Racial/ethnic disparities in access to treatment, time to treatment and complications from treatment, and subsequent survival for hepatocellular carcinoma in California

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ABSTRACT

Background and Aim: Hepatocellular carcinoma (HCC) is one of the most common types of cancer in the world. Its incidence and mortality rate are rising in the United States. HCC affects minority populations disproportionately with higher incidence observed among Asian/Pacific Islanders and Hispanics and higher mortality observed among Black/African Americans and Hispanics. Studies have found Black/African Americans and Hispanics to have lower likelihood in accessing treatment. Because of the rapid tumor doubling time, if left untreated, HCC can quickly lead to a fatal outcome. Longer time to treatment can impact outcomes among patient subgroups, but no studies have assessed racial/ethnic disparities in time to treatment and its effect on survival. Finally, among patients who are able to obtain life-saving surgical treatments, complications from HCC surgery are common. Many existing studies on postsurgical complications are hospital based with small populations. No prior studies assessed racial/ethnic disparities in postoperative complications after having ablation, hepatectomy, or transplantation using a large population-based database. The goal of this population-based study among HCC patients is to examine racial/ethnic disparities in obtaining surgical treatment, delay in getting surgical treatment, and surgical complications.

Methods: 16,375 HCC patients overall were identified from the California Cancer Registry for the period 2012–2017, with 21.3% (n= 3,494) patients identified as having undergone surgical treatments of ablation, resection, and transplantation. Multivariate logistic regression was used to examine racial/ethnic disparities in access to treatment, time to treatment, and complications from treatment. Multivariate Cox proportional hazards regression was used to evaluate racial/ethnic disparities in survival after considering surgical treatments, treatment delay, and surgical complications.

Results: Asian/Pacific Islanders and Black/African Americans were more likely, and Hispanics were less likely, to get surgical treatment relative to non-Hispanic Whites. A higher odds of surgical treatment was also observed among those with private insurance, with high neighborhood SES, and receiving treatment at high volume hospitals. Our study found Asian/Pacific Islanders to have lower likelihood of surgical treatment delay compared to non-Hispanic Whites. Patient neighborhood SES, patient distance from hospital, and hospital surgical volume were also associated with delays. No racial/ethnic differences were observed for neurological, cardiac, pulmonary, gastrointestinal, renal, and infectious types of postsurgical complications combined. However, Black/African Americans demonstrated a lower odds for gastrointestinal complications and Asian/Pacific Islanders demonstrated a lower odds for cardiac complications when compared to non-Hispanic Whites. Higher odds of complications were found among patients with comorbidities or living in low SES neighborhoods. In multivariable models considering access to surgical treatment, increased survival was observed for Asian/PIs and Hispanics, while no difference in survival was observed for Black/African Americans, compared to non-Hispanic Whites. When considering delay in surgical treatment, Asian/PIs, Hispanics, and non-Hispanic Whites undergoing hepatectomy and transplantation had better survival when compared to undergoing ablation. Similar survival results were obtained when considering postoperative surgical complications.

Conclusion: We found improved access to surgical treatment among Black/African Americans driven mainly by hepatectomy. Survival among Black/African Americans also improved

compared to prior estimates. Interactions were observed between race/ethnicity and HCC treatment for both treatment delay and postoperative complications. In both cases, improved survival was observed for Asian/PIs, Hispanics and non-Hispanic Whites undergoing hepatectomy and transplantation compared to undergoing ablation. No such survival difference was observed for Black/African Americans. This calls for further studies to investigate and closely monitor racial/ethnic associations with possible factors such as private insurance and early-stage cancer both of which are associated with better survival. Our findings on postoperative complications underscore the need for disaggregation of complications. HCC is a challenging form of cancer with fatal consequences and racial/ethnic disparities related to HCC can have significant impact on accessing quality treatment and outcomes and necessitates ongoing research to attain equity.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common manifestation of liver and intrahepatic bile duct cancer and is the second leading cause of cancer mortality.[1,2] While the incidence and mortality rates for most cancers are decreasing in the United States, HCC incidence has been steadily increasing[3] with rates changing from 1.5 to 6.2 cases per 100,000 between 1973 and 2011.[4]

While both hepatitis B virus and hepatitis C virus have been the primary etiologic factors for HCC,[5] metabolic disorders such as diabetes[6,7] and obesity[8] also play a role along with non-alcoholic fatty liver disease (NAFLD)[9-11]. Tobacco use[12,13] and alcohol consumption[8,13] are also factors leading to HCC. It has also been suggested that the higher incidence and prevalence of HCC could be a consequence of improved screening and diagnostic capabilities that help better detect HCC cases.[14]

In the U.S., there is significant difference in the distribution of HCC rates by race/ethnicity and the highest rates are observed among Asian/Pacific Islanders (Asian/PI) and Hispanics/Latinos. This disparity is possibly due to differences in the distribution of known risk factors since it has been shown that increased rates of HBV are associated with Asian/PIs[15] while higher rates of HCV and metabolic disorders are more common among Hispanics. While historically Asian/PIs had the highest rates of HCC in the US, recent data has shown that Hispanics have surpassed that and currently have the highest rate for HCC. The prevalence of metabolic disorders such as diabetes and obesity are increasing among Hispanics and are thought to be possible drivers for the increase in HCC incidence along with HCV, alcoholic liver disease, and NAFLD.[16-19] While the distribution of HCC varies by race/ethnicity, studies have also shown disparities in access to treatment and care by race/ethnicity leading to disparities in outcomes.[20,21]

Many studies have consistently shown that Black/African Americans and Hispanics have lower access to care when compared to non-Hispanic Whites.[20,22] This trend has persisted even after adjusting for demographic and clinical characteristics. Variations in care are also noticeable across other race/ethnicity groups when compared to non-Hispanic Whites as shown by several studies. Hepatectomy rates have been shown to be higher among Asian/PIs, while liver transplants are less common among all minority groups relative to non-Hispanic Whites.[23] This disparity is not only present in the pre-treatment phase, but also in the post-treatment phase.[20]

Significant differences in survival have been shown by race/ethnicity with Asian/PIs having increased survival and Black/African Americans and Hispanics having decreased survival. Several contributory factors have been identified, including age, sex, neighborhood SES, and type of surgery. While these factors addressed some of the disparities, racial/ethnic survival differences continue to persist [20,21,23,24] possibly due to important risk factors that have not been addressed.

In addition to having access to life saving HCC surgeries, another important factor that can impact patient survival is delay in time from diagnosis to surgical treatment. Because prognosis from HCC is poor and HCC tumor doubling time is approximately three months, it is imperative that treatment is sought immediately after diagnosis.[25-28] The process to seek treatment can be complex that can involve maneuvering through a maze of different providers and referral centers. All of this can lead to delay in treatment and poor consequent outcomes. While several studies have investigated HCC related therapeutic delay, their primary focus was on patient survival. There is limited information on racial/ethnic disparity in time to treatment from diagnosis including effect of this delay on racial/ethnic disparities in long-term survival.

While not every patient with HCC receives lifesaving HCC surgeries, those who do are also at risk having postoperative complications that can have long-term effects on cancer recurrence and survival. The association between postoperative complications and poor outcomes have been shown in several studies.[29-34] However, most of these studies focused on long-term survival only and information on racial/ethnic disparities related to postoperative complications is rare. Therefore, it is important to identify subgroups with higher postoperative complications and whether postoperative complications contribute to racial/ethnic disparities in survival.

California has the greatest burden of HCC cases in the United States due to its large population.[35] It also ranks fourth highest in terms of HCC incidence and mortality after Texas, Hawaii, and New Mexico.[35] There is a large minority population with 1 of 3 Asians and 1 of 4 Hispanics calling California home.[36] Because both of these population groups have the highest incidence rates for HCC[37] and are growing rapidly, California is an ideal population to identify surgical treatment barriers that could reduce racial/ethnic disparities in access to care and improve survival.

The aim of this current study was to elucidate HCC surgical treatment patterns in California and how these relate to race/ethnicity in terms of access to these treatments, delay in treatment, complications from treatment, and in consequent survival outcomes. Data from the California

Cancer Registry has been extensively used for all analyses in conjunction with specific variables from the California Health Care Access and Information database.

As population demographics change so do disease trends and we need to be better prepared in providing the best care consistently. Identifying contributory factors to racial/ethnic disparity in HCC surgical treatment and outcomes will inform the development of better strategies to mitigate access barriers and promote equity that can result in improved health outcomes.

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Chapter 1. Racial/ethnic disparities in access to treatment and subsequent survival for Hepatocellular Carcinoma in California

ABSTRACT

Background and Aim: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality in the world and both incidence and mortality rates are rising in the United States. Previous studies have reported significant racial/ethnic disparities in accessing surgical treatments and long-term survival for minority populations. This study used current data from the California Cancer Registry to investigate if surgical treatment patterns and survival disparities have changed in more recent times.

Methods: 16,375 patients with HCC were identified from the California Cancer Registry for the period 2012–2017. Multivariate logistic regression was used to examine racial/ethnic disparities in access to treatment and multivariate Cox proportional hazards model was used to assess racial/ethnic disparities in survival after considering surgical treatments that patients had undergone.

Results: Odds ratio (OR) estimates from logistic regression model showed disparities in surgical treatment for HCC with Asians/Pacific Islanders (OR=1.63, 95% CI = 1.47–1.81) and Black/African Americans (OR = 1.24, 95%CI = 1.05–1.47) more likely and Hispanics (OR = 0.88, 95%CI = 0.79–0.97) less likely to get invasive care relative to non-Hispanic Whites. Additionally, hazard ratio (HR) obtained from Cox proportional hazards model showed racial/ethnic differences in overall survival with Asians/Pacific Islanders (HR =0.86, 95%CI = 0.82–0.91) and

Hispanics (HR=0.88, 95%CI = 0.84–0.92) having superior survival compared to non-Hispanic Whites while Black/African Americans (HR=0.95, 95%CI = 0.88–1.02) had similar risk of death as non-Hispanic Whites.

Conclusion: While findings in Asians/Pacific Islanders and Hispanics were consistent with previous findings, we are among the first to report that Black/African Americans were more likely to obtain life-saving surgeries and no longer had worse survival compared to non-Hispanic Whites. This might be explained by better access to healthcare among minorities due to the Affordable Care Act. In our study, older age, male gender, advanced cancer stage, and higher comorbidity score were all associated with lower likelihood of surgical treatment. Additionally, we found higher likelihood of surgical treatment for having private insurance, high neighborhood SES, and receiving treatment at high volume hospitals. This suggests that more resources need to be allocated for patients under financial strain and better access needs to be provided to patients for obtaining surgical treatment at high volume hospitals.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common manifestation of liver and intrahepatic bile duct cancer and represents about 85% of all cases.[1] HCC holds a strong prominence worldwide as the second leading cause of cancer mortality.[2,3] In the United States, HCC incidence has been steadily going up while incidence and mortality rates for most other cancers have been decreasing.[4] This increase is seen across both genders.[4] Between 1973 and 2011, the incidence increased rapidly from 1.5 to 6.2 cases per 100,000.[5]

Both hepatitis B virus (HBV) and hepatitis C virus (HCV) have been shown to be the primary drivers behind HCC.[6] In the developing world, both these viruses along with exposure to aflatoxins are significantly involved in disease incidence. Worldwide, metabolic disorders, such as diabetes[7,8] and obesity[9] are also considered risk factors for HCC, along with non-alcoholic fatty liver disease (NAFLD)[10-12]. In addition, tobacco use[13,14] and alcohol consumption[9,14] increase the risk of HCC. It is also believed that recent improvements in screening and diagnostic capabilities have contributed to better assessment and detection of HCC and consequently, has led to higher incidence and prevalence.[15]

In the U.S., the distribution of HCC rates differs significantly by race/ethnicity, with the highest rates observed among Asians and Hispanics/Latinos. This disparity may be related to differences in the distribution of known risk factors, as Asian populations have increased rates of HBV [16] and Hispanic populations have higher rates of HCV and metabolic disorders.[17,18] In addition, many studies have consistently shown that Black/African Americans and Hispanics with HCC have lower access to treatment when compared to non-Hispanic Whites.[19,20]

Black/African Americans with HCC have also shown poorer survival in many studies.[20-22] These trends persisted even after adjusting for demographic and clinical characteristics.

In a study using California Cancer Registry (CCR) data from 1988–2012, Stewart et al showed racial/ethnic disparity in treatment and survival among liver cancer patients.[20] This study limited surgical treatment to hepatectomy and transplant and examined the combined effect instead of individual treatment effects. In another study, Zak et al used CCR data along with California Health Care Access and Information (HCAI) data for the period 1996–2006 to define the current use of surgical therapies for HCC and identify various patient and hospital characteristics that would be predictors of who received these therapies.[15] This study considered ablation along with hepatectomy and transplant for surgical treatment but did not investigate survival differences related to these specific treatments.

The aim of this study was to fully elucidate current HCC care patterns in California and describe the relationship between race/ethnicity, access to specific surgical treatments and long-term survival using recent data from the CCR for the period 2012 – 2017. All surgical treatments which included ablation, hepatectomy, and transplant were considered, and the individual effect of each surgery was examined. More recent data was used to account for possible changes in disease diagnosis, treatment, and prognosis and to provide updates on current trends, which are not well documented. Important sociodemographic and clinical variables were considered to determine if there have been independent incremental racial/ethnic changes in care patterns that have impacted outcomes.

METHODS

A retrospective cohort study was conducted using CCR data. The CCR is the largest state cancer registry in the U.S covering the entire state of California and represents the union of three regional Surveillance, Epidemiology, and End Results (SEER) registries: Greater California, the Greater Bay and the Los Angeles. California state law mandates the collection of information pertaining to all cases of cancer, with the exception of basal and squamous cell carcinoma of the skin and carcinoma in situ of the cervix. The data collected have fewer than 3% missing race data and less than 3% of cancer cases determined only from death certificate records.[15] Overall, its completeness is more than 95%[20]. The CCR maintains the highest standard for data quality established by the North American Association of Central Cancer Registries (NAACCR) and the National Program for Cancer Registries (NPCR).

Additional data were obtained from HCAI Patient Discharge Database (PDD) and linked with the CCR data. Data from the CCR is linked to HCAI using a probabilistic method that employs patient identifying information, such as patient date of birth, social security number, gender, and other available information. The PDD includes all patient discharge abstracts from general, acute, and nonfederal hospitals in the state. In addition to patient demographic information, the database also contains clinical data, including primary diagnosis and primary procedure based on the *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM)*. It also includes up to 24 additional diagnosis codes and up to 19 additional procedure codes.[15] A unique feature of this database is the inclusion of coding that indicates whether any secondary condition was present during admission. This provides the ability to distinguish between comorbid conditions and hospital-acquired conditions.

In our analysis, HCC patients were identified using the *International Classification of Diseases for Oncology, Third Edition* site code C22.0 and histology codes 8170 – 8175. A total of 18,970 HCC cases were diagnosed between 2012 and 2017 with follow up continuing through December 31, 2018. Our study restricted HCC cases to first primary cancer since the survival experience would be different for those with other cancers. After further exclusion of cases identified through autopsy or death certificates and limiting gender to males and females only, 16,375 HCC cases remained eligible for the study (Figure 1).

Study variables

From the CCR, we obtained different sociodemographic and clinical variables including race/ethnicity, age, sex, neighborhood socioeconomic status (SES), insurance status, tumor stage, surgical treatment type and a derived variable indicating the average annual surgery volume by hospital. Race/ethnicity was stratified into five groups consisting of non-Hispanic Whites, Black/African Americans, Hispanics, Asians/Pacific Islanders (PI) and Others, which consisted of American Indians and Alaskans, Native Hawaiians and any other groups including mixed and unknown groups. Age was dichotomized into less than 65 years, and 65 and above, with the younger age group used at the reference category. SES was presented as quintiles at the neighborhood level (from the U.S. Census) with imputed missing values to ensure all patients had a SES score. Insurance type was coded into one of four categories with private insurance used as the reference category. Private insurance consisted of HMO, PPO, fee for service, managed care, TRICARE, military, Veterans Affairs, or any insurance type not stated while Medicare included all Medicare categories. The Medicaid/Public/Uninsured group consisted of all Medicaid cases along with those not insured or with self-pay, county funded or

Indian/Public Health Services. The last remaining category, Other, consisted of unknown insurance or missing values.

Among the clinical variables, tumor stage was dichotomized into early stage, which consisted of stages I and II, and late stage, which include stages III and IV. Any unstaged, unknown or missing values were combined into an unknown category. We derived the average annual surgery volume variable based on the total number of HCC related surgeries at each hospital over the total number of years included in our study. The average annual surgery volume was broken up into two categories based on median value: 0–5 and greater than 5 average annual surgeries. The main outcome in our primary analysis was HCC related surgeries, including ablation, hepatectomy and transplant and these were identified based on codes for most extensive type of surgery performed during the first course of treatment. If no HCC related surgery was performed and the patient received no treatment or received other non-surgical treatment, then they were added to the no surgery/other category.

We used the PDD data from HCAI to obtain comorbidity data for patients based on the Elixhauser Indices.[23] Patient diagnosis codes were used to calculated 29 Elixhauser Indices of which the indices for lymph, tumor and metastasis were excluded from our study because they are indicative of previous or additional cancer and our study objective is limited to primary cases of a single cancer. The PDD data was examined for presence of any indices during the three years prior to diagnosis of cancer and any indices present were combined into an aggregate score. For patients that did not have any admission during the last three years before diagnosis, indices were searched for the following nine months after diagnosis and combined into an aggregate score when present. The final Elixhauser comorbidity score was considered in three categories consisting of 0–2 comorbidities, 3 or more comorbidities and a no admit category for patients lacking a comorbidity score. The latter category could have happened if a patient had an admission outside of the time period specified for calculating Elixhauser indices or if a patient did not have any hospital admission. The information obtained from the PDD data was linked to the CCR data using patient id.

Statistical Analysis

Contingency table analysis with chi-square tests were used to examine the bivariate relationships between race/ethnicity and surgical treatment along with different sociodemographic and clinical variables. For the variables tumor stage and Elixhauser comorbidity score, the unknown and no admit categories were not included in the primary statistical analyses. However, the impact of unknown values was assessed by separately recategorizing unknown values into one of the two allowable values, rerunning the statistical analysis, and assessing concordance with the analyses where these observations were excluded. If the effect on the main variables, race/ethnicity, remained the same, it would imply that the unknown or no admit data does not create any bias and can be added as a separate category for each respective variable.

We used unconditional logistic regression to quantitate the magnitude of association between race/ethnicity and the receipt of surgical treatment. Four different analyses were conducted which included any surgery vs. none, ablation vs. none, hepatectomy vs. none, and transplantation vs. none. Univariable and multivariable analyses with adjustment for sociodemographic and clinical factors were conducted.

In addition, the association between race/ethnicity and long-term survival of patients was assessed using actuarial methods. Kaplan-Meier survival curves were estimated for HCC patient in each of the race/ethnic groups and the log-rank test was used to test survival differences across race/ethnicity. Cox Proportional Hazards regression modeling was employed to evaluate univariable and multivariable associations between race/ethnicity and survival. In all models, the proportional hazards assumption was assessed using the log(-log) survival curves of the survival distribution function by log(days). It is likely that many patients would have died while waiting for surgery and it would have artificially inflated the risk of death in the non-surgical group. To address this issue, surgical treatment was used as a time-dependent covariate. We examined overall survival with survival time measured in days from cancer diagnosis to date of death from any cause. Patients who were alive at the end of the study period or at the date of last known contact were censored at that time.

All statistical tests were 2-tailed with alpha=0.05. SAS v9.4 was used for all statistical analyses.

RESULTS

Distribution of patient factors

A total of 16,375 patients with HCC were identified; 5,960 (36.4%) patients were non-Hispanic Whites, 5,338 (32.6%) were Hispanic, 3,579 (21.9%) were Asian/PI, 1,198 (7.3%) were Black/African American, and 300 (1.8%) were of other race/ethnicity. Sociodemographic and clinical factors differed by race/ethnicity as shown in Table 1. Asian/PIs (54.4%) had higher proportion of older patients compared to all other race/ethnicities. Racial/ethnic variations were observed in neighborhood SES, with higher proportions of Black/African Americans and Hispanics residing in lower SES neighborhoods, while higher proportions of Asian/PIs and non-Hispanic Whites residing in higher SES neighborhoods. The highest proportion of those in Medicaid, public or uninsured category were Hispanics (39.3%), followed by Black/African Americans (39.1%). The highest proportion of patients with private insurance were non-Hispanic Whites (51.8%) followed by Asian/PIs (45.4%).

Among the clinical factors, early-stage cancer had predominance across all race/ethnicities, with Black/African Americans (57.9%) having the lowest proportion. Lower proportions of Black/African American (38.4%) and Hispanic (36.2%) had surgeries at in high-volume hospitals than Asian/PI (47.8%) and non-Hispanic White (41.8%). The majority of the patients had 3 or more comorbid conditions across all race/ethnicities, with Asian/PIs (68.7%) having the lowest proportion and Black/African Americans (84.8%) and Hispanics (84.4%) having the highest proportion. In our population, 78.4% of the patients did not receive surgery, while the remaining patients received either ablation (10.3%), hepatectomy (8.8%) or liver transplant (2.6%). Compared to other race/ethnicity groups, Asian/PIs (29.6%) had the highest proportion for surgery. Hepatectomy was most common among Asian/PIs (16.7%), followed by Black/African Americans (10.5%). Ablation was more common for non-Hispanic Whites (11.0%) followed by Asian/PIs (10.7). Non-Hispanic Whites (2.9%) had the highest proportion for transplants compared to all other race/ethnicities.

Supplemental analyses for observation with missing stage or no admit Elixhauser comorbidity score values were in concordance with the conclusions of the primary analyses where these observations were deleted (Supplementary tables 1–4). Hence, it was decided to include the unknown stage value and no admit Elixhauser comorbidity score value as additional categories of the respective variables for all subsequent analyses.

Access to surgical treatment

After adjustment for sociodemographic and clinical factors, the odds of surgery was higher for both Asian/PIs (OR = 1.63, 95%CI = 1.47–1.81) and Black/African Americans (OR = 1.24, 95%CI = 1.05–1.47) compared to non-Hispanic Whites. In contrast, Hispanics (OR = 0.88, 95%CI = 0.79–0.97) were less likely to get a surgery than non-Hispanic Whites. When considering individual surgical treatments as outcomes, Hispanics (OR = 0.88, 95%CI = 0.76–1.00) showed lower odds for ablation, while Black/African Americans (OR = 0.50, 95%CI = 0.29–0.84) showed lower odds for transplant. Both Asian/PIs (OR = 2.80, 95%CI = 2.43–3.24) and Black/African Americans (OR = 1.97, 95%CI = 1.57–2.47) demonstrated higher odds of hepatectomy when compared to non-Hispanic Whites possibly driving the previously observed higher odds of any surgery which was statistically significant for both race/ethnicity groups.

