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Treatment and Outcomes of Hepatocellular Carcinoma in Patients with Sickle Cell Disease: A Population-Based study in the U.S.

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Abstract

Background: Sickle cell disease (SCD) is a rare hemoglobinopathy which can result in chronic liver disease and cirrhosis. Patients with SCD have an increased risk of hematologic malignancy, but the prevalence of hepatocellular carcinoma (HCC) in this population is unknown. Herein, the association of SCD with HCC was examined using registry data.

Methods: The SEER-Medicare database was queried to identify patients diagnosed with HCC between 2000 and 2015, and further stratified by SCD status. Propensity matching was performed to examine cancer-related survival and treatment outcomes.

Results: Overall 56,934 patients with HCC were identified, including 81 patients with SCD. Patients with SCD more frequently had cirrhosis [48.1% (39/81) vs 23.5% (13,377/56,853), p<0.01] yet presented with smaller tumors [<5 cm: 51.9% (42/81) vs 38.5% (21,898/56,853), p=0.01]. After propensity matching, SCD was not associated with attenuated survival (aHR 0.73 95%CI 0.52-1.01). When stratified by treatment, patients with SCD had equivalent outcomes to

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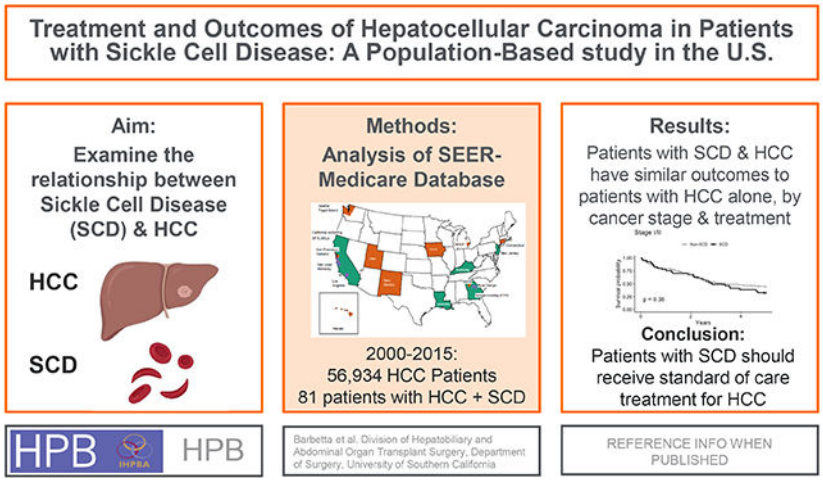
Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

chemotherapy (p=0.65), TACE/TARE (p=0.35), resection (p=0.15) and transplantation (p=0.67) when compared to non-SCD patients.

Conclusion: This study confirms that a subset of patients with SCD will develop HCC. Importantly, therapeutic options for HCC should not be limited by pre-existing SCD, and similar survival should be expected when compared to non-SCD patients.

Graphical Abstract



Introduction

Sickle Cell Disease (SCD) is caused by the presence of pathologic hemoglobin S in homozygous patients (HbSS), leading to the formation of sickled erythrocytes in deoxygenated conditions. The resulting sickled red blood cells cause hemolysis, vaso-occlusive crises, and severe pain. As a consequence of chronic hemolysis and microvascular injury, adult patients with SCD can develop a variety of secondary end-organ complications, including chronic liver disease. A 2016 Medicare report indicated that among >100,000 patients living with SCD in the U.S., 25% have some degree of chronic liver disease [1]. In parallel, the leading cause of death from the Centers for Disease Control national data through 2009 was attributed to chronic liver disease in 10% of patients with SCD [2].

Chronic liver disease in patients with SCD may in part be due to the direct consequences of intrahepatic sickling, resulting in repeated ischemic injury and vascular congestion. Acute sickle intra-hepatic cholestasis is a rare but severe manifestation of SCD that can progress to acute liver failure, with 17% being refractory to exchange transfusion and an associated 50% mortality [3-6]. Patients with SCD are more often at risk for chronic liver disease secondary to the known complications of repeated blood transfusions, including iron overload or acquired viral hepatitis, especially for transfusions received prior to 2000 [1,7,8]. Autopsy studies in patients with SCD have reported that 91% had hepatomegaly, 34% had focal parenchymal necrosis, 20% had portal fibrosis and regenerative nodules, and 11% had cirrhosis [7]. Fewer than a quarter of these patients had a premortem diagnosis of chronic liver disease. Thus, chronic liver disease is often multifactorial in these patients [9,10].

