Influence of Social Determinants of Health on Timeliness to Treatment for Metastatic HCC and the Impact of Affordable Care Act

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Abstract

Background

To achieve progress in cancer treatment, socioeconomic disparities impacting the care need to be recognized and addressed. We hypothesized that social determinants of health may predict a delay in systemic therapy for metastatic hepatocellular carcinoma patients (HCC) and sought to examine the impact of the Affordable Care Act (ACA).

Methods

National Cancer Database (NCDB) was queried for patients with metastatic hepatocellular carcinoma diagnosed from 2004-2015 and considered for first line systemic therapy within 6 months (180 days) of diagnosis. Time to initiation (TTI) was defined as the time in days(d) from diagnosis of cancer to initiation of systemic therapy. Survival was measured in months(m) from the day of diagnosis. Multivariate analyses were performed using 2010 as a cut-off between pre-and post-ACA for analysis.

Results

630 patients meeting the eligibility criteria. Median TTI in the group was 57d. The only factor associated with delayed TTI (defined as the fourth quartile of TTI) in a multivariate logistic regression was non-Hispanic Black (NHB) race Odds Ratio OR 1.94(95%CI 1.0–3.3), p-value=0.052. The OR showed improvement with implementation of ACA – OR3.6(95%CI 1.4-9.4),p-value 0.008 during pre-ACA vs. 1.3(0.5-3.1),p-value=0.6 post-ACA. There was a non-significant trend towards higher mortality among NHB vs. NHW (HR 1.2, 95% CI 1.0-1.6) and lower mortality for those insured vs. uninsured (HR 0.8, 95% CI 0.5-1.1.

Conclusion

Race appears to impact timeliness to therapy in metastatic HCC patients and was positively impacted by ACA. Continued research to monitor disparities in care and identify underlying mechanisms to mitigate them are warranted.

Introduction

Liver cancer is a leading cause of cancer related death worldwide and accounts for 700,000 deaths every year.[1] Specifically in the United States, the rates of primary liver cancer has more than tripled since the 1980s and was associated with more than a doubling of death rates during this period.[1] Hepatocellular carcinoma (HCC) represents the predominant form of primary liver cancers and the rising incidence and mortality of liver cancer has been shown to mirror that of HCC.[2] Studies predict that this trend would continue to rise in the coming years although the rate of rise has decreased.[2,3]

The Affordable Care Act (ACA) was enacted into law in 2010 and aimed to address disparities in healthcare access and outcomes.[4–6] Organizations such as the American College of Physicians (ACP) have proposed further expansion of the provisions set forth by this law with the goal of achieving universal health coverage.[7] HCC represent a cancer subtype with racial disparities in outcomes with higher mortality rates noticed among patients belonging to non-Hispanic Black (NHB) and minority races.[8] This is driven by disparities in access to appropriate systemic or other locoregional and surgical treatments including liver transplants. [8] But as in other cancer types, patients with metastases represent the most vulnerable of the HCC population with limited options of therapy and in turn there is limited data on the impact of socioeconomic factors on this population or that of policies that have been aimed to mitigate these. In this context, we aimed to test the hypothesis that socioeconomic factors impact the delay in timeliness to therapy and outcomes for metastatic hepatocellular cancers and sought to explore the effect of Affordable Care Act (ACA) on this relationship using the National Cancer Database (NCDB).

Method

Patient Selection and Variables

A retrospective analysis using de-identified data accessed from the NCDB was performed.[9] The study was exempt from Institutional Review Board (IRB) oversight and did not require ethics approval. The NCDB was queried for patients diagnosed between 2004-2015 with stage IV hepatocellular carcinoma HCC (Histology code 8170, AJCC pathologic stage IV).

