

# Socioeconomic disparities in long-term heart failure risk of trastuzumab with or without anthracyclines in early-stage breast cancer: a SEER-Medicare database analysis

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Karissa Britten, Marla Lipsyc-Sharf, Eric H. Yang, Susan McCloskey, Mina S. Sedrak, Mediget Teshome, Julia LaBarbera, Aditya Bardia & Nicholas McAndrew

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**Authors:** Karissa Britten<sup>1,5\*</sup>; Marla Lipsyc-Sharf<sup>1</sup>; Eric H Yang<sup>2</sup>; Susan McCloskey<sup>3</sup>; Mina S. Sedrak<sup>1</sup>; Mediget Teshome<sup>4</sup>; Julia LaBarbera<sup>1</sup>; Aditya Bardia<sup>1</sup>; Nicholas McAndrew<sup>1</sup>

**Affiliations:** **1:** Division of Hematology/Oncology, UCLA, Los Angeles, CA **2:** UCLA Cardio-Oncology Program, Division of Cardiology, UCLA, Los Angeles, CA **3:** Department of Radiation Oncology, UCLA, Los Angeles, CA **4:** Division of Breast Surgical Oncology, UCLA, Los Angeles, CA **5:** Department of Medical Oncology, Cedars-Sinai Medical Center, Los Angeles, CA

\*Corresponding Author: Karissa.Britten@cshs.org

### Abstract

While it is well-established that cardiovascular disease and congestive heart failure (CHF) are increased among breast cancer survivors, little is known about how systemic therapy use, medical comorbidities, and socioeconomic factors interact to influence long-term cardiac outcomes. In this study, we performed an analysis of the SEER-Medicare database, including more than 200,000 patients with early-stage breast cancer. Using available zip code and census data, patient disease characteristics and cardiac outcomes were stratified by socioeconomic variables. Overall, patients of Black, Hispanic, and American Indian/Alaskan Native race/ethnicity had increased incidence of large, high-grade tumors and nodal involvement as compared to White and Asian American/Pacific Islander (AAPI) patients. Lower per capita income (PCI), higher percentage of population living in poverty, lower level of education, and not speaking English at home were also associated with increased tumor size, grade, and nodal stage. Adjusting for cardiac covariates and cancer therapy type, a multivariate socioeconomic model revealed that Black patients had higher risk of CHF and AAPI patients had a lower risk compared to White patients. Further adjusting for race/ethnicity, patients living in a zip code in the lowest quartile of PCI also had a higher risk of CHF compared to those in the highest quartile.

## Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer-related deaths among women in the United States<sup>1,2</sup>. Despite this, the vast majority of women are diagnosed with potentially curable, early-stage disease, for which 5-year survival has risen to over 90% in the last 25 years<sup>2</sup>. HER2+ breast cancer – which is characterized by somatic amplification of the HER2 gene and overexpression of the HER2 protein<sup>3</sup> – has seen particularly dramatic improvements in survival, largely resulting from the development of trastuzumab and subsequent HER2-directed therapies. In the US, however, breast cancer incidence and mortality differ substantially by race/ethnicity, socioeconomic status (SES), and other social determinants of health. Incidence is highest among White women (133.7 per 100,000 women), followed by Black (127.8), American Indian/Alaska Native (AIAN; 111.3), Asian American/Pacific Islander (AAPI; 101.3), and Hispanic (99.2) women<sup>2</sup>. However, despite the somewhat lower incidence of breast cancer among Black and AIAN women in the US, age-adjusted mortality is higher than that of White women in these cohorts. Mortality among Black women in particular exceeds that of White women by 40%,<sup>2</sup> even among patients with early-stage HER2+ disease.<sup>4,5</sup> A multitude of studies have additionally shown strong, although less well-defined, relationships between breast cancer outcomes and other socioeconomic variables (SEVs): poverty, lower levels of education, and rurality of residence are all SEVs that have been associated with later-stage disease diagnosis and increased mortality rates among women with breast cancer<sup>6-12</sup>.

As therapeutic advancements continue to improve the survival of patients with breast cancer, clinicians are witnessing an increase in other causes of long-term morbidity and mortality in this population. Cardiovascular disease (CVD) is the leading cause of non-cancer-related mortality in this group, responsible for an estimated 35% of all non-cancer-related deaths in those 50 and older<sup>4</sup>. In particular, several studies have shown increased risk of congestive heart failure (CHF) among breast cancer survivors, particularly among those who have received systemic therapy with trastuzumab and/or anthracyclines<sup>13-15</sup>. In one large study from the UK that included more than 10,000 patients with a prior breast cancer diagnosis, breast cancer survivors were at increased risk of CHF, non-ischemic cardiomyopathy (NICM), and death from CHF or NICM compared to matched controls without cancer<sup>14</sup>.

The anthracyclines and trastuzumab-based monoclonal antibodies are both associated with cardiotoxic effects, and close cardiovascular monitoring is recommended for patients receiving these treatments<sup>16-18</sup>. Anthracyclines – a class of topoisomerase II inhibitor chemotherapy – can cause a well-established type of cardiotoxicity characterized by clinical heart failure, arrhythmia, or myocarditis, which is thought to be caused by irreversible structural cardiomyocyte alterations and cell death<sup>19-21</sup>. Trastuzumab – a monoclonal antibody that binds to the extracellular domain of HER2, which is overexpressed in HER2+ breast cancers<sup>22</sup> – has also been associated with heart failure<sup>23</sup>. This clinical entity is characterized by either clinical heart failure or asymptomatic decline in left ventricular ejection fraction and, in contrast to the structural myocyte damage associated with anthracycline use, is thought to be due to a transient (and potentially reversible) decrease in contractility<sup>19-21</sup>.

Similar to what is seen in the epidemiology of breast cancer itself, the incidence and outcomes of CVD among breast cancer survivors differ substantially by race/ethnicity and SES. Studies have shown that Black breast cancer survivors appear to bear an increased burden of morbidity in this setting: Black women experience higher rates of major adverse cardiovascular events after diagnosis,<sup>24</sup> and also exhibit increased mortality<sup>25,26</sup> when compared to their White counterparts. A variety of other socioeconomic variables have also been associated with increased CVD mortality among breast cancer survivors, including neighborhood median household income and median home values<sup>24</sup>. However, a limited number of studies to date have examined how the interactions between socioeconomic factors,

systemic therapy use, and medical comorbidities impact long-term cardiac outcomes among breast cancer survivors. Further, prior studies have been further limited by relatively small sample sizes, short durations of follow up, and primarily metastatic patient populations.