For these reasons, patients with SCD are at risk of developing hepatocellular carcinoma (HCC). However, no data exist regarding the incidence and treatment of HCC in patients with SCD. In two recently published registry studies examining the role for liver transplantation in 60 patients with SCD from the U.S. and France, only one patient had HCC [11,12]. It is possible that patients with SCD who develop HCC are not being referred for resection or transplantation, perhaps due to a perceived excessive risk of performing surgery in this patient population [13]. Prior studies have shown that patients with SCD carry increased risk of developing hematologic and solid organ malignancy and carry a three-fold increased risk of death when they carry a cancer diagnosis [14,15].

Understanding the prevalence of HCC and treatment outcomes in patients with HCC is important to guide clinicians caring for patients with SCD who develop chronic liver disease. In this study, we examined HCC in patients with SCD using Surveillance Epidemiology and End Results Program linked Medicare (SEER-Medicare) data. We aimed to define the cohort of SCD patients with HCC as well as describe the outcomes as they relate to both cancer stage and associated HCC treatment. Finally, we also studied if race might affect the treatment delivered among patients with SCD and HCC.

Methods

This study was approved by the Institutional Review Board at the University of Southern California.

Data Source

The SEER data, a part of the National Cancer Institute (NCI), is a database of cancer incidence and survival in the US including data from 22 regional cancer registries and thus covering roughly 35% of the US population (Supplemental Figure 1) [16]. The SEER program collects information on patient's demographics, tumor site, morphology, and stage as well as first course treatment and vital status. Linking SEER patients to their Medicare records provided more detailed information about these patients, their cancer, and other clinical conditions of interest. SEER data available from 1995-2015 and Medicare data available from 1995-2016 were examined in this study. The SEER-Medicare 5% non-cancer file was used to identify a SCD population with no history of cancer.

Study Population

All patients with HCC present in the SEER database between 2000 and 2015 were included. Patients with SCD within this dataset were identified by searching for SCD-specific ICD-9/ICD-10 in claim files over the entire study period (ICD-9: 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69, 282.41, 282.42; ICD-10: D57.00, D57.01, D57.02, D57.1, D57.20, D57.211, D57.212, D57.219, D57.40, D57.411, D57.412, D57.419, D57.80, D57.811, D57.812, D57.819). A single occurrence of any code was considered to be a patient with SCD. Patients with sickle cell trait (codes ICD-9: 282.5 and ICD-10: D57.3) were excluded from analysis.

Sociodemographic and Clinical Characteristics

Sociodemographic characteristics were obtained from variables included in the SEER data. Characteristics that can vary over time (e.g. location, marital status) were selected to correspond with the occurrence of their HCC as some patients have other prior cancers. Clinical variables were identified using Medicare claims: Hepatitis B Virus; Hepatitis C Virus; Hepatitis D Virus; Alcohol-related Liver Disorder; Rare Genetic Disorder; and Cirrhosis (Supplemental Table 1). The above codes were required to be present within one-year of diagnosis to be considered as a possible cause of their HCC.

HCC Treatment

Cancer treatments were identified using ICD-9/ICD-10/CPT codes (Supplemental Table 1). These treatments included transplantation, surgical resection, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and chemotherapy. Transplantation codes within two years of diagnosis were considered as treatment. Surgical resection codes within six months from diagnosis were considered as treatment. TACE, TARE, and chemotherapy codes within nine months of diagnosis were considered as treatment.

Statistical Analysis

Treatment received was ordered into a single mutually exclusive variable with the following hierarchy: transplant > surgical resection > TACE > TARE > chemotherapy > no treatment. This variable was then grouped several ways in order to comply with SEER data reporting requirements for cohorts <11 patients as well as fit with analytical needs. For the bivariate analyses (Table 2) treatment is displayed as Surgical (transplant and surgical resection), Non-Surgical (TACE, TARE, and chemotherapy), and No Treatment. In regression models (Table 3) treatment is displayed as Transplant, Surgical Resection, Non-Surgical, and No Treatment. Finally, for the overall Kaplan-Meier survival curves, no grouping was done. SCD and non-SCD HCC patients were compared across several demographic and clinical variables; similar comparisons were also performed on subsets of these groups. Chi-square tests were performed for categorical variables and T-tests were performed for continuous ones; a significance level $\alpha=0.05$ was used. A subsample of non-SCD HCC patients was identified using propensity matching in order overcome bias by balancing across several demographic variables. A 3:1 nearest neighbor matching was performed using a logistic regression model of SCD status controlling for age at diagnosis, sex, race, and urban vs. rural status.