We excluded patients who did not receive any therapy and excluded those who were treated after 6 months. We excluded patients with NCDB class of case categories other than 10-14 (patients who had a diagnosis at the reporting facility and all treatment or a decision not to treat was done elsewhere), as has been previously utilized and reported from the NCDB to minimize reporting errors.[9]

Race was recategorized into four categories – non-Hispanic Whites (NHW), non-Hispanic Blacks (NHB), Hispanics (H) and others. Comorbidity was captured using the Charlson/Deyo comorbidity index. The Charlson/Deyo value is a weighted score derived from the sum of the scores for each of the comorbid conditions listed in the Charlson Comorbidity Score. [9,10] Other sociodemographic variables studied included – gender (male and female), educational status represented in terms of quartiles of the percentage of persons with less than a high school education and median household income - both according to the residents' census tract. Locations were assigned based on data provided by the United States Department of Agriculture Economic Research Service and categorized as rural, urban or metropolitan. Insurance status is captured in the NCDB as it appears on the admission face sheet for the patient and was recoded as insured (Private, Medicaid, Medicare, others) or uninsured. The facility type was assigned according to the Commission on Cancer accreditation category as used in the NCDB. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Statistical Analysis – Time to Therapy Initiation (TTI)

Time to initiation of treatment was defined as time in days from the date of diagnosis of cancer to earliest date of initiation of cancer-directed systemic therapy (TTI). Patients were then classified into quartiles of TTI based on the percentiles for TTI. Those belonging to 4^{th} quartile constituted the delayed treatment group. Univariate logistic regression and stepwise multivariate logistic regression was used to develop a multivariate model to identify predictors for delayed-TTI and assess variation with respect to ACA. The results are reported as Odds Ratio (OR) with 95% Confidence interval (95% CI).

Survival Analysis

Survival was measured in months (m) from the day of diagnosis to the day of censoring (last follow up or day of death). Survival estimates were performed using the Kaplan-Meier method. Cox proportional hazard modeling assessed for significant independent variables impacting the survival that were used to perform multivariate logistic regression.

The study period was divided into pre-ACA and post-ACA using 2010 as cut-off. Summary statistics are presented as percentage for categorical data and median with interquartile range (IQR) for quantitative data.

Data was analyzed using STATA Version 15. Adjusted effect size estimates and 95% confidence intervals are reported using an alpha level of 0.05 to indicate statistical significance. Extremely low values for p-values are represented as <0.005. Most results are rounded to a decimal place of 1 except on occasions where we had to use decimal places up to 3 digits to represent the underlying differences or value for statistical significance.

Results

Cohort characteristics

The dataset included 149,949 patients with hepatocellular carcinoma and 4,648 stage IV HCC of whom 1,784 underwent initial treatment (chemotherapy, immunotherapy and/or stem cell transplant) as per the inclusion criteria. Following exclusion of 1,088 patients treated beyond 6 months and 66 patients with insufficient data for analysis, 630 patients were eligible for analysis (Figure 1). This included 322 (51.1%) pre-ACA and 308 (48.9%) post-ACA patients, respectively.

The median age was 60 (IQR 55-76) years and included 525 (83.3%) males. The majority were NHW 386 (83.3%), had insurance 567 (93.9%), belonged to Metropolitan areas 531 (87.5%), and were treated at Comprehensive Community Cancer Centers 220 (35.8%) or Academic Programs 294 (47.9%). Most patients in this cohort had a comorbidity score of 0 (55.4%) and there was similar distribution in terms of income and education. The median time to initial treatment was 57 (IQR 3-117) days overall. The baseline characteristics of the cohort are summarized in Table 1.

Group with Delayed TTI and Impact of ACA

Median TTI for the 4th quartile group was 153 (IQR 131-164) days from the time of diagnosis. This included 157 patients. Baseline characteristics of this group are summarized in Table 2. This included 83 patients pre-ACA and 74 post-ACA. The only factor associated with delayed TTI in logistic regression analysis was belonging to non-Hispanic Black race (NHB) (odds ratio OR 1.94 (95% CI 1.1-3.3), p-value=0.052). Other variables analyzed included educational status, income group, insurance status, geographical location, comorbidity class, facility of treatment and did not show any significant association with delayed TTI.

In the context of the timing of ACA, the NHB group was associated with a decrease in likelihood for delayed treatment initiation from pre-ACA (OR 3.6, 95% CI 1.4-9.4; p-value = 0.008) to post-ACA (non-significant, OR 1.3, 95% CI 0.5-3.1; p-value = 0.60) when compared to NHW. These results are outlined in Table 3. The prevalence of insurance including Medicaid (as it pertains to ACA) in the entire cohort increased between the two time periods (17.5% post-ACA vs. 12.4% pre-ACA, p-value<0.08 for the entire cohort, 31.1% vs. 23.1%, p-value 0.09 for NHB) but insurance coverage status did not correlate independently with the delay in TTI.