Among other findings, compared to patients who were younger than 65 years, there was a lower odds of surgery with patients 65 years or older (OR = 0.85, 95%CI = 0.78–0.92). Males (OR = 0.88, 95%CI = 0.80–0.97) were less likely to have a surgery compared to females. Compared to the lowest neighborhood SES quintile, patients residing in the highest 4th (OR = 1.20, 95%CI = 1.05–1.37) and 5th (OR = 1.33, 95%CI = 1.15–1.54) SES quintile had a better odds of surgery. Compared to private insurance, all other types led to lower odds of surgery. Our data also showed the odds of surgery to decrease with late-stage cancer (OR = 0.19, 95%CI = 0.17–0.21). Patients treated at hospitals performing higher volume of surgeries had increased odds of surgery. Increasing comorbidity demonstrated lower odds of surgery for those in the category 3+ (OR = 0.55, 95%CI = 0.49–0.62) compared with those in the category 0–2.

Overall survival

Kaplan-Meier analysis showed statistically significant differences in all-cause survival by race/ethnicity (p <0.0001, log-rank test). After sociodemographic, clinical factors and treatment effects were taken into consideration, low risk of death was observed for Asian/PIs (HR = 0.86, 95%CI = 0.82–0.91) and Hispanics (HR = 0.88, 95%CI = 0.84–0.92) compared with non-Hispanic White patients. No differences in risk of death were observed for Black/African Americans (HR = 0.95, 95%CI = 0.88 – 1.02). Compared with non-surgical or other treatment, there was a lower risk of death in patients who received ablation (HR = 0.62, 95%CI = 0.56–0.67), hepatectomy (HR = 0.32, 95%CI = 0.29–0.35) and transplant (HR = 0.17, 95%CI = 0.13–0.22). In addition, we observed the risk of death to increase with the higher age group of those at and above 65 (HR = 1.12, 95%CI = 1.08–1.17). Compared to the lowest neighborhood SES, patients residing in the two highest SES neighborhood had a lower risk of death. Regarding insurance type, all categories showed higher risk of death compared to private insurance. Late tumor stage (HR = 2.85, 95%CI = 2.73–2.97) significantly increased the risk of death. Patients receiving treatment at hospitals performing increased volume of surgeries showed lower risk of death. We also observed an increased risk of death for patients with a Elixhauser comorbidity score 3+ (HR = 1.38, 95%CI = 1.30–1.46) indicating poor outcome for those with three or more comorbid conditions.

DISCUSSION

We conducted an analysis to investigate racial/ethnic disparities in surgical treatment and survival for HCC patients in California and found that Asian/PIs and Black/African Americans are more likely to have surgery compared to non-Hispanic Whites driven primarily by hepatectomy. In contrast, Hispanics are less likely to receive surgical treatments. Prior studies have shown positive relationship between Asian/PIs and surgical treatments and negative association for Hispanics.[19,24,25] However, the positive association between Black/African Americans and surgical treatment based on older study periods has not been demonstrated to our knowledge. In our study, older age, male gender, advanced cancer stage, and higher comorbidity score were all associated with lower chances of surgery, while having private insurance, high neighborhood SES, and receiving treatment at high volume hospitals increased the possibility of getting a surgery.

We observed that Asian/PIs and Hispanics had significantly lower risk of death when compared to non-Hispanic Whites, who had a similar risk of death to Black/African Americans. The superior survival persisted for Asian/PIs and Hispanics after adjusting for treatment effects in addition to sociodemographic and clinical factors, a finding that has been observed in California for the period 1988–2012 previously.[20] That study disaggregated Asian/PIs into several subgroups and the majority of these subgroups demonstrated superior survival. On the other hand, that study also showed significantly worse survival for Black/African Americans, including lower odds of surgical treatment, neither of which were observed in our study. However, in a recent study using Surveillance, Epidemiology, and End Results (SEER) data for the period 2012–

2016, no difference in the likelihood of treatment for tumors less than 5 cm or risk of death was observed between Black/African Americans and non-Hispanic Whites.[26]

The association we observed between Black/African Americans and increased likelihood of surgical treatment might be explained by changing patterns in healthcare access among Black/African Americans during our study period (2012–2017). The Affordable Care Act (ACA), implemented in 2014, was intended to increase healthcare access and bring equity in the healthcare system.[27] Several studies have shown that the ACA along with traditional Medicaid expansion helped reduce racial/ethnic disparities in insurance coverage among Black/African Americans.[27-30] Additionally, a study by Chen et al found significant improvements in reducing the chances of being uninsured, delaying treatment, foregoing treatment, and increasing the chances of physician visits after ACA implementation.[29] This newly accessible healthcare program could have contributed to the changing pattern of treatment access among Black/African Americans in our population.

One of the greatest strengths of our study is the use of a population-based registry data that covers the entire state of California. The CCR has one of the highest quality ratings from the North American Association of Central Cancer Registries (NAACCR). Quality metrics include low levels of loss to follow up with fewer than 3% records obtained from death certificates.[15] This ensures strong external validity. However, this dataset also introduces limitations to the study due to the nature of the data that is collected. Proxy aggregate group-level census-based data are obtained to assign SES. These ecological data may not portray an accurate picture at the individual-level. Any discrepancy can lead to potential error in describing the association between race/ethnicity and availing surgical treatments. An important factor that is missing from the analysis is the subject's fluency in English that can be a barrier to seeking treatment. Neither the CCR nor the HCAI collect data on lifestyle factors such as nutrition, physical activity, and alcohol consumption, all of which can play a role in prognosis. The CCR assigns race/ethnicity information based on the patient's medical records. Unless this information is provided by patient, it is derived based on assumptions or inferences that can be erroneous. If this affects certain minority populations more than others, then it can lead to differential misclassification.

In summary, we examined the association between race/ethnicity and surgical treatment for HCC patients and how it impacts their long-term survival. Racial/ethnic disparities were observed for accessing surgical treatment and survival. According to our findings, Black/African Americans were more likely to get surgical treatment compared to non-Hispanic Whites, a finding driven mainly by hepatectomy that has not been observed previously. More work needs to be done to understand the changing pattern in this important area of HCC treatment and survival for minorities and ensure equity in outcomes.

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Figure 1. Study population selection process

18,970 HCC cases identified using site code C220 and histology code 8170-8175, diagnosed between 2012-2017 with complete follow up till 2018

→ **2,225** cases without first primary tumor excluded

16,745 cases with first primary tumor

→ **362** cases excluded due to being autopsy or death certificate based

16,383 cases with information not coming from autopsy or death certificate

→ **8** cases excluded for having gender other than male and female

16,375 HCC cases in study population

Table 1. Sociodemographic and clinical characteristics by race/ethnicity for hepatocellular carcinoma patients in California from 2012-2017

	Asian / Pacific Islander		African American		Hispanic		Other		Non-Hispanic White		Total		P-value
	(n = 3579)		(n = 1198)		(n = 5338)		(n = 300)		(n = 5960)		(n = 16375)		
	n	%	n	%	n	%	n	%	n	%	n	%	
Age at diagnosis													
0-<65	1633	45.63	722	60.27	3067	57.46	179	59.67	3226	54.13	8827	53.91	<.0001
65+	1946	54.37	476	39.73	2271	42.54	121	40.33	2734	45.87	7548	46.09	
Sex													
Female	959	26.8	299	24.96	1405	26.32	76	25.33	1345	22.57	4084	24.94	<.0001
Male	2620	73.2	899	75.04	3933	73.68	224	74.67	4615	77.43	12291	75.06	
Neighborhood socioeconomic status													
1 - Low SES	507	14.17	402	33.56	1900	35.59	86	28.67	878	14.73	3773	23.04	<.0001
2	791	22.10	328	27.38	1472	27.58	88	29.33	1296	21.74	3975	24.27	
3	837	23.39	238	19.87	987	18.49	51	17.00	1375	23.07	3488	21.30	
4	801	22.38	154	12.85	679	12.72	54	18.00	1322	22.18	3010	18.38	
5 - High SES	643	17.97	76	6.34	300	5.62	21	7.00	1089	18.27	2129	13.00	
Insurance Type													
Private	1626	45.43	480	40.07	2167	40.6	141	47	3085	51.76	7499	45.80	<.0001
Medicaid/Public/Uninsured	1214	33.92	468	39.07	2100	39.34	87	29.00	1450	24.33	5319	32.48	
Medicare	658	18.39	218	18.2	936	17.53	55	18.33	1239	20.79	3106	18.97	
Other	81	2.26	32	2.67	135	2.53	17	5.67	186	3.12	451	2.75	
Tumor stage													
Stage I-II	2060	61.94	631	57.94	3057	62.49	161	60.98	3337	61.18	9246	61.54	0.0791
Stage III-IV	1266	38.06	458	42.06	1835	37.51	103	39.02	2117	38.82	5779	38.46	
Unknown	253		109		446		36		506		1350		
Avg. Annual Surgery Volume													
0-5	1868	52.19	738	61.60	3407	63.83	164	54.67	3468	58.19	9645	58.90	<.0001
>5	1711	47.81	460	38.40	1931	36.17	136	45.33	2492	41.81	6730	41.10	
Elixhauser comorbidity score													
0-2	744	31.29	133	15.23	588	15.57	36	17.14	875	20.8	2376	20.76	<.0001
3+	1634	68.71	740	84.77	3189	84.43	174	82.86	3332	79.2	9069	79.24	
No Admit	1201		325		1561		90		1753		4930		
Surgical Treatment													
No surgery/other	2521	70.44	944	78.80	4419	82.78	240	80.00	4709	79.01	12833	78.37	<.0001
Ablation	383	10.70	112	9.35	496	9.29	34	11.33	657	11.02	1682	10.27	
Hepatectomy	598	16.71	126	10.52	282	5.28	19	6.33	418	7.01	1443	8.81	
Transplantation	77	2.15	16	1.34	141	2.64	7	2.33	176	2.95	417	2.55	

Table 2. Factors associated with receipt of surgical treatment for hepatocellular carcinoma in California from 2012-2017

	Any surgery		Any surgery		Ablation		Hepatectomy		Transplantation	
	Unadjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Race/Ethnicity										
Asian/Pacific Islander	1.58	1.44-1.74	1.63	1.47-1.81	1.07	0.92-1.24	2.80	2.43-3.24	1.10	0.83-1.47
African American	1.01	0.87-1.18	1.24	1.05-1.47	1.00	0.80-1.26	1.97	1.57-2.47	0.50	0.29-0.84
Hispanic	0.78	0.71-0.86	0.88	0.79-0.97	0.88	0.76-1.00	0.86	0.72-1.01	0.85	0.67-1.07
Other	0.94	0.70-1.26	1.02	0.74-1.40	1.06	0.71-1.57	1.02	0.62-1.68	0.80	0.36-1.77
Non-Hispanic White	1.00		1.00		1.00		1.00		1.00	
Age at diagnosis										
0-<65			1.00						1.00	
65+			0.85	0.78-0.92					0.26	0.20-0.34
Sex										
Female			1.00				1.00			
Male			0.88	0.80-0.97			0.79	0.70-0.90		
Neighborhood socioeconomic status										
1 - Low SES			1.00		1.00		1.00			
2			1.02	0.90-1.16	1.02	0.86-1.20	1.02	0.85-1.23		
3			1.11	0.98-1.26	1.06	0.90-1.26	1.12	0.93-1.35		
4			1.20	1.05-1.37	1.25	1.05-1.49	1.11	0.91-1.35		
5 - High SES			1.33	1.15-1.54	1.23	1.02-1.49	1.42	1.16-1.75		
Insurance Type										
Private			1.00		1.00		1.00		1.00	
Medicaid/Public/Uninsured			0.65	0.59-0.72	0.83	0.73-0.94	0.52	0.45-0.60	0.49	0.39-0.63
Medicare			0.81	0.72-0.91	0.82	0.70-0.94	0.78	0.67-0.91	0.73	0.54-1.00
Other			0.50	0.35-0.71	0.44	0.26-0.74	0.48	0.27-0.83	0.74	0.35-1.56
Tumor stage										
Stage I-II			1.00		1.00		1.00		1.00	
Stage III-IV			0.19	0.17-0.21	0.12	0.10-0.15	0.27	0.23-0.31	0.12	0.08-0.17
Unknown			0.13	0.10-0.17	0.22	0.16-0.30	0.05	0.03-0.10	0.05	0.01-0.19
Avg. Annual Hospital Surgery Volume										
0-5			1.00		1.00		1.00		1.00	
>5			2.21	2.03-2.40	2.69	2.40-3.02	1.48	1.32-1.67	3.94	3.11-4.99
Elixhauser comorbidity score										
0-2			1.00		1.00		1.00		1.00	
3+			0.55	0.49-0.62	0.67	0.57-0.79	0.39	0.34-0.44	1.95	1.36-2.80
No Admit			0.44	0.39-0.49	0.84	0.71-0.99	0.16	0.13-0.19	0.92	0.62-1.37

Note: Any surgery model adjusted for all the variables present in the table
Ablation model adjusted for all variables except age at diagnosis, sex
Hepatectomy model adjusted for all variables except age at diagnosis
Transplant model adjusted for all variables except sex, neighborhood socioeconomic status

Table 3. Factors associated with survival from hepatocellular carcinoma in California from 2012-2017

	Overall survival			
	Unadjusted		**Adjusted for sociodemographic, clinical factors, and treatment effects**	
	HR	95% ci	Adjusted HR	95% CI
Race/Ethnicity				
Asian/Pacific Islander	0.78	0.74-0.82	0.86	0.82-0.91
African American	1.05	0.98-1.13	0.95	0.88-1.02
Hispanic	1.00	0.95-1.04	0.88	0.84-0.92
Other	0.91	0.79-1.06	0.83	0.72-0.96
Non-Hispanic White	1.00		1.00	
Age at diagnosis				
0-<65			1.00	
65+			1.12	1.08-1.17
Neighborhood socioeconomic status				
1 - Low SES			1.00	
2			1.01	0.96-1.07
3			0.95	0.90-1.01
4			0.90	0.85-0.95
5 - High SES			0.89	0.83-0.96
Insurance Type				
Private			1.00	
Medicaid/Public/Uninsured			1.20	1.14-1.25
Medicare			1.10	1.05-1.16
Other			1.57	1.41-1.75
Tumor stage				
Stage I-II			1.00	
Stage III-IV			2.85	2.73-2.97
Unknown			2.43	2.26-2.61
Avg. Annual Hospital Surgery Volume				
0-5			1.00	
>5			0.65	0.62-0.68
Elixhauser comorbidity score				
0-2			1.00	
3+			1.38	1.30-1.46
No Admit			0.72	0.68-0.77
Surgical Treatment				
No surgery/other			1.00	
Ablation			0.62	0.57-0.67
Hepatectomy			0.32	0.29-0.35
Transplantation			0.17	0.13-0.22

Note: Model adjusted for all the variables present in the table

Supplemental Table 1. Analysis of unknown stage category related to receipt of surgical treatment for hepatocellular carcinoma

	Stage with Unknowns			Unknowns added to Early Stage			Unknowns added to Late Stage		
Odds Ratio Estimates									
Effect	**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**	
RACE Asian vs White	1.66	1.49	1.85	1.66	1.49	1.84	1.66	1.49	1.85
RACE Black vs White	1.25	1.06	1.48	1.23	1.04	1.45	1.25	1.05	1.47
RACE Hispanic vs White	0.88	0.79	0.97	0.87	0.79	0.97	0.87	0.79	0.97
RACE Other vs White	1.03	0.75	1.42	1.00	0.73	1.37	1.03	0.75	1.41
Tumor Stage III-IV vs Stage I-II	0.21	0.19	0.24	0.22	0.20	0.25	0.21	0.18	0.23
Tumor Stage Unknown vs Stage I-II	0.16	0.11	0.25						
Avg. Annual Surgery Volume >5 vs 0 - 5	2.15	1.97	2.33	2.21	2.03	2.40	2.15	1.98	2.34
Tumor Size 5+ vs 0 - <5	0.78	0.71	0.87	0.75	0.68	0.83	0.79	0.71	0.87
Tumor Size Unknown vs 0 - <5	0.69	0.41	1.19	0.12	0.08	0.17	0.54	0.38	0.78
INSURANCE Medicaid/Public/Uninsured vs Private	0.65	0.59	0.72	0.66	0.60	0.73	0.66	0.59	0.72
INSURANCE Medicare vs Private	0.81	0.72	0.90	0.82	0.73	0.91	0.81	0.72	0.91
INSURANCE Other vs Private	0.51	0.35	0.73	0.50	0.35	0.72	0.51	0.35	0.73
Neighborhood Socioeconomic Status 2 vs 1	1.02	0.90	1.16	1.02	0.90	1.15	1.02	0.90	1.16
Neighborhood Socioeconomic Status 3 vs 1	1.11	0.98	1.26	1.12	0.98	1.27	1.11	0.98	1.26
Neighborhood Socioeconomic Status 4 vs 1	1.19	1.04	1.36	1.19	1.04	1.36	1.19	1.04	1.36
Neighborhood Socioeconomic Status 5 vs 1	1.33	1.15	1.54	1.34	1.15	1.54	1.33	1.15	1.54
SEX 1 vs 2	0.88	0.81	0.97	0.88	0.80	0.97	0.88	0.81	0.97
AGE 65+ vs 0-<65	0.86	0.79	0.94	0.86	0.78	0.93	0.86	0.79	0.94
Elixhauser Comorbidity Score 3+ vs 0-2	0.55	0.49	0.61	0.54	0.48	0.60	0.55	0.49	0.61
Elixhauser Comorbidity Score no admit vs 0-2	0.43	0.38	0.48	0.42	0.38	0.48	0.43	0.38	0.48

Supplemental Table 2. Analysis of unknown stage category related to survival from hepatocellular carcinoma

		Stage with Unknowns			Unknowns added to Early Stage			Unknows added to Late Stage		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits	
RACE (non-Hispanic White)	Asian	0.85	0.81	0.90	0.86	0.81	0.90	0.85	0.81	0.90
RACE (non-Hispanic White)	Black	0.94	0.88	1.02	0.95	0.88	1.03	0.94	0.87	1.01
RACE (non-Hispanic White)	Hispanic	0.88	0.84	0.92	0.89	0.85	0.93	0.88	0.84	0.92
RACE (non-Hispanic White)	Other	0.83	0.72	0.97	0.85	0.74	0.99	0.83	0.71	0.96
Tumor Stage (Stage I-II)	Stage III-IV	2.42	2.30	2.54	2.32	2.21	2.43	2.36	2.25	2.48
Tumor Stage (Stage I-II)	Unknown	1.93	1.72	2.17						
Tumor Size (<5)	5+	1.37	1.30	1.43	1.39	1.32	1.45	1.39	1.33	1.46
Tumor Size (<5)	Unknown	1.52	1.33	1.74	2.82	2.60	3.07	1.25	1.15	1.37
Avg. Annual Surgery Volume (<=5)	>5	0.67	0.64	0.70	0.66	0.64	0.69	0.67	0.64	0.70
Elixhauser Comorbidity Score (0-2)	3+	1.40	1.33	1.49	1.41	1.33	1.49	1.40	1.33	1.48
Elixhauser Comorbidity Score (0-2)	no admit	0.74	0.69	0.79	0.74	0.69	0.79	0.74	0.69	0.79
INSURANCE (Private)	Medicaid/Public/Uninsured	1.19	1.14	1.24	1.18	1.13	1.23	1.19	1.14	1.24
INSURANCE (Private)	Medicare	1.10	1.04	1.16	1.09	1.04	1.15	1.10	1.04	1.16
INSURANCE (Private)	Other	1.50	1.34	1.67	1.51	1.35	1.68	1.49	1.34	1.67
Neighborhood socioeconomic status (1)	2	1.01	0.96	1.07	1.01	0.96	1.07	1.01	0.96	1.07
Neighborhood socioeconomic status (1)	3	0.95	0.90	1.01	0.95	0.89	1.00	0.95	0.90	1.01
Neighborhood socioeconomic status (1)	4	0.90	0.85	0.96	0.90	0.85	0.96	0.90	0.85	0.96
Neighborhood socioeconomic status (1)	5	0.89	0.83	0.95	0.89	0.83	0.95	0.89	0.83	0.95
AGE (<65)	65+	1.10	1.06	1.15	1.11	1.07	1.16	1.10	1.06	1.15
Ablation (no surgery)		0.64	0.59	0.70	0.63	0.58	0.69	0.64	0.59	0.70
Hepatectomy (no surgery)		0.30	0.28	0.34	0.30	0.27	0.33	0.31	0.28	0.34
Transplant (no surgery)		0.17	0.13	0.23	0.17	0.13	0.22	0.17	0.13	0.23

Supplemental Table 3. Analysis of no admit Elixhauser comorbidity score category related to receipt of surgical treatment for hepatocellular carcinoma

	Elixhauser comorbidty score with no admits			no admits added to Elixhauser comorbidity score 0-2			no admits added to Elixhauser comorbidity score 3+		
Odds Ratio Estimates									
Effect	**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**	
RACE Asian vs White	1.66	1.49	1.85	1.68	1.51	1.86	1.62	1.46	1.80
RACE Black vs White	1.25	1.06	1.48	1.21	1.03	1.43	1.25	1.06	1.47
RACE Hispanic vs White	0.88	0.79	0.97	0.85	0.77	0.95	0.88	0.79	0.97
RACE Other vs White	1.03	0.75	1.42	1.01	0.74	1.38	1.03	0.75	1.41
Tumor Stage III-IV vs Stage I-II	0.21	0.19	0.24	0.21	0.19	0.24	0.21	0.19	0.24
Tumor Stage Unknown vs Stage I-II	0.16	0.11	0.25	0.16	0.1	0.24	0.16	0.11	0.25
Avg. Annual Surgery Volume >5 vs 0 - 5	2.15	1.97	2.33	2.16	1.98	2.34	2.14	1.97	2.33
Tumor Size 5+ vs 0 - <5	0.78	0.71	0.87	0.84	0.76	0.92	0.80	0.72	0.88
Tumor Size Unknown vs 0 - <5	0.69	0.41	1.19	0.67	0.4	1.15	0.67	0.39	1.15
INSURANCE Medicaid/Public/Uninsured vs Private	0.65	0.59	0.72	0.67	0.6	0.73	0.67	0.60	0.73
INSURANCE Medicare vs Private	0.81	0.72	0.9	0.82	0.73	0.92	0.82	0.74	0.92
INSURANCE Other vs Private	0.51	0.35	0.73	0.51	0.36	0.73	0.52	0.36	0.74
Neighborhood Socioeconomic Status 2 vs 1	1.02	0.90	1.16	1.03	0.91	1.16	1.02	0.90	1.15
Neighborhood Socioeconomic Status 3 vs 1	1.11	0.98	1.26	1.10	0.97	1.25	1.10	0.97	1.25
Neighborhood Socioeconomic Status 4 vs 1	1.19	1.04	1.36	1.18	1.03	1.34	1.18	1.03	1.34
Neighborhood Socioeconomic Status 5 vs 1	1.33	1.15	1.54	1.33	1.15	1.53	1.31	1.13	1.52
SEX 1 vs 2	0.88	0.81	0.97	0.88	0.8	0.97	0.88	0.80	0.97
AGE 65+ vs 0-<65	0.86	0.79	0.94	0.83	0.76	0.91	0.86	0.79	0.94
Elixhauser Comorbidity Score 3+ vs 0-2	0.55	0.49	0.61	0.94	0.87	1.03	0.50	0.45	0.56
Elixhauser Comorbidity Score no admit vs 0-2	0.43	0.38	0.48						

