Temporal Trends of Nonalcoholic Fatty Liver Disease–Related Hepatocellular Carcinoma in the Veteran Affairs Population

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BACKGROUND & AIMS: **Nonalcoholic fatty liver disease (NAFLD) is a risk factor for hepatocellular carcinoma (HCC). However, no systemic studies from the United States have examined temporal trends, HCC surveillance practices, and outcomes of NAFLD-related HCC.**

METHODS: **We identified a national cohort of 1500 patients who developed HCC from 2005 through 2010 from Veterans Administration (VA) hospitals. We reviewed patients' full VA medical records; NAFLD was diagnosed based on histologic evidence for, or the presence of, the metabolic syndrome in the absence of hepatitis C virus (HCV) infection, hepatitis B, or alcoholic liver disease. We compared annual prevalence values for the main risk factors (NAFLD, alcohol abuse, and HCV), as well a HCC surveillance and outcomes, among HCC patients.**

RESULTS: **NAFLD was the underlying risk factor for HCC in 120 patients (8.0%); the annual proportion of NAFLD-related HCC remained relatively stable (7.5%–12.0%). In contrast, the proportion of HCC cases associated with HCV increased from 61.0% in 2005 (95% confidence interval, 53.1%–68.9%) to 74.9% in 2010 (95% confidence interval, 69.0%–80.7%). The proportion of HCC cases associated with only alcohol abuse decreased from 21.9% in 2005 to 15.7% in 2010, and the annual proportion of HCC cases associated with hepatitis B remained relatively stable (1.4%–3.5%). A significantly lower proportion of patients with NAFLD-related HCC had cirrhosis (58.3%) compared with patients with alcohol- or HCV-related HCC (72.4% and 85.6%, respectively; $P < .05$). A significantly higher percentage of patients with NAFLD-related HCC did not receive HCC surveillance in the 3 years before their HCC diagnosis, compared with patients with alcohol- or HCV-associated HCC. A lower proportion of patients with NAFLD-related HCC received HCC-specific treatment (61.5%) than patients with HCV-related HCC (77.5%; $P < .01$). However, the 1-year survival rate did not differ among patients with HCC related to different risk factors.**

CONCLUSIONS: **NAFLD is the third most common risk factor for HCC in the VA population. The proportion of NAFLD-related HCC was relatively stable from 2005 through 2010. Although patients with NAFLD-related HCC received less HCC surveillance and treatment, a similar proportion survive for 1 year, compared with patients with alcohol-related or HCV-related HCC.**

Keywords: Liver Cancer; NASH; Incidence; Time.

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States.[1,2] Most of this increase has been attributed to the aging of individuals infected with hepatitis C (HCV) in the 1960s and 1970s.[3] However, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in the United States.[4] It is estimated that 10% to 46% of individuals in the United States have NAFLD, and 3% to 5% may have nonalcoholic steatohepatitis (NASH).[5,6] NAFLD and NASH also likely are contributing to the burden of advanced liver disease. Indeed, most patients

Abbreviations used in this paper: **AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CPT, Common Procedural Terminology; EMR, electronic medical records; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; MedSAS, Medical SAS; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VA, Veterans Administration.**

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with cryptogenic cirrhosis are now thought to have NAFLD or NASH.[7,8] In 2010, NASH was the fourth most common cause of liver transplantation in the United States.[9] A recent systematic review showed that NAFLD-/NASH-related cirrhosis is associated with a higher risk of HCC, although the risk was reportedly lower than that related to HCV cirrhosis.[10] Given the sheer number of patients with NAFLD/NASH, it is possible that even a small risk of HCC may translate into a large number of HCC patients. However, the burden of NAFLD-related HCC is not well defined.