Socioeconomic Factors and Mortality

The median survival was 6.6 (3.1-14.3) months for the entire cohort. There were trends towards poorer survival in NHB vs. NHW – 4.6 (95% CI 2.2-10.1) months vs. 6.7 (95% CI 3.3-14.7) months, male vs. female – 6.5 (95% CI 3.0-13.5) months vs. 7.8 (95% CI 4.3-20.0) months, and uninsured 4.2 (95% CI 2.8 – 7.3) months vs. insured 6.8 (95% CI 3.3-14.7). On multivariate cox regression analysis for mortality, female sex and insurance status as insured were associated lower were statistically significant (Table 4). Other variables analyzed included educational status, income group, geographical location, comorbidity class, facility of treatment and did not show any significant association to be included in the cox regression model.

Discussion

HCC is a cancer impacting the elderly population and this is reflected in the present study group. While comparing this study to other studies, it should be kept in mind that we only included patients that were able to receive some form of therapy in order to test the hypothesis involving the delay in treatment. The demographic data may be slightly different when all comers with the disease are considered. The fact that most patients had a comorbidity score of 0 is also likely due to the fact that we only selected patients undergoing therapy. Despite this, the median survival was only 6.6 months reflecting the aggressiveness of the disease. In support of our hypothesis that socioeconomic factors may be associated with delay in TTI, the study suggests that disparity in terms of access to treatment is significant even for this group of patients. We were able to demonstrate that NHB are the most

disadvantaged among the group of patients with metastatic HCC in terms of timeliness to therapy. We also found that the significant association was prominent only in the pre-ACA period.

The disparity in terms of treatment and outcomes in HCC has previously been demonstrated, predominantly involving race with the worst outcomes for NHB.[11,12,13,14,15,16,17,18,19,20,21,22] A major reason for the poorer outcomes for NHB when considering all patients has been the lower likelihood of undergoing transplantation even when controlling for factors such as tumor stage, resection status, and transplant eligibility (Odds Ratio of 0.5 – 0.7 when compared to Whites).[11,12,13, 14,15,17,21] Similar to our study showing prolonged time to systemic therapy, prolonged time to surgical intervention even when patients are eligible has been demonstrated.[14] Income status and insurance were identified as significant factors impacting the treatment for HCC.[12,20] Also of note, the impact of race on disparities does appear to improve when adjustments are made for socioeconomic factors suggesting that this indeed is involved in the pathway linking racial status and disparity in treatment.[15]

It is also important to be aware that minorities suffer from highest incidence of HCC and NHB have a higher likelihood for advanced stage of diagnosis.[13,18,19] Whether the poor outcome in NHB patients with HCC is a result of diagnosis at an advanced stage or lack of treatment is unclear as studies show variable results. While some studies show poor outcomes even when adjusted for stage, others show that the differences improve when stage and ability to undergo treatment/transplantation are adjusted .[14,17,18,19] It does appear that early stage NHB patients who are able to undergo transplantation are able to have similar outcomes as Whites.[17] While these trends were reflected in the present study it did not meet statistical significance. Nevertheless, the present study is relevant as studies specifically looking at metastatic cancer patients are not available although these represent the patients with the most aggressive disease and worst outcomes. Studies examining the impact of ACA in this patient population are also lacking.