Supplemental Table 4. Analysis of no admit Elixhauser comorbidity score category related to survival from hepatocellular carcinoma

		Elixhauser comorbidity			no admits added to			no admits added to		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian	0.85	0.81	0.90	0.85	0.81	0.90	0.82	0.77	0.86
RACE (non-Hispanic White)	Black	0.94	0.88	1.02	0.94	0.87	1.01	0.95	0.88	1.03
RACE (non-Hispanic White)	Hispanic	0.88	0.84	0.92	0.88	0.84	0.92	0.89	0.85	0.94
RACE (non-Hispanic White)	Other	0.83	0.72	0.97	0.83	0.72	0.96	0.84	0.73	0.97
Tumor Stage (Stage I-II)	Stage III-IV	2.42	2.30	2.54	2.42	2.31	2.54	2.43	2.31	2.55
Tumor Stage (Stage I-II)	Unknown	1.93	1.72	2.17	1.93	1.72	2.16	1.92	1.71	2.15
Tumor Size (<5)	5+	1.37	1.30	1.43	1.38	1.32	1.45	1.39	1.33	1.46
Tumor Size (<5)	Unknown	1.52	1.33	1.74	1.52	1.33	1.74	1.46	1.28	1.67
Avg. Annual Surgery Volume (<=5)	>5	0.67	0.64	0.70	0.67	0.64	0.70	0.66	0.63	0.69
Elixhauser Comorbidity Score (0-2)	3+	1.40	1.33	1.49	1.72	1.65	1.78	1.14	1.07	1.20
Elixhauser Comorbidity Score (0-2)	no admit	0.74	0.69	0.79						
INSURANCE (Private)	Medicaid/Public/Uninsured	1.19	1.14	1.24	1.19	1.14	1.25	1.25	1.19	1.30
INSURANCE (Private)	Medicare	1.10	1.04	1.16	1.10	1.05	1.16	1.15	1.09	1.21
INSURANCE (Private)	Other	1.50	1.34	1.67	1.50	1.34	1.67	1.51	1.36	1.69
Neighborhood socioeconomic status (1)	2	1.01	0.96	1.07	1.01	0.96	1.07	1.01	0.96	1.06
Neighborhood socioeconomic status (1)	3	0.95	0.90	1.01	0.95	0.90	1.00	0.94	0.89	0.99
Neighborhood socioeconomic status (1)	4	0.90	0.85	0.96	0.90	0.85	0.96	0.88	0.83	0.94
Neighborhood socioeconomic status (1)	5	0.89	0.83	0.95	0.89	0.83	0.95	0.86	0.80	0.92
AGE (<65)	65+	1.10	1.06	1.15	1.09	1.05	1.14	1.09	1.05	1.14
Ablation (no surgery)		0.64	0.59	0.70	0.65	0.60	0.70	0.65	0.60	0.70
Hepatectomy (no surgery)		0.30	0.28	0.34	0.32	0.29	0.35	0.34	0.31	0.38
Transplant (no surgery)		0.17	0.13	0.23	0.18	0.13	0.23	0.20	0.16	0.26

Chapter 2. Racial/ethnic disparities in surgical treatment delay and survival for Hepatocellular Carcinoma cases in California

ABSTRACT

Background: Hepatocellular carcinoma is the most common manifestation of liver and intrahepatic bile duct cancer and is the second leading cause of cancer mortality worldwide. Due to rapid tumor doubling time, treatment delay after diagnosis of hepatocellular carcinoma can lead to significant tumor progression and decreased survival. Studies have shown mixed impacts of treatment delay displaying either detrimental effect, no effect, or beneficial effect. In addition, there is scarce information regarding racial/ethnic disparities in treatment delay and consequent survival for patients with hepatocellular carcinoma. The purpose of this study was to investigate racial/ethnic disparities in time to treatment after diagnosis of hepatocellular carcinoma and impact of treatment delay on survival of hepatocellular carcinoma cases in California. The study utilized a large population-based database to investigate and report its findings.

Methods: A retrospective study consisting of 3,494 hepatocellular carcinoma cases was conducted using data from the California Cancer Registry for the period 2012 to 2017. Surgical treatment delay was defined as absence of surgical treatment from diagnosis date for a period of 90 days. Racial/ethnic disparities in treatment delay was investigated along with survival outcomes by considering the independent effect of treatment delay. In addition, we studied the interaction between race/ethnicity and surgical treatment delay.

Results: Asian/PIs (29.7%) had the lowest proportion for surgical treatment delay followed by Black/African Americans (39.0%), non-Hispanic Whites, (40.9%) and Hispanics (45.3%). We found that Asian/Pacific Islanders (OR = 0.76, 95%CI = 0.63–0.92) were less likely to experience surgical treatment delays than non-Hispanic White patients; surgical treatment delays were similar between Black/African Americans (OR = 1.10, 95%CI = 0.82–1.49), Hispanic (OR = 1.14, 95%CI = 0.94–1.37) and non-Hispanic Whites. In addition, greater distance from patience residence to hospital increased the odds of surgical treatment delay, while high neighborhood SES, high volume hospitals performing greater number of surgeries, and higher comorbidity score decreased the odds. Having a hepatectomy decreased the odds while having a transplant increased the odds of having a surgical treatment delay. Surgical treatment delay (HR = 0.68, 95%CI = 0.60–0.77) appeared to be associated with improved survival, with similar associations observed by race/ethnicity.

Conclusion: Our study showed that Asian/PIs were less likely to have surgical treatment delay and delays were associated with patient neighborhood SES, hospital proximity and hospital surgical volume. Treatment delay had a favorable effect on survival, which might be explained by case prioritization where patients with more severe conditions received earlier treatment but had poor prognosis for survival.

INTRODUCTION

One of the most common forms of cancer in the world is hepatocellular carcinoma (HCC).[1,2] By some estimates, it ranks fifth in terms of the number of people affected by it and ranks second in cancer related mortality.[3] While hepatitis B virus and hepatitis C virus have been primary risk factors[4], increasing rates of obesity, diabetes, fatty liver diseases and other risk factors have made HCC difficult to manage and control.[5] In the U.S., HCC incidence has been steadily increasing with rates changing from 1.5 to 6.2 cases per 100,000 between 1973 and 2011.[6] Although advances in surgical techniques and postsurgical management have helped control morbidity and mortality, HCC mortality rates still remain one of the highest in the world.[7-9]

In the U.S., HCC rates vary by race/ethnicity with Asians and Hispanics having the highest rates. This could likely be due to differences in the distribution of risk factors across different racial and ethnic groups. While it has been shown that access to treatment and care varies by race/ethnicity, there is still inadequate information regarding racial/ethnic disparities in time to receiving surgical treatment.

Because prognosis from HCC is poor, it is important to initiate treatment as early as possible. However, accessing care for many patients can be a daunting task and can lead to significant delays because it requires multiple steps and interactions with several healthcare providers. Treatment strategies for HCC involves highly complex care that are only available at tertiary referral centers. Access to these referral centers can require overcoming several barriers associated with race/ethnicity, including clinical and socioeconomic factors.[10] This differential time in accessing care along racial/ethnic lines can have profound implications on treatments received and patient survival.

Several studies have examined HCC-related therapeutic delay but their focus has been on patient survival and results have been mixed. Three different single facility-based studies found therapeutic delay to be associated with worse survival.[11-13] Only one of the studies included a broad range of treatments, while the other two studies were limited to either radiofrequency ablation or locoregional therapy. Other studies were able to show no effect of therapeutic delay on survival.[14,15] However, only one of the studies used a large nationwide clinical oncology database and defined treatment to include a broad array of interventions. Another facility-based study found no impact of therapeutic delay for liver resection for overall survival but did observe improved survival for modest delays in specific subset of patients.[16] Finally, a few studies found treatment delay to be associated with improved survival and only one of them use a large nationwide clinical oncology database.[17,18]

None of these studies specifically investigated racial/ethnic disparities in therapeutic delay and its effect on survival along racial/ethnic lines. Additionally, only a limited number of studies used large population-based databases, and most have been restricted to single facilities like hospitals and focused on specific number of treatment options which inhibits generalizability. The two studies that did use the large population-based databases used data from the same source but with different time periods and found conflicting results. The effect of treatment delay on survival based on large population-based databases is still unclear.

Our goal is to examine racial/ethnic disparities in surgical treatment delay and subsequent long-term survival using data from a large population-based cancer registry. It is important to focus on surgical treatment delay since only surgical modalities have been proven to be effective against HCC while non-surgical modalities such as chemotherapy and radiotherapy have been largely ineffective.[19-21] Also, surgical treatment delay can lead to rapid progression of tumors into significantly large size that can lead to ineligibility for surgery and increased fatality. Finally, this study will provide additional perspective into the discordant results of the two existing studies that used large population-based databases.

To our knowledge, this will be the first time data from a large population-based registry in California, the California Cancer Registry, will be used to study racial/ethnic differences in surgical therapeutic delay and subsequent survival outcomes using recent data and covering the surgical modalities of ablation, hepatectomy, and transplantation.

METHODS

A retrospective cohort study was conducted using data from the California Cancer Registry (CCR) linked with inpatient hospital data from the California Health Care Access and Information (HCAI). The CCR consists of the union of three National Cancer Institute-funded Surveillance, Epidemiology, and End Results (SEER) regional registries including the Greater California Registry, the Greater Bay Area Registry and Los Angeles Registry. The CCR serves as the combined data repository for all cancer cases in California and is regarded as the largest population-based registry in the U.S. Due to a state mandate, all newly diagnosed cancer cases are required to be reported except for basal and squamous cell carcinoma of the skin and carcinoma in site of the cervix. Data quality at the CCR meets exceptionally high standards as established by the North American Association of Central Cancer Registries (NAACR) and the National Program for Cancer Registries (NPCR). More than 95% of the data are almost complete[22] with less than 3% missing race information and fewer than 3% of the data are obtained solely from death records.[23] The CCR provides a rich array of different classes of data elements including patient demographics and clinical information including detailed cancer-related data.

The California HCAI Patient Discharge Database (PDD) data contains patient discharge abstracts related to all inpatient hospital visits in California. The database provides patient demographic and clinical information including primary diagnosis code and procedure code along with 24 additional secondary diagnosis codes and up to 19 secondary procedure codes based on the *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM)*.[23] The HCAI PDD data were linked to the CCR data using a probabilistic method using patient specific information that includes patient date of birth, gender, social security number, and other relevant information.

The study identified all reports of HCC between January 2012 and December 2017 with follow-up through 2018. Patients were identified using the *International Classification of Diseases for Oncology, Third Edition* site code C22.0 along with histology codes 8170–8175. This yielded 18,970 HCC patients. We limited our analysis to only primary HCC because the survival patterns of other liver cancer histologies would be different. We also excluded patients identified only through autopsy and death certificates and included only males and females for sex while deleting the few missing or other gender values. This resulted in 16,375 patients. Because we were interested in surgical therapeutic delay, all our patients had to have a surgery to assess the primary effect of interest—surgical treatment delay. This restriction led to an elimination of 12,833 patients without HCC surgery. After further removal of cases with missing diagnosis dates, surgery dates, and surgery dates preceding diagnosis dates, our final study population consisted of 3,494 HCC patients with surgical treatment (Figure 1).

Study variables

The CCR was the source for most of the variables used in our study. Demographic variables included race/ethnicity, age, sex, socioeconomic status (SES), and insurance status while clinical variables included tumor stage and surgical treatment type. In addition, we also derived a variable which measured the average annual surgery volume by hospital. The race/ethnicity variable consisted of five different groups which included non-Hispanic Whites, Asian American/Pacific Islanders (PI), Black/African Americans, Hispanics, and others. The "other" group consisted of American Indians and Alaskans, Native Hawaiians and any other groups including mixed and unknown groups. Age was dichotomized into less than 65 years and 65 and above, and the former group was used as the reference category. SES quintiles used in our study were derived at the neighborhood level from the U.S. Census and were grouped into quintiles. For the primary analyses, missing values were assigned an imputed value to ensure all patients had a SES score. We categorized insurance type into private insurance, Medicare, Medicaid/Public/Uninsured and Other. Private insurance consisted of HMO, PPO, fee for service, managed care, TRICARE, military, Veterans Affairs, or any insurance type not specified. All Medicare categories were included in the Medicare group, while the Medicaid/Public/Uninsured group consisted of Medicaid, uninsured, self-pay, county founded or Indian/Public Health Services. If patients had unknown insurance or missing values for insurance, then they were assigned to the other category.

Tumor stage was one of the clinical variables used in our study and was grouped into stages I and II (early stage) and stages III and IV (late stage). A third unknown stage category was also created to include unstaged, unknown or missing stage values. One of the primary outcomes of interest was delayed time to HCC surgical treatment, where treatment included ablation, hepatectomy and transplantation. We identified these surgical procedures using codes for the most extensive type of surgery performed in the first course of treatment. The last variable obtained from the CCR was the average annual surgery volume, which was derived by counting the total number of HCC related surgeries over the study period for each hospital and dividing by the total number of years in the study. This provided the average number of HCC-related surgeries performed annually at each hospital and was broken up into the two categories based on median value. The category 0–5 represented hospitals performing up to five HCC surgeries on average per year, while the category greater than 5 surgeries represented hospitals performing more than five surgeries on average per year.

The PDD data from HCAI was used to obtain comorbidity scores from the Elixhauser Indices. The 29 Elixhauser Indices representing different health conditions (co-morbidities) were identified using both the primary diagnosis code and 24 secondary diagnosis codes. Indices for lymph, tumor and metastasis were excluded from the comorbidity score calculation since these would be indicative of previous cancer and our study is restricted to primary cases of a single cancer. The initial timeframe used to identify Elixhauser Indices included three years prior to diagnosis of cancer. Any indices present were combined into an aggregate Elixhauser comorbidity score. For patients who did not have any indices present in the three years prior to diagnosis of cancer, nine months of data after diagnosis of cancer was also examined to search for presence of any of the Elixhauser Indices which were combined into an aggregate sum when present. The final Elixhauser comorbidity score was broken up into three categories with 0–2 representing presence of up to two comorbid conditions while 3+ was used for the presence of three or more comorbid conditions. The third category, “no admit,” was used for patients if they lacked any admission during the specified time period considered for presence of Elixhauser Indices. In addition to the Elixhauser comorbidity score, the PDD data was also the source of distance information from patient residence to hospital where patient sought treatment. The approximate distance was calculated using patient residence zip code and hospital zip code and was broken up into three categories. The category 0–5 consisted of patient residence within up to a five-mile radius from the hospital while the category indicating greater than 5 represented all patient residence beyond the five-mile radius. The median value for patient distance was used for this categorization. Patients who lacked a zip code were assigned to the “No Zip” category.

In our study, the primary outcome of interest was surgical treatment delay which was defined as present if the time from diagnosis to HCC surgery exceeded 90 days. We specifically chose 90 days since it is considered tumor doubling time.[13-15,24] If surgical treatment delay exists and a patient’s tumor indeed doubles in size then the patient risks developing late-stage cancer and thus, being ineligible for surgery.

Statistical Analysis

Bivariate relationship between surgical therapeutic delay and race/ethnicity was examined using contingency table analysis with chi-square tests. Similar analyses were also conducted to determine the association between surgical therapeutic delay and different sociodemographic and clinical variables. In order to quantitate the magnitude of the association between race/ethnicity and presence of surgical therapeutic delay, unconditional logistic regression was used. Both univariate and multivariate models were conducted with the multivariate model adjusting for relevant sociodemographic and clinical factors.

Additionally, the effect of surgical therapeutic delay on the association between race/ethnicity and long-term survival of patients was also examined using actuarial methods. We estimated Kaplan-Meier survival curves for HCC patients by race/ethnicity and tested for differences using the log-rank test. Cox Proportional Hazards regression model was used to evaluate the association between race/ethnicity and survival. Surgical treatment delay was specifically used in the multivariate model among other relevant variables to estimate its effect on patient survival. We further studied the interactive effects of race/ethnicity and surgical treatment delay and surgical treatment type on survival. Proportional hazards assumption was assessed in all instances of modeling using log(–log) survival curves of the survival distribution function by log(days). Our interest was in overall survival and accordingly, survival time was measured from date of diagnosis to death from any cause. We censored patients if they were alive at the end of the study period or based on their last known date of contact.

For all regression modeling, we opted to keep unknown or missing values of certain variables as a separate category for those respective variables. These included unknown category for stage, no admit category for Elixhauser comorbidity score, and no admit/no zip category for patient distance. However, we ran additional analyses to ensure our analytic approach had limited effect on the main variables of interest in our models. These analyses included separately recategorizing the unknown or missing values into one of the two allowable values for stage, Elixhauser comorbidity score, and patient distance, rerunning the statistical analysis, and assessing concordance with the analyses where the missing or unknown values were excluded.

All statistical tests in our study were 2-tailed with statistical significance defined as $p<0.05$ (two-sided). SAS v9.4 was used for all statistical analyses.

RESULTS

Distribution of patient factors

Out of 3,494 HCC cases receiving HCC surgical treatment, 38.6% experienced surgical treatment delay (Table 1). Among all racial/ethnic groups, Asian/PIs had the lowest proportion for surgical treatment delay (29.7%) followed by Black/African Americans (39.0%) and non-Hispanic Whites (40.9%). Hispanics had the highest proportion for surgical treatment delay (45.3%).

Our data also demonstrated that Asian/PIs had the highest proportion of older patients and patients with fewer comorbid conditions. Patients across all race/ethnicities were predominantly male and had private insurance. Compared to other racial/ethnic groups, non-Hispanic Whites had the highest proportion of private insurance. Higher proportions of Asian/PIs and non-Hispanic Whites resided in upper neighborhood SES quintiles, while higher proportions of Black/African Americans and Hispanics resided lower neighborhood SES quintiles. Asian/PIs had the highest proportion when it came to seeking care at high volume hospitals and living close to the treating hospital. Our data revealed that hepatectomy was most common among Asian/PIs followed by Black/African Americans, while ablation and transplantation were most common for Hispanic and non-Hispanic Whites.

Supplementary analyses adding a category for unconfirmed and unknown values for the variables stage, Elixhauser comorbidity score, and patient distance showed concordant results for the main variables of interest to analyses that excluded unconfirmed/unknown values (Supplemental tables 1–6). This allowed us to keep separate unknown or missing categories for the variables stage, Elixhauser comorbidity score, and patient distance in all our final regression models.

Treatment delay experience

Asian/PIs (OR = 0.61, 95%CI = 0.51–0.73) demonstrated a lower odds for surgical treatment delay compared to non-Hispanic Whites (Table 2). Black/African Americans (OR =0.92, 95%CI = 0.70–1.22) showed similar odds for surgical treatment delay as non-Hispanic Whites, while Hispanics (OR = 1.20, 95%CI = 1.01–1.42) showed higher odds for surgical treatment delay. After adjusting for sociodemographic and clinical factors, Asian/PIs (OR = 0.77, 95%CI = 0.64–0.93) continued to have lower odds for surgical therapeutic delay while both Black/African Americans (OR = 1.10, 95%CI = 0.82–1.49) and Hispanics (OR = 1.14, 95%CI = 0.94–1.37) showed no difference in surgical treatment delay when compared to non-Hispanic Whites. Having increased patient distance from the hospital (OR = 1.28, 95%CI = 1.08–1.52) increased the odds of having a surgical treatment delay. In contrast, having the highest SES quintile (OR = 0.72, 95%CI = 0.55–0.93), visiting hospitals with high average annual surgical volume (OR = 0.65, 95%CI = 0.56–0.76), and having three or more comorbid conditions as measured by the

Elixhauser comorbidity score (OR = 0.78, 95%CI = 0.65–0.95) greatly decreased the odds of having surgical treatment delay. Regarding individual surgical treatments, having a hepatectomy (OR = 0.39, 95%CI = 0.33–0.47) decreased the odds of a surgical treatment delay when compared to ablation while having a transplantation (OR = 2.18, 95%CI = 1.72–2.77) greatly increased the odds of having a surgical treatment delay.

Overall survival

Kaplan-Meier analysis showed statistically significant differences for overall survival by race/ethnicity (p <0.0001, log-rank test). Asian/PIs (HR = 0.77, 95%CI = 0.67–0.89) showed a lower risk of death while both Black/African Americans (HR = 1.18, 95%CI = 0.95–1.46) and Hispanics (HR = 1.12, 95%CI = 0.97-1.29) demonstrated the same risk of death when compared to non-Hispanic Whites (Table 3).

After taking sociodemographic, clinical factors and surgical treatment delay into consideration, Asian/PIs (HR = 0.73, 95%CI = 0.63–0.85) continued to demonstrate superior survival than non-Hispanic Whites while Black/African Americans (HR = 1.01, 95%CI = 0.81–1.25) and Hispanics (HR = 1.00, 95%CI = 0.86–1.16) continued to show similar survival as non-Hispanic Whites.

When we considered interactions between race/ethnicity and surgical treatment delay and surgical treatment in our adjusted survival model, we only observed significant differences in the association of surgical treatments and survival by race/ethnicity. Among Asian/PIs, Hispanics, and Non-Hispanic Whites, we observed lower risk of death for both hepatectomy and transplant compared with ablation but did not observe significant associations between surgery type and survival among Black/African Americans (Figure 2). Surgical treatment delay

(HR = 0.67, 95%CI = 0.59–0.76) appeared to have a protective effect on death, with similar associations observed by race/ethnicity.

DISCUSSION

In this retrospective cohort study using a large population-based cancer registry, we investigated racial/ethnic disparities in therapeutic delay for HCC surgical treatment. Our study revealed that only 29.7% of Asian/PIs had a surgical treatment delay followed by Black/African Americans (39.4%), non-Hispanic Whites (40.9%), and Hispanics (45.3%). We also observed that Asian/PIs are less likely to have therapeutic delay, while Black/African Americans and Hispanics were as likely to have delays in surgical treatment in comparison to non-Hispanic Whites. Surgical treatment delays were more likely if patients lived far from the hospital and were less likely if patients resided in high SES neighborhoods, received care at hospitals performing high volume of surgeries, and had higher number of comorbid conditions. In addition, compared with ablation, having hepatectomy decreased the odds of surgical treatment delay, while transplantation increased the odds of having a surgical treatment delay.

