%), and have hypertension (65.57% versus 52.27%), HLD (39.37% versus 30.05%), anemia (30.72% versus 18.47%), and chronic obstructive pulmonary disorder (21.59% versus 15.35%) (all p < 0.001), while being significantly less likely to have STEMI (0.49% versus 0.80%) and NSTEMI/UA (2.42% versus 2.71%). These trends held for the above primary malignancies compared to patients without cancer, except for the following primary malignancies having significantly higher frequency of non-STEMI/unstable angina (UA): prostate (3.42%) and skin (3.04%) (all p < 0.001).

3.3. PCI Mortality Disparities by Sex

Among the 4,6659,200 hospitalized adult cancer patients, females were less likely than males to have ACS (41.52% versus 58.58%); however, they were less likely to undergo PCI even if they had ACS (37.86% versus 58.48%) with mortality risk matched to males for minor, moderate, and extreme risk (all p < 0.001). Among hospitalized adult patients overall, fully adjusted regression stratified by cancer and sex status found greater mortality reduction after PCI for males (OR 0.66, 95%CI 0.63–0.69; p < 0.001) versus females (OR 0.72, 95%CI 0.68–0.76; p < 0.001) without cancer. In the subgroup of patients with cancer, the mortality reduction was even greater for PCI among males (OR 0.56; 95%CI 0.50–0.62; p < 0.001) versus females (OR 0.61; 95%CI 0.53–0.69; p < 0.001. (Table 1) Of note, nonwhite race had statistically significant increased mortality amongst both males and females. Increasing income was associated with an albeit small, but statistically significant odds ratio reduction in females.

In sub-group multivariable regression among patients with cancer and PCI, mortality was significantly increased for females (OR 3.77, 95%CI 3.10–4.58, p < 0.001). Among the most common primary malignancies among patients undergoing PCI without significant baseline sex predominance (i.e.
prostate and breast), there was a greater mortality reduction for men versus women in skin cancer (OR 0.59, 95%CI 0.44–0.79, p < 0.001 for men; OR 0.63, 95%CI 0.42–0.95, p = 0.028 for women) and GI cancers (OR 0.46, 95%CI 0.36–0.59, p < 0.001 for men; OR 0.60, 95%CI 0.44–0.81, p = 0.001 for women), though the difference was revered for non-solid cancers (OR 0.55, 95%CI 0.44–0.69, p < 0.001 for men; OR 0.44, 95%CI 0.32–0.61, p < 0.001 for women).

### 3.4. PCI Mortality Disparities by Race and Region

There were significant regional disparities of PCI frequency among patients with cancer, with the top two regions representing 22.22% of regions but 38.61% of PCIs. The regions with the highest frequency of PCI among patients with cancer included South Atlantic (22.20%), East North Central (16.41%), Mid-Atlantic (14.40%), and West South Central (12.75%), and Pacific (11.38%) (all p < 0.001). The regions with the greatest racial difference between non-white and white patients in PCI frequencies across regions included: Pacific (14.23% versus 10.34%), East North Central (14.57% versus 18.47%), West South Central (14.42% versus 9.07%), West North Central (2.35% versus 6.99%), and East South Central (4.19% versus 7.48%) (all p < 0.001) (Fig. 1).

In the sub-group propensity score adjusted multivariable regression among patients with cancer stratified by race, the significantly reduced mortality was greater for whites (OR 0.50, 95%CI 0.46–0.55, p < 0.001) than non-whites (OR 0.58, 95%CI 0.49–0.68, p < 0.001). There was no significant association between mortality and income among non-whites, but among whites there was a significant stepwise increase in mortality reduction with increased income quartile compared to the lowest quartile from the 2nd (OR 0.96, 95%CI 0.92–0.99, p = 0.014) to the 3rd (OR 0.90, 95%CI 0.87–0.94, p < 0.001) to the 4th (OR 0.88, 95%CI 0.85–0.92, p < 0.001). In sub-group multivariable regression among patients with cancer and PCI, mortality was significantly increased among non-whites (OR 1.23, 95%CI 1.02–1.48, p = 0.032).

### 3.5. PCI Mortality Disparities by Cancer

In propensity score adjusted multivariable regression stratified by cancer, PCI had greater mortality reduction among patients with cancer (OR 0.52, 95%CI 0.48–0.56, p < 0.001) versus without it (OR 0.61, 95%CI 0.59–0.64, p < 0.001). In multivariable regression analysis stratified by historical versus active cancer, there were greater mortality reductions with PCI for patients with active versus historical cancer overall as well as for prostate, breast, and non-solid malignancies while the difference was inverted for skin and GI (Fig. 2). In multivariable regression analysis stratified by metastatic versus non-metastatic malignancy, there were greater mortality reductions with PCI for patients with metastatic versus non-metastatic malignancy overall as well as for prostate, though this difference was inverted for breast, skin, and GI (Fig. 3).