While the mechanisms underlying the disparities are unclear, the improvement in access in the years following the introduction of ACA does point towards insurance as a prominent factor. Previously, it has been shown that commercial insurance was associated with higher odds for curative treatment and improved survival.[23] In the cohort analyzed in this study, insurance was not independently associated with the delayed therapy group suggesting existence of other factors affecting access to care which could include health awareness and social support. While we expected to find association with insurance, income status, and educational status these were not significant. We did note improvement in Medicaid coverage (for the entire study cohort and specifically for NHB) in the post-ACA period as noted in the results and similar to previous studies that adjusted for temporal changes in coverage.[24] But the Medicaid expansion by itself would not explain the impact of ACA on time to treatment initiation as insurance status was not a significant factor on the analysis as previously noted. This could be attributed to other aspects of ACA associated with reducing cost barriers and improving health care access that couldn't be examined in the present study but has been established in other studies.[24,25]

The patient protection and Affordable Care Act (ACA) was a major health policy intervention in the last decade and aimed to mitigate health inequities predominantly by expanding health care coverage.[4,5] Preliminary studies indicate improved outcomes in diseases such as colorectal cancer and ovarian cancer through improved cost sharing and improved access to earlier diagnosis and treatment.[26,27,6] Gain in terms of time to diagnosis resulting in stage migration and timely treatment have been demonstrated in ovarian cancer.[28] A particular tenet of ACA has been the expansion of Medicaid coverage and that was shown to differentially improve receipt of timely treatment among African American patients diagnosed with advanced or metastatic solid tumors.[29] Similar to these studies, we were able to demonstrate improvement in terms of therapy enrollment in the years following ACA while adjusting for other factors. Unfortunately, the NCDB does not record states to which patients belong and therefore comparison between states is not possible.

A major limitation of the present study is the retrospective nature of this analysis that may result in unaccounted biases and unmeasured confounders. This is due to lack of granular data on liver functional status, Childs score, performance status, all factors that would affect whether or not patients receive treatments as well as potential delays in treatment. Mortality differentials are applicable to only those who underwent the treatment which was the study group and does not include those who could not seek treatment based on socioeconomic reasons. Such a study design was made as our hypothesis was to test the disparity in this particular patient group that received treatment. Certainly, there would be patients that did not undergo therapy and suffered death while waiting for therapy or due to the treatment delay. The NCDB tries to attain 90% adherence on mortality reporting consistent with Commission on Cancer (CoC) quality standards and likely reflect a good estimate of the real-world outcomes , but errors may have happened in capturing the follow-up information given the retrospective nature of the database. It captures 70% of all diagnosed malignancies in the United States although details specific to HCC is not available.[30] Use of multiple surrogates for socio-economic status (income, education, geographical location) and their respective adjustments during analysis improved the robustness and generalizability of the results. The fact also remains that metastatic HCC represents a disease with limited therapy options, but this argument is not relevant in addressing the disparity in treatments.

Conclusions

Our study suggests that non-Hispanic Black race may be predictive of delay in therapy, a finding which was positively changed in the years following ACA. Continued research to monitor disparities in care and identify underlying mechanisms to mitigate them is warranted.

Declarations

Funding: This study received no funding.

Conflict of Interest: No author present on this article has any conflicts of interest.

Ethical approval: This study does not contain any identifiable data and was exempt from institution review board oversight and ethical approval process.

Authors Contributions: Study concept and design: TJ, VB, DM, RW. Analysis and interpretation of data: TJ, RW. Drafting of the manuscript: TJ, VB, RW. Critical revision of the manuscript for important intellectual content: TJ,VB,GF,DM,RW. Administrative, technical, or material support:DM, RW

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Data Statement: Authors TJ and RW had full access to all the data in the study. We take full responsibility for the integrity of the data and the accuracy of the analysis as well as sharing the data with any interested investigators.

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Tables

Table 1. Baseline Characteristics of Patients Selected for the Analysis

Characteristic (n=630)	Distribution Median (IQR) Or N(Percentage)	
Age in years	60 (55-69)	
Days to therapy	57 (3-117)	
Follow up in months	6.4 (3.0-13.4)	
Survival in months	6.6 (3.1-14.3)	
Sex		
Male	525 (83.3)	
Female	105 (16.7)	
Race		
Non-Hispanic Whites	386 (61.3)	
Non-Hispanic Blacks	84 (13.3)	
Hispanic	61 (9.7)	
Others	99 (15.7)	
Insurance		
Uninsured		37 (6.1)
Insured		567 (93.9)
Private	240 (42.3)	
Medicaid	94 (16.6)	
Medicare	219 (38.6)	
Details Unknown	14 (2.5)	
Median Income		
<$38,000	137 (22.2)	
$38,000-$47,999	146 (23.6)	
$48,000-$62,999	162 (26.2)	
>=$63,000	173 (28.0)	
Education		
≥21%	127 (20.6)	
13.0-20.9%	196 (31.7)	
7.0-12.9%	182 (29.5)	
<7.0%	113	

