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Hepatocellular Carcinoma Incidence Rates Are 2%-3% in US Patients with Cirrhosis Regardless of Etiology

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This article reviews Reddy KR, McLerran D, Marsh T et al. Incidence and risk factors for hepatocellular carcinoma in cirrhosis: the multicenter Hepatocellular Carcinoma Early Detection Strategy (HEDS) study. Gastroenterology 2023;165(4): 1053-1063.e6.

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STRUCTURED ABSTRACT

Question: What is the incidence of hepatocellular carcinoma (HCC) among US patients with cirrhosis and which demographic and clinical characteristics predict the development of HCC?

Design: Multicenter, prospective cohort study.

Setting: Seven centers across the US between April 2013 and December 2021.

Patients: Study patients had cirrhosis (diagnosed using histology or a combina-

tion of imaging and laboratory findings) and a Model for End-Stage Liver Disease (MELD) score <15. Exclusion criteria included: (a) clinically significant hepatic decompensation (defined as Grade 3–4 encephalopathy, refractory ascites, Child-Turcotte-Pugh class C); (b) listing for transplant; (c) history of cancer within 5 years; (d) unexplained liver masses; and (e) significant comorbid conditions with life expectancy <1 year.

Patients were followed every 6 months (per standard of care at each site) until HCC development, liver transplant, or death. Patients underwent HCC surveillance according to provider preference (or the respective site's protocol) and included bi-annual ultrasound or computed tomography/magnetic resonance imaging (CT/MRI) with or without serum alpha-fetoprotein (AFP). Baseline clinical, demographic and laboratory data were collected, and lifestyle exposures were assessed through validated questionnaires.

Outcomes: The primary endpoint was development of HCC, defined per AASLD guidelines (i.e., diagnosed either on biopsy or by radiographic identification of an LI-RADS 5 lesion). Incident HCC were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system, the most widely used staging system which includes tumor burden, liver function, and performance status. The BCLC system includes 5 stages: 0 (very early), A (early), B (intermediate), C (advanced), and D (terminal). Stage 0 indicates the tumor is less than 2cm, patient feels well and is active, and Child-Pugh A. Stage A means there is a single tumor of any size or up to 3 tumors all less than 3cm, patient feels well and are active, and Child-Pugh A or B.

Data Analysis: The annual incidence rate of HCC was estimated per 100 person-years and reported with 95% Poisson confidence intervals. Fisher's exact test, Wilcoxon test and multivariable logistic regression were used to examine the association between risk factors and incident HCC. All risk factor analyses excluded patients diagnosed with HCC within 6 months of study enrollment and patients with <6 months of follow-up.

Funding: National Institutes of Health.

Results: Among 1,723 patients followed for a median of 2.2 years (range, 0–8.7 years), the annual incidence rate of HCC was 2.4% (95% confidence interval [CI], 1.8%-3.1%). Among the 109 patients that developed HCC, 81% had very early or

early-stage HCC, defined as BCLC stage 0/A. Patients included in analyses evaluating risk factors for HCC development included 95 patients with HCC diagnosed >6 months after study enrollment and 1,230 patients without HCC with at least 6 months of study follow-up.

HCC incidence rates differed by cirrhosis etiology, with highest rates seen in Hepatitis C virus (HCV) infection (3.02%, 95% CI 2.04%– 4.26%) and alcohol-related liver disease (2.69%, 95% CI 1.37%–4.6%), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) (2.06%, 95% CI 1.01%–3.61%), and lower rates observed in Hepatitis B virus (HBV) infection (1.08%, 95% CI 0%–8%), autoimmune hepatitis (0.69%, 95% CI 0.02–3.22), and cholestatic liver disease (1.78%, 95% CI 0.37–4.74).

In univariate analysis, the following clinical characteristics and laboratory parameters were significantly associated with HCC: male gender (70.5% vs 51.9%; $P<0.001$), age (median, 62 years vs 59.5 years; $P=0.03$), obesity (63.2% vs 50.3%; $P=0.02$), smoking history (ever vs never; $P=0.04$), family history of liver cancer (9% vs 3.9%; $P=0.05$), baseline AFP ($P<0.001$), albumin, aspartate aminotransferase (AST), total bilirubin ($P=0.01$), international normalized ratio (INR) ($P=0.004$), platelet count ($P=0.002$), MELD score (10.0 vs 8.0; $P=0.004$), history of HCV (56.4% vs 40.9%; $P=0.005$) and years with cirrhosis (median, 3.85 vs 2.73 years; $P=0.004$). In multivariate analysis, male gender (odds ratio [OR] 2.47; 95% CI 1.54–4.07), obesity (OR 1.7; 95% CI 1.08–2.73), older age (per 5 years; OR 1.17; 95% CI 1.03–1.33), family history of liver cancer (OR 2.69; 95% CI 1.11–5.86), and years with cirrhosis (OR 1.06; 95% CI 1.02–1.1) predicted incident HCC.