Our group previously presented data from the SEER-Medicare database describing long-term cardiotoxicity associated with trastuzumab (T) and/or anthracyclines (A) in early-stage breast cancer (EBC) patients (to be published separately).<sup>27</sup> Here, we present an analysis of disparities in outcomes stratified by available socioeconomic variables (SEVs) from individual zip code and census data.

## Results

### *Study Population*

Of the 214,014 patients with early breast cancer (EBC) included in our initial primary analysis, census data was available for 206,605 patients. Of those, 8,302 patients (4.0%) received trastuzumab (T) with non-anthracycline (A) chemotherapy, 1,977 (1.0%) received both T and A, and 13,176 (6.4%) received A without T. The remainder received neither T nor A.

### *Clinicopathologic Features*

Overall, patients of Black, Hispanic, and AIAN race/ethnicity had significantly increased prevalence of large, high-grade tumors and increased nodal involvement as compared to White and AAPI patients (Table 1, Figures 1-3). 14.6% of Black patients, 13.1% of Hispanic patients, and 12.1% of AIAN patients were diagnosed with T3-4 tumors, compared to 9.8% and 10.2% in White and AAPI patients, respectively. Similarly, 45.2% of Black women, 38.5% of Hispanic women, and 38.5% of AIAN women were found to have grade 3 disease, compared to 29.2% and 32.5% in White and AAPI women, respectively. Further, 37.6% of Black patients, 37.9% of Hispanic patients, and 34.5% of AIAN patients had nodal involvement (N1-N3) at time of diagnosis, compared to 28.1% and 28.4% of White and AAPI patients, respectively (Table 1).

Other SEVs associated with these higher risk features included lower level of education, lower PCI, higher percent of population living below poverty, and higher percent of households not speaking English at home (Table 1, Figures 1-3). Level of education, PCI, and percent of population living below poverty were all linearly associated with tumor size, grade, and nodal (N) stage: the proportion of patients with T3-T4 tumors, high-grade pathology, and nodal involvement decreased in a linear fashion with improvements in level of education, PCI, and percent of population living below poverty. Only the highest quartile of not speaking English at home (i.e., a larger proportion of households where English is not spoken in the home) was associated with a higher prevalence of these features.

### *Cardiovascular Comorbidities*

The rate of significant cardiovascular comorbidities also varied by race/ethnicity and SEVs (Table 2). Black patients demonstrated significantly increased prevalence of coronary artery disease (CAD, 32.4%), hypertension (HTN, 85.0%), and diabetes mellitus (DM, 53.9%) compared to White patients (31.6, 76.6, and 37.5%, respectively). Patients of Hispanic, API, and AIAN ethnicity also had significantly increased prevalence of DM (56.9, 49.6, and 48.3%, respectively). Further, the prevalence of CAD, HTN, DM, and emphysema were highest among patients living in a zip code in the lowest quartile of PCI and the highest quartile of population living below poverty. While the rates of CAD and DM were also highest among patients in the highest quartile of not speaking English at home, the prevalence of HTN was greatest in the lowest quartile. While the rates of DM and emphysema were also highest among those

who did not graduate from high school, CAD and HTN were most prevalent among those with a college education.

#### *Risk of Congestive Heart Failure*

A univariate cox proportional hazards model showed that all SEVs were associated with significant differences in the risk of developing CHF; however, a multivariate analysis including all SEVs revealed that level of education, not speaking English at home, and percent of population living below poverty were no longer significant, and thus were removed from subsequent models. Adjusting for significant cardiac covariates and exposure variables, the multivariate socioeconomic model revealed that Black patients had a 23% higher risk of CHF (HR 1.23, 95% CI 1.19-1.27,  $p < 0.001$ ) and AAPI patients had a 12% lower risk of CHF (HR 0.88, 95% CI 0.83-0.93,  $p < 0.001$ ) compared to White patients (Table 3, Figures 4-5). Hispanic and AIAN patients did not have a significantly different risk of CHF compared to White patients (HR 0.99, 95% CI 0.92-1.08,  $p = 0.986$ ; HR 1.13, 95% CI 0.96-1.35,  $p = 0.149$ , respectively; Table 3, Figures 4-5). Adjusting for race/ethnicity and cardiac comorbidities, patients living in a zip code in the lowest quartile of PCI had an 18% higher risk of CHF (HR 1.18, 95% CI 1.15-1.22,  $p < 0.001$ ) as compared to those in the highest quartile (Table 4, Figures 4-5).

Risk of CHF associated with the exposure variables showed similar trends as those reported in the primary analysis: patients receiving both T and A remained at highest risk of developing CHF (HR 1.23, 95% CI 1.13-1.34,  $p < 0.001$ ) compared to the baseline population (who had received neither T nor A), followed by A without T (HR 1.20, 95% CI 1.16-1.24,  $p < 0.001$ ) and T without A (HR 1.15, 95% CI 1.09-1.21,  $p < 0.001$ ; Tables 3-4, Figures 4-5).

#### Discussion

To our knowledge, this is the first study using a multivariate analysis to demonstrate how socioeconomic factors, systemic therapy use, and medical comorbidities interact to impact the long-term development of congestive heart failure among a large population of patients with early-stage breast cancer. Among patients with EBC, patients of Black, Hispanic, and AIAN race/ethnicity had increased prevalence of large, high-grade tumors and nodal involvement as compared to White and AAPI patients. Other SEVs associated with these higher risk features included lower level of education, lower PCI, higher percent of population living below poverty, and higher percent of households not speaking English at home. Further, the proportion of patients with high-risk clinical features decreased in a nearly linear fashion with improvements in level of education, PCI, and percent of population living below poverty. A multivariable analysis accounting for SEVs, cardiovascular comorbidities, and treatment received revealed a persistently increased risk of CHF in Black patients, a persistently decreased risk in AAPI patients, a persistently increased risk in patients living in low PCI zip codes, and no change in the pattern of cardiotoxic risk seen with anthracyclines and/or trastuzumab as previously reported.

