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We read with great interest the recent paper by Poynard and colleagues wherein the authors propose a validation of the multivariable hepatocellular carcinoma (HCC) risk calculator, LCR1-LCR2, in patients with chronic hepatitis C and volunteer a new algorithm for HCC surveillance in this setting.[1]

Although regularly challenged due to persisting controversies with regards to efficacy, harms and cost-effectiveness, ultrasound screening every 6 months in patients with cirrhosis is recommended by international societies.[2-6] If surveillance in patients with equivalent METAVIR F3 fibrosis (histology or non-invasive tests) remains controversial, there is a consensus not to implement surveillance below this threshold with respect to the low HCC incidence reported by numerous prospective cohorts over the last 20 years, including in patients who have achieved HCV clearance.[4-6] Nevertheless, identifying non-cirrhotic patients at higher risk of developing HCC who could benefit from surveillance programs following HCV eradication is an unmet need.

The HECAM-FibroFrance Group previously reported and externally validated the LCR1 and LCR2 tests to identify individuals at high risk of HCC in a cohort of patients with any cause of chronic liver disease.[7,8] LCR1-LCR2 is a multi-analyte blood test combining proteins involved in liver cell repair (apolipoprotein-A1, haptoglobin), known HCC risk factors (gender, age, gamma-glutamyltransferase), a marker of fibrosis (alpha2-macroglobulin) and alfa-fetoprotein, a specific marker of HCC. In this issue of *JHEP Reports*, the HECAM consortium and the ANRS CO22 Hepather cohort present an external validation of LCR1-LCR2 in patients with chronic hepatitis C from the ANRS CO22 Hepather cohort.[1]

The ANRS CO22 Hepather cohort is a French national, multicenter, prospective, observational cohort study of patients with past or present viral hepatitis infection included between Aug 6, 2012, and Dec 31, 2015 in 32 expert hepatology centers in France, with ongoing follow-up. For the purpose of this study, the population was limited to patients with active hepatitis C infection at inception, irrespective of fibrosis stage, treated or not with antivirals, and no history of decompensated cirrhosis or liver transplantation or with interferon-based antiviral treatment. This was an ambispective study meaning that patients were included prospectively but LCR1-LCR2 data could be assessed retrospectively in patients missing components of those tests at baseline. The co-primary study outcome was the negative predictive value (NPV) of LCR1-LCR2 for the occurrence of HCC at 5 years and survival without HCC according to the predetermined LCR1-LCR2 cut-offs (LCR1 low risk <0.0154-LCR2 low risk <0.044), adjusted for HCC risk variables and for the response to HCV treatment, quantified using time-dependent Cox proportional hazards models.

A total of 4,903 patients were included in the study, 18.2% with baseline cirrhosis and 77% with sustained virological response (SVR), with a median follow-up of 5.8 years. The LCR1-LCR2 algorithm classified 3,755 (76.6%) patients into the low-risk and 1,148 (23.4%) patients into the high-risk categories. At 5 years, a total of 137 cases of HCC had occurred: 24 in LCR1-LCR2 low-risk patients compared to 113 in LCR1-LCR2 high-risk patients. The NPV was 99.4% (95% CI 99.1–99.6), similar to the 99.5% (99.0–99.7) observed in the original study developed in patients with any cause of chronic liver disease. Importantly, findings were robust after adjustment for exposure to antivirals, age, gender, geographical origin, HCV genotype-3, alcohol consumption, type 2-diabetes and arterial hypertension. Most incident HCCs were potentially curable and all were smaller than 30 mm.

The authors conclude that, according to the LCR1-LCR2 algorithm, in patients with chronic hepatitis C irrespective of fibrosis stage and SVR status, HCC risk is minimal in 76% of cases. Therefore, these low-risk patients could be reassured at least for 5 years and surveillance strategies could focus on the remaining 25% at high risk.

All international guidelines endorse lifelong HCC surveillance in patients with cirrhosis who achieved HCV clearance[9] using semi-annual ultrasound, with known sensibility issues.[10] Refining HCC risk prediction in these patients mostly aims at identifying those remaining at a very high risk and in whom personalized management using more effective (but also more expensive) surveillance tools such as contrast-enhanced imaging techniques or circulating biomarkers could be implemented. For instance, it has been suggested that MRI could increase rates of early HCC

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detection and be cost-effective altogether in patients with an annual HCC incidence above 3%.[11] However, such high-HCC risk subgroups can be easily identified using existing scoring systems with varying levels of complexity based on the combination of routine parameters estimating coexisting comorbidities, persisting liver inflammation or functional impairment.[12] The present study did not address the specific issue of HCC risk stratification in hepatitis C cirrhotic patients after SVR. The implementation in clinical practice of new patented algorithms in patients with cirrhosis will only be justified if i) these algorithms outperform those already available at no additional cost, ii) intensification of surveillance procedures in high-risk patients is proven to be cost-effective in randomized trials.

The issue of HCC risk stratification in patients without advanced fibrosis is different. As in patients with NAFLD, the overall benefit of including a high-volume population in surveillance programs is highly questionable given the expected extremely low HCC incidence. In this setting, HCC risk prediction is not possible based on routine parameters: hence, the use of algorithms combining new biological features such as apolipoprotein-A1, haptoglobin or alpha2-macroglobulin in the LCR1-LCR2 score may fill the gap for HCC risk stratification in F0-F2 patients. The Hepather cohort included patients in whom liver fibrosis assessment did not necessarily rely on liver biopsy, reflecting real-life clinical practice. As stated by the authors, defining the gold standard of fibrosis assessment remains an unsolved issue. The LCR1-LCR2 algorithms, by combining surrogate markers of liver fibrosis and parameters potentially associated with hepatocarcinogenesis, may reveal unexpected phenotypes in non-cirrhotic patients with an HCC incidence justifying semi-annual ultrasound. Defining, in the population of patients with chronic liver disease (not only chronic hepatitis C) without advanced fibrosis, the subset of patients in whom HCC surveillance is cost-effective and safe is the next challenge physicians, taxpayers and stakeholders need to tackle.

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