Survival time was calculated as years from date of diagnosis to either date of death or last known follow-up date in the Medicare data. Kaplan-Meier curves were constructed comparing five-year survival probability between SCD and non-SCD patients stratified by HCC stage and also treatment received. Additionally, a Cox Proportional Hazard model was constructed to measure the effect treatment and SCD status have on survival while controlling for potentially confounding demographic and clinical variables. These additional variables were identified in a two-step selection process. Focusing on a subset of a priori variables (age at diagnosis, sex, race, urban vs. rural status, HCC stage, and comorbidities), the effect of these variables on treatment received were first measured using a Multinomial

Logistic Regression model controlling for SCD status and then measured on overall survival using a Cox Proportional Hazard model, controlling for SCD status and treatment received. Those variables found to be statistically significant ($p<0.05$) in both steps were included in the final survival model. These selected variables were also used to examine the relationship SCD status and race (Black compared to non-Black) have on treatment received in Multinomial Logistic regression model. SEER does not allow reporting of cohorts, either directly or through back calculation, smaller than 11, and in these instances, sample sizes are replaced with "**". All statistical analysis and figures were done in R version 4.0.3.

Results

Study Demographics

A total of 56,934 patients were identified with HCC diagnosed between 2000 and 2015, and a subset of 81 patients had SCD (Study inclusion/exclusion outlined in Supplemental Figure 2). Both SCD and non-SCD cohorts had similar characteristics at the time of HCC diagnosis including sex, marital status, residential area or SEER-regions, level of education, and household income (Table 1). Interestingly, almost half of the SCD patient were white (44.4%). Patients with SCD and HCC were less likely to be Black when compared to SCD patients with non-HCC cancers ($p<0.01$) or patients with SCD from the non-cancer reference cohort ($p<0.01$) (Supplemental Figure 3).

HCC Features in patients with SCD

A temporal distribution in era of cancer diagnosis was observed, with the majority of the SCD population being diagnosed with HCC after 2006 (Table 2, $p=0.01$). Patients with SCD were more likely to have tumors measuring <5 cm [51.9% vs 38.5%, $p=0.01$] and present with either stage I or II disease [49.4% vs 41.4% of non-SCD patients, $p=0.05$]. The SCD population with HCC was more likely to have other associated liver diagnoses, including a higher frequency of cirrhosis [48.1% vs 23.5%], Hepatitis C [34.6% vs 18.1%], and alcoholic liver disease [22.2% vs 9.7%] ($p<0.01$ for all diagnoses vs the non-SCD group). Examination of treatment delivered showed that patients with SCD were more likely to receive cancer treatment of any type when compared to non-SCD patients (Table 2, $p<0.01$).

To address the imbalance in number of patients and covariates between the patient groups, a nearest neighbor propensity matching was performed (3:1), resulting in 81 patients with SCD and a reference group of 243 matched non-SCD patients (Table 2). Non-SCD patients were more often from Northeast region (65.4%) while the majority of SCD patients (66.7%) were from the West ($p<0.01$) and had a lower level of education ($p<0.01$) (Table 1). Even after matching, patients with SCD were more likely to have cirrhosis [48.1% vs 24.7%, $p<0.01$], alcoholic liver disease [22.2% vs 9.9%] $p=0.01$), and Hepatitis C [34.6% vs 17.7%, $p<0.01$] when compared to the non-SCD group. Similar to what was observed in the unmatched cohorts, patients with SCD were more likely to receive any cancer treatment when compared to the non-SCD matched cohort (63.0% vs 32.5%, $p<0.001$). Surgical treatment, consisting of either resection or transplantation, was performed more often in patients with SCD [18.5% vs 10.7% of non-SCD patients, $p<0.01$]. Non-surgical treatments including radiofrequency ablation, chemoembolization and chemotherapy were

administered in 44.4% of SCD patients versus only 21.8% of non-SCD patients (p<0.01), with chemoembolization being the most common cancer treatment in both groups (Table 2).

Examination of the potential impact of SCD and race on HCC treatment

A multinomial logistic regression model was used to analyze the effect of SCD on type of cancer treatment received. Patients with SCD were more likely to undergo liver transplantation (OR 3.19, 95% CI: 1.16-8.76, p=0.02), surgical resection (OR: 3.12 95% CI 1.21-8.09, p=0.019), or non-surgical treatment (OR: 3.71 95% CI 2.09-6.6, p<0.01) when compared to non-SCD patients (unadjusted, Table 3A). Multivariable analysis showed that the SCD population had a more than three-fold adjusted increase in odds of receiving surgery (p=0.02) or non-surgical treatment (p<0.01) when compared to non-SCD patients (Table 3A).

