ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Level of α-Fetoprotein Predicts Mortality Among Patients With Hepatitis C–Related Hepatocellular Carcinoma

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BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) can result from hepatitis C virus (HCV)-related liver disease and is the fastest-growing cause of cancer-related death in the United States. α-fetoprotein (AFP) has been used as a prognostic factor for HCC, but the value of AFP as a prognostic factor for HCV-related HCC in the United States is unknown. We investigated whether higher levels of AFP at the time of diagnosis are associated with increased mortality of patients with HCV-related HCC. **METHODS:** In a retrospective study, we collected data from a cohort of HCV-infected veterans, identifying incident HCC cases from October 1, 1998, to January 1, 2007 (n = 1480 patients). The mean serum levels of AFP, obtained within 60 days before to 30 days after HCC diagnosis, were determined for 1064 patients and categorized as less than 10 ng/mL (18%), 10 to less than 100 ng/mL (30%), 100 to less than 1000 ng/mL (22%), or 1000 ng/mL or more (29%). Cox proportional hazard models were used to associate serum levels of AFP with mortality, adjusting for demographic features, clinical factors, and treatment. **RESULTS:** The median survival times were significantly lower among patients with higher levels of AFP: 709 days for patients with less than 10 ng/mL, 422 days for patients with 10 to less than 100 ng/mL, 208 days for patients with 100 to less than 1000 ng/mL, and 68 days for patients with 1000 ng/mL or more. In the multivariate analysis, increased levels of AFP (10 to <100, 100 to <1000, and ≥1000) were associated significantly with increased mortality, compared with a serum AFP level of less than 10; hazard ratios were 1.50, 2.23, and 4.35, respectively. **CONCLUSIONS: Serum AFP level at the time of diagnosis with HCV-related HCC is an independent predictor of mortality.**

Keywords: Liver Disease; Risk; Prognosis; Epidemiology; Blood Test.

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy.[1] The incidence of HCC has been increasing recently in the United States, becoming the fastest growing cause of cancer-related death.[1–4] The 5-year survival rates are poor, ranging between 0% and 10% among patients detected at a symptomatic stage.[2] The increased incidence of HCC can be attributed mostly to increases in hepatitis C virus (HCV)-related liver disease.[3,4] There are approximately 2.7 million people in the United States with chronic HCV.[5] Individuals with HCV-related cirrhosis have a 2% to 8% annual incidence of HCC.[2,3] Therefore, a better understanding of the prognostic factors in HCV-related HCC is needed in the United States.

Prognosis of patients with HCC is related to the degree of liver dysfunction, tumor size, and overall functional status.[2,6–9] Studies also have examined serum α-fetoprotein (AFP) as a modality for HCC surveillance as well as a prognostic factor for HCC.[8,9] These studies have shown that higher AFP levels at the time of HCC diagnosis are associated with worse survival,[8–11] even after adjusting for tumor size and stage.[3,6,7,10–13] Therefore, AFP has been incorporated into at least 3 of the major staging and prognostic scoring systems of HCC: the Cancer of the Liver Italian Program (CLIP), the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH), and the Chinese University Prognostic Index (CUPI).[6,7,14,15] There are several other prognostic systems that have not incorporated AFP.[16]

The value of AFP as a prognostic factor for HCC among patients with HCV-related HCC in the United States is unknown. The studies that examined AFP levels as a part of CLIP, GRETCH, or CUPI were not conducted in the United States and evaluated patients with liver disease of various etiologies.[6,14,15] The CLIP validation study contained the largest proportion of patients with HCV-related liver disease (85.5%), although these proportions were considerably smaller in the GRETCH (18%) and CUPI (3.3%) studies.[6,14,15] These findings may not be generalizable to HCV-related HCC. For example, it has been reported that AFP levels are higher in hepatitis B virus (HBV)-positive patients than HBV-negative patients irrespective

Abbreviations used in this paper: **AFP, α-fetoprotein; CHF, congestive heart failure; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; MELD, Model for End-stage Liver Disease; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; VA, Veterans Administration.**

1542-3565/$36.00
doi:10.1016/j.cgh.2011.07.026

of HCC.[9,10] In addition, several established clinical and pathogenic differences exist between HBV- and HCV-related HCC.[3,13] Given these differences and the fact that AFP is an inexpensive, widely available, and an easily interpretable test, it is important to examine the prognostic properties of AFP in an HCV-specific HCC population in the United States.

The Veterans Administration (VA) has the largest integrated health care system in the United States. The VA provides care to a large number of patients with HCV and collects a substantial amount of clinical data on these individuals. By using information obtained from the VA HCV Clinical Case Registry we conducted a retrospective cohort study of HCV-infected patients who developed HCC to determine whether AFP levels at the time of HCC diagnosis are predictive of mortality.