Consistent with our results, other studies have also shown that Black, Hispanic, and American Indian women are more likely to be diagnosed with high-grade and/or locally advanced tumors compared to White women<sup>2,10,29-34</sup>, with Black women having the highest rates of high-grade and locally advanced disease. In some studies, these disparities persist even after controlling for other indicators of socioeconomic status, such as income and level of education<sup>35</sup>. Beyond race/ethnicity, other studies have also shown later stage disease at presentation to be independently associated with socioeconomic variables including poverty<sup>10,36,37</sup>, rurality of residence<sup>38</sup>, and level of education<sup>39</sup>. This increase in T/N stage among certain socioeconomic groups is also thought to be multifactorial, due to complex disparities in healthcare access and delivery. It is important to note, however, that while inequities in access to and/or utilization of healthcare may account for much of the disparity seen in stage of disease

at diagnosis, it cannot account for the higher-grade tumors seen in these populations. The increased prevalence of TNBC in these populations (particularly among black patients)<sup>2,29,32,34,40,41</sup>, molecular subtype does not fully account for the differences seen in the present study. Other factors that have been proposed as driving these more aggressive disease characteristics among certain ethnicities include obesity<sup>42</sup> and differences in tumor biology (such as increased loss or hypermethylation of tumor suppressor genes<sup>36,40,43-46</sup> and elevated levels of pro-inflammatory cytokines<sup>47,48</sup>). More research is needed to elucidate these associations between race/ethnicity and high-grade breast cancers.

Consistent with prior research of both the general population and breast cancer survivors specifically, our study showed increased rates of cardiac comorbidities among certain ethnicities and SEVs. Our study additionally showed that, even after adjusting for these cardiac comorbidities and exposure to therapy (including trastuzumab and/or anthracyclines), Black EBC survivors had a higher long-term risk of CHF (HR 1.23) compared to White patients, while AAPI patients were at lower risk (HR 0.88). After additionally adjusting for race/ethnicity, EBC survivors living in a zip code in the lowest quartile of PCI were also at a significantly increased risk of developing CHF as compared to patients in the highest quartile. This important finding suggests that race/ethnicity is not the only factor associated with these disparities, and patients with lower household incomes are at increased risk of CHF regardless of race/ethnicity or underlying cardiac comorbidities.

Data surrounding the prevalence of CHF among Black women in the general population is scant. According to three large studies, the lifetime risk of heart failure was 32-39% for non-Hispanic White women and 24-46% for Black women, although it is worth noting that Black women represented just 2-16% of each study population, which likely for the large range of values reported<sup>49,50</sup>. While it is well-documented that the overall Black population (and Black men in particular) are at higher risk for developing CHF than their White counterparts<sup>49-51</sup>, it is still unclear if this holds true for Black women. Many studies have attributed these race-based differences in CHF risk to the increased rate of cardiac comorbidities (and subsequent suboptimal management of these risk factors) among Black patients<sup>51-53</sup>. Our study, however, shows that Black women who are EBC survivors were more likely to develop CHF regardless of the presence of major cardiac comorbidities.

Prior research has also shown disparate outcomes in the development of cardiotoxicity following treatment with anthracyclines and/or trastuzumab. In several large meta-analyses reporting outcomes for tens of thousands of patients over several decades, African American ethnicity was consistently reported as a significant risk factor for anthracycline-induced cardiotoxicity<sup>54-57</sup>. Similarly, experience over the last two decades has revealed that Black women are also at increased risk for developing trastuzumab-induced cardiotoxicity even when adjusting for relevant cardiac risk factors and other measures of socioeconomic status<sup>58</sup>. Unfortunately, exact incidences of chemotherapy-induced cardiotoxicity among different races/ethnicities are unclear, largely due to a lack of adequate inclusion of minority populations in clinical trials and a lack of reporting of cardiotoxicity stratified by race. Overall, a relatively small number of studies have specifically investigated racial differences in cardiotoxicity among patients with breast cancer<sup>59</sup>. Recent observational data examining major cardiac events among triple-negative breast cancer survivors who received anthracyclines additionally showed increased risk of CHF for those living in rural area or an area with 20% of higher poverty levels<sup>60</sup>.

The reasons for these disparate outcomes in long-term incidence of CHF and/or cardiotoxicity among breast cancer survivors are unknown. It is worth noting, however, that there are several overlapping risk factors for both breast cancer and heart disease, all of which vary tremendously by race/ethnicity and other socioeconomic factors. Increased alcohol consumption<sup>61-67</sup>, physical inactivity<sup>68-73</sup>, tobacco use<sup>74-77</sup>,

and obesity<sup>78-84</sup> are all well-established risk factors for both breast cancer and CVD/CHF that have higher incidences among ethnic minorities (including Black, Hispanic, and AIAN women) and those of lower SES<sup>85-92</sup>. Further, obesity<sup>93,94</sup>, alcohol consumption<sup>95</sup>, and physical inactivity<sup>96-98</sup> have been linked specifically to increased risk of cardiotoxicity with anthracycline use. Additionally, disparities in access to care (including lack of insurance coverage, lack of transportation, and lack of access to specialty care) almost certainly impact the screening, surveillance, and management of treatment-associated cardiotoxicity in breast cancer survivors. Additional research is needed to investigate the degree to which these socioeconomic and lifestyle factors shape the long-term incidence of heart disease among breast cancer patients.

The concept of “allostatic load” has recently emerged as a more comprehensive framework to explain some of the observed socioeconomic disparities in breast cancer outcomes. The term was first introduced in the 1990s as a way to represent the biologic impact of chronic/cumulative environmental stressors on health outcomes: as stressors increase, so do neuroendocrine responses (mediated by a variety of physiologic mechanisms, including B-adrenergic signaling, inflammatory biomarkers, upregulation of gene expression, and epigenetic changes), leading to worse health outcomes<sup>99-107</sup>. As expected, the distribution of allostatic load varies by race/ethnicity and other indicators of socioeconomic status, and increased allostatic load appears to be associated with a variety of poor health outcomes, including both cancer and cardiovascular disease<sup>108,109</sup>. In breast cancer specifically, increased allostatic load has been shown to be further correlated with increased incidence of large, poorly-differentiated, and ER-negative tumors, especially among black women<sup>110,111</sup>. Despite the data available across many different disease subtypes, however, the clinical criteria used to quantify allostatic load (ranging from C-reactive protein levels to systolic blood pressure) are not standardized and vary significantly across trials. Further research is needed to validate this framework as a predictive mediator of socioeconomic status and disparities in breast cancer outcomes. Increased allostatic load may be a possible explanation for the independently increased risks of CHF seen in Black patients and those living in the lowest PCI population.

