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Hepatocellular Carcinoma Survival in Uninsured and Underinsured Patients

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Abstract

Background—The incidence of hepatitis C virus (HCV) and hepatocellular carcinoma (HCC) is increasing. The purpose of this study is to establish baseline survival in a medically-underserved population and to evaluate the effect of HCV seropositivity on our patient population.

Materials and Methods—We reviewed clinicopathologic parameters from a prospective tumor registry and medical records from the Harris County Hospital District (HCHD). Outcomes were compared using Kaplan-Meier survival analysis and log-rank tests.

Results—A total of 298 HCC patients were identified. The median survival for the entire cohort was 3.4 mo. There was no difference in survival between the HCV seropositive and the HCV seronegative groups (3.6 mo versus 2.6 mo, $P = 0.7$). Patients with a survival <1 mo had a significant increase in αfetoprotein (AFP), international normalized ratio (INR), model for end-stage liver disease (MELD) score, and total bilirubin and decrease in albumin compared with patients with a survival ≥1 mo.

Conclusions—Survival for HCC patients in the HCHD is extremely poor compared with an anticipated median survival of 7 mo reported in other studies. HCV seropositive patients have no survival advantage over HCV seronegative patients. Poorer liver function at diagnosis appears to be related to shorter survival. Further analysis into variables contributing to decreased survival is needed.

Keywords

hepatitis C virus; HCV; hepatocellular carcinoma; HCC; survival

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States has risen to 4.1 per 100,000 from 1.6 per 100,000 over the last 30 y. Although Asian/Pacific Islanders have the highest age-adjusted incidence of HCC, the fastest rise in incidence rates in the last 15 y was seen in American Indian/Alaska natives, followed by African-Americans, Caucasians, and Hispanics [1]. With approximately 600,000 new cases reported worldwide each year, HCC remains a significant, global healthcare issue [2].

Along with alcohol abuse, hepatitis B (HBV) and hepatitis C virus (HCV) seropositivity are the leading risk factors for HCC. In the United States, effective HBV vaccination programs

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have resulted in HCV infection being largely responsible for the dramatic rise in the incidence of HCC [3].

Both HBV and HCV can cause carcinogenesis by hepatic fibrosis. HBV, however, is a DNA virus that can integrate into the hepatocyte DNA. This results in genomic instability and provides an additional pathway for tumorigenesis [4]. Since HCV causes tumorigenesis by hepatic fibrosis, HCV seropositive patients with HCC tend to have more advanced cirrhosis and poorer liver function than patients with HBV-related HCC. While no significant difference in survival has been identified in HBV-related HCC and HCV-related HCC, some have noted that the HCV positive patients do better with transplantation as opposed to resection [5], presumably due to greater liver function capacity postoperatively.

With a population approaching 4 million people, Harris County is the largest county in Texas and one of the largest counties in the United States. The Harris County Hospital District (HCHD) is one of the largest public hospital districts in the United States, with more than 240,000 in-patient days per year. As a county hospital system in Texas, HCHD primarily serves the indigent, uninsured, and underinsured. This translates into a patient population that is mostly minority, largely socioeconomically disadvantaged, and with a significant immigrant faction.

Currently there are an estimated 480,000 carriers of HCV in the state of Texas and, similar to worldwide trends, the incidences of HCV, HBV, and HCC appear to be increasing. We undertook this project to evaluate the baseline survival of patients with HCC within the HCHD system. These patients often lack comprehensive primary care and access to screening modalities and therefore present with advanced disease. Since the rate of survival in patients with HCC is directly related to early detection [6], we expect to see poor survival data in this cohort. Additionally, we investigated the association of HCV seropositivity on survival in this unique cohort.

METHODS

The paper and electronic medical records of HCHD patients with a diagnosis of HCC from 1999 to 2009 were reviewed. Patient demographics, αfetoprotein (AFP) at diagnosis, albumin at diagnosis, international normalized ratio (INR) at diagnosis, total bilirubin at diagnosis, platelet count at diagnosis, model for end-stage liver disease score (MELD) at diagnosis, HBV status, HCV status, stage at diagnosis, and length of survival were recorded. When clinicopathologic and stage data could not be found, the patients were not excluded from the study, but the missing data were omitted from the analysis.