	(18.3)
Comorbidity Score	
0	349 (55.4)
1	159 (25.2)
2	66 (10.5)
≥3	56 (8.9)
Location	
Metropolitan	531 (87.5)
Urban	70 (11.5)
Rural	6 (0.99)
Facility Type	
Community Cancer Center	44 (7.2)
Comprehensive Community Cancer Center	220 (35.8)
Academic/Research Program	294 (47.9)
Year Group	
2004-2005	57 (9.1)
2006-2007	61 (9.7)
2008-2009	128 (20.3)
2010-2011	142 (22.5)
2012-2013	153 (24.3)
2014-2015	89 (14.1)
Affordable Care Act (ACA) groups	
Pre-ACA	322 (51.1)
Post-ACA	308 (48.9)

Table 2. Characteristics of Patients belonging to delayed-TTI Group

Characteristic (n=157)	Distribution Median (IQR) Or Frequency (%)
Age in years	61 (54-69)
Days to therapy	153 (131-164)
Follow up in months	4.7 (2.4-10.0)
Survival in months	4.9 (2.4-10.6)
Sex	
Male	132 (84.1)
Female	25 (15.9)
Race	
Non-Hispanic Whites	93 (59.2)
Non-Hispanic Blacks	29 (18.5)
Hispanic	10 (6.4)
Others	25 (15.9)
Insurance	
Uninsured	8 (5.1)
Insured	140 (94.6)
Private	53 (37.9)
Medicaid	22 (15.7)
Medicare	63 (45.0)
Details Unknown	2 (1.4)
Median Income	
<$38,000	36 (23.5)
$38,000-$47,999	35 (22.9)
$48,000-$62,999	35 (22.9)
>=$63,000	47 (30.7)
Education	
≥21%	29 (19.0)
13.0-20.9%	46 (30.1)
7.0-12.9%	43 (28.1)
<7.0%	35 (22.9)
Comorbidity Score	
0	80 (51.0)
1	39 (24.8)
2	20 (12.7)
≥3	18 (11.5)
Location	
Metropolitan	136 (90.1)
Urban	14 (9.3)
Rural	1 (0.7)
Facility Type	
Community Cancer Center	13 (8.4)
Comprehensive Community Cancer Center	63 (40.9)
Academic/Research Program	67 (43.5)
Year Group	

2004-2005	11 (7.0)
2006-2007	15 (9.6)
2008-2009	38 (24.2)
2010-2011	38 (24.2)
2012-2013	32 (20.4)
2014-2015	23 (14.7)
Affordable Care Act (ACA) groups	
Pre-ACA	83 (52.9)
Post-ACA	74 (47.1)

Table 3 Demonstrating the Change in the Association of non-Hispanic Black Racial status with Delayed TTI when Stratified by Timing of ACA

Race Category	Pre-ACA (n=322)		Post-ACA (n=308)	
	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value
Non-Hispanic Whites	Reference		Reference	
Non-Hispanic Blacks	3.6 (1.4-9.4)	0.008	1.3 (0.5-3.1)	0.60

Table 4 Multivariate Cox Regression Analysis of Socioeconomic Factors Impacting Survival [a]

Characteristic	Median Survival (IQR) months	Hazard Ratios (95%CI)	p-value
Sex			
Male	6.5 (3.0-13.5)	Reference	
Female	7.8 (4.3-20.0)	0.8 (0.6-1.0)	0.04
Race			
Non-Hispanic Whites	6.7 (3.3-14.7)	Reference	
Non-Hispanic Blacks	4.6 (2.2-10.1)	1.2 (1.0-1.6)	0.24
Hispanic	7.3 (3.6-15.9)	0.9 (0.6-1.2)	
Insurance			
Uninsured	4.2 (2.8-7.3)	Reference	
Insured	6.8 (3.3-14.7)	0.7 (0.5-1.0)	0.05