When considering survival, a significant finding was the protective effect of surgical treatment delay. While this relationship might appear conflicting or contradictory, a few studies have demonstrated similar findings.[17,18] Further, the relationship between race/ethnicity and survival did not change even after adjustment for sociodemographic and clinical factors, including surgical treatment delay. The association observed between surgical treatment delay and survival may be explained by case prioritization where patients with more severe and aggressive conditions were selected for surgery without much delay. These patients would also have worse prognosis due to the severity of their health conditions. On the other hand, patients with relatively better health conditions could be made to wait longer and these patients would also have better survival outcomes. Consistent with our findings, Xu et al observed that patients with delayed treatment had better survival using a large nationwide, facility-based, comprehensive clinical oncology dataset.[17] In addition, they found a 26% decreased risk of death for Asians, which is close to our finding of 25% reduced risk of death. Alongside that, their study showed no survival difference for Black/African Americans and Hispanics compared with non-Hispanic Whites with estimates that closely resembled our findings even though surgical treatments excluded transplantation. In another study, Akce et al found a protective effect of treatment delay that included curative surgery, liver-directed therapy or chemotherapy using data from the Department of Veterans Affairs.[18]

The association between race/ethnicity and surgical treatment on survival differed by race/ethnicity. Both hepatectomy and transplantation was associated with a decrease in the risk of death for Asian/PI, Hispanic, and non-Hispanic White patients compared with ablation, but this association was not observed in Black/African Americans where survival was similar by surgery type. Prior studies have shown superior performance of both hepatectomy and transplantation when compared to ablation,[25-27] but prior studies have not considered whether surgical treatment outcomes differed by race/ethnicity.

Surgical treatment delays were more likely if patients lived far from the hospital and were less likely with patients residing in high SES neighborhoods, receiving care at hospitals performing high volume of surgeries, and having higher number of comorbid conditions. In addition, having hepatectomy decreased the odds of surgical treatment delay, while transplantation increased the odds of having a surgical treatment delay. The multitude steps and time involved from cancer diagnosis to treatment can make it a burden on patients living far from the hospital which can subsequently lead to delay in treatment.[15] Patient distance from treating facility can also lead to missed appointments which can further cause delay. Hospital type can play in role in reducing treatment delay.[15] High volume hospitals may have more experienced providers and staff who can work efficiently to ensure short time to treatment. Several studies have shown early treatment without delay to be associated with clinical factors such as late tumor stage, elevated alpha-fetoprotein, large tumor size, or tumor aggressiveness.[15,17] This is understandable since treatment delay in such cases can lead to fatal outcome. Also, cancer treatment is a lengthy process and can lead to financial strain and treatment nonadherence.[14] This can occur even with health insurance coverage which itself can direct the quality of treatment. The association observed in our study between high neighborhood SES and lower likelihood of treatment delay could be a consequence of financial advantage which can lead to better access and resources for immediate treatment. Treatment delay due to patients undergoing transplantation can be caused by several reasons including necessary locoregional therapy and limited organ availability.[14]

While this study leveraged a large population-based database that included detailed information on racial/ethnic, sociodemographic, and clinical factors, and hence, providing generalizability, there are several limitations that may impact the observed results. Our study lacked treatment facility information which can be a confounding factor with treatment delay on survival. In addition, disease etiology and clinical indicators, such as liver functional status, Model for End Stage Liver Disease (MELD) score, which are readily available in hospital-based studies, could not be included. Also, the socioeconomic status information provided by the CCR is not at the individual level but derived from an aggregate census-based value at the neighborhood level and might not represent the true relationship. This can possibly lead to misclassification error affecting the associations being studied. The CCR database also lacks information on lifestyle factors, such as alcohol consumption, obesity, and diabetes which may be important modulators of the relationship between race/ethnicity and treatment delay. There are instances where surgical treatment cannot commence until lifestyle changes are made thus leading to further treatment delay.

In summary, our study showed that Asian/PIs were less likely to have surgical treatment delay, but no differences were observed for other racial/ethnic groups. Residing far from the treating hospital increased the odds of surgical treatment delay, while residing in a high SES neighborhood, getting treatment at high volume hospitals, and higher number of comorbid conditions decreased the odds. Efforts should be made to reach out to patients living far from the hospital to ensure they receive appropriate care. More resources should be made available to patients under financial strain. The transition from cancer diagnosis to treatment can be a complex process and it needs to be simplified to ensure equity both in access to treatment and time to treatment. We also found surgical treatment delay to be associated with a protective effect on death. However, this should not be interpreted as a reason to delay treatment. Rather, this decision should rest on clinicians who understand the disease burden, general health, and fitness for surgery of the patient. Future studies on racial/ethnic disparities should incorporate facility type and additional clinical information, which might provide further insight between race/ethnicity, surgical treatment delay, and survival outcomes.

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Figure 1. Study population selection process

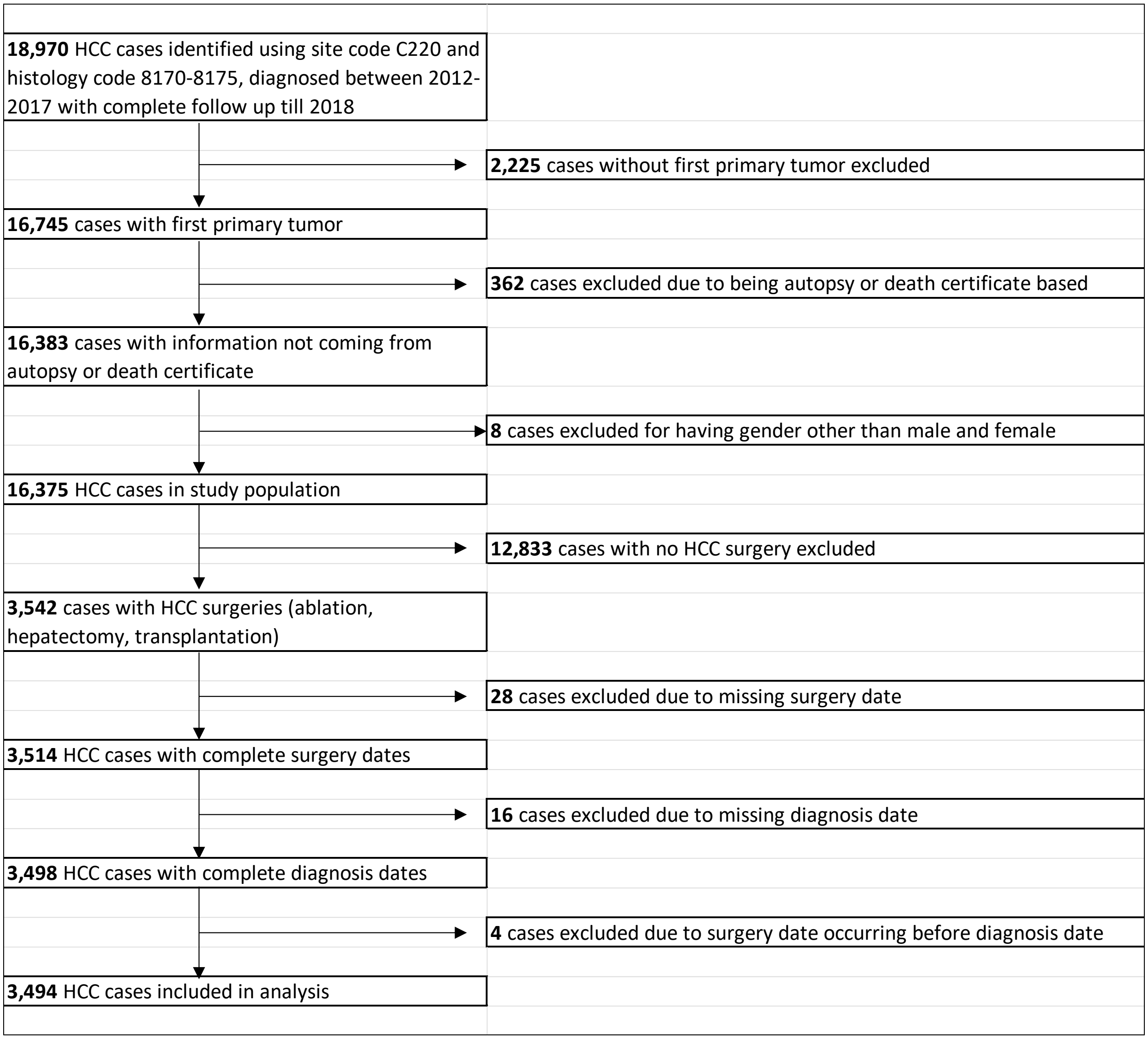

Figure 2. Forest plot of surgical treatment comparison by race/ethnicity

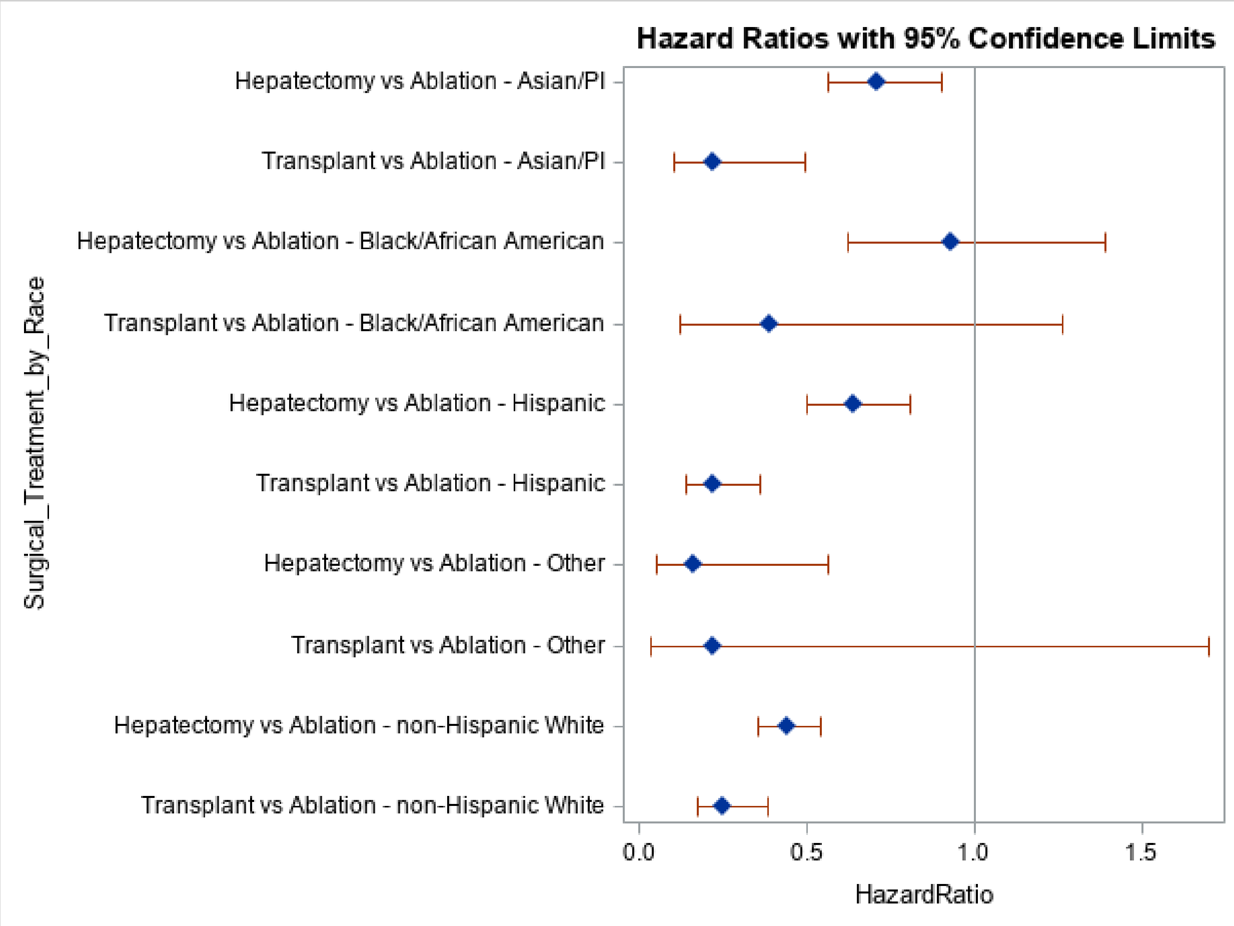

Table 1. Sociodemographic and clinical characteristics by surgical treatment delay for hepatocellular carcinoma patients in California from 2012-2017

	Asian / Pacific Islander		African American		Hispanic		Other		Non-Hispanic White		Total		P-value
	(n = 1048)		(n = 251)		(n = 905)		(n = 59)		(n = 1231)		(n = 3494)		
	n	%	n	%	n	%	n	%	n	%	n	%	
Age at diagnosis													
0-<65	520	49.62	163	64.94	562	62.1	37	62.71	703	57.11	1985	56.81	<.0001
65+	528	50.38	88	35.06	343	37.9	22	37.29	528	42.89	1509	43.19	
Sex													
Female	282	26.91	68	27.09	278	30.72	20	33.9	324	26.32	972	27.82	0.1497
Male	766	73.09	183	72.91	627	69.28	39	66.1	907	73.68	2522	72.18	
Neighborhood socioeconomic status													
1 - Low SES	134	12.79	75	29.88	274	30.28	13	22.03	148	12.02	644	18.43	<.0001
2	223	21.28	59	23.51	226	24.97	22	37.29	226	18.36	756	21.64	
3	233	22.23	59	23.51	189	20.88	7	11.86	268	21.77	756	21.64	
4	241	23.00	39	15.54	142	15.69	12	20.34	310	25.18	744	21.29	
5 - High SES	217	20.71	19	7.57	74	8.18	5	8.47	279	22.66	594	17.00	
Insurance type													
Private	547	52.19	110	43.82	447	49.39	36	61.02	765	62.14	1905	54.52	<.0001
Medicaid/Public/Uninsured	298	28.44	93	37.05	288	31.82	14	23.73	214	17.38	907	25.96	
Medicare	198	18.89	45	17.93	161	17.79	9	15.25	233	18.93	646	18.49	
Other	5	0.48	3	1.20	9	0.99	0	0	19	1.54	36	1.03	
Tumor stage													
Stage I-II	898	86.60	215	86.35	781	87.36	48	87.27	1069	87.69	3011	87.17	0.9402
Stage III-IV	139	13.40	34	13.65	113	12.64	7	12.73	150	12.31	443	12.83	
Unknown	11		2		11		4		12		40		
Avg. annual surgery volume													
0-5	359	34.26	107	42.63	365	40.33	18	30.51	446	36.23	1295	37.06	0.0142
>5	689	65.74	144	57.37	540	59.67	41	69.49	785	63.77	2199	62.94	
Patient distance													
0-5	352	40.18	72	33.64	256	32.2	17	33.33	323	29.99	1020	33.85	<.0001
>5	524	59.82	142	66.36	539	67.8	34	66.67	754	70.01	1993	66.15	
No Admit/No Zip	172		37		110		8		154		481		
Elixhauser comorbidity score													
0-2	315	41.83	44	22.8	145	21.29	10	22.22	268	29.68	782	30.37	<.0001
3+	438	58.17	149	77.2	536	78.71	35	77.78	635	70.32	1793	69.63	
No Admit	295		58		224		14		328		919		
Surgical treatment													
Ablation	377	35.97	110	43.82	484	53.48	33	55.93	644	52.32	1648	47.17	<.0001
Hepatectomy	595	56.77	125	49.80	281	31.05	19	32.20	414	33.63	1434	41.04	
Transplantation	76	7.25	16	6.37	140	15.47	7	11.86	173	14.05	412	11.79	
Surgical treatment delay													
1 (>90 days)	311	29.68	98	39.04	410	45.30	25	42.37	504	40.94	1348	38.58	<.0001
0 (<90 days)	737	70.32	153	60.96	495	54.70	34	57.63	727	59.06	2146	61.42	

Table 2. Factors associated with surgical treatment delay for hepatocellular carcinoma in California from 2012-2017

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Race/Ethnicity				
Asian/Pacific Islander	0.61	0.51-0.73	0.77	0.64-0.93
Black/African American	0.92	0.70-1.22	1.10	0.82-1.49
Hispanic	1.20	1.01-1.42	1.14	0.94-1.37
Other	1.06	0.63-1.80	1.20	0.68-2.09
Non-Hispanic White	1.00		1.00	
Age at diagnosis				
0-<65			1.00	
65+			0.89	0.76-1.04
Sex				
Female			1.00	
Male			1.17	0.99-1.38
Neighborhood socioeconomic status				
1 - Low SES			1.00	
2			0.84	0.67-1.06
3			1.06	0.84-1.33
4			1.03	0.82-1.31
5 - High SES			0.72	0.55-0.93
Insurance type				
Private			1.00	
Medicaid/Public/Uninsured			1.12	0.94-1.34
Medicare			1.12	0.91-1.37
Other			0.36	0.16-0.83
Tumor stage				
Stage I-II			1.00	
Stage III-IV			1.09	0.87-1.37
Unknown			0.39	0.18-0.82
Avg. annual hospital surgery volume				
0-5			1.00	
>5			0.65	0.56-0.76
Patient distance				
0-5			1.00	
>5			1.28	1.08-1.52
No Admit/No Zip			0.56	0.42-0.76
Elixhauser comorbidity score				
0-2			1.00	
3+			0.78	0.65-0.95
No Admit			1.86	1.43-2.42
Surgical treatment				
Ablation			1.00	
Hepatectomy			0.39	0.33-0.47
Transplantation			2.18	1.72-2.77

Note: Model adjusted for all the variables present in the table

Table 3. Factors associated with survival from hepatocellular carcinoma in California from 2012-2017

	Unadjusted		Adjusted for sociodemographic, clinical factors, and treatment effects		Includes interaction between Race/ethnicity and Surgical Treatment	
	HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI
Race/Ethnicity *						
Asian/Pacific Islander	0.77	0.67-0.89	0.73	0.63-0.85		
African American	1.18	0.95-1.46	1.01	0.81-1.25		
Hispanic	1.12	0.97-1.29	1.00	0.86-1.16		
Other	0.83	0.51-1.35	0.62	0.38-1.01		
Non-Hispanic White	1.00		1.00			
Age at diagnosis						
0-<65			1.00		1.00	
65+			1.16	1.02-1.31	1.17	1.04-1.32
Sex						
Female						
Male						
Neighborhood socioeconomic status						
1 - Low SES			1.00		1.00	
2			0.90	0.76-1.07	0.92	0.77-1.09
3			0.88	0.74-1.05	0.89	0.75-1.07
4			0.82	0.68-0.98	0.82	0.69-0.99
5 - High SES			0.65	0.53-0.81	0.67	0.54-0.82
Insurance type						
Private			1.00		1.00	
Medicaid/Public/Uninsured			1.23	1.07-1.41	1.25	1.09-1.44
Medicare			1.13	0.97-1.32	1.12	0.96-1.32
Other			1.55	0.98-2.45	1.50	0.95-2.37
Tumor stage						
Stage I-II			1.00		1.00	
Stage III-IV			2.98	2.59-3.43	3.05	2.65-3.52
Unknown			2.22	1.46-3.38	2.14	1.40-3.26
Avg. annual hospital surgery volume						
0-5						
>5						
Patient distance						
0-5			1.00		1.00	
>5			0.79	0.70-0.89	0.78	0.69-0.89
No Admit/No Zip			0.60	0.45-0.81	0.60	0.45-0.80
Elixhauser comorbidity score						
0-2			1.00		1.00	
3+			1.54	1.32-1.79	1.52	1.31-1.77
No Admit			0.90	0.72-1.12	0.89	0.71-1.11
Surgical treatment *						
Ablation			1.00			
Hepatectomy			0.59	0.52-0.67		
Transplantation			0.24	0.19-0.32		
Surgery Delay						
0			1.00		1.00	
1			0.68	0.60-0.77	0.67	0.59-0.76

* Adjusted hazard ratios not provided due to presence of interaction in model
Note: Model adjusted for all the variables present in the table

Supplemental Table 1. Analysis of unknown stage category related to surgical treatment delay for hepatocellular carcinoma

	Stage with Unknowns			Unknowns added to Early Stage			Unknowns added to Late Stage		
Odds Ratio Estimates									
Effect	**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**	
RACE Asian vs White	0.76	0.63	0.92	0.76	0.63	0.92	0.76	0.63	0.92
RACE Black vs White	1.11	0.83	1.50	1.12	0.83	1.50	1.11	0.83	1.50
RACE Hispanic vs White	1.14	0.94	1.38	1.14	0.94	1.38	1.14	0.94	1.38
RACE Other vs White	1.20	0.69	2.10	1.14	0.65	1.98	1.14	0.65	1.98
Surgical Treatment hepatectomy vs ablation	0.39	0.33	0.47	0.40	0.33	0.47	0.40	0.34	0.48
Surgical Treatment transplant vs ablation	2.24	1.77	2.84	2.27	1.79	2.87	2.27	1.79	2.87
Elixhauser Comorbidity Score 3+ vs 0-2	0.78	0.64	0.94	0.78	0.64	0.94	0.78	0.64	0.95
Elixhauser Comorbidity Score no admit vs 0-2	1.84	1.41	2.39	1.83	1.41	2.38	1.83	1.41	2.38
Neighborhood Socioeconomic Status 2 vs 1	0.84	0.66	1.05	0.83	0.66	1.05	0.83	0.66	1.05
Neighborhood Socioeconomic Status 3 vs 1	1.05	0.84	1.33	1.05	0.83	1.32	1.05	0.83	1.32
Neighborhood Socioeconomic Status 4 vs 1	1.03	0.81	1.30	1.03	0.81	1.30	1.02	0.81	1.30
Neighborhood Socioeconomic Status 5 vs 1	0.71	0.54	0.91	0.71	0.54	0.91	0.71	0.54	0.92
PATIENT_DISTANCE >5 vs 0 - 5	1.29	1.09	1.53	1.30	1.09	1.53	1.29	1.09	1.53
PATIENT_DISTANCE no admit/no zip vs 0 - 5	0.57	0.42	0.77	0.57	0.42	0.77	0.57	0.42	0.77
Avg. Annual Surgery Volume >5 vs 0 - 5	0.66	0.57	0.77	0.67	0.57	0.78	0.66	0.57	0.77
Tumor Stage III-IV vs Stage I-II	1.09	0.87	1.37	1.11	0.88	1.39	1.00	0.80	1.24
Tumor Stage Unknown vs Stage I-II	0.39	0.18	0.82						
SEX 1 vs 2	1.19	1.01	1.40	1.18	1.00	1.39	1.18	1.00	1.39
INSURANCE Medicaid/Public/Uninsured vs Private	1.13	0.94	1.35	1.12	0.94	1.34	1.12	0.94	1.34
INSURANCE Medicare vs Private	1.07	0.88	1.31	1.07	0.88	1.30	1.07	0.88	1.30
INSURANCE Other vs Private	0.36	0.16	0.84	0.36	0.16	0.84	0.37	0.16	0.85

Supplemental Table 2. Analysis of unknown stage category related to survival from hepatocellular carcinoma

