

Predicting Liver Cancer in People Cured of Hepatitis C

Readily available clinical parameters can identify those at greatest risk for hepatocellular carcinoma.

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Three new methods using demographic characteristics, liver disease severity and readily available biomarkers can help predict who will develop liver cancer after successful treatment for hepatitis C virus, according to a set of studies presented last month at the Digital International Liver Congress.

Over years or decades, chronic hepatitis C can lead to the development of cirrhosis and hepatocellular carcinoma (HCC), the most common type of liver cancer liver. Although people who are cured of hep C are less likely to develop HCC, the risk is not eliminated entirely, especially for those who have already progressed to cirrhosis. HCC is often diagnosed late, when it is more difficult to treat, and better methods to predict who is most likely to develop liver cancer are urgently needed.

Jessica Azzi, PharmD, of the ANRS-AFEF HEPATHER Study Group in Paris, and colleagues analyzed predictive factors and developed a prognostic score for HCC after sustained virological response (SVR) to direct-acting antiviral (DAA) therapy.

The analysis included 3,929 people with chronic hepatitis C who were cured with DAAs. Of the 2,829 patients with cirrhosis, 191 (6.8%) developed liver cancer. In contrast, only 15 of the 1,097 people (1.4%) with moderate to advanced fibrosis developed HCC.

The researchers identified 11 variables associated with the development of HCC, including male sex, age greater than 64, hepatitis C virus (HCV) genotype 3, prolonged prothrombin time (a measure of blood clotting ability), alpha-fetoprotein (AFP, a liver cancer biomarker), FIB-4 score (a fibrosis index based on laboratory tests), elevated cholesterol, esophageal varices (enlarged veins), prior treatment with interferon-based therapy, duration of HCV infection and below-normal body weight.

They then assigned points for each of these variables and calculated a composite HCC risk score. Scores below 6 were considered low risk, scores of 6 to 11 were medium risk and scores of 11 or above were high risk.

After three years of follow-up, just 2% of people with low risk scores developed HCC, rising to 7% for those with medium risk scores and 23% for those with high risk scores. Those with high scores saw a steep increase in liver cancer even during the first year of follow-up, while those with low or medium scores experienced a more gradual rise.

The score offers a “practical and easy tool to use in clinical practice to estimate HCC risk” and can help identify a high-risk subgroup of people for whom liver cancer screening would be cost effective, Azzi said.

In another French study, Pierre Nahon, MD, PhD, of Jean Verdier Hospital in Paris, and colleagues aimed to identify routinely measured biomarkers and changes in AFP levels that could predict higher risk of HCC in people with cirrhosis. They used data from ANRS CirVir, a prospective cohort of people with compensated cirrhosis who underwent regular HCC surveillance.

The analysis included 717 participants who were followed for a median of 5.6 years; 413 of them (58%) achieved SVR. Levels of liver enzymes (ALT, AST and GGT), bilirubin, AFP, albumin, platelets and prothrombin time were assessed every six months.

Prior to SVR, the investigators identified three clusters: people with inflammation and high AFP levels (26%), those who experienced liver failure (28%) and those with the least impaired lab values (46%). People with inflammation and high AFP had the highest risk of developing HCC, with the liver failure cluster not far behind. Those with the least impaired lab values had a much lower risk.

Among those who achieved SVR, 26% had persistent liver impairment, 23% continued to have elevated liver biomarkers and 22% had the least impaired values. In this group, people with persistent liver impairment (16%) or elevated biomarkers (14%) had a higher HCC risk, while those with the least impaired values had a low rate (8%). Nahon suggested that people with persistent liver impairment after being cured of hep C may have been treated too late.

The investigators concluded that the pre-SVR inflammation and liver failure clusters represent two different risk profiles that together accounted for more than half of people who developed liver cancer. These profiles can persist even after SVR, identifying subgroups who remain at risk for HCC.

Finally, Gamal Shiha, MD, PhD, of the Egyptian Liver Research Institute and Hospital near Cairo, and colleagues developed a noninvasive scoring model for individualized HCC risk prediction. He noted that a one-size-fits-all screening strategy for a growing population of people treated for hepatitis C may not be feasible, particularly in low- and middle-income countries.

After screening more than 200,000 people for hep C in 73 villages in Egypt and treating those with active infection, the researchers identified 2,372 individuals without existing liver cancer who achieved SVR and completed at least a year of follow-up; nearly three quarters had cirrhosis, while the rest had advanced fibrosis.

Over a median two years of follow-up, 109 people (4.6%) developed HCC after the end of treatment. All but eight already had cirrhosis before starting hep C treatment. Older age (over 54), male sex, pretreatment fibrosis stage (cirrhosis versus advanced cirrhosis) and AFP and albumin levels were identified as risk factors for the development of liver cancer.

The researchers then developed a composite score by assigning points for each relevant variable. Participants were stratified into three groups with low risk (a score of 6.0 or lower; 58%), intermediate risk (6.0 to 7.5; 25%) or high risk (over 7.5; 18%). The score demonstrated high predictive accuracy, with HCC incidence rates of 1.2% for the low-risk group, 3.3% for the intermediate-risk group and 7.1% for the high-risk group.

The score was then validated in two other patient cohorts. In an internal cohort of 422 people with cirrhosis and 265 with advanced fibrosis, two people (0.2%) in the low-risk group, two (2.1%) in the intermediate group and 10 (8.7%) in the high-risk group developed liver cancer. In an external cohort of 947 patients with cirrhosis and 394 with advanced fibrosis, only one person (0%) in the low-risk group, six people (2.1%) in the intermediate group and 39 (6.1%) in the high-risk group developed HCC.

The researchers concluded that this simple score using readily available parameters can accurately stratify patients according to HCC risk. Shiha suggested that identifying people who will not benefit from continued HCC surveillance based on their estimated risk could enable a personalized surveillance strategy targeting those at highest risk.

“The proposed scores potentially represent a useful clinical tool to help inform patients about the risk of developing HCC after HCV is cured,” said Jordi Bruix, MD, PhD, of the University of Barcelona, commenting on the three studies in an [EASL press release](#). “These data also reinforce the importance of implementing HCC screening programs in DAA-treated patients and the need to reinforce research efforts to identify the causes of liver cancer development despite cure of HCV.”

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