In addition to the unclear contribution of NAFLD to the current burden of HCC in the United States, the clinical and prognostic features of NAFLD-related HCC are also only emerging. Available data suggest that patients with HCC resulting from NAFLD are older, have less aggressive tumors. and are less likely to be diagnosed by surveillance compared with HCC caused by viral hepatitis. However, most of this information is based on reports from referral centers and does not represent community practice.[11–13]

By using data obtained from the national Veterans Affairs Health Administration (VA) system, we estimated the prevalence of HCC attributable to NAFLD, alcohol abuse, and HCV in a representative sample of 1500 patients who were diagnosed with HCC during fiscal years 2005 to 2010. We also compared receipt of surveillance before HCC diagnosis, the stage of HCC at diagnosis, and subsequent outcomes (receipt of HCC treatment and overall survival) in patients with NAFLD-related HCC compared with patients with HCC from other etiologies.

Methods

Data Sources

Data were obtained from VA administrative data files and a review of patient electronic medical records (EMRs). Administrative data included the Medical SAS (MedSAS) Outpatient and Inpatient files, and the VA Vital Status File. The MedSAS files contain patient demographic data as well as diagnoses according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) and procedures according to Common Procedural Terminology (CPT) codes. We determined the date of death, if any, in the Vital Status File, which uses an algorithm to select the "best" date of death using the VA MedSAS Inpatient file, Beneficiary Identification and Records Locator System Death File, Medicare Vital Status file, and Social Security Administration death file.[14] Patient EMR information was obtained by accessing the Compensation and Pension Records Interchange, which is a VA application that provides access to the EMR found in the Computerized Patient Record System at any VA facility nationwide. EMRs were reviewed manually using a structured data abstraction tool by trained medical record abstractors (S.T. and S.M.).

Study Population

We identified a national cohort of 10,695 patients who had an HCC diagnosis in all VA hospitals during October 1, 2004, to September 30, 2011 (fiscal years, 2005–2010). The HCC diagnosis was identified based on the presence of ICD-9 CM code 155.0 (malignant neoplasm of liver) and in the absence of code 155.1 (intrahepatic cholangiocarcinoma).[15] We subsequently selected a random computer-generated sample of 2719 patients for medical record review to confirm the HCC diagnosis, and to determine if eligibility criteria (described later) were met. We included patients in the study cohort if they had an HCC diagnosis made by histopathology or imaging criteria according to the 2005 American Association for the Study of Liver Disease or European Association for the Study of Liver Disease guidelines.[16,17] We excluded 830 of 2719 patients because the HCC diagnosis could not be confirmed. Furthermore, we excluded patients without recent VA health care use (at least 1 inpatient or outpatient encounter at any VA facility within 1 year before the date of HCC diagnosis), cases presenting with HCC recurrence and first HCC diagnosis before the study period, and patients who received treatment before establishing guideline-based diagnosis (n = 389). Thus, our final study cohort included 1500 patients with verified HCC.

Patient Characteristics and Hepatocellular Cancer Management

We ascertained age, sex, race/ethnicity, clinical characteristics including Model for End-Stage Liver Disease score, indicators of advanced liver disease (ascites, encephalopathy, varices), medical comorbidities (diabetes, chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, hypertension, peripheral vascular disease, and end-stage renal disease), and mental health disorders (bipolar disorder, psychosis, posttraumatic stress disorder) for each patient. We ascertained the Barcelona Clinic Liver Cancer (BCLC) HCC stage (A–D) at diagnosis by capturing tumor number and size from the imaging report and performance status from physician notes. We classified patients as having cirrhosis if they had evidence of cirrhosis on a liver biopsy obtained any time before the diagnosis of HCC, features suggestive of cirrhosis on abdominal imaging, or had abnormal values on 2 of 3 laboratory results available within 6 months before and 4 weeks after HCC diagnosis (albumin level, < 3.0 g/L; platelet count, $< 200{,}000$ μL; INR, >1.1). HCC surveillance was defined as receiving abdominal ultrasound, computed tomography, or magnetic resonance imaging with an indication of screening/surveillance for HCC, or any α-fetoprotein (AFP) test within the 3 years before HCC diagnosis. All of the earlier-described information was abstracted manually from the EMR. HCC-specific treatment was defined as receipt of liver