Survival was determined as the difference between the date of diagnosis and the date of death, confirmed by the Social Security Death Index. If the date of death could not be verified, the date of last contact in the HCHD system was used. Diagnosis was made by one of three methods: pathologic confirmation, the presence of a liver mass with an AFP greater than or equal to 400 ng/mL, or a progressively enlarging liver mass in the setting of cirrhosis in which the clinical picture is consistent with HCC. Survival analysis was performed using the Kaplan-Meier method with differences determined by the log rank test. Significance was defined as $P < 0.05$.

RESULTS

The medical records and tumor registry for 298 HCC patients was reviewed. The entire cohort was predominately minority: 35% African-American, 35% Hispanic, 14% Asian, and 16% Caucasian. Although funding information was unknown for 62% of the cohort, 33% of patients were “self-pay,” i.e., they had no private or government-sponsored health insurance,

and 5% of patients had Medicaid or Medicare. A total of 183 were HCV seropositive (61%) and 115 seronegative (39%). The HCV seropositive group had a significantly higher number of females than the HCV negative group (Table 1). The composition by race and stage also showed significant differences. More African-Americans were seen in the HCV positive group and more Asians in the HCV negative group. Both groups had greater than 60% of patients who presented with either stage III or stage IV disease.

Comparing the AFP, total bilirubin, INR, albumin, MELD score, and platelets at diagnosis, only the platelet count had a statistically significant difference (Table 2). The mean platelet count for the HCV seropositive group was 173, while the HCV seronegative group had a mean platelet count of 236 ($P = 0.001$).

Approximately 29% of patients in the cohort received some sort of therapy for HCC: 19% received intravenous or oral chemotherapy, 8% received transarterial chemoembolization, and 5% underwent resection.

The entire group had an overall median survival of 3.4 mo (range 0 to 63.8 mo) after the diagnosis of HCC was made (Table 3). The median survival for HCV seropositive patients was 3.6 mo (range 0–54.7 mo) and 2.9 mo for HCV seronegative patients (range 0–63.8 mo). There is no significant difference between these two groups ($P = 0.7$) (Fig. 1A, Table 4).

Comparing survival of all patients by stage, there was a significant difference seen ($P = 0.0046$) (Fig. 1B, Table 3). Patients with stages I and II disease at presentation had a median survival of 6.7 mo (range 0–63.8 mo) and 7.7 mo (range 0.1–44.1 mo), respectively. This decreased to 3.5 mo (range 0–62.2 mo) and 1.7 mo (range 0–49.8 mo) for patients who presented with stage III and stage IV disease (Fig. 1B).

Due to the observation that median survival for the entire cohort was much lower than expected, we examined those patients with survival less than 1 month (LOS < 1 mo) and compared that subgroup with those whose survival was greater than or equal to 1 mo (LOS ≥ 1 mo). There was no difference between groups for stage, gender, race, or age (Table 4). Serum AFP, total bilirubin, INR, albumin, MELD score, and platelets for the LOS < 1 month group were all significantly different from LOS ≥ 1 mo (see Table 5).

DISCUSSION

Our series reports a far lower rate of both surgical therapy and median survival than previously published studies. The SHARP trial, which enrolled Childs' A cirrhotics with advanced disease who were not candidates for or failed resection and locoregional therapies, reported an overall median survival of 7.9 mo in the placebo group (those not given sorafenib) [7]. Kim *et al.* recently reported the results of a large SEER HCC study in which the median survival for all patients diagnosed this past decade ($n = 9953$) was 7 mo [8]. The median survival for all patients in these two studies is similar to the survival for the stages I and II patients in our cohort. The poor outcome for all patients regardless of stage suggests that either the HCHD patients present with more advanced HCC, are not effectively screened, receive fewer therapies for HCC, or have a greater degree of medical comorbidity that negatively affects survival (Table 6).

Indeed, our cohort has very high AFP levels at diagnosis (median 30,689 and 18,076 in HCV positive and negative groups, respectively). The placebo arm of the SHARP trial had a median baseline AFP of 99, with a range from 0 to 500,000. This suggests a significant tumor burden at diagnosis and may provide a partial explanation for the poorer survival outcomes seen.