		Stage with Unknowns			Unknowns added to Early Stage			Unknowns added to Late Stage		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits	
RACE (non-Hispanic White)	Asian	0.73	0.63	0.85	0.73	0.63	0.85	0.73	0.63	0.85
RACE (non-Hispanic White)	Black	1.01	0.81	1.25	1.01	0.81	1.25	1.01	0.81	1.25
RACE (non-Hispanic White)	Hispanic	1.00	0.86	1.16	1.00	0.87	1.16	1.00	0.86	1.15
RACE (non-Hispanic White)	Other	0.62	0.38	1.01	0.65	0.40	1.06	0.61	0.37	0.98
Tumor Stage (Stage I-II)	Stage III-IV	2.98	2.59	3.43	2.95	2.56	3.39	2.90	2.53	3.32
Tumor Stage (Stage I-II)	Unknown	2.22	1.46	3.38						
Surgical Treatment (ablation)	Hepatectomy	0.59	0.52	0.67	0.58	0.51	0.66	0.60	0.52	0.68
Surgical Treatment (ablation)	Transplant	0.24	0.19	0.32	0.24	0.18	0.32	0.25	0.19	0.32
Elixhauser comorbidity score (0-2)	3+	1.54	1.32	1.79	1.54	1.32	1.79	1.54	1.33	1.80
Elixhauser comorbidity score (0-2)	no admit	0.90	0.72	1.12	0.90	0.72	1.13	0.90	0.72	1.12
PATIENT_DISTANCE (0 - 5)	>5	0.79	0.70	0.89	0.79	0.70	0.89	0.79	0.70	0.89
PATIENT_DISTANCE (0 - 5)	no admit/no zip	0.60	0.45	0.81	0.62	0.46	0.83	0.60	0.45	0.80
INSURANCE (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.23	1.07	1.42	1.23	1.07	1.41
INSURANCE (Private)	Medicare	1.13	0.97	1.32	1.13	0.97	1.33	1.13	0.96	1.32
INSURANCE (Private)	Other	1.55	0.98	2.45	1.53	0.97	2.42	1.56	0.98	2.46
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.91	0.77	1.08	0.90	0.76	1.07
Neighborhood socioeconomic status (1)	3	0.88	0.74	1.05	0.88	0.74	1.06	0.88	0.73	1.05
Neighborhood socioeconomic status (1)	4	0.82	0.68	0.98	0.82	0.68	0.99	0.81	0.68	0.98
Neighborhood socioeconomic status (1)	5	0.65	0.53	0.81	0.66	0.54	0.81	0.65	0.53	0.80
AGE (<65)	65+	1.16	1.02	1.31	1.16	1.02	1.31	1.16	1.03	1.31
Surgery Treatment Delay (0)	1	0.68	0.60	0.77	0.67	0.59	0.76	0.69	0.60	0.78

Supplemental Table 3. Analysis of no admit Elixhauser comorbidity score category related to receipt of surgical treatment for hepatocellular carcinoma

	Elixhauser comorbidity score with no admits			no admits added to Elixhauser comorbidity scor 0-2			no admits added to Elixhauser comorbidity scor 3+		
Odds Ratio Estimates									
Effect	**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**	
RACE Asian vs White	0.76	0.63	0.92	0.76	0.63	0.92	0.79	0.66	0.96
RACE Black vs White	1.11	0.83	1.50	1.12	0.83	1.51	1.08	0.81	1.46
RACE Hispanic vs White	1.14	0.94	1.38	1.14	0.95	1.38	1.12	0.93	1.35
RACE Other vs White	1.20	0.69	2.10	1.20	0.69	2.09	1.16	0.66	2.02
Surgical Treatment hepatectomy vs ablation	0.39	0.33	0.47	0.35	0.30	0.41	0.34	0.29	0.41
Surgical Treatment transplant vs ablation	2.24	1.77	2.84	2.24	1.77	2.83	2.07	1.64	2.61
Elixhauser Comorbidity Score 3+ vs 0-2	0.78	0.64	0.94	0.61	0.52	0.72	0.92	0.76	1.11
Elixhauser Comorbidity Score no admit vs 0-2	1.84	1.41	2.39						
Neighborhood Socioeconomic Status 2 vs 1	0.84	0.66	1.05	0.83	0.66	1.04	0.83	0.66	1.05
Neighborhood Socioeconomic Status 3 vs 1	1.05	0.84	1.33	1.05	0.83	1.32	1.05	0.83	1.32
Neighborhood Socioeconomic Status 4 vs 1	1.03	0.81	1.30	1.03	0.81	1.30	1.03	0.82	1.30
Neighborhood Socioeconomic Status 5 vs 1	0.71	0.54	0.91	0.70	0.54	0.90	0.72	0.56	0.93
PATIENT_DISTANCE >5 vs 0 - 5	1.29	1.09	1.53	1.30	1.10	1.54	1.32	1.12	1.57
PATIENT_DISTANCE no admit/no zip vs 0 - 5	0.57	0.42	0.77	0.82	0.64	1.06	1.12	0.88	1.43
Avg. Annual Surgery Volume >5 vs 0 - 5	0.66	0.57	0.77	0.66	0.56	0.77	0.66	0.56	0.76
Tumor Stage III-IV vs Stage I-II	1.09	0.87	1.37	1.10	0.88	1.38	1.07	0.85	1.34
Tumor Stage Unknown vs Stage I-II	0.39	0.18	0.82	0.39	0.19	0.83	0.40	0.19	0.84
SEX 1 vs 2	1.19	1.01	1.40	1.18	1.00	1.39	1.18	1.00	1.39
INSURANCE Medicaid/Public/Uninsured vs Private	1.13	0.94	1.35	1.12	0.93	1.34	1.09	0.91	1.30
INSURANCE Medicare vs Private	1.07	0.88	1.31	1.09	0.89	1.32	1.06	0.87	1.29
INSURANCE Other vs Private	0.36	0.16	0.84	0.35	0.15	0.81	0.35	0.15	0.80

Supplemental Table 4. Analysis of no admit Elixhauser comorbidity score category related to survival from hepatocellular carcinoma

		Elixhauser comorbidity score			no admits added to Elixhauser			no admits added to Elixhauser		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits	
RACE (non-Hispanic White)	Asian	0.73	0.63	0.85	0.73	0.63	0.85	0.72	0.62	0.84
RACE (non-Hispanic White)	Black	1.01	0.81	1.25	1.01	0.81	1.26	1.03	0.83	1.29
RACE (non-Hispanic White)	Hispanic	1.00	0.86	1.16	1.00	0.86	1.16	1.02	0.88	1.19
RACE (non-Hispanic White)	Other	0.62	0.38	1.01	0.62	0.38	1.01	0.65	0.40	1.06
Tumor Stage (Stage I-II)	Stage III-IV	2.98	2.59	3.43	2.98	2.59	3.43	3.02	2.62	3.48
Tumor Stage (Stage I-II)	Unknown	2.22	1.46	3.38	2.22	1.46	3.37	2.16	1.42	3.28
Surgical Treatment (ablation)	Hepatectomy	0.59	0.52	0.67	0.60	0.53	0.68	0.64	0.57	0.73
Surgical Treatment (ablation)	Transplant	0.24	0.19	0.32	0.25	0.19	0.32	0.26	0.20	0.35
Elixhauser comorbidity score (0-2)	3+	1.54	1.32	1.79	1.60	1.41	1.82	1.41	1.21	1.63
Elixhauser comorbidity score (0-2)	no admit	0.90	0.72	1.12						
PATIENT_DISTANCE (0 - 5)	>5	0.79	0.70	0.89	0.79	0.70	0.89	0.77	0.68	0.87
PATIENT_DISTANCE (0 - 5)	no admit/no zip	0.60	0.45	0.81	0.57	0.44	0.73	0.39	0.31	0.50
INSURANCE (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.23	1.07	1.41	1.23	1.07	1.41
INSURANCE (Private)	Medicare	1.13	0.97	1.32	1.13	0.97	1.32	1.13	0.97	1.33
INSURANCE (Private)	Other	1.55	0.98	2.45	1.56	0.98	2.47	1.61	1.02	2.55
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.90	0.76	1.07	0.91	0.77	1.08
Neighborhood socioeconomic status (1)	3	0.88	0.74	1.05	0.88	0.74	1.05	0.86	0.72	1.03
Neighborhood socioeconomic status (1)	4	0.82	0.68	0.98	0.82	0.68	0.98	0.81	0.68	0.98
Neighborhood socioeconomic status (1)	5	0.65	0.53	0.81	0.66	0.53	0.81	0.65	0.53	0.80
AGE (<65)	65+	1.16	1.02	1.31	1.15	1.02	1.30	1.14	1.01	1.29
Surgery Treatment Delay (0)	1	0.68	0.60	0.77	0.68	0.60	0.77	0.66	0.58	0.75

Supplemental Table 5. Analysis of no admits/no zip patience distance category related to receipt of surgical treatment for hepatocellular carcinoma

	Patient Distance with no admits/no zip			No admits/no zip added to 0 - 5			No admits/no zip added to >5		
Odds Ratio Estimates									
Effect	**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**		**Point Estimate**	**95% Wald Confidence**	
RACE Asian vs White	0.76	0.63	0.92	0.77	0.63	0.93	0.75	0.62	0.91
RACE Black vs White	1.11	0.83	1.50	1.10	0.82	1.49	1.09	0.81	1.47
RACE Hispanic vs White	1.14	0.94	1.38	1.14	0.94	1.38	1.13	0.94	1.37
RACE Other vs White	1.20	0.69	2.10	1.19	0.68	2.09	1.18	0.68	2.07
Surgical Treatment hepatectomy vs ablation	0.39	0.33	0.47	0.38	0.32	0.45	0.38	0.32	0.45
Surgical Treatment transplant vs ablation	2.24	1.77	2.84	2.24	1.77	2.83	2.36	1.86	2.98
Elixhauser Comorbidity Score 3+ vs 0-2	0.78	0.64	0.94	0.77	0.64	0.94	0.76	0.63	0.93
Elixhauser Comorbidity Score no admit vs 0-2	1.84	1.41	2.39	1.41	1.13	1.77	1.21	0.97	1.50
Neighborhood Socioeconomic Status 2 vs 1	0.84	0.66	1.05	0.83	0.66	1.05	0.84	0.66	1.05
Neighborhood Socioeconomic Status 3 vs 1	1.05	0.84	1.33	1.04	0.83	1.32	1.05	0.83	1.32
Neighborhood Socioeconomic Status 4 vs 1	1.03	0.81	1.30	1.02	0.80	1.29	1.02	0.81	1.29
Neighborhood Socioeconomic Status 5 vs 1	0.71	0.54	0.91	0.70	0.54	0.91	0.71	0.55	0.92
PATIENT_DISTANCE >5 vs 0 - 5	1.29	1.09	1.53	1.46	1.25	1.71	1.17	0.99	1.38
PATIENT_DISTANCE no admit/no zip vs 0 - 5	0.57	0.42	0.77						
Avg. Annual Surgery Volume >5 vs 0 - 5	0.66	0.57	0.77	0.66	0.57	0.77	0.66	0.56	0.77
Tumor Stage III-IV vs Stage I-II	1.09	0.87	1.37	1.10	0.87	1.38	1.08	0.86	1.36
Tumor Stage Unknown vs Stage I-II	0.39	0.18	0.82	0.38	0.18	0.81	0.37	0.18	0.78
SEX 1 vs 2	1.19	1.01	1.40	1.18	1.00	1.39	1.18	1.00	1.39
INSURANCE Medicaid/Public/Uninsured vs Private	1.13	0.94	1.35	1.12	0.94	1.34	1.10	0.92	1.32
INSURANCE Medicare vs Private	1.07	0.88	1.31	1.09	0.89	1.32	1.09	0.90	1.33
INSURANCE Other vs Private	0.36	0.16	0.84	0.36	0.16	0.84	0.36	0.16	0.83

Supplemental Table 6. Analysis of no admits/no zip patience distance category related to survival from hepatocellular carcinoma

		Patient Distance with no admits/no zip			No admits/no zip added to 0 - 5			No admits/no zip added to >5		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits	
RACE (non-Hispanic White)	Asian	0.73	0.63	0.85	0.73	0.63	0.85	0.73	0.63	0.85
RACE (non-Hispanic White)	Black	1.01	0.81	1.25	1.00	0.80	1.24	1.00	0.80	1.25
RACE (non-Hispanic White)	Hispanic	1.00	0.86	1.16	1.00	0.86	1.16	1.00	0.86	1.16
RACE (non-Hispanic White)	Other	0.62	0.38	1.01	0.61	0.38	1.00	0.61	0.38	1.00
Tumor Stage (Stage I-II)	Stage III-IV	2.98	2.59	3.43	2.98	2.59	3.44	2.98	2.59	3.43
Tumor Stage (Stage I-II)	Unknown	2.22	1.46	3.38	2.13	1.40	3.24	2.17	1.42	3.29
Surgical Treatment (ablation)	Hepatectomy	0.59	0.52	0.67	0.57	0.50	0.65	0.58	0.51	0.67
Surgical Treatment (ablation)	Transplant	0.24	0.19	0.32	0.24	0.18	0.32	0.25	0.19	0.33
Elixhauser comorbidity score (0-2)	3+	1.54	1.32	1.79	1.54	1.32	1.79	1.54	1.32	1.79
Elixhauser comorbidity score (0-2)	no admit	0.90	0.72	1.12	0.73	0.60	0.89	0.81	0.67	0.98
PATIENT_DISTANCE (0 - 5)	>5	0.79	0.70	0.89	0.84	0.75	0.94	0.78	0.69	0.87
PATIENT_DISTANCE (0 - 5)	no admit/no zip	0.60	0.45	0.81						
INSURANCE (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.23	1.07	1.42	1.23	1.07	1.41
INSURANCE (Private)	Medicare	1.13	0.97	1.32	1.14	0.97	1.33	1.14	0.97	1.33
INSURANCE (Private)	Other	1.55	0.98	2.45	1.55	0.98	2.45	1.54	0.98	2.44
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.89	0.75	1.06	0.90	0.76	1.07
Neighborhood socioeconomic status (1)	3	0.88	0.74	1.05	0.87	0.73	1.05	0.88	0.74	1.05
Neighborhood socioeconomic status (1)	4	0.82	0.68	0.98	0.81	0.67	0.97	0.82	0.68	0.98
Neighborhood socioeconomic status (1)	5	0.65	0.53	0.81	0.65	0.53	0.80	0.66	0.53	0.81
AGE (<65)	65+	1.16	1.02	1.31	1.17	1.04	1.32	1.16	1.03	1.31
Surgery Treatment Delay (0)	1	0.68	0.60	0.77	0.68	0.60	0.77	0.68	0.60	0.78

Chapter 3. Racial/ethnic disparities in postoperative complications after HCC surgery and effect on survival

ABSTRACT

Background and Aim: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality in the world. Although morbidity and mortality rates have improved, it remains high. While surgical treatment has proven effective, postsurgical complications can influence both cancer recurrence and survival. Previously, studies have shown racial/ethnic disparities in accessing surgical treatment. Studies on racial/ethnic disparities related to postsurgical complications are rare. This study examines racial/ethnic disparities in postsurgical complications after surgery for HCC and how complications impact survival.

Methods: 3,494 hepatocellular carcinoma cases were identified from the California Cancer Registry and postsurgical complications including neurological, cardiac, pulmonary, gastrointestinal (GI), renal, and infectious complications were obtained from hospital inpatient and emergency department data for the period 2012 to 2017. Multivariable logistic regression analyses determined the likelihood of any as well as select classes of complications, and Cox proportional hazards regression assessed the impact of complications on survival.

Results: Our study demonstrated overall complications to be present in similar proportions across patients of all race/ethnicities (Asian/PI, 25.9%; Black/African American, 26.3%; non-Hispanic White, 28.4%; Hispanic, 28.9%). No differences in overall complications were observed by race/ethnicity in multivariable models. However, when we considered specific classes of complications, Black/African Americans (Odds Ratio (OR) = 0.64, 95% confidence interval (CI) = 0.42–0.98) had lower odds for GI complications while Asian/PIs (OR = 0.69, 95%CI = 0.52–0.91) and Hispanics (OR = 0.75, 95%CI = 0.56–1.00) had lower odds for cardiac complications compared with non-Hispanic Whites. Patients residing in the highest SES neighborhoods (OR = 0.70, 95%CI = 0.53–0.92) had decreased odds of complications, while patients receiving care at high volume hospitals (OR = 1.21, 95%CI = 1.02–1.43), with greater number of comorbid conditions (OR = 1.90, 95%CI = 1.56–2.31), or who had surgical treatment of hepatectomy (OR = 2.23, 95%CI = 1.85–2.69) or transplantation (OR = 2.54, 95%CI = 1.98–3.27) experienced an increased odds of having complications. Having postsurgical complications was independently associated with an increased the risk of death.

Conclusions: Occurrence of postsurgical complications was an adverse independent predictor for survival and varied by race/ethnicity for GI and cardiac complications. Our finding of higher complication rates in high surgical volume hospitals warrants further investigation to determine if this finding is related to more high-risk surgeries occurring in these centers or patients with more comorbid conditions attending these centers. Complications were also associated with patients who live in lower SES neighborhoods suggesting that efforts should be made to provide more support and better access to resources for patients under financial strain.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer worldwide and the second leading cause of cancer mortality.[1-3] HCC has a high prevalence in Asia and its incidence is increasing in the West.[4] Despite the high number of affected people, the prognosis of HCC has improved over the last two decades especially in developed countries where cases are diagnosed at early stages and effective treatments are administered.[5,6] Although surgical techniques along with postoperative management have greatly improved mortality rates, complications, such as ascites, liver function impairment, biliary fistula, hepatic abscess, pleural effusion, still remain high.[7] This has been observed in several studies on resection of the liver.[8,9] A few studies have reported postoperative complication rates as high as 30%–40% following resection of the liver.[10,11]

Postoperative complications following HCC surgery can be associated with cancer recurrence and survival. Using 274 hospital patients, Zhou et at. found a positive association between postoperative complications and risk of HCC recurrence following resection of the liver.[12] In a larger study of 2,442 patients from multiple hospitals, Yang et al. observed that patients with postoperative complications after resection of the liver had decreased overall survival and recurrence-free survival.[13] Many other studies have looked at overall survival as their primary endpoint and have found postoperative complications to negatively impact long-term survival.[14-17] However, most of these studies are limited to postoperative complications that arose after having either ablation or resection of the liver and focused on a single type of complication or a combination of different complications. Also, many of the studies are hospital based with smaller population size and limited external validity. In general, the overall goals for existing studies were to identify risk factors for postoperative complications and how it impacted long-term survival.

In the U.S., race/ethnicity is strongly associated with HCC incidence and prevalence. Studies have shown that Asian/Pacific Islanders and Hispanics have higher incidence rates of HCC possibly due to different etiologies. Increased rates of hepatitis B virus are seen more commonly in Asian/Pacific Islanders while metabolic disorders including diabetes, obesity, etc. are more common among Hispanics.[18-20] Additionally, Black/African Americans have consistently demonstrated poor survival from HCC compared to non-Hispanic Whites.[21-23]

There are few studies assessing racial/ethnic disparities and postoperative complications after HCC surgery. Many of the studies on postoperative complications from HCC surgery are based in Asia where racial/ethnic diversity is limited relative to the U.S. Additionally, the focus of most of these studies were to identify risk factors for postoperative complications and its effect on survival. It is possible that different racial/ethnic groups can experience variations in postoperative complications, information important to better preparing and addressing the needs of patients undergoing HCC surgery.

Our goal in this study was to examine racial/ethnic disparities in postoperative complications from HCC surgery and associated long-term survival using cancer registry data from California alongside hospital inpatient and emergency department data. To our knowledge, this is one of the first studies to use large population-based data to study racial/ethnic disparities in the occurrence of postoperative complications, including neurological, cardiac, pulmonary, gastrointestinal, renal, and infectious, from all type of HCC surgery (ablation, resection, and transplantation.

METHODS

We conducted a retrospective cohort study using data from the California Cancer Registry (CCR) linked with the California Department of Healthcare Access and Information (HCAI). The linkage between CCR and HCAI is achieved by using a probabilistic method that employs patient identifying information, such as patient date of birth, social security number, gender, and other relevant information. The CCR collects data on all cases of cancer other than basal and squamous cell carcinoma of the skin and carcinoma in situ of the cervix. The registry is well known for its high data quality with very little loss to follow-up and completeness. Less than 3% of data in the CCR are obtained from death records[24] and its completeness is more than 95%.[21] The dataset contains a multitude of sociodemographic and clinical information and maintains the highest level of data quality standards defined by the North American Association of Central Cancer Registries and the National Program for Cancer Registries. The HCAI database consists of all inpatient hospital discharge data along with emergency visit data from general, acute, and nonfederal hospitals in the state of California. Besides patient demographic information, important clinical information is also present including primary diagnosis and procedure codes along with 24 additional diagnoses codes and up to 19 additional procedure codes based on the *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM)*.[24]

Primary cases of HCC were identified based on the *International Classification of Diseases for Oncology, Third Edition* site code C22.0 and histology codes 8170–8175. There were 18,970 patients identified based on these criteria for the period 2012 to 2017 with a follow-up time until 2018. All patients had to have primary HCC due to differences in survival experiences of other cancer types. Our primary goal was to study postoperative complications related to HCC surgery. Therefore, the population of HCC cases was restricted to only those who had either ablation, hepatectomy, or transplantation, which was identified from the CCR data based on the most extensive type of surgery performed during the first course of treatment. Based on these surgical and other restrictions, our final study population included 3,494 cases (Figure 1).

Study variables

The complications of interest broadly fell into six different classes consisting of neurological, cardiac, pulmonary, gastrointestinal, renal, and infectious categories (Supplemental Tables 1a–1f). Neurological complications included cerebral infarction, while cardiac complications consisted of myocardial infarction, congestive heart failure, arrhythmia, and venous thrombosis. The pulmonary category included only pneumonia, the renal category included urinary tract infection and renal failure, and the infectious category included sepsis. The gastrointestinal category (GI) consisted of bile leakage, ascites, liver failure, gastrointestinal bleeding, and ileus. As the CCR data do not provide information on complications that can arise from surgical treatments, the occurrence of these conditions was obtained from HCAI Patient Discharge Data (PDD) and Emergency Department (ED) data.

The PDD data includes all inpatient hospital visit data in California and the ED data includes patient emergency visit information. Both datasets provide primary diagnosis for every visit and an additional 24 secondary diagnoses using International Classification of Diseases (ICD) code. Because our study period overlapped the transition period from ICD-9 to ICD-10, we employed both set of codes for identifying postoperative complications. All 25 diagnosis codes for each patient record were scanned for any of the complications of interest and if identified, were flagged. Any complication for which the date of diagnosis fell within 60 days from the date of surgery was included in the study. Some studies have used a cumulative 30-day interval to account for postoperative complications.[13-15] However, in a study by Martinelli et al investigating thrombosis after liver transplantation for HCC, thrombosis occurrence period was divided into two segments with 30 days after surgery treated as early period and thereafter as late period.[25] Because thrombosis is one of the complications of interest in our study, we chose to use 60 days to ensure sufficient time was provided to capture all instances of complications. The presence of any complication and specific classes of complications were summarized for each patient.