There are several limitations to our study. First, the racial/ethnic categories included in the SEER database (and our analyses) underappreciate the great diversity of racial and ethnic groups in the United States. Future studies could consider including genetic ancestry, in addition to the race/ethnicity categories included in SEER, in analyses. Further, in using the SEER-Medicare database, our study primarily includes individuals aged 65 and older, although a small number of Medicare beneficiaries who received coverage before age 65 due to disability have been included. It is worth noting that these individuals may not be representative of the general population of breast cancer survivors (regardless of age). There are also several other medical comorbidities, environmental risk factors, and breast cancer treatments that may potentially impact the long-term development of CHF in breast cancer survivors which were not included in the present study, including chronic kidney disease, obesity, tobacco use, and use of endocrine therapy. Also, while 2016 was the most recently available data at the time of data request, a repeat analysis with longer follow-up may be additionally informative, however practice patterns have not significantly changed in the United States since 2016 for HER2+ patients in a way relevant to this analysis, and this study likely reflects the contemporary patient population. Additionally, other validated measures of disparities such as the Social Vulnerability Index or Area Deprivation Index were not used in the present study, and future analyses could consider incorporating such composite outcomes. Finally, population sizes for each specific socioeconomic and/or clinicopathologic variable (e.g., Black race/ethnicity, grade 3 disease, etc.) were not sufficiently large to perform meaningful sub-analyses of the primary outcome. While some of these higher order analyses (i.e., risk of CHF by tumor

characteristics, etc.) will be reported in the primary analysis, this will not include stratification by socioeconomic variable.

In conclusion, among EBC survivors, Black women and individuals living in a zip code with low PCI had a higher long-term risk of CHF regardless of underlying cardiac comorbidities. Including these variables in a multivariable model does not seem affect cardiotoxic risk profiles of anthracyclines and/or trastuzumab based regimens described in our prior analysis. Additionally, individuals of Black, Hispanic, or AIAN race/ethnicity or those living in areas with lower levels of education, lower PCI, higher percent of population living below poverty, and higher percent of households not speaking English at home had increased prevalence of large, high-grade tumors and nodal involvement. While no evidence-based guidelines currently exist for specialized cardiac monitoring among high-risk patients after a diagnosis of early-stage breast cancer, our study identifies several populations at increased risk for the development of CHF after breast cancer treatment who should be considered for closer cardiac monitoring or additional risk factor modification.

### Methods

The processes by which the primary analysis was performed has been previously described,<sup>27</sup> and will be reiterated below with additional details unique to this sub-analysis included as well.

#### *SEER-Medicare Linked Database*

The SEER Program is a national cancer registry managed by the National Cancer Institute of the United States. The SEER registry has been individually linked with the Medicare database to associate billing and treatment variables with these important cancer statistics. At the time of data request for this study, 2016 was the most recently available dataset. All patient data were extracted from the original text files using SAS statistical software (SAS Institute Inc., Cary, NC, USA) and stored securely on an institutional server according to the SEER data usage agreement.

#### *Cohort Selection Criteria*

Patients diagnosed with stage I-III breast cancer with available zip code and census data between 2005 and 2016 were included in this sub-analysis, excluding patients with only *in situ* disease at diagnosis. Patients with a history of CHF prior to initial breast cancer diagnosis were also excluded using both the chronic conditions flag dataset (starting 2 years prior to study period) as well as any history of coding for CHF prior to an index breast cancer diagnosis. Patients with an index breast cancer diagnosis prior to 2005, which preceded the approval of adjuvant trastuzumab, use were also excluded.

#### *Primary Outcome, Exposure, and Comorbidity Variables*

The primary outcome of interest was development of CHF after breast cancer diagnosis, as defined by a single instance of inpatient or outpatient billing by ICD9 (years 2005-2015) or ICD10 (years 2015-2016) codes. To maximize outcome capture, a broad range of CHF diagnosis codes were included (Supplemental Table 1). The primary exposure variables were receipt of trastuzumab (including biosimilars) and/or an anthracycline, as defined by their respective health care common procedure coding system (HCPCS) codes (Supplemental Table 1). These codes did not include those for various cardiomyopathies to ensure uniformity in the study population and to reduce the risk of misclassification. Clinically important cardiac comorbidities included history of hypertension, valvular heart disease, hyperthyroidism, diabetes, emphysema, or coronary artery disease defined using ICD9/ICD10 codes (Supplemental Table 1). Variables regarding history of left-sided radiation, age, and race were taken directly from the SEER PEDSF dataset (since renamed the SEER cancer file). Details on breast cancer subtypes for the overall study population are reported in the primary analysis.

### *Socioeconomic Variables*

The SEVs selected in this analysis included race/ethnicity, per capita income (PCI), overall level of education, percent living below poverty, and percent not speaking English in the household. The terminology for racial and ethnic groups included in this study reflect the terminology used in the SEER census data. Continuous variables were transformed into categorical variables and represented as quartiles. This census data was individually linked to each patient using the state lived in and encrypted zip code available at the year of diagnosis.

### *Statistical Analysis Plan*

Summary statistics of clinical characteristics were compared among the various SEVs using the Chi<sup>2</sup> test. For all “time-to-event” survival analyses, development of CHF was defined as the time from the date of breast cancer diagnosis to the date of first coding for any CHF variable. Because the SEER-Medicare database does not include the day of diagnosis, but only a month and year of diagnosis, the 15<sup>th</sup> of the month was chosen as the day of breast cancer diagnosis for all patients. The reference population (i.e., the “baseline” CHF prevalence) used for Cox regression of the primary exposure variables was patients with stage I-III breast cancer who received neither trastuzumab nor an anthracycline. An initial univariate Cox proportional hazards regression was utilized to estimate the individual risk of heart failure (i.e., the hazard ratio, HR) between each SEV and the outcome variable. To control for potential imbalance and confounding of cardiac comorbidity variables, a multivariate Cox proportional hazards regression analysis was performed using all prospectively identified, clinically relevant covariates, regardless of their significance in the univariate analysis. A stepwise-down multivariate Cox model was finally constructed including all significant SEVs, as well as the cardiac comorbidity variables and exposure variables, using an alpha of 0.05. Multivariate Cox regression, as opposed to a propensity scoring system, was chosen for this analysis to decrease bias given the high number of patients, confounding variables, and events in the study population.<sup>28</sup> All descriptive and statistical tests were performed using the Stata Statistical Software Package version MP-17.0 (StataCorp, College Station, TX, USA).