COMMENTARY

Why is This Important?

HCC, the most common type of primary liver cancer, is the fastest rising cause of cancer-related deaths in the U.S., and >80% of cases occur in patients with cirrhosis.[1,2] Major risk factors for HCC, aside from male sex and older age, include hepatitis B virus (HBV) infection, HCV infection, MASLD (previously known as non-alcoholic fatty liver disease-NAFLD), alcohol consumption, diabetes and smoking. The risk of HCC varies across cirrhosis etiologies, and the landscape of HCC is shifting from predominately viral (HCV, HBV) to eradicated HCV and non-viral (MASLD and alcohol-related liver disease) etiologies with lower annual incidence rates.[3] These lower incidence rates hinder surveillance effectiveness in patients with MASLD, ALD, and eradicated HCV, by increasing the number needed to screen

(NNS)—the number of patients that must be screened to identify one early-stage HCC. Thus, better risk stratification tools are needed to identify at risk patients.

Most prior studies on HCC incidence and risk factors have been retrospective, performed outside of the US, and/or conducted in cohorts of patients lacking diversity in liver disease etiology. This decade-long, NIH-funded study is the largest prospective cohort to date to examine the magnitude of HCC risk and risk factors for HCC in contemporary patients with cirrhosis. Additionally, this study used validated surveys and manual chart reviews to evaluate risk factors not included in other studies, including family history of liver cancer, tobacco use, alcohol consumption, coffee/tea consumption, etc.

Key Study Findings

In a geographically diverse cohort of patients with cirrhosis enrolled from 2013 to 2021 with median follow-up time of 2.2 years (4,510 person-years), the annual incidence rate for HCC was 2.4% (95% CI 1.8%–3.1%).

HCC incidence rates differed by cirrhosis etiology with highest rates seen in HCV (3.02%, 95% CI 2.04%–4.26%) and alcohol-related liver disease (2.69%, 95% CI 1.37- 4.6), followed by MASLD (2.06%, 95% CI 1.01%–3.61%). Obesity OR 1.7 (95% CI 1.08–2.73) was the only modifiable risk factor identified in this study.

Caution

The study cohort, while geographically diverse, lacked racial and ethnic diversity and included only 7.1% Black, 2.1% Asian/Pacific Islander, and 9.5% Hispanic/Latino participants. Data on aspirin use, which has been associated with reduced HCC risk in population-based studies,[4-5] was not collected.

My Practice

We follow the updated 2023 AASLD guidance for HCC surveillance,[6] which recommends performing biannual ultrasound in addition to AFP in all patients with cirrhosis, regardless of etiology. This practice is supported by this prospective study, as the annual incidence rate for HCC exceeded 1% for all etiologies of cirrhosis, exceeding the established threshold for which surveillance is currently considered to be cost-effective. We also perform surveillance in patients with cirrhosis and treated HCV who have achieved viral cure (i.e., sustained viral response), as well as those with chronic HBV who are at high risk (determined by PAGE-B score $\geq$10 or age + endemic country of origin from Asia or Africa).[6]

Obesity was the only modifiable risk factor identified for HCC in this study. This reiterates the importance of counseling patients on lifestyle modifications and healthy weight loss to mitigate HCC risk. As only a minority of patients can lose weight and maintain weight loss with lifestyle modifications

alone, it will become increasingly important to 1) identify and risk stratify patients with MASLD; and 2) refer patients early for multidisciplinary treatment, including bariatric surgery or pharmacologic obesity treatment and pharmacologic MASLD treatment once available.

For Future Research

The burden of HCC is not equally distributed in the US, with higher incidence and mortality rates observed among Black, Hispanic, Asian/Pacific Islander and American Indian/Alaskan Native populations compared to non-Hispanic Whites.[3,7] Thus, future studies should be performed in racially and ethnically diverse cohorts. Additionally, limited information is available to guide clinicians on how to counsel patients regarding their individual risk of HCC. While some risk stratification tools are available, none have been sufficiently externally validated and it remains unclear how to implement these tools into clinical practice.

Conflicts of Interest

Dr. Arvind reports no conflicts of interest. Dr. Rich has served as consultant for AstraZeneca, Eisai, and Elevar Therapeutics.

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