### 4. Discussion

Social disparities in general cardiology include gaps in mortality, resource utilization, and complication rates. Our study is consistent with prior social and medical trends observed in the general population for ACS. We demonstrated that among patients with cancer, females are less likely than males to undergo
medically indicated PCI and are less likely to survive. Different regions and races in the USA also observed varying frequency of PCI. As we expand the technical knowledge of treating cardiovascular disease in malignancy, so should our understanding of medical inequities in this vulnerable population.

The undertreatment of female compared to male patients with cancer for ACS found in our study is consistent with analogous studies done in the general population. Shehab et al [10] and Radovanovic et al [11] demonstrate that women without cancer were less likely to undergo invasive procedures including angiography (27% vs 34%; P < 0.001), PCI (10.5% vs 15.6%; P < 0.001) and reperfusion therapy (6.9% vs 4.0%, P < 0.001), respectively. These trends remain despite comparable success rates of PCI found in both genders (OR 1.09, 95% CI 1.04-1.14) [12]. Numerous studies also demonstrate women experience disparities according to race. Multi-ethnic Asian women with STEMI are less likely to undergo coronary angiography (40.91% vs. 48.93%, p < 0.001) and PCI (32.03% vs. 40.04%, p < 0.001) compared to men [13], with similar trends demonstrated in the Middle Eastern population [10].

Multiple proposals have been made to justify sex disparities in the treatment for ACS. Physicians frequently cited their reason for not intervening in women with ACS as cases not being supported by proficient evidence (men 5.3% vs women 10.1%, P = .017) [14]. The atypical presentation of female patients with ACS influences medical decision making as physicians seek alternative non-invasive diagnostic imaging [15]. Although done with good intentions, these approaches lead to delay in coronary angiography and appropriate cardiac medication for women. Our study is the first nationally representative study showing that PCI benefits inpatient mortality in cancer patients regardless of their demographic. Among patients with cancer, those with active and metastatic cancer experienced even greater mortality reductions than those with historical and non-metastatic disease. These differences in disease status can further the disparities seen in the female and other vulnerable populations discussed previously. Thus, regardless of cancer status or demographics, PCI should not be withheld when medically indicated.

Although we found improved inpatient mortality in women, various studies have shown higher risk for bleeding difficulties in women undergoing invasive coronary procedures. (OR = 5.39, 95% CI 2.26 to 12.8) [16]. This may raise concern in oncologic patients, who are at higher risk of bleeding than patients without cancer (6.5% vs. 3%, P < 0.001) [17], which suggests why patients with cancer are undertreated and blood thinners are avoided in this patient population. The undertreatment of female patients with cancer for ACS is multifactorial and requires further research to identify the causes.

Along with lower likelihood of PCI and increased complication rates, the mortality reduction after PCI in females with cancer is lower than that of males. This advantage in mortality for males could be secondary to the undertreatment of female patients with fewer invasive procedures, and with less aggressive medical management at discharge. Numerous studies have described the lower utilization of cardiac related medications in females compared to males [10, 13, 18]. Similarly, cancer patients are undertreated and less likely to be on secondary preventive drugs like aspirin, statins, and beta blockers [17, 19]. This puts female patients with cancer at a huge disadvantage. Considering our study findings,
we aim to encourage physicians to be more diligent in treating the female population more aggressively for ACS. This is in line with the recent JACC guidelines on coronary artery vascularization, which recommended treating patients regardless of their sex, ethnicity, or race [20]. According to our data cancer should not be seen as a deterrent to manage these patients regardless of gender.

Regional and racial differences in managing ACS have been discussed in the literature. Yet, the studies are limited for these differences in hospitalized cancer patients. Our study findings demonstrate lower PCI frequency for hospitalized cancer patients in the Mountain and New England regions when compared to the South Atlantic and East North Central regions. Like our findings, Kolte et al group found Northeast regions were less likely to receive PCI and CABG in comparison to the Midwest, West, and South regions [20, 21]. Some possible explanations for these findings include higher use of medications [22]. Krumholz was able to show more betablocker usage (72% vs 52% other regions, P < .001) and aspirin use (80% vs 76% other regions, P < .001) in the NE region compared to other regions. Earlier follow up with primary care physician or cardiologist [23], and more cardiac rehab referrals in the Northeast region [24] when compared to other regions in the US namely, the Midwest and South regions. All these interventions highlight the superior outcomes with ACS treatment in Northeast regions. Kolte et al group showed worse in-hospital mortality despite reperfusion and revascularization rates in other regions when compared to the Northeast. Our study findings on hospitalized patients with cancer who underwent PCI did not show significant mortality disparities in the different regions. This is parallel to other findings done showing narrowing of regional differences in myocardial infarction-associated mortality over the years [25]. One possible theory for this improvement in ACS mortality in different regions is the implementation of guidelines and participation in quality improvement programs [26]. Laskey et al group devised a program recommending early aspirin use, and discharge prescriptions of angiotensin-converting enzyme inhibitors, beta blockers, and statins in both rural and urban areas. No significant mortality differences were noted between the two regions when conforming to these guidelines. In a similar study, Hispanic patients in different US cities who enrolled in a program to help enforce guideline directed medical therapy showed no regional variation in in-hospital mortality [26, 27]. This will ultimately help avoid lapses or discrimination of different patient populations. It is known cancer and ACS share multiple risk factors, and it is not infrequent that patients will often have both diseases [28]. Thus, managing these risk factors appropriately can help improve mortality rates. These programs focused on implementing guidelines have been shown to help with performance measures in ACS patients [29]. The same should apply to the cancer patient population as well. With implementation of more clear and useful guidelines, as well as ensuring patients are discharged on the appropriate medication regimen, these regional differences in ACS mortality will continue to shrink for the overall US population including cancer patients.