### **Declarations**

- 1) **Data Availability:** This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.
- 2) **Code Availability:** Not applicable.
- 3) **Acknowledgements:** The authors acknowledge the efforts of the National Cancer Institute; Information Management Services, Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention’s (CDC) National Program of Cancer Registries, under cooperative agreement 1NU58DP007156; the National Cancer Institute’s Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute.
- 4) **Author Contributions:** KB and NM wrote the main manuscript text and prepared all tables/figures. KB, MLS, EHY, SM, MSS, MT, JL, AB, and NM reviewed and approved the manuscript.
- 5) **Competing Interests:** The above-mentioned authors have no competing interests to disclose.

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Table 1. Clinicopathologic Features by Socioeconomic Variable

Figure 1. Prevalence of T3-T4 Staging at Diagnosis by Socioeconomic Variable

Figure 2. Prevalence of N2-N3 Staging at Diagnosis by Socioeconomic Variable

Figure 3. Prevalence of Grade 3 Pathology at Diagnosis by Socioeconomic Variable

Table 2. Prevalence of Select Cardiac Comorbidities by Socioeconomic Variable

Table 3. 5-Year Incidence and Risk of Heart Failure by Race/Ethnicity

Table 4. 5-Year Incidence and Risk of Heart Failure by Per Capita Income Quartile

Figure 4. Multivariate Analysis: Risk of CHF by Race, PCI, and Treatment Type

Figure 5. Multivariate Analysis: Risk of CHF by Race, PCI, and Treatment Type

Estimate Type	Variable	All cases	White	Black	AAPI	Hispanic	AIAN
5-Year KM Rate	No T, No AC	12.9%	12.3%	16.3%	9.1%	11.9%	11.2%
5-Year KM Rate	T	18.3%	18.1%	20.5%	18.2%	15.6%	12.4%
5-Year KM Rate	T+AC	24.0%	23.8%	28.9%	17.5%	29.9%	20.0%
5-Year KM Rate	AC	21.7%	20.2%	31.1%	19.1%	20.6%	25.0%
HR (95% CI, P-value)	Multivariate	NA	1.00	1.23 (1.19-1.28, <0.001)	0.88 (0.83-0.93, <0.001)	0.99 (0.92-1.08, 0.99)	1.13 (0.96-1.34, 0.149)