Next, we explored whether race was associated with the type of cancer treatment delivered among patients with SCD and HCC. Given that SCD is associated with Black race and that race represents a social determinant of health that can impact rates of cancer treatment, we compared Black versus the remaining combined non-Black racial categories. There were differences between Black and non-Black patients with SCD and HCC, with the Black subgroup more often being single, from the South, and having a lower household income when compared to non-Black patients with SCD. However, no differences in the type of cancer treatment received were observed in univariate or multivariate analyses by race (**data not shown**).

Survival analysis and risk factors including race

Survival analysis stratified by HCC stage showed that while SCD and non-SCD patients with stage I and II of disease had similar overall (p=0.38), SCD patients with stage III or IV of disease had a better survival (p=0.016) (Figure 1). Survival analyses stratified by treatment type demonstrated that patients with SCD who underwent liver transplant had an equivalent outcome when compared to non-SCD patients (p=0.67). As well, the overall survival of SCD and non-SCD patients who underwent to surgical resection was equivalent (p=0.15) (Figure 2). Among non-surgical treatments, patients with SCD who received TACE/TARE and chemotherapy showed similar overall survival when compared to non-SCD patients who received similar treatments (p=0.35 and p=0.65 respectively, Figure 2).

Next, a multivariate Cox regression analysis was performed to understand the relationship between treatment, SCD status, and survival while considering other potential confounders. After controlling for SCD status, liver transplantation and surgery were associated with improved overall survival (Table 3B). Specifically, the adjusted overall survival was greater in patients who underwent liver transplantation (aHR 0.32 95% CI 0.15-0.7, p<0.01) or surgery (aHR= 0.25 95% CI 0.12-0.51, p<0.01) (Table 3B). After controlling for SCD status, survival was decreased in all patients with alcohol related liver disease (aHR= 1.96, 95% CI 1.31-2.94, p<0.01), advanced age (>75 years: aHR=2.5 [95% CI 1.66-3.76], p<0.01), or more advanced stages of cancer (stage III or IV: aHR= 2.5 [95% CI 1.66-3.76, p<0.01).

Notably, the presence of SCD was not associated with a greater risk of death (aHR 0.75 [95% CI 0.55-1.03], p=0.08).

Survival analysis of the SCD population stratified by race demonstrated that Black patients with SCD without a cancer diagnosis had a shorter overall survival when compared to the Black SCD population with HCC as well as the non-Black SCD population both with and without cancer (p<0.01) (Supplemental Figure 4).

Discussion

A deeper understanding of the chronic manifestations of SCD and advances in management have improved the life expectancy in adults with SCD [17]. With improved survival comes the challenge of managing complexes disease states that present later in life, including chronic liver disease and HCC. Through exploration of the SEER-Medicare database, this study has identified a cohort of patients with SCD who have also been diagnosed with HCC. When compared to non-SCD patients, the SCD population had smaller, earlier stage HCC at the time of diagnosis. Additionally, we have identified risk factors amongst the SCD cohort, such as increased frequency of cirrhosis, viral hepatitis, and alcohol related liver disease, which place patients at risk for hepatocarcinogenesis. Interestingly, despite the complexity of this chronic disease, SCD patients had similar or improved survival stage for stage as well as similar survival when stratified by HCC treatment to non-SCD patients.

While the association between hematologic malignancies and SCD has been described in case series, few studies have focused on solid organ tumors [18,19]. In one study using registry data from England, Seminog et al. established an association between SCD and four solid organ tumors including, colon, non-melanoma skin, kidney and thyroid cancer [20]. While the underlying etiology of these cancers, including HCC, are likely multifactorial, repeated hypoxic insults during vaso-occlusive events in SCD may contribute [9,10]. In HCC, hypoxia plays a crucial rule in aggressive cancer specific phenotypes as well as in therapeutic failure [21-23]. Also, blood transfusion, a mainstay in management of SCD, places patients at greater risk for the development of HCC due to the development of chronic viral hepatitis [24]. In this study, we observed that patients with SCD more often presented with cirrhosis as well as Hepatitis B and C when compared to non-SCD patients (Table 2). The association between viral hepatitis and SCD patients with HCC is expected, as routine testing of transfused blood did not begin until 1971 for hepatitis B and 1990 for hepatitis C. Indeed, a study by Hassan et al. observed that 58% of SCD patients transfused prior to 1992 had HCV antibodies [25]. Therefore, the association between HCC and SCD is unsurprising given the hepatotoxic nature of both the underlying disease and risks associated with its management.

Multidisciplinary management of the SCD population is complex, particularly when patients are diagnosed with equally challenging conditions such as cancer that require a unique set of subspecialists. While it might be assumed that patients with SCD would have worse cancer associated outcomes, we observed that stage for stage, these patients have at least similar if not improved survival compared to non-SCD patients (Figure 1). Additionally, on multivariate analysis, there was no association between SCD and death in HCC. Given the rarity of both SCD and HCC, our cohort is small, but our findings are consistent with that

of other groups. In a registry study of 6,423 patients with SCD diagnosed with a variety of different cancers, Brunson et al. observed that while overall survival was attenuated in SCD patients, cancer-specific survival was equivalent to non-SCD patients [14]. We can therefore echo the sentiment that cancer treatments should not be restricted in patients with SCD.