Demographic and clinical information, including race/ethnicity, age, sex, neighborhood socioeconomic status (SES), insurance status, tumor stage, surgical treatment type, and a derived variable that calculated the average annual surgery volume for each hospital, were obtained from the CCR. Race/ethnicity and was categorized as Asian/PI, Black/African Americans, Hispanics, non-Hispanic Whites, and other. The other category included Native Americans and Alaskans, Native Hawaiians and any other race including mixed and unknown races. Non-Hispanic Whites were used as the reference category in our analyses. Age was dichotomized into 0 to less than 65 years of age and 65 years or older and the younger age was used as the reference category. Sex was limited to male and female only and any other coding (including missing) were excluded. The CCR provides neighborhood SES data from the U.S. Census and American Community Survey as quintiles. Missing values are imputed to ensure all cases have a SES score and we used the lowest quintile as the reference category in our analyses. Health insurance information was also included which was categorized into Private, Medicaid/Public/Uninsured, Medicare, and Other. Private category consisted of HMO, PPO, fee for service, managed care, TRICARE, military, Veterans Affairs, or any other insurance not stated. Medicaid/Public/Uninsured included all Medicaid cases along with those not insured or with self-pay, county funded or Indian/Public Health Services while Medicare consisted of all Medicare categories. The final category, other, comprised of unknown insurance or missing values.

Average annual surgery volume was derived based on the total number of HCC surgeries performed at each hospital over the study period. Each hospital that cases visited was assigned an average value and higher values represented higher number of surgeries performed and possibly better outcomes due to having more experienced surgeons and better resources.[26] The average annual surgery volume was dichotomized into 0–5 and >5, based on the median, representing the average number of surgeries performed at a hospital annually.

For clinical factors, tumor stage was dichotomized into early stage (including stages I and II) and late stage (including stages III and IV). A third unknown category was also added for unknown, unstaged, or missing stage values. The Elixhauser comorbidity score indicating comorbidity status and derived using the Elixhauser Indices, was obtained using the PDD data. There were

29 Elixhauser Indices that were calculated using patient diagnosis codes from the PDD database of which indices for lymph, tumor and metastases were excluded. This exclusion was necessary since they would be indicative of previous or additional cancer which overlaps with our study objective of a primary case of a single cancer. The presence of any indices was searched in the PDD data for up to three years prior to diagnosis of cancer. Any indices present were summed into an aggregate score. If the search for indices in the three years prior to diagnosis did not yield any results then the data for the next nine months after diagnosis of cancer was reviewed for presence of any indices and if present, were summed into an aggregate score. The final Elixhauser comorbidity score was broken up into three categories which included 0–2, 3+, and no admit. The 0–2 category was assigned to cases with up to two comorbid conditions while the 3+ was assigned to cases with at least three comorbidities. If cases did not have any admission during the course of their disease or in the time period specified, then they were assigned to the no admit category.

Statistical Analysis

Contingency table analyses with chi-square tests were performed to examine the bivariate association between postoperative complications and race/ethnicity including other factors of interest in our study. For the variables tumor stage and Elixhauser comorbidity score, which consists of unknown or missing categories, additional analyses were conducted separately to determine their inclusion in the primary analyses. These including recategorizing the unknown or missing values into one of the two allowable values for each variable or excluding them altogether, rerunning the statistical analysis and comparing the results. If similar results were observed, then it would suggest no additional bias was present due to the missing or unknown values and that these unknown or missing values could be added as a separate category for each respective variable.

We employed univariable and multivariable unconditional logistic regression to assess the magnitude of the association between race/ethnicity and postoperative complications. These regression analyses were conducted for all complications combined and separately for each class of complication which included GI, cardiac and renal complications. Not all class specific complications were analyzed due to limitations in population sample size. The magnitude of association was summarized as the odds ratio and 95% confidence interval.

We also assessed the association between race/ethnicity and overall survival using actuarial methods. We estimated Kaplan-Meier survival curves for HCC patients by race/ethnicity and used the log-rank test to assess survival differences. In addition, we evaluated survival differences by race/ethnicity using both univariable and multivariable Cox proportional hazards models. We also tested for interactions in our survival model between race/ethnicity with complications and surgical treatment. We ensured that the proportional hazards assumption was met by using the log(-log) survival curves of the survival distribution function by log(days). The proportional hazards ratio (HR) and 95% confidence interval were used to summarize the magnitude of association of race/ethnicity and other covariates with survival. Because it is possible that some cases would die before experiencing a postoperative complication and artificially inflate the risk of death in the group not experiencing complications, postoperative complication was used as a time-dependent covariate. In all our analyses, survival time was measured in days from cancer diagnosis until time of death from any cause. We resorted to censoring patients if they were alive at the end of the study period or at the date of last known contact. This analysis was conducted separately for all combined complications and each class of complication meeting sample size requirements.

In all our statistical analyses, tests used alpha=0.05 (2-tailed); all analyses were conducted using SAS v9.4.

RESULT

Distribution of patient factors

Our study population consisted of 3,494 cases of which 27.7% experienced a postoperative complication. The proportion of complications across all race/ethnicity were similar among Asian/PI (25.9%), Black/African American (26.3%), non-Hispanic White (28.4%), and Hispanic (28.9%) patients. A higher proportion of Asian/PIs (50.4%) were older than compared to other race/ethnicities. A high proportion of both Black/African Americans and Hispanics lived in lower SES neighborhoods, while the opposite was true for Asian/PIs and non-Hispanic Whites. Most patients across all race/ethnicities had private insurance. Asian/PI patients had fewer comorbid conditions than patients of other race/ethnicities. Our data indicated that Asian/PI and non-Hispanic White patients frequented high-volume hospitals more than Black/African American and Hispanic patients. Hepatectomy was more frequent among Asian/PI patients (56.8%) compared to patients of other race/ethnicities, while ablation was more common among Hispanic (53.5%) and non-Hispanic White (52.3%) patients. A higher proportion for transplantation was also observed for Hispanic (15.5%) and non-Hispanic White (14.1%) compared with Asian/PI and Black/African American.

In supplemental analyses excluding missing or unknown values for stage and Elixhauser comorbidity score variables, findings were similar with the results of the primary analysis when these values were included (Supplementary Tables 2–16). Therefore, we included the missing and unknown values for tumor stage and Elixhauser comorbidity score as separate categories in all subsequent analyses.

All postoperative complications

Patients of all race/ethnicities had similar odds of experiencing postoperative complications (Table 2). Patients residing in the highest (vs lowest) SES neighborhoods had lower odds of experiencing postoperative complications (OR = 0.70, 95%CI = 0.53–0.92). Patients seeking care at high volume hospitals (OR = 1.21, 95%CI = 1.02–1.43), with a higher Elixhauser comorbidity score (OR = 1.90, 95%CI = 1.56–2.31), and who underwent the surgical procedure of hepatectomy (OR = 2.23, 95%CI = 1.85–2.69) or transplantation (OR = 2.54, 95%CI = 1.98–3.27) had an increased odds of having a postoperative complication. Patients who had advanced tumor stage (OR = 1.25, 95%CI = 1.00–1.58) also had an increased odds of having a postoperative complication but it was borderline significant.

Overall survival related to all postoperative complications

Kaplan-Meier analysis revealed significant differences in survival by race/ethnicity with statistical comparisons performed using the log-rank test. Compared to non-Hispanic Whites, Asian/PIs (HR = 0.77, 95%CI = 0.67–0.90) demonstrated superior survival in multivariable Cox proportional hazards regression model (Table 3). Adjusting for complications did not impact racial/ethnic differences in survival. As found previously, an interaction between race/ethnicity and surgical treatment was observed and controlled for in our adjusted model. In addition, residing in higher neighborhood SES quintiles of 4 (HR = 0.80, 95%CI = 0.66–0.96) and 5 (HR = 0.66, 95%CI = 0.54–0.81) was associated with significantly better survival. On the other hand, older age (HR = 1.21, 95%CI = 1.07–1.37), late tumor stage (HR = 2.94, 95%CI = 2.55–3.38), higher Elixhauser comorbidity score (HR = 1.50, 95%CI = 1.29–1.74), Medicaid/Public insurance (HR = 1.25, 95%CI = 1.09–1.43), and having postoperative complications (HR = 1.29, 95%CI = 1.14–1.47) were associated with worse survival. No interaction of race/ethnicity and postoperative complications with survival was observed.

GI postoperative complications

When considering only GI complications, Black/African Americans (OR = 0.64, 95%CI = 0.42–0.98) demonstrated lower odds for GI complications when compared to non-Hispanic Whites (Table 4). Additionally, patients with older age (OR = 0.78, 95%CI = 0.64–0.95) had lower odds for GI complications, while patients with high Elixhauser comorbidity score (OR = 2.11, 95%CI = 1.64–2.70) and who underwent surgical procedures of hepatectomy (OR = 1.73, 95%CI = 1.39–2.16) and transplantation (OR = 1.56, 95%CI = 1.16–2.11) had greater odds for GI complications. Additionally, having a GI related postsurgical complication was associated with worse survival (HR = 1.34, 95%CI = 1.15–1.56) (Table 5).

Cardiac postoperative complications

Asian/PIs (OR = 0.69, 95%CI = 0.52-0.91) and Hispanics (OR = 0.75, 95%CI = 0.56–1.00) had lower odds of developing cardiac postsurgical complications (Table 4). Older age (OR = 1.39, 95%CI = 1.09–1.78), male gender (OR = 1.31, 95%CI = 1.01–1.70), Medicare recipient (OR =

1.34, 95%CI = 1.00–1.79), high Elixhauser comorbidity score (OR = 1.77, 95%CI = 1.34–2.34), and having surgical procedures of hepatectomy (OR = 2.46, 95%CI = 1.88–3.21) and transplantation (OR = 1.84, 95%CI = 1.26–2.68) increased the odds of having a cardiac related postsurgical complication. Patients with a cardiac related postsurgical complication (HR = 1.50, 95%CI = 1.27–1.78) experienced significantly decreased survival (Table 5).

Effect of renal postoperative complications

There were no racial/ethnic differences in the odds of experiencing postsurgical renal complications (Table 4). Increasing neighborhood SES status was associated with decreased the odds of having a postsurgical renal complication. Alternatively, high Elixhauser comorbidity score (OR = 2.68, 95%CI = 1.98–3.63) and the surgical procedures of hepatectomy (OR = 2.36, 95%CI = 1.81–3.06) and transplantation (OR = 5.43, 95%CI = 4.03–7.32) greatly increased the odds. Our data showed that having a postsurgical renal complication significantly decreased survival (HR = 1.54, 95%CI = 1.30–1.82) (Table 5).

DISCUSSION

In this large retrospective cohort study that included the population of California, we focused on several classes of complications that patients undergoing HCC intervention such as ablation, hepatectomy, or transplantation often experience, observing an overall complication rate of 27.6%. Our findings are consistent with prior studies that have found these complications to be common after HCC surgery, ranging between 30%–40%.[10,11] While the overall complication rate was similar by race/ethnicity, Black/African Americans were less likely to have GI complications and Asian/PIs and Hispanics were less likely to have cardiac complications than Non-Hispanic White patients. Complications were lower among patients residing in high SES neighborhoods and were higher among patients receiving treatment at high volume hospitals, with greater number of comorbid conditions, or who had either hepatectomy or transplantation. Notably, having any of the complications we considered in this study was associated with decreased overall survival.

Our findings indicated that Black/African Americans, Asian/PIs, and Hispanics were less likely to have select postsurgical complication rates. Although there are studies on postsurgical complications after HCC surgery, none of them focused on racial/ethnic disparities. However, studies conducted on other cancers investigating racial/ethnic disparities for surgical outcomes have generally demonstrated that minority groups, particularly Black/African Americans, experience poorer postoperative outcomes.[27-31] The lack of an association between Asian/PIs, Black/African Americans, Hispanics and postsurgical complications relative to non-Hispanic Whites in our study may be explained by improved access to healthcare access in this racial/ethnic group. The Affordable Care Act (ACA) which was implemented in 2014 to increase healthcare access and reduce inequity in the healthcare system could have played an important role in this.[32] Several studies have already shown that the ACA along with the Medicaid expansion have helped reduce disparities in insurance coverage among Black/African Americans.[32-35] Having insurance coverage could possibly imply diagnosis at earlier stage, less aggressive tumor characteristics, and treatment in better performing hospitals. It would also imply better management of comorbid conditions, access to experienced providers, and appropriate therapy. This previously inaccessible benefit could have contributed significantly to the reduction of postoperative complications in minority groups. A study by McMorrow et al did find uninsured disparities to decrease for Black/African Americans and Hispanic adults.[35]

While studies comparing all surgical treatments for HCC are rare, a study by Lei et al showed no difference in outcomes between resection and transplantation.[36] Both of these procedures are more invasive than ablation and both had similar higher odds of complications in our study. Van den Berg et al showed an association between low SES and worse outcome in a colorectal cancer study.[37] Similar to our findings, Shinkawa et al was able to show an association between postoperative complications after hepatectomy and comorbidities using age adjusted Charlson comorbidity index.[38] Results from studies on association between high volume hospitals and mortality have generally shown better survival with higher volume hospitals.[39-41] However, a nationwide Dutch study found no association between hospital volume and both morbidity and mortality.[42] Our results indicating higher odds of complications in higher surgical volume hospitals could be due to a number of factors including having a mix of patients with high acuity disease that more typically get referred to these hospitals. These would include patients with more unfavorable and aggressive biologic disease, more extensive spread, and more advanced liver disease. These patients might require more complex surgeries, such as hepatectomies and transplantations, that have higher complication rates.

We observed poor survival for individuals who had any complications as well as for specific complications. Our findings are not unexpected since postoperative complications occurrence as an independent risk factor for survival has been demonstrated in many studies.[12-16,43,44] Among individual classes of complications, renal complications demonstrated the highest risk of death. This is likely due to the inclusion of renal failure as one of the components of renal complications. High mortality rates among hospitalized patients with acute renal failure, particularly with dialysis, have been demonstrated in several studies.[45-50] In addition, little change has occurred in the mortality rate for renal failure over a significant period of time.[51]

While studies have been able to show the association between postsurgical outcomes and poor prognosis, there is gap in knowledge in understanding the mechanism between them. Findings on postsurgical complications show the occurrence of systemic inflammation which in turn might lead to poor short- and long-term outcomes for many cancers.[14,43,52,53] Harimoto et al suggested the possibility of a dose response relationship between complication severity and worse overall and recurrence-free survival in their study findings.[15] However, more studies need to be done to clarify the underlying mechanism between postsurgical complications and survival.

One of the biggest strengths of this study is the use of a large high-quality population-based cancer registry. The CCR covers the entire state of California with a very diverse population thus providing good external validity. Despite this strength, there are also a few important limitations in our study. HCC most frequently occurs in patients with cirrhosis and cirrhosis severity significantly impacts the type of HCC treatment and the risk of HCC surgery. Our current dataset did not include information on cirrhosis. We did not use a comprehensive list of all types of complications that can arise after HCC surgery, but included common complications were found to be associated with survival in prior studies.[13-16,43,54-58] This can affect our outcomes especially if there is variation by race/ethnicity for complications not covered in our study. Our ability to identify variations by race/ethnicity could also have been impacted by the relatively small number of Black/African American patients in this study (n=251). The CCR collects SES data that is not at the individual level which can lead to misclassification bias. Also, no information is collected on lifestyle factors such as alcohol consumption and physical activity which are known to be associated with poorer outcomes. Additionally, only complications that require an inpatient hospitalization or ED visit are captured by the HCAI data, therefore any complications treated exclusively in an outpatient setting are not included in our analyses. Hence, it is likely that we captured more serious complications, although we lacked specific details on severity, which can affect survival of the patient. Finally, we used a 60-day cumulative incidence period from date of surgery as cutoff point for complications. It is possible that this longer duration of time might have captured conditions that might not be fully reflective of complications from HCC surgery.

In summary, complications are common after HCC surgery and associated with a detrimental effect on survival. While we did not observe racial/ethnic differences in overall postsurgical complications, Black/African Americans were less likely to have GI complications and Asian/PIs and Hispanics were less likely to have cardiac complications than Non-Hispanic White patients. As expected, patient comorbidities and more invasive HCC surgeries increased the likelihood of complications. Our finding of higher complication rates in high surgical volume hospitals warrants further investigation to determine if this finding is related to variations in case mix. Complications were also associated with neighborhood SES, suggesting that efforts should be made to provide support and access to resources for patients under financial strain.

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Figure 1. Study population selection process

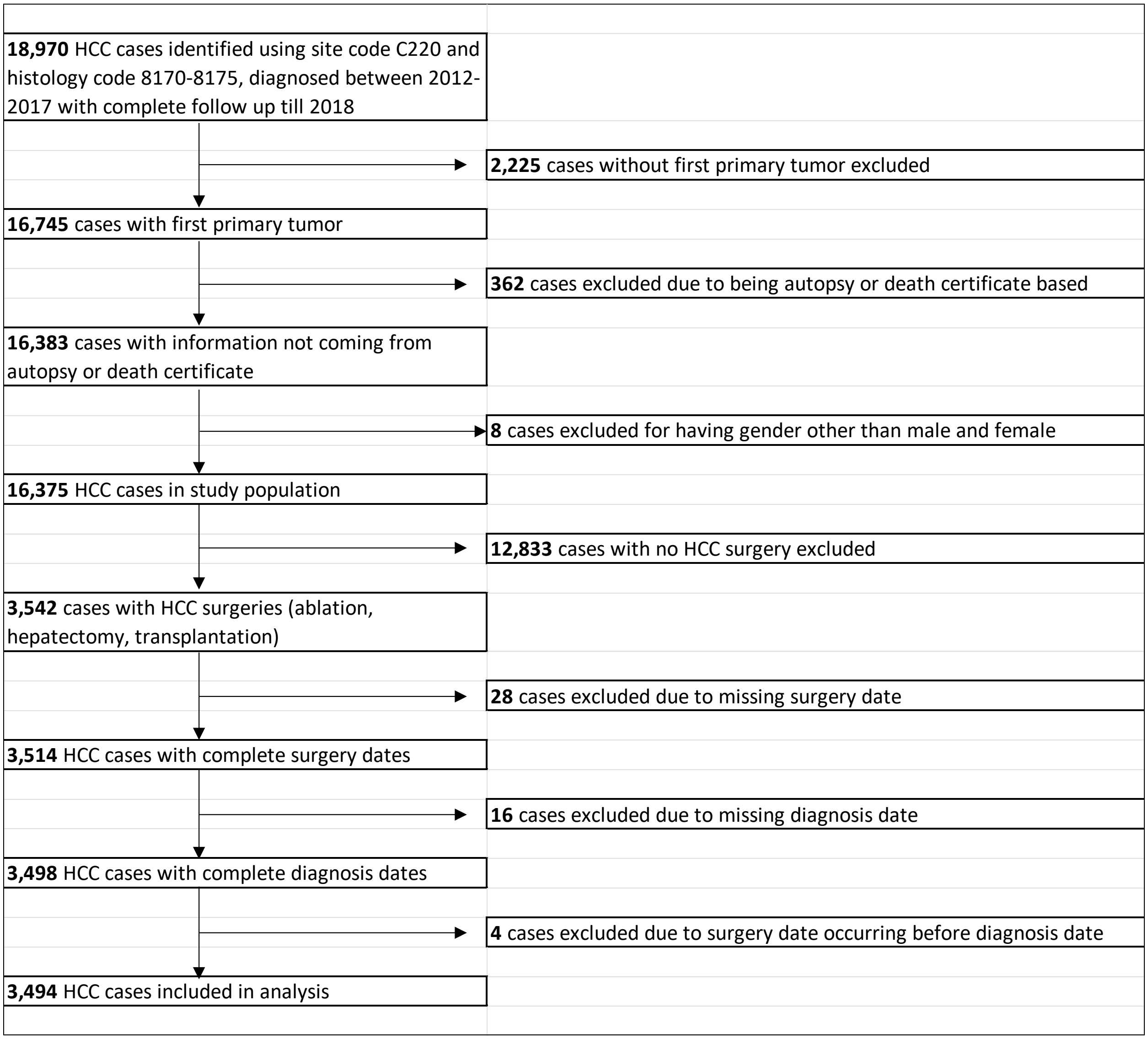

Table 1. Race/ethnicity, sociodemographic and clinical characteristics by postoperative complications status for hepatocellular carcinoma patients in California from 2012-2017

	Asian / Pacific Islander		African American		Hispanic		Other		Non-Hispanic White		Total		P-value
	(n = 1048)		(n = 251)		(n = 905)		(n = 59)		(n = 1231)		(n = 3494)		
	n	%	n	%	n	%	n	%	n	%	n	%	
Age at diagnosis													
0-<65	520	49.62	163	64.94	562	62.10	37	62.71	703	57.11	1985	56.81	<.0001
65+	528	50.38	88	35.06	343	37.90	22	37.29	528	42.89	1509	43.19	
Sex													
Female	282	26.91	68	27.09	278	30.72	20	33.90	324	26.32	972	27.82	0.1497
Male	766	73.09	183	72.91	627	69.28	39	66.10	907	73.68	2522	72.18	
Neighborhood socioeconomic status													
1 - Low SES	134	12.79	75	29.88	274	30.28	13	22.03	148	12.02	644	18.43	<.0001
2	223	21.28	59	23.51	226	24.97	22	37.29	226	18.36	756	21.64	
3	233	22.23	59	23.51	189	20.88	7	11.86	268	21.77	756	21.64	
4	241	23.00	39	15.54	142	15.69	12	20.34	310	25.18	744	21.29	
5 - High SES	217	20.71	19	7.57	74	8.18	5	8.47	279	22.66	594	17.00	
Insurance type													
Private	547	52.19	110	43.82	447	49.39	36	61.02	765	62.14	1905	54.52	<.0001
Medicaid/Public/Uninsured	298	28.44	93	37.05	288	31.82	14	23.73	214	17.38	907	25.96	
Medicare	198	18.89	45	17.93	161	17.79	9	15.25	233	18.93	646	18.49	
Other	5	0.48	3	1.20	9	0.99	0	0	19	1.54	36	1.03	
Tumor stage													
Stage I-II	898	86.6	215	86.35	781	87.36	48	87.27	1069	87.69	3011	87.17	0.9402
Stage III-IV	139	13.4	34	13.65	113	12.64	7	12.73	150	12.31	443	12.83	
Unknown	11		2		11		4		12		40		
Avg. annual surgery volume													
0-5	359	34.26	107	42.63	365	40.33	18	30.51	446	36.23	1295	37.06	0.0142
>5	689	65.74	144	57.37	540	59.67	41	69.49	785	63.77	2199	62.94	
Elixhauser comorbidity score													
0-2	315	41.83	44	22.8	145	21.29	10	22.22	268	29.68	782	30.37	<.0001
3+	438	58.17	149	77.2	536	78.71	35	77.78	635	70.32	1793	69.63	
No Admit	295		58		224		14		328		919		
Surgical treatment													
Ablation	377	35.97	110	43.82	484	53.48	33	55.93	644	52.32	1648	47.17	<.0001
Hepatectomy	595	56.77	125	49.8	281	31.05	19	32.2	414	33.63	1434	41.04	
Transplantation	76	7.25	16	6.37	140	15.47	7	11.86	173	14.05	412	11.79	
Complications													
Present	272	25.95	66	26.29	262	28.95	17	28.81	349	28.35	966	27.65	0.5842
Absent	776	74.05	185	73.71	643	71.05	42	71.19	882	71.65	2528	72.35	