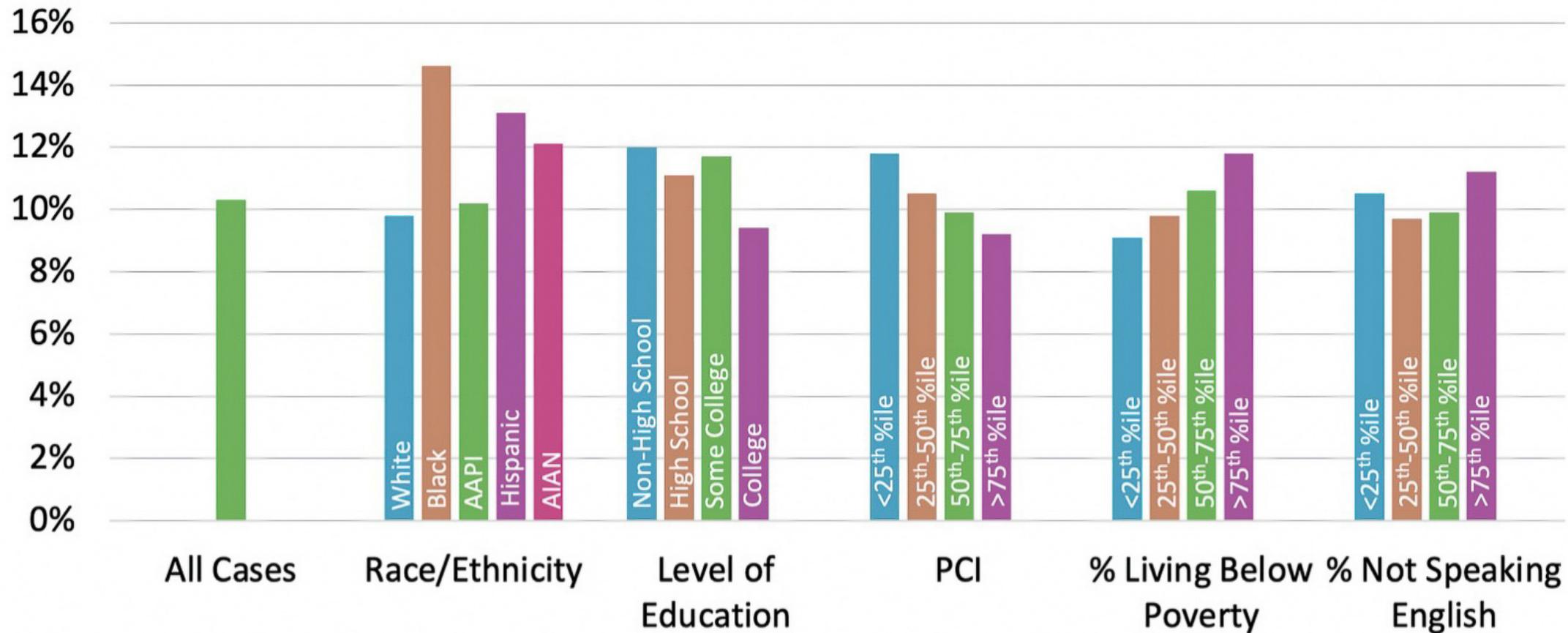
Variable	All cases	Race/Ethnicity					Level of Education (Majority per Zip)				Per Capita Income by Quartile				Percent Living Below Poverty by Quartile				Percent Not Speaking English by Quartile						
		White	Black	AAP	Hispanic	AIAN	Non-	HS	Some	College	<25 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	>75 <sup>th</sup>	<25 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	>75 <sup>th</sup>	<25 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	>75 <sup>th</sup>			
<b>Tumor Size</b>																									
<b>T1</b>	128175 (61.5)	106643 (63.1)	10700 (51.6)	6,831 (59.0)	2059 (50.6)	504 (56.2)	477 (57.1)	470 (58.2)	4361 (58.1)	24834 (63.9)	28800 (57.4)	30609 (60.9)	31772 (63.1)	32818 (65.0)	33024 (65.0)	31563 (62.9)	30711 (60.1)	28750 (45.4)	31528 (61.9)	31683 (63.4)	31577 (62.6)	29260 (58.6)			
<b>T2</b>	58804 (28.2)	45751 (27.1)	6997 (33.8)	3,561 (30.8)	1478 (36.3)	285 (31.8)	258 (30.9)	246 (30.4)	2265 (30.2)	10390 (26.7)	15498 (30.9)	14385 (28.6)	13662 (27.1)	13074 (25.9)	13176 (25.9)	13677 (27.3)	14313 (28.4)	15469 (30.9)	14129 (27.7)	13447 (26.9)	13899 (27.5)	15160 (30.3)			
<b>T3</b>	12981 (6.2)	9957 (5.9)	1803 (8.7)	696 (6.0)	327 (8.0)	66 (7.4)	619 (7.4)	562 (6.7)	537 (7.2)	2281 (5.9)	3405 (6.8)	3085 (6.1)	3048 (6.1)	2920 (5.8)	2905 (5.7)	2980 (5.9)	3141 (6.2)	3437 (6.9)	3094 (6.1)	2965 (5.9)	3080 (6.1)	3324 (6.7)			
<b>T4</b>	8614 (4.1)	6556 (3.9)	1227 (5.9)	484 (4.2)	208 (5.1)	42 (4.7)	386 (4.6)	359 (4.4)	334 (4.5)	1368 (3.5)	2495 (5.0)	2216 (4.4)	1892 (3.8)	1691 (3.4)	1716 (3.4)	1930 (3.9)	2196 (4.4)	2453 (4.9)	2231 (4.4)	1907 (3.8)	1929 (3.8)	2228 (4.5)			
<b>Tumor Grade</b>																									
<b>1</b>	4690 (23.3)	4013 (24.6)	2994 (15.0)	2411 (21.6)	733 (18.4)	184 (20.9)	178 (22.0)	174 (22.3)	1651 (22.8)	9345 (24.8)	10278 (21.2)	11455 (23.5)	11642 (23.9)	11984 (24.5)	11506 (23.4)	11902 (24.5)	11607 (23.8)	10368 (21.5)	11446 (23.3)	11526 (23.8)	11810 (24.2)	10601 (21.9)			
<b>2</b>	7565 (45.5)	7568 (46.3)	7925 (39.8)	5125 (45.9)	1715 (43.1)	357 (40.6)	347 (42.9)	338 (43.1)	3101 (42.7)	17476 (46.4)	21305 (44.0)	21875 (45.0)	22512 (46.1)	23210 (47.4)	23209 (47.2)	22486 (46.2)	21913 (44.9)	21323 (44.1)	22104 (45.0)	22160 (45.7)	22743 (46.5)	21924 (45.4)			
<b>3</b>	4764 (31.2)	4768 (29.2)	9015 (45.2)	3625 (32.5)	1529 (38.5)	338 (38.5)	284 (35.1)	271 (34.6)	2505 (34.5)	10834 (28.8)	16829 (34.8)	15337 (31.5)	14661 (30.0)	13729 (28.1)	14424 (29.4)	14264 (29.3)	15250 (31.3)	16636 (34.4)	15609 (31.8)	14833 (30.6)	14348 (29.3)	15784 (32.7)			
<b>Nodal Stage</b>																									
<b>N0</b>	150035 (70.6)	123573 (71.9)	13231 (62.4)	8403 (71.6)	2601 (62.1)	607 (65.5)	567 (66.6)	556 (67.6)	5144 (67.3)	28611 (72.5)	34536 (67.3)	35864 (70.0)	36895 (72.0)	37799 (73.3)	37846 (73.3)	36683 (72.0)	35994 (70.1)	34630 (67.6)	36618 (70.6)	36472 (71.6)	36875 (71.7)	35188 (69.0)			
<b>N1</b>	4375 (20.6)	3411 (19.8)	5429 (25.6)	2373 (20.2)	1036 (24.7)	210 (22.7)	198 (23.3)	188 (22.9)	1773 (23.2)	7867 (19.9)	11340 (22.1)	10664 (20.8)	10174 (19.8)	9874 (19.3)	9944 (19.3)	10185 (20.0)	10658 (20.8)	11276 (22.0)	10495 (20.2)	10150 (19.9)	10426 (20.3)	10992 (21.6)			
<b>N2</b>	12263 (5.8)	9342 (5.4)	1697 (8.0)	636 (5.4)	343 (8.2)	75 (8.1)	579 (6.8)	534 (6.5)	505 (6.6)	1991 (5.0)	3556 (6.9)	3074 (6.0)	2786 (5.4)	2361 (4.6)	2541 (4.9)	2657 (5.2)	3042 (5.9)	3538 (6.9)	3158 (6.1)	2809 (5.5)	2730 (5.3)	3081 (6.1)			
<b>N3</b>	6413 (3.0)	4898 (2.9)	864 (4.1)	330 (2.8)	211 (5.0)	35 (3.8)	280 (3.3)	252 (3.1)	219 (2.9)	1009 (2.6)	1887 (3.7)	1627 (3.2)	1419 (2.8)	1266 (2.5)	1316 (2.6)	1441 (2.8)	1659 (3.2)	1786 (3.5)	1585 (3.1)	1511 (3.0)	1401 (2.7)	1705 (3.4)			