This study suggests that underlying SCD should not limit surgical treatment of HCC. Patients with SCD had similar survival when undergoing surgical resection for HCC to those patients without SCD. Multiple studies have explored outcomes related to common surgical procedures in patients with SCD, such as laparoscopic cholecystectomy and orthopedic procedures, and have found that while operative intervention is safe, there is increased risk of perioperative complications in this population [26,27]. A possible explanation for improved survival in the SCD population in the present study involves the extensive perioperative evaluation that represents standard of care in the multidisciplinary management of cancer. Preoperative optimization or the concept of “pre-habilitation” has been shown to improve outcomes in liver resections [28]. While this concept has not yet become standard of care in all patients, it has been long recognized that optimization of patients with SCD is essential to prevent perioperative complications. Evaluation and optimization of all organ systems must be addressed prior to surgery given the systemic complications of SCD [29]. Thorough preoperative assignment and mitigation of preoperative risk factors may contribute to better overall outcomes. We observed equivalent survival in SCD and non-SCD patients who underwent liver transplantation for HCC. In our prior propensity matched cohort analysis comparing Black patients with and without SCD who underwent liver transplant for all causes, we observed that SCD patients were sicker at the time of transplant but, despite this, experienced equivalent graft and patient survival [11]. Thus, major liver resection or even liver transplantation should be considered for patients with SCD and HCC that otherwise meet criteria for these procedures.

There are limitations to this study. A major limitation is the small sample size, despite using a large national cancer registry. Indeed, in 2015 the SEER registries included 10 states (Supplemental Figure 1): California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah and two metropolitan areas: Detroit and Seattle, thus representing only a few of the states that have large populations of SCD patients (e.g. California, Louisiana, Georgia, and New Jersey). States with the largest SCD populations overall (Florida, New York, and Texas) are notability absent from the data. This likely influences the cohort of SCD patients we were able to identify and their demographics, especially the race distribution[30,31]. SCD and HCC are both rare diseases and while this study represents the largest cohort to our knowledge, the ability to fully understand the association between these two diseases is limited. Additionally, there are inherent limitations with the utilization of the SEER and Medicare databases, including inaccurate and incomplete data collection and entry and recognition that these datasets were not designed to answer the questions of our study. The retrospective nature of the study does not allow for the complete understanding of why various treatment regimens were pursued.

Also, our results may be affected by population selection bias. In our study, the median age at death in patients with SCD was 67 years, which was similar to the non-SCD group. However, two previous studies demonstrated that the lifespan has paradoxically decreased

for adult patients with SCD, with a median age at death of 38 years for males and 42 for females[2,32]. A more recent simulated cohort modeling study supports this observation, where the projected life expectancy was 54 years for patients with SCD vs 74 for non-SCD patients [33]. The younger age at death of the SCD population in Supplemental Figure 4 might also explain our small sample size, as these patients may not live long enough to reach the ages captured by SEER-Medicare files. We can speculate that the longer life span we observed in patients with SCD in the SEER dataset could be due to several factors. It is possible that patients with SCD who live long enough to develop HCC have a less severe clinical manifestation of SCD and its associated complications or different access to tertiary care in urban centers that could lead to longer survival. Differences in access to care and again the younger age at death are also reflected in our results (Supplemental Figure 4), which confirmed that Black patients with SCD and no history of cancer had a shorter lifespan. This observation may have limited our ability to detect HCC-related disparities faced by patients with SCD, especially among ethnic and racial minorities [34]. Despite these limitations, this study does give valuable insight into two diseases which could not otherwise be described given their rarity.