5. Conclusion

Cardio-oncology is an emerging field that seeks to establish the standard of cardiac care in patients with cancer and address the socioeconomic inequalities that may exist within. Our nationally representative study supports with cancer are less likely to undergo PCI and survive compared to males. PCI utilization
was also found to be different according to region, and white vs non-white race. Lastly, patients of non-white race and those within lower income quartiles had lesser mortality reductions after PCI. Social disparities are as prevalent in Cardio-oncology as any other specialty in the medical literature. As we recognize the existence of these disparities, we hope that the medical community will be motivated to further understand the mechanisms that drive them.

**Abbreviations**

PCI = percutaneous coronary intervention; NIS = National Inpatient Sample; Diagnosis Related Group (DRG); ACS = Acute Coronary Syndrome; ML = Machine learning; RMSE = Root Mean Squared Error; HCUP = Healthcare Cost and Utilization Project; ICD-10 = International Classification of Disease, Tenth Revision; IRB = Institutional Review Board; HIPAA = Health Insurance Portability and Accountability Act; ML-PSr = Machine Learning-Augmented Propensity Score Adjusted Multivariable Regression; SD = Standard Deviation; CI = Confidence Interval; STEMI = ST elevation Myocardial Infarction; COPD = Chronic Obstructive Pulmonary Disease; UA = Unstable Angina.

**Declarations**

6.1 Ethical Approval and Consent to Participate
The NIS is classified as a limited data set by the United States' Agency for Healthcare Research and Quality under the Department of Health and Human Services. As an HCUP limited data set, the NIS does not require IRB approval under HIPAA. The study was performed under the ethical principles in the 1975 Declaration of Helsinki and related global bioethical standards

6.2 Consent for Publication
Not Applicable

6.3 Availability of Data and Materials
The data generated or analyzed during this study are available from the corresponding author on reasonable request.

6.4 Competing Interests
The authors declare that they have no competing interests

6.5 Funding
No funding to declare.

6.6 Authors’ Contributions
Design of the Work – JWK, DJM, EK, MC, CI
Acquisition of Data – DJM, CI

Analysis of Data – JWK, DJM, CI

Interpretation of Data – JWK, DJM, KH, SS, NP, JLM, MC, CI

Visualization – JWK, DJM, JP, SS, NP, KM

Original Draft – JWK, MAK, AJ, KH, GI, SK, KM,


Supervision – JWK, GI, NP, JLM, MC, CI

All authors read and approved the final manuscript

6.7 Acknowledgements

Not applicable

References


Tables

Table 1. Propensity score adjusted multivariable regression of PCI and mortality by sex among patients with cancer (N=4,659,200)

<table>
<thead>
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<tr>
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</table>
### Females

| Mortality | Odds Ratio | Std. Err. | t    | P > |t|   | 95% Conf. Interval |
|-----------|------------|-----------|------|-----|-----|-------------------|
| PCI       | 0.61       | 0.04      | -7.40| 0.00| 0.53| 0.69              |
| Age       | 1.00       | 0.00      | -2.96| 0.00| 1.00| 1.00              |
| Nonwhite  | 1.14       | 0.03      | 5.82 | 0.00| 1.09| 1.19              |
| Income    | 0.98       | 0.01      | -2.15| 0.03| 0.96| 1.00              |
| Metastases| 1.75       | 0.03      | 28.56| 0.00| 1.68| 1.82              |
| Mortality risk | 6.87   | 0.13      | 98.16| 0.00| 6.61| 7.14              |
| ACS       | 5.31       | 0.60      | 14.76| 0.00| 4.25| 6.63              |

### Figures

**Figure 1**

Significant PCI disparities among cancer patients by race and region, N=30,195,722 (p<0.001)
Figure 2

Machine learning-augmented multivariable regression of mortality and PCI by historical versus active cancer

*Fully adjusted for age, sex, race, income, NIS-calculated mortality risk by DRG, and ACS; p<0.05 for all results.

Figure 3
Machine learning-augmented multivariable regression of mortality and PCI by metastatic versus non-metastatic cancer*

*Fully adjusted for age, sex, race, income, NIS-calculated mortality risk by DRG, and ACS; p<0.05 for all results (clinically it would be incorrect to analyze non-solid malignancy by metastatic versus non-metastatic disease).