Editorial

Hepatocellular carcinoma (HCC) risk stratification after virological cure for hepatitis C virus (HCV)-induced cirrhosis: time to refine predictive models

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Direct-acting antivirals (DAAs) have revolutionized antiviral treatment for chronic hepatitis C virus (HCV) infection, especially with the interferon-free regimens of the past 5 years. Having a cure for a virus that has been identified (only) 30 years ago is unique in medical history. Importantly, even in case of advanced liver disease, cohort studies showed that patients attaining a sustained virological response (SVR) have a 3- to 4-fold reduced risk of hepatocellular carcinoma (HCC) (1-3). Despite this favourable perspective, the risk of HCC is not eradicated upon viral clearance among patients with cirrhosis. In fact, albeit within a biased population of predominantly male American veterans with frequent comorbidities, the annual HCC rate following SVR was substantial and appeared to remain rather stable over long periods of follow-up (4). As SVR is now increasingly achieved in HCV-infected patients with the highest risk of cirrhosis-related complications due to the general use of highly effective DAAs with good safety profile, we should expect to encounter HCC following HCV eradication more frequently in the upcoming years. Guidelines indeed recommend physicians to continue costly and intensive HCC surveillance following successful antiviral therapy in all patients with cirrhosis (5,6). As our experience with advanced liver disease and SVR increases and prolongs, research will focus on long-term individual HCC risk stratification. How can we optimize the cost-efficacy of surveillance programs? Which patients can and should be safely discharged?

The December (Nobel Prize) issue of *Journal of Hepatology* added new insights to the growing amount of data on HCC risk stratification (7). Predictive machine learning approaches were applied in HCC risk stratification among patients with HCV-related cirrhosis which consider more specific interactions between prognostic factors. So far, assessment of clinical parameters by "standard" statistical methodologies has not yet delivered a sufficiently powerful and reliable HCC risk tool. At least, not to identify patients who are free from long-term risks. New innovative efforts should thus indeed be explored to refine prognostic HCC models, and the study presented by Dr. Audureau et al. should be appreciated for this.

For their analyses, the authors included 836 patients from the French CirVir Cohort in a derivation cohort, which were recruited in 35 French centers between 2006 and 2012. Due to the timeframe of inclusion, the cohort was followed for a median duration of more than 5 years but mostly consisted of patients treated with interferon-based therapy. The SVR rate was therefore just above 50%. During follow-up 156 patients were diagnosed with HCC, leading to an overall 5-year cumulative incidence of 19.3%. Importantly, patients without SVR were separately analysed from those with SVR as risk factors indeed differed between the response groups. First, Fine-Gray competing risk regression models (accounting for competing risk of death or liver transplant) were used to identify predictors of HCC occurrence. For patients with ongoing HCV infection, six familiar predictors of HCC were identified: past excessive alcohol intake, HCV genotype 1, elevated alpha-fetoprotein

and gamma glutamyltransferase, and reduced platelet count and albumin. Although adequate natural history models remain with relevant purpose, direct clinical use for the individual patient is less likely due to the rapid cure of newly diagnosed HCV infection. In this light, the estimated independent associations between HCC occurrence and elevated aspartate aminotransferase (AST, with a cut-off ≥1.5× upper limit of normal), reduced platelet count (with a cut-off <70 10^3/μL) and lower prothrombin time percentage (PT, cut-off ≤85%) at the time of SVR may be of higher interest. Hereafter, more advanced mathematical models were designed. A single decision tree was build based on the five most important predictors within that algorithm, which resulted in 8 different risk groups (5 before SVR, 3 after SVR). With a C-statistic of 0.68, however, the discriminative performance of this prognostic model was modest. In addition, calibration analyses among the SVR patients in ANRS C022 Hepather validation cohort, with similar characteristics and HCC surveillance protocols, were not reassuring. Among those included in the lowest risk group based on an AST <2.5× ULN and PT >85% at SVR, the predicted 5-year HCC risk of 0.5% underestimated the observed 5-year HCC rate of 7.9%. The C-statistic in the validation cohort also declined to 0.62. Finally, the authors took their analyses one step further with a random survival forest approach. Even though these complex prognostic models may not be straightforward to visualize and interpret, they are considered to result in a more accurate prediction. The three most important liver-related variables in this model (PT, alanine aminotransferase, and platelet count) are in line with our general understanding of risk in liver diseases, as they represent liver function, persisting liver inflammation and the degree of portal hypertension. This model indeed had the best predictive accuracy, which remained adequate in the validation cohort (c-statistic 0.70). Still, overestimation of an actually low risk of HCC appeared to be a problem with this model and this will not facilitate physicians to confidently discharge patients from active follow-up. The limitations with respect to the calibration of the estimates of the models may be partly attributed to the fact that they were based on only 19 HCC events after SVR, also because only a minority of patients were cured with DAAs. While short-term implementation in daily clinical decisions may therefore be unlikely, the potential and relevance of the sophisticated methodology are evident.

Even though HCC surveillance requires better clinical evidence, especially after SVR, there will be no discussion that it is futile for patients who will not develop HCC (8). In fact, there are potential harms of surveillance to consider, which become more relevant as the rate of HCC lowers and long-term survival increases with SVR in patients with HCV-induced cirrhosis (2). Harms of surveillance include false positive findings resulting in unnecessary extra diagnostic evaluation (with radiation exposure, contrast injury and potential biopsy-related complications) as well as psychological distress. While these harms form an important argument in the justification of a randomized controlled trial to assess the clinical efficacy of surveillance, such a trial will be challenging to perform (8). Reliable identification of patients with a negligible risk of HCC may thus represents a more practical way forward. Repeated measurement of non-invasive markers of liver disease severity following antiviral therapy is gaining attention for this purpose (1,9). In the largest cohort of >29,000 DAA-treated American Veterans, those with a decrease of pre-treatment FIB-4 index ≥3.25 to a FIB-4 index <3.25 post SVR had a 50% lower risk of HCC as compared to those with a persisting high FIB-4 index. Still, their annual HCC rate of ~2% remained substantial (1). Although further exploration of the course of such variables in relation to HCC is warranted, for instance by machine learning, it can be questioned whether the readily available parameters in clinical practice will have sufficient predictive power to exclude a residual HCC risk. Combining such effort with translational studies to identify novel predictive biomarkers and genetic profiling may be needed to definitely personalize decisions on HCC surveillance (10-12).

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Footnote

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