In conclusion, while rare, given the hepatic insult of both the nature and management of SCD, there is a risk of developing HCC in this patient population. The association between HCC and SCD was more commonly observed in patients with SCD and underlying hepatitis B and C, as well as those with cirrhosis. This study suggests that management of HCC, including application of appropriate therapeutic options, should not be limited by SCD and that this patient population can expect similar survival to non-SCD patients. Further prospective studies are necessary to understand the prevalence and risk of HCC in adult patients with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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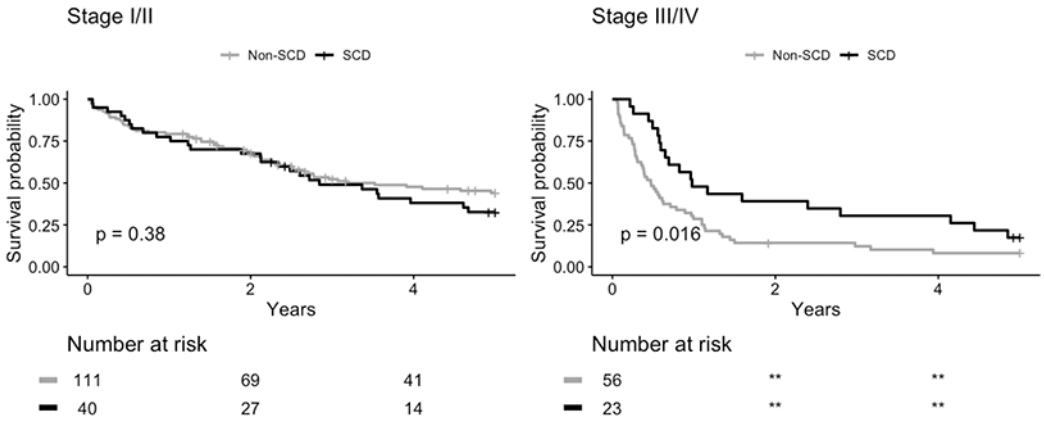

Figure 1. Overall patient survival of SCD and non-SCD patients, stratified by cancer stage.

Note: Due to data reporting requirements, all instances where a subsample of n<11 could be reported or back calculated have been replaced with "**" due to the SEER data use agreement.

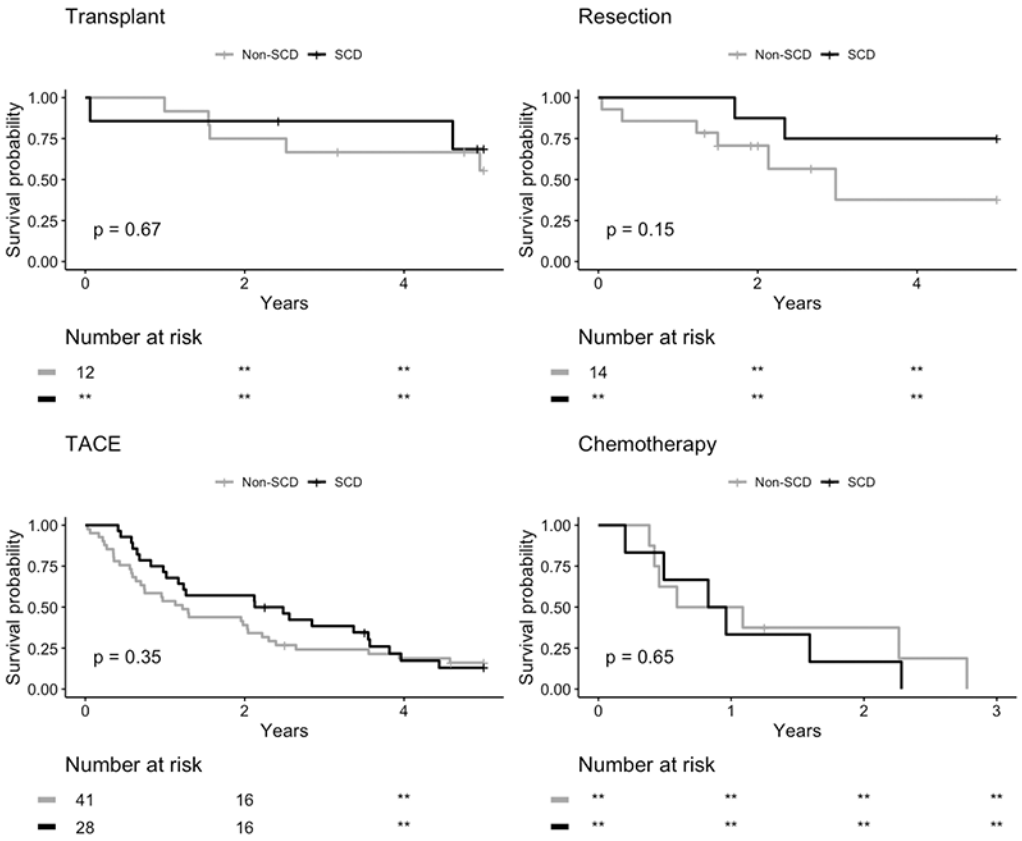

Figure 2. Overall survival of SCD and non-SCD HCC patients, stratified by type of treatment.

Note: Due to data reporting requirements, all instances where a subsample of n<11 could be reported or back calculated have been replaced with "**" due to the SEER data use agreement.