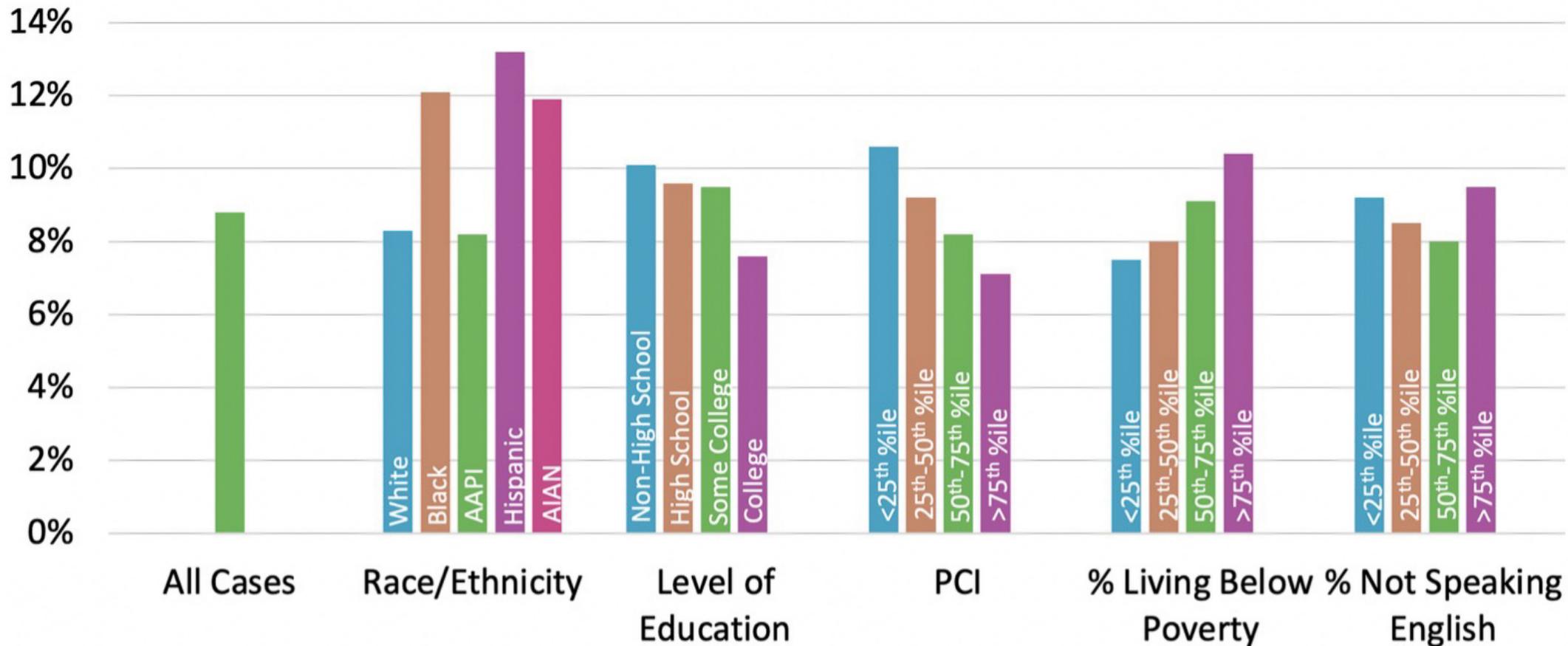


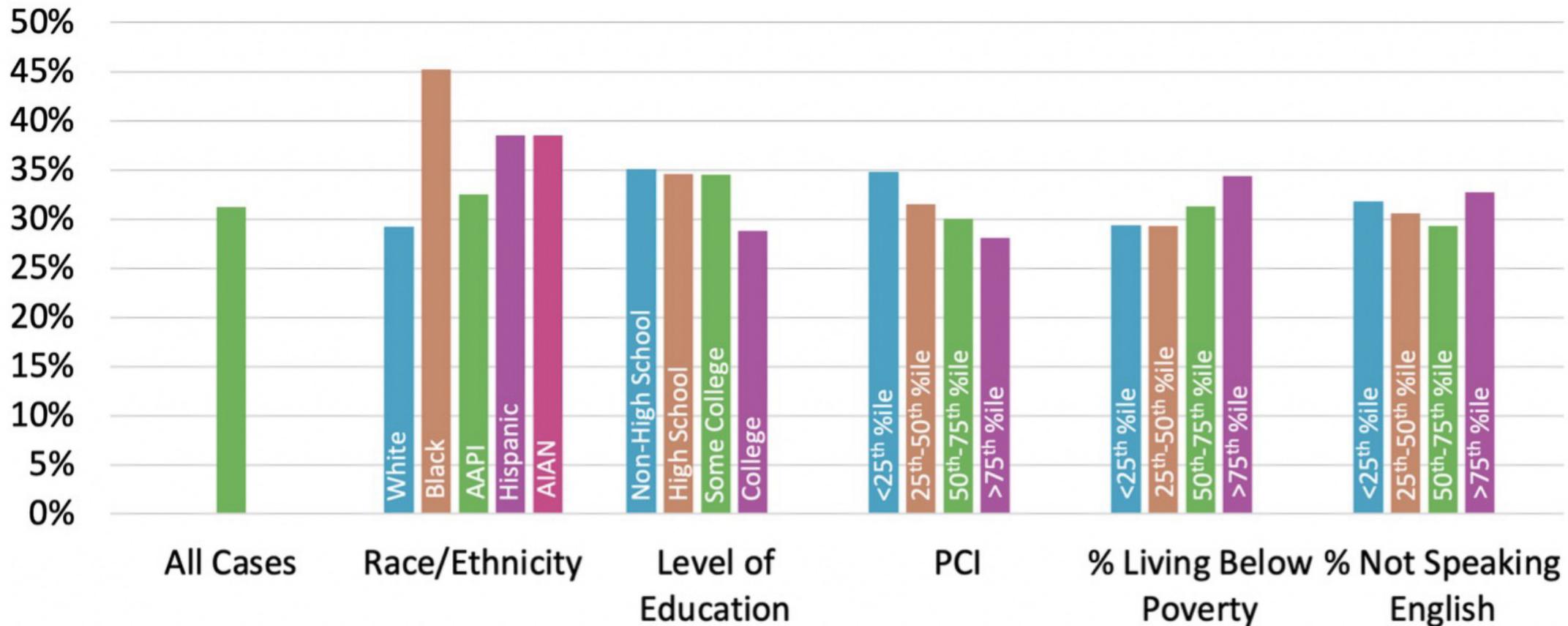
V a r i a b l e	A l i c a s e s	Race/Ethnicity					Level of Education (Majority per Zip)				Per Capita Income by Quartile				Percent Living Below Poverty by Quartile				Percent Not Speaking English by Quartile			
		W h i t e	B l a c k	A A P I	H i s - p a n i c	A I A N	N o n - H S	H S	S o m e C o l l e g e	C o l l e g e	<25 <sup>t</sup> h	2 5 <sup>t</sup> h_	5 0 <sup>t</sup> h_	> 7 5 <sup>t</sup> h	<25 <sup>t</sup> h	2 5 <sup>t</sup> h_	5 0 <sup>t</sup> h_	> 7 5 <sup>t</sup> h	<25 <sup>t</sup> h	2 5 <sup>t</sup> h_	5 0 <sup>t</sup> h_	> 7 5 <sup>t</sup> h
C A D	66 72 7 (3 1. 2)	54 72 1 (3 1. 6)	6 9 4 (2 2. 4)	3 1 2 (2 6. 3)	1 2 3 (2 5. 7)	2 3 9 (2 5. 7)	2 1 4 (2 2. 6)	2 8 3 (2 2. 4)	1 8 9 (2 2. 4)	11 32 1 (2 8. 5)	1761 9 (34.1 )	15 94 6 (3 0. 9)	15 63 4 (3 0. 3)	15 71 0 (3 0. 4)	1909 6 (30.9 )	15 47 5 (3 0. 2)	15 96 9 (3 0. 9)	17 39 1 (3 3. 7)	1672 7 (32.1 )	15 87 2 (3 1. 0)	15 77 9 (3 0. 5)	16 55 3 (3 2. 2)
	H T N	16 53 04 (7 7. 2)	13 27 46 (7 6. 7)	1 8 1 (8 5. 0)	8 8 6 (7 5. 1)	3 1 9 (7 4. 6)	6 9 4 (7 2. 2)	6 0 0 (7 2. 3)	5 4 6 (7 0. 9)	28 79 3 (7 2. 5)	4210 8 (81.4 )	40 40 2 (7 8. 3)	39 22 4 (7 6. 0)	38 32 4 (7 4. 2)	3969 2 (76.3 )	38 56 9 (7 5. 1)	40 05 0 (7 7. 5)	41 80 3 (8 1. 0)	4185 2 (80.2 )	39 84 7 (7 7. 7)	39 27 3 (7 5. 8)	39 14 2 (7 6. 1)
D M	86 13 8 (4 0. 3)	64 98 9 (3 7. 5)	1 5 7 (4 5. 6)	2 8 0 (4 5. 9)	4 4 9 (4 8. 3)	3 5 8 (4 1. 7)	3 2 4 (3 3. 0)	2 9 1 (3 3. 4)	14 03 1 (3 5. 3)	2421 9 (46.8 )	20 68 0 (4 0. 1)	19 85 1 (3 8. 5)	18 51 1 (3 5. 8)	1983 5 (38.1 )	19 22 3 (3 7. 5)	53 3 3 (9. 7)	23 69 3 (4 5. 9)	2015 4 (38.6 )	19 90 5 (3 8. 8)	20 08 9 (3 3. 8)	23 13 6 (4 5. 0)	
	V a l v u l a r d i s e a s e	63 70 4 (2 9. 8)	53 06 9 (3 0. 7)	6 1 5 (2 8. 7)	2 7 6 (2 3. 4)	1 0 5 (2 3. 7)	1 8 5 (1 9. 9)	2 5 3 (2 4. 4)	1 8 0 (2 2. 6)	11 74 6 (2 9. 6)	1538 2 (29.7 )	15 26 9 (2 9. 6)	15 18 0 (2 9. 4)	16 14 5 (3 1. 3)	1634 6 (31.4 )	15 07 1 (2 9. 4)	15 25 1 (2 9. 5)	15 33 6 (2 9. 7)	1609 1 (30.8 )	16 13 4 (3 1. 5)	15 21 9 (2 9. 4)	14 56 0 (2 8. 3)
H y p e r - t h y r	15 68 4 (7. 3)	12 69 8 (7. 3)	1 6 8 (7. 9)	7 9 5 (6. 7)	3 0 5 (7. 2)	5 4 (5. 8)	5 9 (5. 9)	4 4 (5. 8)	4 8 (5. 8)	29 37 (7. 4)	3887 (7.5)	35 95 (7. 0)	36 82 (7. 1)	40 83 (7. 9)	3919 (7.5)	37 29 (7. 3)	36 73 (7. 1)	39 35 (7. 6)	3645 (7.0)	37 67 (7. 4)	38 41 (7. 4)	40 03 (7. 8)