Methods

Data Source

Data were obtained from the national VA HCV Clinical Case Registry. Patients were identified based on positive HCV antibody test or International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes for HCV (V02.62, V070.41, V070.51, V070.44, and V070.54) at any of the 128 VA health care facilities nationwide. Data elements include demographics, laboratory tests, and inpatient and outpatient diagnosis and current procedural terminology codes. Details on the Clinical Case Registry data are published elsewhere.[17] The date of death was obtained from the VA vital status file. Follow-up information was available through September 30, 2009.

Study Population

The details of this study cohort have been described previously.[18] All HCV-infected patients 18 years of age or older with incident HCC were identified between October 1, 1998, and January 1, 2007. Patients with HCV were defined by 1 positive HCV antibody test combined with at least 1 HCV ICD-9-CM code. The date of first occurrence of a positive HCV antibody test or HCV ICD-9-CM code served as the HCV index date. HCC was defined using a previously validated algorithm.[19] To ensure that patients were using the VA for their health care, inclusion required at least 1 inpatient or outpatient encounter at any VA facility within the 2 years before and 1 year after the HCC diagnosis date. Patients who developed HCC or died within 12 months after the HCV or cirrhosis index date were excluded.

Study Variables and Definitions

The main exposure variable of interest was serum AFP level at HCC diagnosis. The main outcome variable was time to death after HCC diagnosis. Serum AFP level at the time of HCC diagnosis was defined as the serum AFP level within 60 days before to 30 days after HCC diagnosis. Those patients without AFP levels documented during this time period were recorded as not having serum AFP tested. If patients had more than 1 AFP level recorded during this time period the mean value was used, resulting in each patient having only 1 AFP level analyzed.

Cirrhosis was identified by one of several previously validated ICD-9-CM codes (571.2, 571.5, or 571.6) and a cirrhosis index date was based on the first appearance of a cirrhosis code.[20] Liver disease severity was assessed with the Model for End-stage Liver Disease (MELD) score, which was calculated using laboratory values for serum creatinine, bilirubin, and international normalized ratio within 6 months before or after the HCV index date.[21] The Child–Pugh class would have been more informative for this cohort, but based on the lack of detailed information on encephalopathy and ascites with its treatment in the Clinical Case Registry we were unable to determine an accurate class. Therefore, MELD was the next best choice for determining liver disease severity. Laboratory data were used to determine HBV surface antigen status. Alcohol, cocaine, and cannabis use were identified by positive laboratory tests or ICD-9-CM codes. We also assessed the presence of ICD-9-CM codes for ascites, varices, encephalopathy, medical comorbidities (diabetes, coronary artery disease, chronic obstructive pulmonary disease, respiratory failure, congestive heart failure [CHF], hypertension, human immunodeficiency virus, and end-stage renal disease), and mental health disorders (anxiety, post-traumatic stress disorder, depression, bipolar disorder, and psychosis), as well as to calculate the Deyo et al[22] comorbidity index. HCC treatment was ascertained by ICD-9-CM procedure and current procedural terminology codes for liver transplant, surgical resection, local ablation with alcohol or radiofrequency ablation (RFA), as well as transarterial chemoembolization (TACE) within 90 days before and 24 months after the HCC diagnosis date.

The study protocol was approved by the Baylor College of Medicine Institutional Review Board and the Office of Human Subjects Research of the National Institutes of Health.

Data analysis. The primary outcome measure was time to death after HCC diagnosis. Follow-up evaluation started at HCC diagnosis and ended on September 30, 2009. Any patients alive at the end of the follow-up period were censored. In preliminary analyses, AFP levels were examined as a continuous variable and logarithmic transformation was used for normalization. The main analysis examined the serum AFP level for each patient within the specified 60 days before to 30 days after HCC diagnosis or the mean AFP value in the presence of multiple tests. Based on the results from preliminary analyses and clinical knowledge, the AFP levels at the time of HCC diagnosis were converted to a categoric variable with 4 groups: less than 10 ng/mL, 10 to less than 100 ng/mL, 100 to less than 1000 ng/mL, and 1000 ng/mL or more. For each group, survival rates were estimated using a Kaplan–Meier approach. In a multivariate Cox proportional hazards regression model, the demographic and clinical variables listed earlier were tested as potential determinants of survival. Variables with a P value of less than .10 in univariable Cox regression model were evaluated further using a stepwise regression analysis to identify independent prognostic factors. Only variables with a P value of less than .10 were retained in the final model. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated for each predictor variable with the final level of significance set at 0.05. The graphic and numeric methods of Lin et al[23] were performed to check the functional form of AFP and the proportional hazards assumption for the Cox model.

We also conducted sensitivity analyses in which we examined only the first AFP level among patients with more than one AFP level within 60 days before to 30 days after the HCC diagnosis date. We also analyzed the change in serum AFP level in patients who had more than one AFP test during the period that spanned 2 years before to 30 days after the HCC diagnosis. The change in AFP level was based on a slope estimated from linear regression and categorized as no increase, less than a 2-fold increase, a 2- to