Table 1:

Demographic characteristics of the overall study population and when compared to a propensity-matched reference group of non-SCD patients.

	Overall				Propensity Matched Reference Group			
Characteristics, n (%)	**Total (n=56,934)**	**Non-SCD (n=56,853)**	**SCD (n=81)**	***p*-value**	**Total (n=324)**	**Non-SCD (n=243)**	**SCD (n=81)**	***p*-value**
Age at Diagnosis								
< 65	18164 (31.9%)	18135 (31.9%)	29 (35.8%)	0.02	116 (35.8%)	87 (35.8%)	29 (35.8%)	0.99
65-74	19999 (35.1%)	19962 (35.1%)	37 (45.7%)		148 (45.7%)	111 (45.7%)	37 (45.7%)	
75+	18771 (33%)	18756 (33%)	15 (18.5%)		60 (18.5%)	45 (18.5%)	15 (18.5%)	
Sex								
Male	40732 (71.5%)	40678 (71.5%)	54 (66.7%)	0.4	216 (66.7%)	162 (66.7%)	54 (66.7%)	0.99
Race/Ethnicity								
White	37160 (65.3%)	37124 (65.3%)	36 (44.4%)	<0.01	141 (43.5%)	105 (43.2%)	36 (44.4%)	0.99
Black	6455 (11.3%)	6440 (11.3%)	15 (18.5%)		60 (18.5%)	45 (18.5%)	15 (18.5%)	
Asian	5924 (10.4%)	5910 (10.4%)	14 (17.3%)		56 (17.3%)	42 (17.3%)	14 (17.3%)	
Hispanic	3055 (5.4%)	**	**		31 (9.6%)	**	**	
Other/N. Am./Unknown	4340 (7.6%)	**	**		36 (11.1%)	**	**	
Marital Status								
Single	24611 (43.2%)	27148 (47.7%)	27110 (47.7%)	0.98	155 (47.8%)	117 (48.1%)	38 (46.9%)	0.95
Partnered	29786 (52.3%)	29786 (52.3%)	29743 (52.3%)		169 (52.2%)	126 (51.9%)	43 (53.1%)	
SEER Region								
Northeast	8132 (14.3%)	8119 (14.3%)	13 (16%)	0.19	172 (53.1%)	159 (65.4%)	13 (16%)	<0.01
Midwest	4359 (7.7%)	**	**		31 (9.6%)	**	**	
South	10176 (17.9%)	**	**		13 (4%)	**	**	
West	34267 (60.2%)	34213 (60.2%)	54 (66.7%)		108 (33.3%)	54 (22.2%)	54 (66.7%)	
Urban vs. Rural								
Urban	51092 (89.7%)	**	**	0.15	312 (96.3%)	**	**	0.99
Percent High School Graduate								
<80%	21288 (37.4%)	21254 (37.4%)	34 (42%)	0.50	108 (33.3%)	74 (30.5%)	34 (42%)	0.03
80%-89%	18282 (32.1%)	18255 (32.1%)	27 (33.3%)		97 (29.9%)	70 (28.8%)	27 (33.3%)	
90%+	17364 (30.5%)	17344 (30.5%)	20 (24.7%)		119 (36.7%)	99 (40.7%)	20 (24.7%)	

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	Overall				Propensity Matched Reference Group			
Characteristics, n (%)	**Total (n=56,934)**	**Non-SCD (n=56,853)**	**SCD (n=81)**	***p*-value**	**Total (n=324)**	**Non-SCD (n=243)**	**SCD (n=81)**	***p*-value**
Median Household Income								
<$35,000	9480 (16.7%)	9468 (16.7%)	12 (14.8%)	0.64	60 (18.5%)	48 (19.8%)	12 (14.8%)	0.24
$35,000-$64,999	29107 (51.1%)	29068 (51.1%)	39 (48.1%)		131 (40.4%)	92 (37.9%)	39 (48.1%)	
$65,000+	18347 (32.2%)	18317 (32.2%)	30 (37%)		133 (41%)	103 (42.4%)	30 (37%)	

Note: Due to data reporting requirements, all instances where a subsample of n<11 could be reported or back calculated have been replaced with "**".

Table 2:

HCC characteristics of the overall study population and when compared to a propensity-matched reference group of non-SCD patients.