o id																						
E m p h y - s e m a	51 69 4 (2 4. 1)	44 20 0 (2 5. 5)	4 6 2 (2 1. 6)	1 6 3 (1 7. 3. 8)	7 4 8 (1 7. 7)	1 9 5 (2 1. 0)	1 8 0 (2 1. 0)	1 7 7 (2 1. 4)	1 5 7 (2 0. 5)	74 18 (1 8. 7)	1471 6 (28.5 )	13 39 0 (2 5. 9)	11 73 0 (2 2. 7)	10 31 7 (2 0. 0)	1101 2 (21.2 )	11 64 3 (2 2. 7)	13 18 8 (2 5. 5)	14 33 0 (2 7. 8)	1398 3 (26.8 )	12 63 9 (2 4. 7)	11 81 9 (2 2. 8)	11 73 2 (2 2. 8)

Estimate Type	Variable	All cases	<25 <sup>th</sup>	25 <sup>th</sup> -50 <sup>th</sup>	50 <sup>th</sup> -75 <sup>th</sup>	>75 <sup>th</sup>
5-Year KM Rate	No T, No AC	12.9%	15.4%	13.3%	12.3%	11.2%
5-Year KM Rate	T	18.3%	20.7%	17.9%	19.3%	15.3%
5-Year KM Rate	T+AC	24.0%	27.9%	22.4%	22.2%	22.9%
5-Year KM Rate	AC	21.7%	25.9%	22.1%	20.1%	17.5%
HR (95% CI, P-value)	Multivariate	NA	1.18 (1.15-1.22, <0.001)	1.13 (1.09-1.16, <0.001)	1.09 (1.06-1.12, <0.001)	1.00







Category	Variable	HR	95% CI	p-value	Standard Error
<b>Race</b>	Black	1.23	1.19-1.27	<0.001	0.021
	AIAN	1.13	0.96-1.34	0.149	0.099
	AAPI	0.88	0.83-0.93	<0.001	0.024
	Hispanic	0.99	0.92-1.08	0.986	0.042
	Other	0.84	0.71-0.99	0.034	0.071
<b>PCI</b>	<25th %ile	1.18	1.15-1.22	<0.001	0.019
	25th-50th %ile	1.13	1.09-1.16	<0.001	0.018
	50th-75th %ile	1.09	1.06-1.12	<0.001	0.018
<b>Treatment Type</b>	T + A	1.23	1.13-1.34	<0.001	0.052
	A (no T)	1.20	1.16-1.24	<0.001	0.022
	T (no A)	1.15	1.09-1.21	<0.001	0.030