Table 2. Factors associated with presence of postoperative complications for hepatocellular carcinoma in California from 2012-2017

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Race/Ethnicity				
Asian/Pacific Islander	0.89	0.74-1.07	0.83	0.68-1.02
Black/African American	0.90	0.66-1.23	0.74	0.53-1.04
Hispanic	1.03	0.85-1.25	0.94	0.76-1.16
Other	1.02	0.58-1.82	0.90	0.49-1.67
Non-Hispanic White	1.00		1.00	
Age at diagnosis				
0-<65			1.00	
65+			1.15	0.97-1.36
Neighborhood socioeconomic status				
1 - Low SES			1.00	
2			0.82	0.64-1.05
3			0.83	0.64-1.06
4			0.89	0.69-1.14
5 - High SES			0.70	0.53-0.92
Tumor stage				
Stage I-II			1.00	
Stage III-IV			1.25	1.00-1.58
Unknown			1.62	0.74-3.53
Avg. annual hospital surgery volume				
0-5			1.00	
>5			1.21	1.02-1.43
Elixhauser comorbidity score				
0-2			1.00	
3+			1.90	1.56-2.31
No Admit			0.29	0.21-0.39
Surgical treatment				
Ablation			1.00	
Hepatectomy			2.23	1.85-2.69
Transplantation			2.54	1.98-3.27

Note: Model adjusted for all the variables present in the table

Table 3. Race/ethnicity, postoperative complications and other factors associated with survival from hepatocellular carcinoma in California from 2012-2017

	Unadjusted		Adjusted for sociodemographic, clinical factors, and treatment effects		Includes interaction between Race/ethnicity and Surgical Treatment	
	HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI
Race/Ethnicity *						
Asian/Pacific Islander	0.77	0.67-0.89	0.77	0.67-0.90		
Black/African American	1.18	0.95-1.46	0.98	0.79-1.23		
Hispanic	1.12	0.97-1.29	0.98	0.85-1.14		
Other	0.83	0.51-1.35	0.64	0.39-1.04		
Non-Hispanic White	1.00		1.00			
Age at diagnosis						
0-<65			1.00		1.00	
65+			1.20	1.06-1.35	1.21	1.07-1.37
Sex						
Female						
Male						
Neighborhood socioeconomic status						
1 - Low SES			1.00		1.00	
2			0.91	0.76-1.08	0.92	0.77-1.09
3			0.85	0.71-1.02	0.86	0.72-1.03
4			0.80	0.66-0.96	0.80	0.67-0.97
5 - High SES			0.66	0.54-0.81	0.67	0.54-0.83
Insurance type						
Private			1.00		1.00	
Medicaid/Public/Uninsured			1.23	1.07-1.41	1.25	1.09-1.43
Medicare			1.11	0.95-1.30	1.10	0.94-1.29
Other			1.76	1.12-2.79	1.73	1.09-2.74
Tumor stage						
Stage I-II			1.00		1.00	
Stage III-IV			2.87	2.50-3.31	2.94	2.55-3.38
Unknown			2.39	1.57-3.63	2.31	1.52-3.52
Avg. annual hospital surgery volume						
0-5			1.00		1.00	
>5						
Elixhauser comorbidity score						
0-2			1.00		1.00	
3+			1.51	1.30-1.76	1.50	1.29-1.74
No Admit			0.77	0.64-0.94	0.77	0.63-0.93
Surgical treatment *						
Ablation			1.00			
Hepatectomy			0.58	0.51-0.67		
Transplantation			0.21	0.16-0.28		
Postsurgical complications						
0			1.00		1.00	
1			1.28	1.13-1.46	1.29	1.14-1.47

* Adjusted hazard ratios not provided due to presence of interaction in model
Note: Model adjusted for all the variables present in the table

Table 4. Factors associated with presence of gastrointestinal, cardiac and renal postoperative complications for hepatocellular carcinoma in California from 2012-2017

	Gastrointestinal		Cardiac		Renal	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Race/Ethnicity						
Asian/Pacific Islander	0.99	0.78-1.27	0.69	0.52-0.91	0.96	0.73-1.28
Black/African American	0.64	0.42-0.98	0.68	0.43-1.09	1.03	0.67-1.57
Hispanic	1.03	0.81-1.31	0.75	0.56-1.00	1.11	0.84-1.46
Other	1.35	0.69-2.66	0.38	0.12-1.26	0.73	0.30-1.82
Non-Hispanic White	1.00		1.00		1.00	
Age at diagnosis						
0-<65	1.00		1.00			
65+	0.78	0.64-0.95	1.39	1.09-1.78		
Sex						
Female			1.00			
Male			1.31	1.01-1.70		
Neighborhood socioeconomic status						
1 - Low SES					1.00	
2					0.70	0.51-0.97
3					0.66	0.48-0.91
4					0.67	0.48-0.93
5 - High SES					0.56	0.38-0.81
Insurance type						
Private			1.00			
Medicaid/Public/Uninsured			1.05	0.79-1.40		
Medicare			1.34	1.00-1.79		
Other			0.48	0.11-2.04		
Elixhauser comorbidity score						
0-2	1.00		1.00		1.00	
3+	2.11	1.64-2.70	1.77	1.34-2.34	2.68	1.98-3.63
No Admit	0.33	0.22-0.49	0.23	0.13-0.39	0.54	0.35-0.84
Surgical treatment						
Ablation	1.00		1.00		1.00	
Hepatectomy	1.73	1.39-2.16	2.46	1.88-3.21	2.36	1.81-3.06
Transplantation	1.56	1.16-2.11	1.84	1.26-2.68	5.43	4.03-7.32

Note: Model adjusted for all the variables present in the table unless left blank

Table 5. Race/ethnicity, gastrointestinal, cardiac and renal postoperative complications and other factors associated with survival from hepatocellular carcinoma in California from 2012-2017

	Gastrointestinal		Cardiac		Renal	
	Adjusted HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI
Race/Ethnicity						
Asian/Pacific Islander	0.77	0.66-0.89	0.77	0.66-0.90	0.78	0.67-0.91
Black/African American	0.99	0.80-1.24	0.98	0.78-1.22	0.95	0.76-1.19
Hispanic	0.98	0.84-1.13	0.99	0.85-1.14	0.98	0.85-1.14
Other	0.61	0.38-1.00	0.65	0.40-1.06	0.65	0.40-1.05
Non-Hispanic White	1.00		1.00		1.00	
Age at diagnosis						
0-<65	1.00		1.00		1.00	
65+	1.21	1.07-1.37	1.19	1.05-1.34	1.19	1.05-1.34
Neighborhood socioeconomic status						
1 - Low SES	1.00		1.00		1.00	
2	0.90	0.76-1.07	0.90	0.76-1.07	0.91	0.77-1.08
3	0.84	0.70-1.01	0.85	0.71-1.01	0.87	0.73-1.04
4	0.80	0.66-0.96	0.80	0.66-0.96	0.81	0.68-0.98
5 - High SES	0.66	0.53-0.81	0.65	0.53-0.80	0.66	0.54-0.82
Insurance type						
Private	1.00		1.00		1.00	
Medicaid/Public/Uninsured	1.24	1.08-1.42	1.23	1.07-1.41	1.22	1.06-1.40
Medicare	1.12	0.95-1.30	1.11	0.95-1.29	1.11	0.95-1.30
Other	1.71	1.08-2.70	1.76	1.11-2.79	1.77	1.12-2.80
Tumor stage						
Stage I-II	1.00		1.00		1.00	
Stage III-IV	2.91	2.53-3.35	2.88	2.50-3.31	2.86	2.48-3.29
Unknown	2.45	1.61-3.72	2.45	1.61-3.73	2.33	1.53-3.53
Elixhauser comorbidity score						
0-2	1.00		1.00		1.00	
3+	1.53	1.31-1.78	1.51	1.30-1.76	1.50	1.29-1.75
No Admit	0.76	0.63-0.93	0.76	0.63-0.92	0.75	0.62-0.91
Surgical treatment						
Ablation	1.00		1.00		1.00	
Hepatectomy	0.60	0.52-0.68	0.59	0.52-0.67	0.58	0.51-0.67
Transplantation	0.21	0.16-0.28	0.22	0.16-0.28	0.19	0.15-0.26
Postsurgical GI complications						
0	1.00		1.00		1.00	
1	1.34	1.15-1.56	1.50	1.27-1.78	1.54	1.30-1.82

Note: Model adjusted for all the variables present in the table

Supplemental Table 1a. ICD-9, ICD-10 codes for neurological complications

Brain/Cerebral infarction		
ICD-9	ICD-10	ICD-10
434.01	I6330	
434.11	I6340	
434.91	I6350	

Supplemental Table 1b. ICD-9, ICD-10 codes for cardiac complications

Myocardial infarction		Congestive heart		Arrhythmia		Venous thrombosis	
ICD-9	ICD-10	ICD-9	ICD-10	ICD-9	ICD-10	ICD-9	
410.x	I21.x	398.91	I0981	427.0	I469	415.11	I2690
	I22.x	402.01	I110	427.1	I471	415.13	I2692
	I25.2	402.11	I130	427.2	I472	415.19	I2699
	I2109	402.91	I132	427.3	I479	673.2	I8010
	I2111	404.01	I425	427.4	I4891	453.40	I80209
	I2119	404.03	I426	427.5	I4892	453.41	I80219
	I2129	404.11	I427	427.6	I4901	453.42	I82220
	I213	404.13	I428	427.7	I4902	671.31	I82221
	I214	404.91	I43	427.8	I491	671.33	I82290
	I252	404.93	I501	427.9	I493	671.42	I82409
		425.4	I5020		I4940	671.44	I82419
		425.5	I5021		I4949	453.2	I82429
		425.6	I5022		I495	453.8	I82439
		425.7	I5023		I498	451.11	I82449
		425.8	I5030		I499	451.19	I82499
		425.9	I5031		R001	451.81	I824Y9
		428.x	I5032			997.2	I824Z9
			I5033			997.3	I82609
			I5040			453.9	I82619
			I5041			453.89	I82629
			I5042				I82890
			I5043				I8291
			I509				I82A19
							I82B19
							I82C19
							J95851
							J95859
							J9588
							J9589
							O2231
							O2232
							O2233
							O871
							O88211
							O88212
							O88213
							O88219
							O8822
							O8823
							T800XXA
							T81718A
							T81719A
							T8172XA
							T82817A
							T82818A

Supplemental Table 1c. ICD-9, ICD-10 codes for pulmonary complications

Pneumonia	
ICD-9	ICD-10
480.xx	A221
481.xx	A3791
482.xx	A481
483.xx	B250
484.xx	B440
485.xx	J120
486.xx	J121
	J122
	J1281
	J1289
	J129
	J13
	J14
	J150
	J151
	J1520
	J15211
	J15212
	J1529
	J153
	J154
	J155
	J156
	J157
	J158
	J159
	J160
	J168
	J17
	J180
	J181
	J189

Supplemental Table 1d. ICD-9, ICD-10 codes for gastrointestinal complications

Bile leakage		Ascites		Liver failure		Gastrointestinal		Ileus	
ICD-9	ICD-10	ICD-9	ICD-10	ICD-9	ICD-10	ICD-9	ICD-10	ICD-9	ICD-10
567.81	K653	789.5	R180	570	K7200	456.0	I8501	560.1	K560
			R188		K762	456.20	I8511		K567
						530.7	K226		
						530.82	K228		
						531.00	K250		
						531.01	K252		
						531.20	K254		
						531.21	K256		
						531.40	K260		
						531.41	K262		
						531.60	K264		
						531.61	K266		
						532.00	K270		
						532.01	K272		
						532.20	K274		
						532.21	K276		
						532.40	K280		
						532.41	K282		
						532.60	K284		
						532.61	K286		
						533.00	K2901		
						533.01	K2921		
						533.20	K2941		
						533.21	K2951		
						533.40	K2961		
						533.41	K2971		
						533.60	K2981		
						533.61	K2991		
						534.00	K5521		
						534.01	K5711		
						534.20	K5713		
						534.21	K5731		
						534.40	K5733		
						534.41	K625		
						534.60	K661		
						534.61	K920		
						535.01	K921		
						535.11	K922		
						535.21			
						535.31			
						535.41			
						535.51			
						535.61			
						537.83			
						562.02			
						562.03			
						562.12			
						562.13			
						568.81			
						569.3			
						569.85			
						578.0			
						578.1			
						578.9			

Supplemental Table 1e. ICD-9, ICD-10 codes for renal complications

Urinary tract infection		Renal failure	
ICD-9	ICD-10	ICD-9	ICD-10
590	K900	584	N170
595.0	K901	586	N171
597	K902		N172
599	K903		N178
	K904		N179
	K9089		N19
	K909		
	K912		
	N10		
	N110		
	N118		
	N12		
	N139		
	N151		
	N159		
	N16		
	N2884		
	N2885		
	N2886		
	N3000		
	N3001		
	N360		
	N361		
	N362		
	N3641		
	N3642		
	N365		
	N368		
	N369		
	N390		
	N398		
	N399		
	R310		
	R311		
	R312		
	R319		

Supplemental Table 1f. ICD-9, ICD-10 codes for infectious complications

Sepsis	
ICD-9	ICD-10
380	I76
381	A207
381.0	A227
381.1	A392
381.2	A393
381.9	A394
384.2	A400
384.0	A401
384.1	A403
384.3	A408
384.4	A409
384.9	A411
331	A413
202	A414
223	A419
362	A427
382	B007
383	A021
545	A267
388	A327
389	A412
449	B377
790.7	A3710
995.90	A3711
995.91	A4101
995.92	A4150
	A4152
	A4153
	A4159
	A4181
	A4189
	H7290
	H7291
	H7292
	H7293
	R7881
	R6510
	A4151
	A5486
	R6520
	R6521

Supplemental Table 2. Effect of missing stage on presence of overall postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.84	0.69	1.03	0.84	0.68	1.03
RACE Black/AA vs non-Hispanic White	0.74	0.53	1.04	0.74	0.53	1.04
RACE Hispanic vs non-Hispanic White	0.94	0.77	1.17	0.95	0.77	1.17
RACE Other vs non-Hispanic White	0.90	0.49	1.68	0.94	0.50	1.79
Elixhauser Comorbidity Score 3+ vs 0-2	1.91	1.57	2.33	1.92	1.57	2.34
Elixhauser Comorbidity Score no admit vs 0-2	0.29	0.21	0.39	0.30	0.22	0.41
Surgical Treatment Hepatectomy vs Ablation	2.23	1.85	2.68	2.25	1.87	2.71
Surgical Treatment Transplant vs Ablation	2.49	1.94	3.19	2.52	1.96	3.24
Tumor Stage Stage III-IV vs Stage I-II	1.27	1.01	1.60	1.27	1.01	1.59
Tumor Stage Unknown vs Stage I-II	1.63	0.75	3.57			
Insurance Medicaid/Public/Uninsured vs Private	0.93	0.76	1.13	0.93	0.76	1.14
Insurance Medicare vs Private	1.23	1.00	1.52	1.26	1.02	1.55
Insurance Other vs Private	0.65	0.29	1.45	0.65	0.29	1.45
Neighborhood Socioeconomic Status 2 vs 1	0.81	0.63	1.04	0.79	0.62	1.02
Neighborhood Socioeconomic Status 3 vs 1	0.81	0.63	1.05	0.81	0.63	1.04
Neighborhood Socioeconomic Status 4 vs 1	0.88	0.68	1.13	0.86	0.67	1.12
Neighborhood Socioeconomic Status 5 vs 1	0.69	0.52	0.92	0.69	0.52	0.92
Avg. Annual Surgery Volume >5 vs 0 - 5	1.20	1.01	1.42	1.18	1.00	1.40

Supplemental Table 3. Effect of missing stage on survival related to overall postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian	0.77	0.67	0.90	0.78	0.67	0.91
RACE (non-Hispanic White)	Black	0.98	0.79	1.23	0.99	0.79	1.24
RACE (non-Hispanic White)	Hispanic	0.98	0.85	1.14	0.99	0.85	1.15
RACE (non-Hispanic White)	Other	0.64	0.39	1.04	0.59	0.35	1.01
Tumor Stage (Stage I-II)	Stage III-IV	2.87	2.50	3.31	2.88	2.50	3.32
Tumor Stage (Stage I-II)	Unknown	2.39	1.57	3.63			
Surgical Treatment (Ablation)	Hepatectomy	0.58	0.51	0.67	0.59	0.52	0.67
Surgical Treatment (Ablation)	Transplant	0.21	0.16	0.28	0.21	0.16	0.28
Elixhauser Comorbidity Score (0-2)	3+	1.51	1.30	1.76	1.54	1.32	1.79
Elixhauser Comorbidity Score (0-2)	no admit	0.77	0.64	0.94	0.78	0.64	0.95
Insurance (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.23	1.07	1.41
Insurance (Private)	Medicare	1.11	0.95	1.30	1.13	0.96	1.32
Insurance (Private)	Other	1.76	1.12	2.79	1.77	1.12	2.80
Neighborhood socioeconomic status (1)	2	0.91	0.76	1.08	0.91	0.76	1.08
Neighborhood socioeconomic status (1)	3	0.85	0.71	1.02	0.85	0.71	1.01
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.81	0.67	0.98
Neighborhood socioeconomic status (1)	5	0.66	0.54	0.81	0.67	0.55	0.83
COMPLICATIONS (0)	1	1.28	1.13	1.46	1.28	1.12	1.45
Age (<65)	65+	1.20	1.06	1.35	1.19	1.06	1.35

Supplemental Table 4. Effect of missing Elixhauser comorbidity score on presence of overall postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.84	0.69	1.03	0.82	0.66	1.02
RACE Black/AA vs non-Hispanic White	0.74	0.53	1.04	0.78	0.55	1.10
RACE Hispanic vs non-Hispanic White	0.94	0.77	1.17	0.95	0.76	1.18
RACE Other vs non-Hispanic White	0.90	0.49	1.68	0.88	0.46	1.67
Elixhauser Comorbidity Score 3+ vs 0-2	1.91	1.57	2.33	1.99	1.63	2.43
Elixhauser Comorbidity Score no admit vs 0-2	0.29	0.21	0.39			
Surgical Treatment Hepatectomy vs Ablation	2.23	1.85	2.68	2.21	1.81	2.68
Surgical Treatment Transplant vs Ablation	2.49	1.94	3.19	1.68	1.29	2.20
Tumor Stage Stage III-IV vs Stage I-II	1.27	1.01	1.60	1.30	1.02	1.65
Tumor Stage Unknown vs Stage I-II	1.63	0.75	3.57	2.20	0.92	5.25
Insurance Medicaid/Public/Uninsured vs Private	0.93	0.76	1.13	0.96	0.78	1.19
Insurance Medicare vs Private	1.23	1.00	1.52	1.31	1.05	1.63
Insurance Other vs Private	0.65	0.29	1.45	0.51	0.21	1.23
Neighborhood Socioeconomic Status 2 vs 1	0.81	0.63	1.04	0.85	0.66	1.11
Neighborhood Socioeconomic Status 3 vs 1	0.81	0.63	1.05	0.85	0.65	1.11
Neighborhood Socioeconomic Status 4 vs 1	0.88	0.68	1.13	0.94	0.72	1.24
Neighborhood Socioeconomic Status 5 vs 1	0.69	0.52	0.92	0.76	0.56	1.02
Avg. Annual Surgery Volume >5 vs 0 - 5	1.20	1.01	1.42	1.27	1.06	1.52

Supplemental Table 5. Effect of missing Elixhauser comorbidity score on survival related to overall postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian	0.77	0.67	0.90	0.81	0.69	0.96
RACE (non-Hispanic White)	Black	0.98	0.79	1.23	0.98	0.77	1.25
RACE (non-Hispanic White)	Hispanic	0.98	0.85	1.14	0.96	0.81	1.12
RACE (non-Hispanic White)	Other	0.64	0.39	1.04	0.61	0.36	1.05
Tumor Stage (Stage I-II)	Stage III-IV	2.87	2.50	3.31	2.71	2.32	3.16
Tumor Stage (Stage I-II)	Unknown	2.39	1.57	3.63	2.40	1.41	4.08
Surgical Treatment (Ablation)	Hepatectomy	0.58	0.51	0.67	0.57	0.50	0.66
Surgical Treatment (Ablation)	Transplant	0.21	0.16	0.28	0.21	0.16	0.28
Elixhauser Comorbidity Score (0-2)	3+	1.51	1.30	1.76	1.51	1.30	1.76
Elixhauser Comorbidity Score (0-2)	no admit	0.77	0.64	0.94			
Insurance (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.28	1.10	1.49
Insurance (Private)	Medicare	1.11	0.95	1.30	1.06	0.89	1.26
Insurance (Private)	Other	1.76	1.12	2.79	1.54	0.92	2.58
Neighborhood socioeconomic status (1)	2	0.91	0.76	1.08	0.90	0.74	1.08
Neighborhood socioeconomic status (1)	3	0.85	0.71	1.02	0.85	0.70	1.04
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.80	0.65	0.98
Neighborhood socioeconomic status (1)	5	0.66	0.54	0.81	0.65	0.52	0.82
COMPLICATIONS (0)	1	1.28	1.13	1.46	1.31	1.15	1.50
Age (<65)	65+	1.20	1.06	1.35	1.18	1.03	1.35

Supplemental Table 6. Effect of missing stage on presence of GI postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.99	0.78	1.27	0.98	0.77	1.26
RACE Black/AA vs non-Hispanic White	0.64	0.42	0.98	0.64	0.42	0.98
RACE Hispanic vs non-Hispanic White	1.03	0.81	1.31	1.04	0.82	1.33
RACE Other vs non-Hispanic White	1.35	0.69	2.66	1.33	0.66	2.68
Elixhauser Comorbidity Score 3+ vs 0-2	2.11	1.64	2.70	2.14	1.67	2.74
Elixhauser Comorbidity Score no admit vs 0-2	0.33	0.22	0.49	0.34	0.23	0.51
Surgical Treatment Hepatectomy vs Ablation	1.73	1.39	2.16	1.77	1.42	2.20
Surgical Treatment Transplant vs Ablation	1.56	1.16	2.11	1.60	1.18	2.15
Age 65+ vs 0-<65	0.78	0.64	0.95	0.79	0.65	0.97