	Overall				Propensity Matched Reference Group			
Characteristics, n (%)	**Total (n=56,934)**	**Non-SCD (n=56,853)**	**SCD (n=81)**	***p*-value**	**Total (n=324)**	**Non-SCD (n=243)**	**SCD (n=81)**	***p*-value**
Diagnosis Year								
2000-2005	15090 (26.5%)	15078 (26.5%)	12 (14.8%)	0.01	90 (27.8%)	78 (32.1%)	12 (14.8%)	0.01
2006-2010	18202 (32%)	18165 (32%)	37 (45.7%)		116 (35.8%)	79 (32.5%)	37 (45.7%)	
2011+	23642 (41.5%)	23610 (41.5%)	32 (39.5%)		118 (36.4%)	86 (35.4%)	32 (39.5%)	
Stage								
I/II	23562 (41.4%)	23522 (41.4%)	40 (49.4%)	0.05	152 (46.9%)	112 (46.1%)	40 (49.4%)	0.30
III/IV	13394 (23.5%)	13371 (23.5%)	23 (28.4%)		79 (24.4%)	56 (23%)	23 (28.4%)	
Unknown	19978 (35.1%)	19960 (35.1%)	18 (22.2%)		93 (28.7%)	75 (30.9%)	18 (22.2%)	
Tumor Size								
0-49mm	21940 (38.5%)	21898 (38.5%)	42 (51.9%)	0.01	148 (45.7%)	106 (43.6%)	42 (51.9%)	0.12
50+mm	18909 (33.2%)	18881 (33.2%)	28 (34.6%)		106 (32.7%)	78 (32.1%)	28 (34.6%)	
Unknown	16085 (28.3%)	16074 (28.3%)	11 (13.6%)		70 (21.6%)	59 (24.3%)	11 (13.6%)	
Comorbidities								
Alcohol-related Liver Disorder	5555 (9.8%)	5537 (9.7%)	18 (22.2%)	<0.01	42 (13%)	24 (9.9%)	18 (22.2%)	0.01
Cirrhosis	13416 (23.6%)	13377 (23.5%)	39 (48.1%)	<0.01	99 (30.6%)	60 (24.7%)	39 (48.1%)	<0.01
Hepatitis B or D	1767 (3.1%)	**	**	<0.01	16 (4.9%)	**	**	<0.01
Hepatitis C	10300 (18.1%)	10272 (18.1%)	28 (34.6%)	<0.01	71 (21.9%)	43 (17.7%)	28 (34.6%)	<0.01
Treatment								
No Treatment	42025 (73.8%)	41995 (73.9%)	30 (37%)	<0.01	194 (59.9%)	164 (67.5%)	30 (37%)	<0.01
Surgical	4859 (8.5%)	4844 (8.5%)	15 (18.5%)		41 (12.7%)	26 (10.7%)	15 (18.5%)	
Non-Surgical	10050 (17.7%)	10014 (17.6%)	36 (44.4%)		89 (27.5%)	53 (21.8%)	36 (44.4%)	

Note: Due to data reporting requirements, all instances where a subsample of n<11 could be reported or back calculated have been replaced with "**".

Table 3.

Multinomial logistic regression analysis examining the effect of SCD on type of HCC treatment (Part A) and Cox proportional hazard model predicting overall survival (Part B).

A. Model predicting type of treatment*						
	Unadjusted Odds Ratios (95% CI)			**Adjusted Odds Ratios (95% CI)**		
Effect	**OR**	**95% CI**	***p*-value**	**Treatment OR**	**95% CI**	***p*-value**
SCD (vs. Non-SCD)	**No Treatment (ref)**			**No Treatment (ref)**		
	Transplant			**Transplant**		
	3.19	1.16-8.76	**0.02**	2.67	0.90-7.88	**0.08**
	Surgical Resection			**Surgical Resection**		
	3.12	1.21-8.09	**0.02**	3.85	1.41-10.46	**0.01**
	TACE/TARE/Chemotherapy			**TACE/TARE/Chemotherapy**		
	3.71	2.09-6.6	**<0.01**	3.71	2.03-6.78	**<0.01**

B. Model predicting overall survival		
	aHR (95% CI)	***p*-value**
Treatment (ref = No Treatment)		
Transplant	0.32 (0.15 0.7)	<0.01
Surgical Resection	0.25 (0.12 0.51)	<0.01
Non-Surgical Therapy	0.78 (0.58 1.06)	0.12
Sickle Cell Disease Status (ref = Non-SCD)	0.75 (0.55 1.03)	0.08
HCC Stage (ref = Stage I/II)		
III/IV	2.56 (1.83 3.59)	<0.01
Unknown	2.33 (1.69 3.2)	<0.01
Age at Diagnosis (ref = < 65 years)		
65-74 years	1.79 (1.3 2.46)	<0.01
75+ years	2.5 (1.66 3.76)	<0.01
Alcohol Related Liver Disease (ref = No)	1.96 (1.31 2.94)	<0.01

*Adjusting factors in Multinomial Logistic Regression Model: age, alcohol related liver disease and stage of disease.