The HCHD has no formal screening regimens and we do not know what percentage of our patients received screening. Anecdotally, most patients in our cohort were first found to have a liver mass in the emergency room, further demonstrating that screening the population is not widespread. The American Association for the Study of Liver Disease recommends that surveillance for chronic HCV and/or HBV seropositive patients with cirrhosis should consist of biannual liver ultrasound and serum AFP measurements [9]. However, in the U.S., these screening recommendations are not routinely followed. There are no current United States Preventative Services Task Force (USPSTF) recommendations for HCC screening, and the last update was 2004. Nor does the USPSTF recommend screening for HBV or HCV in the adult population at low risk for disease (current grade D recommendation) and also those who are high risk for disease (grade I recommendation) [10, 11]. Since resection and transplantation are the only curative therapies for HCC, early diagnosis is key for survival. Multiple studies have shown increased survival with screening programs aimed at high risk patients [12, 13]. The data on the cost-effectiveness of biannual or annual screening of cirrhoticswith ultrasound and AFP remains controversial. This underscores the need for data to support a cost effective screening program in the United States.

In the Western Hemisphere, 30%–40% of patients diagnosed with hepatocellular carcinoma undergo treatments with curative intent. Due to widespread screening in the Eastern Hemisphere, 60%–90% of HCC patients in some developed countries, i.e., Japan, undergo treatment with curative intent [14]. Kim *et al.* found that nearly 72% of patients received no surgical intervention, while 6% underwent ablation/destruction procedures and 23% underwent resection/transplantation. In our cohort, only 5% of patients underwent treatment with curative intent (resection, in this case). The remainder of the patients treated for HCC received chemotherapy or TACE, both of which are not potentially curative. Intravenous chemotherapy, including doxorubicin, cisplatin, gemcitabine, and 5-FU, has not been shown to improve survival in patients with HCC. It is important to note that a number of patients in the present study were seen prior to FDA approval of the oral tyrosine kinase inhibitor sorafenib (November 2007). In terms of curative treatments, the HCHD is able to offer resection and ablation; transplantation services are not provided. Chemotherapy and TACE are also provided. This underscores the need for an active screening program in the HCHD for high risk patients so that HCC can be found at stages in which curative therapies may be employed.

We do not have data to suggest that our patients have more medical comorbidities than other studies' cohorts. Future investigation into the prevalence of coronary artery disease, diabetes, and other medical problems would be useful to evaluate if greater medical comorbidities partially explain the poorer survival in our cohort.

With respect to the significant clinicopathologic values, the LOS < 1 month group had significantly decreased albumin and increased AFP, total bilirubin, MELD score, and INR compared to the LOS ≥ 1 month group. These laboratory values likely indicate an advanced degree of liver disease and cirrhosis, which, in combination with a presumably high tumor burden as indicated by the high AFP levels, may account for the decreased survival in that group. It is unclear at this time how to address the problem of patients presenting with concomitant end-stage liver disease and HCC. Advanced liver disease is likely to be a significant factor contributing to the entire cohort's poor survival.

This is a retrospective study with inherent limitations and biases. As with any retrospective cohort study, disadvantages include limited control over the approach to sampling the population and over the nature and quality of the predictor variables. As these data come from a prospectively collected tumor registry, there is no a priori hypothesis, and the

opportunity for unsystematic data collection is significant. Since there was no randomization between HCV seropositive and HCV seronegative patients, confounding variables could also be imbalanced.

Since the incidence of HCC is increasing, the poor overall survival of HCC patients detailed in this study and other recent studies is concerning. Coupled with the fact that effective screening guidelines are lacking and available treatments are marginally effective, HCC is likely to remain a significant cause of cancer mortality. Worldwide, curative treatment options include resection, transplantation, and ablation. These all require identifying the tumor at an early stage in a patient with adequate liver function. Aggressive screening programs in the Eastern Hemisphere have been implemented and appear to have increased the portion of patients who are surgical candidates. Investigation into the cost and effectiveness of HCC screening programs in the U.S. is needed.

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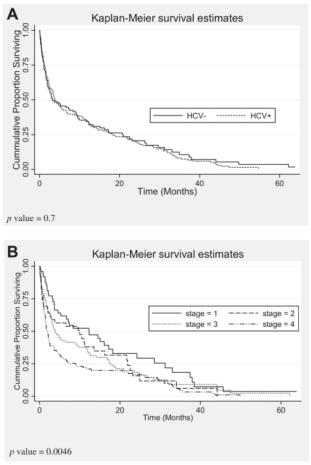

FIG. 1.