Supplemental Table 7. Effect of missing stage on survival related to GI postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.77	0.66	0.89	0.77	0.67	0.90
RACE (non-Hispanic White)	Black/AA	0.99	0.80	1.24	1.00	0.80	1.25
RACE (non-Hispanic White)	Hispanic	0.98	0.84	1.13	0.99	0.85	1.14
RACE (non-Hispanic White)	Other	0.61	0.38	1.00	0.57	0.34	0.98
Tumor Stage (Stage I-II)	Stage III-IV	2.91	2.53	3.35	2.92	2.53	3.36
Tumor Stage (Stage I-II)	Unknown	2.45	1.61	3.72			
Surgical Treatment (Ablation)	Hepatectomy	0.60	0.52	0.68	0.60	0.53	0.68
Surgical Treatment (Ablation)	Transplant	0.21	0.16	0.28	0.22	0.16	0.28
Elixhauser Comorbidity Score (0-2)	3+	1.53	1.31	1.78	1.55	1.33	1.81
Elixhauser Comorbidity Score (0-2)	no admit	0.76	0.63	0.93	0.77	0.64	0.94
Insurance (Private)	Medicaid/Public/Uninsured	1.24	1.08	1.42	1.23	1.07	1.42
Insurance (Private)	Medicare	1.12	0.95	1.30	1.14	0.97	1.33
Insurance (Private)	Other	1.71	1.08	2.70	1.71	1.08	2.71
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.90	0.76	1.07
Neighborhood socioeconomic status (1)	3	0.84	0.70	1.01	0.84	0.70	1.01
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.81	0.67	0.97
Neighborhood socioeconomic status (1)	5	0.66	0.53	0.81	0.67	0.54	0.82
Age (<65)	65+	1.21	1.07	1.37	1.21	1.07	1.37
COMPLICATIONS_GI (0)	1	1.34	1.15	1.56	1.31	1.12	1.52

Supplemental Table 8. Effect of missing Elixhauser comorbidity score on presence of GI postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.99	0.78	1.27	0.99	0.77	1.28
RACE Black/AA vs non-Hispanic White	0.64	0.42	0.98	0.64	0.41	0.99
RACE Hispanic vs non-Hispanic White	1.03	0.81	1.31	1.01	0.79	1.31
RACE Other vs non-Hispanic White	1.35	0.69	2.66	1.45	0.73	2.89
Elixhauser Comorbidity Score 3+ vs 0-2	2.11	1.64	2.70	2.17	1.69	2.78
Elixhauser Comorbidity Score no admit vs 0-2	0.33	0.22	0.49			
Surgical Treatment Hepatectomy vs Ablation	1.73	1.39	2.16	1.65	1.31	2.06
Surgical Treatment Transplant vs Ablation	1.56	1.16	2.11	1.10	0.79	1.52
Age 65+ vs 0-<65	0.78	0.64	0.95	0.79	0.64	0.97

Supplemental Table 9. Effect of missing Elixhauser comorbidity score on survival related to GI postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.77	0.66	0.89	0.80	0.68	0.95
RACE (non-Hispanic White)	Black/AA	0.99	0.80	1.24	1.00	0.78	1.27
RACE (non-Hispanic White)	Hispanic	0.98	0.84	1.13	0.95	0.81	1.12
RACE (non-Hispanic White)	Other	0.61	0.38	1.00	0.59	0.34	1.00
Tumor Stage (Stage I-II)	Stage III-IV	2.91	2.53	3.35	2.75	2.36	3.21
Tumor Stage (Stage I-II)	Unknown	2.45	1.61	3.72	2.50	1.47	4.26
Surgical Treatment (Ablation)	Hepatectomy	0.60	0.52	0.68	0.58	0.51	0.67
Surgical Treatment (Ablation)	Transplant	0.21	0.16	0.28	0.21	0.16	0.29
Elixhauser Comorbidity Score (0-2)	3+	1.53	1.31	1.78	1.53	1.31	1.78
Elixhauser Comorbidity Score (0-2)	no admit	0.76	0.63	0.93			
Insurance (Private)	Medicaid/Public/Uninsured	1.24	1.08	1.42	1.29	1.11	1.50
Insurance (Private)	Medicare	1.12	0.95	1.30	1.06	0.89	1.27
Insurance (Private)	Other	1.71	1.08	2.70	1.48	0.88	2.48
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.89	0.74	1.08
Neighborhood socioeconomic status (1)	3	0.84	0.70	1.01	0.84	0.69	1.02
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.80	0.65	0.98
Neighborhood socioeconomic status (1)	5	0.66	0.53	0.81	0.65	0.51	0.81
Age (<65)	65+	1.21	1.07	1.37	1.20	1.05	1.37
COMPLICATIONS_GI (0)	1	1.34	1.15	1.56	1.36	1.17	1.59

Supplemental Table 10. Effect of missing stage on presence of cardiac postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.69	0.52	0.91	0.69	0.52	0.92
RACE Black/AA vs non-Hispanic White	0.68	0.43	1.09	0.68	0.43	1.08
RACE Hispanic vs non-Hispanic White	0.75	0.56	1.00	0.73	0.54	0.98
RACE Other vs non-Hispanic White	0.38	0.12	1.26	0.41	0.12	1.34
Elixhauser Comorbidity Score 3+ vs 0-2	1.77	1.34	2.34	1.77	1.33	2.34
Elixhauser Comorbidity Score no admit vs 0-2	0.23	0.13	0.39	0.23	0.14	0.40
Surgical Treatment Hepatectomy vs Ablation	2.46	1.88	3.21	2.48	1.90	3.24
Surgical Treatment Transplant vs Ablation	1.84	1.26	2.68	1.86	1.27	2.71
Age 65+ vs 0-<65	1.39	1.09	1.78	1.39	1.09	1.78
Insurance Medicaid/Public/Uninsured vs Private	1.05	0.79	1.40	1.08	0.81	1.43
Insurance Medicare vs Private	1.34	1.00	1.79	1.36	1.02	1.82
Insurance Other vs Private	0.48	0.11	2.04	0.48	0.11	2.06
Sex 1 vs 2	1.31	1.01	1.70	1.33	1.03	1.73

Supplemental Table 11. Effect of missing stage on survival related to cardiac postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.77	0.66	0.90	0.78	0.67	0.91
RACE (non-Hispanic White)	Black/AA	0.98	0.78	1.22	0.98	0.79	1.23
RACE (non-Hispanic White)	Hispanic	0.99	0.85	1.14	1.00	0.86	1.16
RACE (non-Hispanic White)	Other	0.65	0.40	1.06	0.61	0.36	1.04
Tumor Stage (Stage I-II)	Stage III-IV	2.88	2.50	3.31	2.88	2.50	3.32
Tumor Stage (Stage I-II)	Unknown	2.45	1.61	3.73			
Surgical Treatment (Ablation)	Hepatectomy	0.59	0.52	0.67	0.59	0.52	0.67
Surgical Treatment (Ablation)	Transplant	0.22	0.16	0.28	0.22	0.17	0.29
Elixhauser Comorbidity Score (0-2)	3+	1.51	1.30	1.76	1.54	1.32	1.79
Elixhauser Comorbidity Score (0-2)	no admit	0.76	0.63	0.92	0.77	0.64	0.94
Insurance (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.22	1.06	1.41
Insurance (Private)	Medicare	1.11	0.95	1.29	1.13	0.96	1.32
Insurance (Private)	Other	1.76	1.11	2.79	1.77	1.12	2.80
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.90	0.76	1.07
Neighborhood socioeconomic status (1)	3	0.85	0.71	1.01	0.84	0.71	1.01
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.81	0.67	0.97
Neighborhood socioeconomic status (1)	5	0.65	0.53	0.80	0.66	0.53	0.81
COMPLICATIONS_CARDIAC (0)	1	1.50	1.27	1.78	1.50	1.26	1.77
Age (<65)	65+	1.19	1.05	1.34	1.18	1.05	1.34

Supplemental Table 12. Effect of missing Elixhauser comorbidity score on presence of cardiac postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.69	0.52	0.91	0.68	0.50	0.91
RACE Black/AA vs non-Hispanic White	0.68	0.43	1.09	0.70	0.44	1.13
RACE Hispanic vs non-Hispanic White	0.75	0.56	1.00	0.76	0.56	1.03
RACE Other vs non-Hispanic White	0.38	0.12	1.26	0.26	0.06	1.08
Elixhauser Comorbidity Score 3+ vs 0-2	1.77	1.34	2.34	1.80	1.36	2.38
Elixhauser Comorbidity Score no admit vs 0-2	0.23	0.13	0.39			
Surgical Treatment Hepatectomy vs Ablation	2.46	1.88	3.21	2.44	1.86	3.21
Surgical Treatment Transplant vs Ablation	1.84	1.26	2.68	1.52	1.02	2.27
Age 65+ vs 0-<65	1.39	1.09	1.78	1.41	1.09	1.81
Insurance Medicaid/Public/Uninsured vs Private	1.05	0.79	1.40	1.11	0.83	1.48
Insurance Medicare vs Private	1.34	1.00	1.79	1.39	1.03	1.86
Insurance Other vs Private	0.48	0.11	2.04	0.52	0.12	2.21
Sex 1 vs 2	1.31	1.01	1.70	1.28	0.98	1.67

Supplemental Table 13. Effect of missing Elixhauser comorbidity score on survival related to cardiac postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.77	0.66	0.90	0.81	0.69	0.96
RACE (non-Hispanic White)	Black/AA	0.98	0.78	1.22	0.97	0.76	1.24
RACE (non-Hispanic White)	Hispanic	0.99	0.85	1.14	0.96	0.81	1.13
RACE (non-Hispanic White)	Other	0.65	0.40	1.06	0.63	0.37	1.08
Tumor Stage (Stage I-II)	Stage III-IV	2.88	2.50	3.31	2.71	2.32	3.16
Tumor Stage (Stage I-II)	Unknown	2.45	1.61	3.73	2.53	1.48	4.31
Surgical Treatment (Ablation)	Hepatectomy	0.59	0.52	0.67	0.58	0.50	0.66
Surgical Treatment (Ablation)	Transplant	0.22	0.16	0.28	0.22	0.16	0.29
Elixhauser Comorbidity Score (0-2)	3+	1.51	1.30	1.76	1.52	1.30	1.77
Elixhauser Comorbidity Score (0-2)	no admit	0.76	0.63	0.92			
Insurance (Private)	Medicaid/Public/Uninsured	1.23	1.07	1.41	1.27	1.09	1.48
Insurance (Private)	Medicare	1.11	0.95	1.29	1.06	0.89	1.26
Insurance (Private)	Other	1.76	1.11	2.79	1.53	0.91	2.56
Neighborhood socioeconomic status (1)	2	0.90	0.76	1.07	0.89	0.74	1.07
Neighborhood socioeconomic status (1)	3	0.85	0.71	1.01	0.84	0.69	1.03
Neighborhood socioeconomic status (1)	4	0.80	0.66	0.96	0.80	0.65	0.98
Neighborhood socioeconomic status (1)	5	0.65	0.53	0.80	0.63	0.50	0.80
COMPLICATIONS_CARDIAC (0)	1	1.50	1.27	1.78	1.51	1.27	1.80
Age (<65)	65+	1.19	1.05	1.34	1.17	1.02	1.33

Supplemental Table 14. Effect of missing stage on presence of renal postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.96	0.73	1.28	0.97	0.74	1.29
RACE Black/AA vs non-Hispanic White	1.03	0.67	1.57	1.04	0.68	1.60
RACE Hispanic vs non-Hispanic White	1.11	0.84	1.46	1.13	0.86	1.49
RACE Other vs non-Hispanic White	0.73	0.30	1.82	0.82	0.33	2.05
Surgical Treatment Hepatectomy vs Ablation	2.36	1.81	3.06	2.36	1.82	3.07
Surgical Treatment Transplant vs Ablation	5.43	4.03	7.32	5.47	4.06	7.39
Elixhauser Comorbidity Score 3+ vs 0-2	2.68	1.98	3.63	2.66	1.96	3.59
Elixhauser Comorbidity Score no admit vs 0-2	0.54	0.35	0.84	0.55	0.35	0.85
Neighborhood Socioeconomic Status 2 vs 1	0.70	0.51	0.97	0.70	0.51	0.96
Neighborhood Socioeconomic Status 3 vs 1	0.66	0.48	0.91	0.67	0.48	0.92
Neighborhood Socioeconomic Status 4 vs 1	0.67	0.48	0.93	0.66	0.48	0.92
Neighborhood Socioeconomic Status 5 vs 1	0.56	0.38	0.81	0.55	0.38	0.80

Supplemental Table 15. Effect of missing stage on survival related to renal postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.78	0.67	0.91	0.79	0.68	0.92
RACE (non-Hispanic White)	Black/AA	0.95	0.76	1.19	0.96	0.77	1.20
RACE (non-Hispanic White)	Hispanic	0.98	0.85	1.14	0.99	0.85	1.15
RACE (non-Hispanic White)	Other	0.65	0.40	1.05	0.60	0.35	1.03
Tumor Stage (Stage I-II)	Stage III-IV	2.86	2.48	3.29	2.86	2.48	3.29
Tumor Stage (Stage I-II)	Unknown	2.33	1.53	3.53			
Surgical Treatment (Ablation)	Hepatectomy	0.58	0.51	0.67	0.59	0.51	0.67
Surgical Treatment (Ablation)	Transplant	0.19	0.15	0.26	0.19	0.15	0.26
Elixhauser Comorbidity Score (0-2)	3+	1.50	1.29	1.75	1.52	1.30	1.77
Elixhauser Comorbidity Score (0-2)	no admit	0.75	0.62	0.91	0.76	0.63	0.93
Insurance (Private)	Medicaid/Public/Uninsured	1.22	1.06	1.40	1.22	1.06	1.40
Insurance (Private)	Medicare	1.11	0.95	1.30	1.13	0.96	1.32
Insurance (Private)	Other	1.77	1.12	2.80	1.78	1.12	2.81
Neighborhood socioeconomic status (1)	2	0.91	0.77	1.08	0.91	0.77	1.08
Neighborhood socioeconomic status (1)	3	0.87	0.73	1.04	0.87	0.72	1.04
Neighborhood socioeconomic status (1)	4	0.81	0.68	0.98	0.83	0.69	0.99
Neighborhood socioeconomic status (1)	5	0.66	0.54	0.82	0.68	0.55	0.84
Age (<65)	65+	1.19	1.05	1.34	1.19	1.05	1.34
COMPLICATIONS_RENAL (0)	1	1.54	1.30	1.82	1.57	1.33	1.85

Supplemental Table 16. Effect of missing Elixhauser comorbidity score on presence of renal postsurgical complications

LOGISTIC REGRESSION						
POSTSURGICAL COMPLICATIONS						
Odds Ratio Estimates	with Stage 'unknown'			without Stage 'unknown'		
Effect	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
RACE Asian/PI vs non-Hispanic White	0.96	0.73	1.28	0.92	0.69	1.24
RACE Black/AA vs non-Hispanic White	1.03	0.67	1.57	1.09	0.71	1.68
RACE Hispanic vs non-Hispanic White	1.11	0.84	1.46	1.10	0.83	1.47
RACE Other vs non-Hispanic White	0.73	0.30	1.82	0.78	0.32	1.94
Surgical Treatment Hepatectomy vs Ablation	2.36	1.81	3.06	2.30	1.75	3.01
Surgical Treatment Transplant vs Ablation	5.43	4.03	7.32	4.32	3.14	5.94
Elixhauser Comorbidity Score 3+ vs 0-2	2.68	1.98	3.63	2.74	2.03	3.71
Elixhauser Comorbidity Score no admit vs 0-2	0.54	0.35	0.84			
Neighborhood Socioeconomic Status 2 vs 1	0.70	0.51	0.97	0.79	0.57	1.10
Neighborhood Socioeconomic Status 3 vs 1	0.66	0.48	0.91	0.69	0.49	0.97
Neighborhood Socioeconomic Status 4 vs 1	0.67	0.48	0.93	0.72	0.51	1.02
Neighborhood Socioeconomic Status 5 vs 1	0.56	0.38	0.81	0.59	0.40	0.87

Supplemental Table 17. Effect of missing Elixhauser comorbidity score on survival related to renal postoperative complications

SURVIVAL ANALYSIS							
OVERALL SURVIVAL							
Hazards Ratio Estimates		with Stage 'unknown'			without Stage 'unknown'		
Parameter (ref: group)		Hazard Ratio	95% Hazard Ratio Limits		Hazard Ratio	95% Hazard Ratio Limits	
RACE (non-Hispanic White)	Asian/PI	0.78	0.67	0.91	0.82	0.69	0.97
RACE (non-Hispanic White)	Black/AA	0.95	0.76	1.19	0.95	0.74	1.21
RACE (non-Hispanic White)	Hispanic	0.98	0.85	1.14	0.95	0.81	1.12
RACE (non-Hispanic White)	Other	0.65	0.40	1.05	0.62	0.36	1.07
Tumor Stage (Stage I-II)	Stage III-IV	2.86	2.48	3.29	2.69	2.31	3.14
Tumor Stage (Stage I-II)	Unknown	2.33	1.53	3.53	2.32	1.36	3.95
Surgical Treatment (Ablation)	Hepatectomy	0.58	0.51	0.67	0.57	0.50	0.66
Surgical Treatment (Ablation)	Transplant	0.19	0.15	0.26	0.19	0.14	0.26
Elixhauser Comorbidity Score (0-2)	3+	1.50	1.29	1.75	1.50	1.29	1.75
Elixhauser Comorbidity Score (0-2)	no admit	0.75	0.62	0.91			
Insurance (Private)	Medicaid/Public/Uninsured	1.22	1.06	1.40	1.27	1.09	1.47
Insurance (Private)	Medicare	1.11	0.95	1.30	1.06	0.89	1.26
Insurance (Private)	Other	1.77	1.12	2.80	1.54	0.92	2.58
Neighborhood socioeconomic status (1)	2	0.91	0.77	1.08	0.90	0.75	1.09
Neighborhood socioeconomic status (1)	3	0.87	0.73	1.04	0.87	0.72	1.06
Neighborhood socioeconomic status (1)	4	0.81	0.68	0.98	0.82	0.67	1.00
Neighborhood socioeconomic status (1)	5	0.66	0.54	0.82	0.65	0.52	0.82
Age (<65)	65+	1.19	1.05	1.34	1.18	1.03	1.35
COMPLICATIONS_RENAL (0)	1	1.54	1.30	1.82	1.56	1.31	1.85

CONCLUSION

We investigated racial/ethnic disparities among HCC patients in California focusing on access to surgical treatment, delay in surgical treatment after diagnosis, and postoperative complications. Further, we examined the effects of these factors on long-term survival and whether considering these factors impacted racial/ethnic disparities in survival.

In chapter 1, we noticed racial/ethnic disparities in obtaining HCC surgical treatment. Both Asian/PIs and Black/African Americans demonstrated higher odds for surgical treatment, while Hispanics displayed lower odds relative to non-Hispanic Whites. The interesting finding in our study was the increased odds for HCC surgical treatment among Black/African Americans who have historically demonstrated low odds of treatment in many prior studies.[1,2] This finding may relate to better access to healthcare among minorities after the implementation of the Affordable Care Act in 2014. Our study further revealed that the increased odds of surgical treatment for both Asian/PIs and Black/African Americans was driven mainly by hepatectomy. After adjusting for surgical treatment and other sociodemographic and clinical factors, our results demonstrated that Asian/PIs and Hispanics have superior survival after HCC than non-Hispanic Whites, while Black/African Americans had similar survival relative to non-Hispanic Whites. In past studies, Black/African Americans usually demonstrated higher risk of death than non-Hispanic Whites,[1,3] so our study highlights a significant survival improvement for this group. We found older age, male gender, late-stage cancer, and higher comorbid conditions to have a decreased likelihood for surgical treatment while high neighborhood SES, high volume hospitals, and private insurance were associated with an increased likelihood for surgical treatment. This suggests increased efforts to identify cancer early to improve the likelihood of getting surgical treatment. Also, additional resources should be allocated for patients under financial strain and access to high volume hospitals should be made easier for patients.

In chapter 2, we investigated racial/ethnic disparities in surgical treatment delay from HCC diagnosis. Our results indicated only Asian/PIs to have lower odds of delay compared to non-Hispanic Whites. Our analyses also demonstrated that hepatectomy was associated with a lower odds of treatment delay, while transplantation was associated with a higher odds of treatment delay. The delay due to transplantation is understandable given that some patients might need additional therapy prior to transplantation. Delays could also be due to organ shortages. Treatment delay demonstrated a protective effect on survival, which may be explained by case prioritization where advanced HCC cases with poor outcomes are treated without delay compared to cases with limited tumor progression and better prognosis. However, the protective effect of treatment delay should not be interpreted as a reason to delay treatment. Instead, the timing of surgical treatment should be left to the treating physician and not be related to comorbid conditions, patient neighborhood SES, patient distance from hospital, or hospital surgical volume, all of which were associated with delay. Our findings suggest increased efforts to reach out to patients living far from the hospital to ensure they receive appropriate and timely care.

In chapter 3, we studied the association between race/ethnicity and postoperative complications, as complications can lead to longer hospital stays,[4] higher reoperation rates[5] and increased medical costs[6]. We found no difference by race/ethnicity for developing overall postoperative complications comprised of neurological, cardiac, pulmonary, gastrointestinal, renal, and infectious complications, but observed that Black/African Americans were less like to have gastrointestinal related postoperative complications and Asian/PIs were less likely to have cardiac related postoperative complications. And many studies, including ours, have shown that postoperative complications can have a negative impact on survival. While recent developments in both surgical techniques and postsurgical management have made great strides in reducing postoperative complications, it is still common, occurring in 27.7% of patients in our study. To reduce postoperative complications, it is imperative that we understand the risk factors to minimize the incidence of complications, including neighborhood SES, and prior comorbidities observed in this study.

In summary, we found improved access to surgical treatment among Black/African Americans driven mainly by hepatectomy. Survival among Black/African Americans also improved compared to prior estimates. Interactions were observed between race/ethnicity and HCC treatment for both treatment delay and postoperative complications. In both cases, improved survival was observed for Asian/PIs, Hispanics and non-Hispanic Whites undergoing hepatectomy and transplantation compared to undergoing ablation. No such survival difference was observed for Black/African Americans. This calls for further studies to investigate and closely monitor racial/ethnic associations with possible factors such as private insurance and early-stage cancer both of which are associated with better survival. Our findings on postoperative complications underscore the need for disaggregation of complications. Our results indicated racial/ethnic variation for presence of specific postoperative complications. This offers the potential for more precise intervention by race/ethnicity. HCC is a challenging form of cancer with fatal consequences and racial/ethnic disparities related to HCC can have significant impact on accessing quality treatment and outcomes and necessitates ongoing research to attain equity.

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