[a]Other factors analyzed for the model were income, educational status, comorbidity, facility type and geographical location and were not found to be significant on univariate analysis to be included in the model

Figures

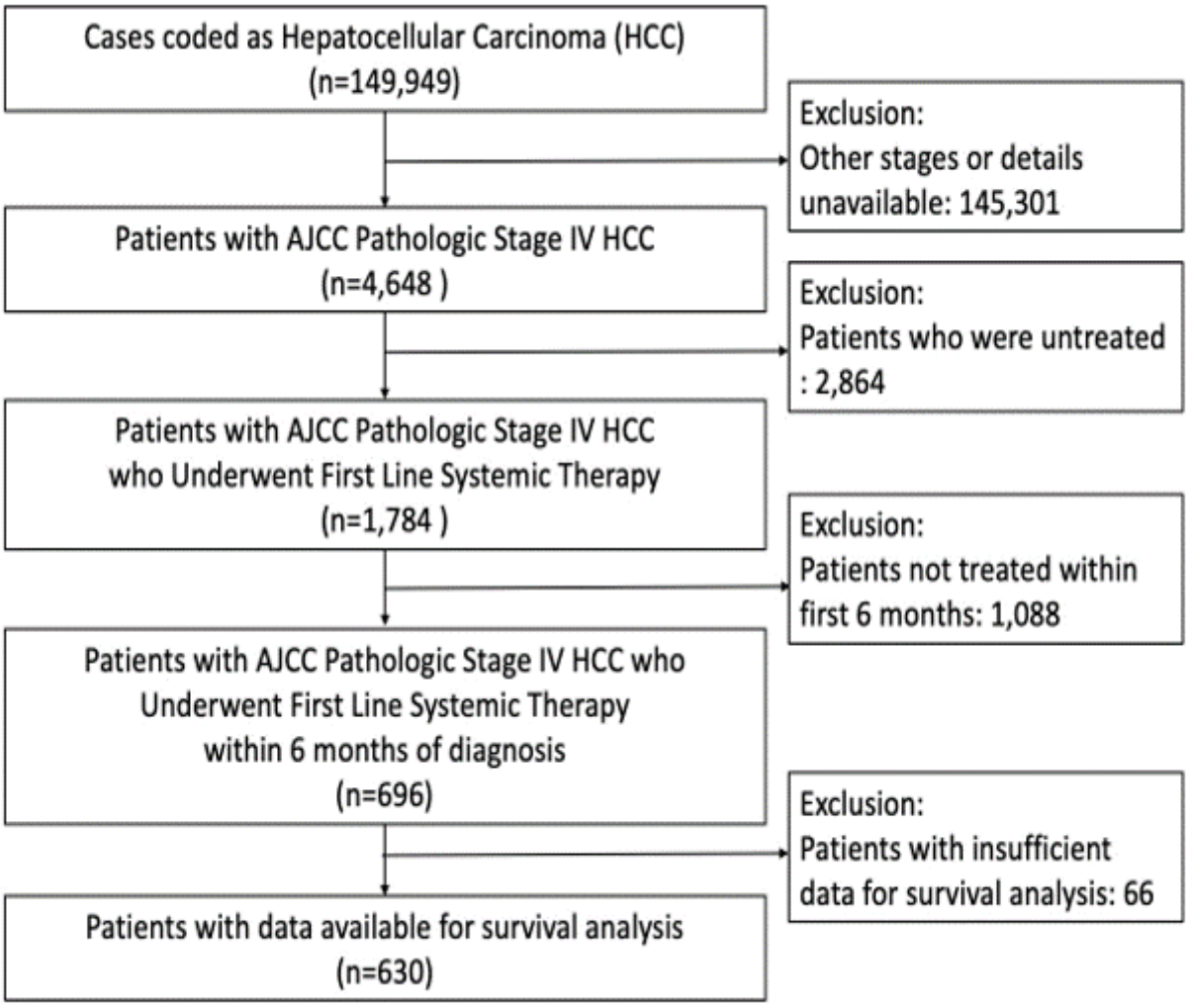

Figure 1

Flow Diagram Demonstrating Selection of Patients for the Study