(A) Kaplan-Meier survival curve comparing patients by HCV status. (B) Kaplan-Meier survival curve comparing patients by stage.

TABLE 1

Baseline Characteristics of the Patients

	HCV negative		HCV positive		
Variable	**Number**	**Percent**	**Number**	**Percent**	***P***
Median age	55	-	52	-	0.070
Gender					0.001
Male	83	72%	160	87%	
Female	32	28%	23	13%	
Race					0.000
Caucasian	14	12%	32	17%	
African-American	25	22%	78	43%	
Hispanic	51	44%	57	31%	
Asian	25	22%	16	9%	
Stage at diagnosis					0.006
I	23	23%	28	18%	
II	13	13%	26	17%	
III	21	21%	51	32%	
IV	43	43%	52	33%	

TABLE 2

Median Laboratory Values at Presentation

	HCV negative (IQR)	HCV positive (IQR)	*P*
α-Fetoprotein	526 (19–6,778)	693 (38–10,631)	0.167
Total bilirubin	1.4 (0.8–2.8)	1.6 (0.9–3.0)	0.677
INR	1.3 (1.1–1.5)	1.3 (1.2–1.5)	0.494
Albumin	2.8 (2.8–3.2)	2.6 (2.1–3.1)	0.888
Platelets	239 (105–319)	138 (93–211)	0.001
MELD score	10 (6–15)	12 (8–16)	0.058

IQR = interquartile range (25th–75th percentile).

TABLE 3

Median Survival, in Months (range mo)

Overall	3.4 (0–63.8)
Stage	
I	6.7 (0–63.8)
II	7.2 (0.1–44.1)
III	3.5 (0–62.2)
IV	1.7 (0–49.8)

TABLE 4

Median Survival in HCV Seropositive and Seronegative Patients (range, mo)

	HCV patient status		
	Negative	**Positive**	***P* value**
Overall	2.9 (0–63.8)	3.6 (0–54.7)	0.7
Stage			
I	7.4 (0–63.8)	6.1 (0.7–45.6)	
II	6.3 (0–22.5)	8.0 (0.1–44.1)	
III	7.3 (0–44.1)	3.3 (0–47.4)	
IV	1.5 (0–34.9)	2.3 (0–36.6)	
Gender			
Male	2.1 (0.1–62.2)	3.4 (0–54.7)	
Female	8.3 (0.1–63.8)	9.4 (0–48.2)	
Race			
Caucasian	2.0 (0–29.7)	4.8 (0.1–32.0)	
African-American	2.9 (0–16.2)	3.1 (0–45.6)	
Hispanic	5.1 (0–63.8)	4.3 (0–28.5)	
Asian	1.9 (0.1–62.2)	3.7 (0–54.7)	

TABLE 5

Characteristics of Patients with Survival Less Than and Greater Than 1 Month

	LOS < 1 mo	LOS ≥ 1 mo	*P* value
Number	72	226	
Median age	53	54	0.444
Stage			0.114
I	6 (9.1%)	45 (21.2%)	
II	11 (16.7%)	28 (13.2%)	
III	23 (34.8%)	70 (33.0%)	
IV	26 (39.4%)	69 (32.5%)	
Gender			0.444
Male	63 (87.5%)	180 (79.6%)	
Female	9 (12.5%)	46 (20.4%)	
Race			0.277
Caucasian	13 (18.1%)	33 (14.6%)	
African-American	27 (37.5%)	76 (33.6%)	
Hispanic	23 (31.9%)	85 (37.6%)	
Asian	9 (12.5%)	32 (14.2%)	

LOS = length of survival.

TABLE 6

Median Laboratory Values at Presentation in Patients with Survival Less Than and Greater Than 1 Month

	LOS < 1 mo (IQR)	LOS ≥ 1 mo (IQR)	*P*
α-Fetoprotein	6693 (111–37,722)	286 (27–4172)	0.002
Total bilirubin	2.7 (1.4–6.2)	1.4 (0.8–2.5)	0.005
INR	1.5 (1.3–1.8)	1.3 (1.1–1.5)	0.003
Albumin	2.2 (1.8–2.8)	2.8 (2.3–3.2)	0.003
Platelets	135 (98–213)	164 (97–275)	0.064
MELD score	15 (9–21)	11 (8–15)	0.002

IQR = interquartile range (25th–75th percentile); LOS = length of survival.