Editorial

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Towards personalized screening for hepatocellular carcinoma: Still not there

Vincenza Calvaruso[1,*], Jordi Bruix[2]

[1]GI & Liver Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo; [2]BCLC group, Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBEREHD

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In patients with HCV-related cirrhosis the annual risk of hepatocellular carcinoma (HCC) is 2–4%.[1] However, with the advent of highly effective and well tolerated direct-acting antivirals (DAAs), the number of patients cured of HCV has increased dramatically.[2] Many studies have confirmed the benefit of sustained virological response (SVR) on all liver outcomes. However, data from the largest HCV international cohorts provided clear evidence that SVR significantly lowers the risk of HCC without removing the risk altogether.[3,4] A recent long-term evaluation of HCC occurrence in the Veterans cohort found that the incidence rate of HCC remained stable between 1.5 to 2.3/100 person years in patients with cirrhosis and the risk of HCC did not regress even 3.6 years after DAA-induced SVR.[5] Therefore, the identification of patients with HCV who remain at high risk of HCC despite viral clearance remains an unsolved clinical need. Moreover, thanks to the benefits of SVR on liver function, patients with cirrhosis will survive longer and a greater number will thus be susceptible to HCC. For this reason, many groups focused their research on the identification of potential predictors of HCC in order to provide a rationale to tailor different surveillance regimens according to HCC risk. Until now, these studies analysed variables related to stage of liver disease. As expected, Child-Pugh class and/or platelets and albumin together with viral response have been proposed as predictors of different risk classes.[4] The more recent restrospective analysis of Iannou *et al.*[6] defined increasing risk classes according to FIB-4 score. Pons *et al.*[7] confirmed, in a cohort of patients with compensated advanced chronic liver disease, that liver cancer remains the most frequent complication after oral antiviral therapy and found that liver stiffness and albumin levels after treatment can help to identify patients at higher or lower risk of HCC.

In this issue of *Journal of Hepatology*, Audureau and colleagues[8] developed algorithms based on predictive machine learning approaches to refine individualized predictions of HCC risk according to HCV eradication in patients with cirrhosis included in the large French ANRS CO12 CirVir cohort. Since patients were recruited from 2006 onwards, many of them were treated with interferon-based regimens and therefore the overall SVR rate in the whole cohort was 51.9%. Even if this clinical situation can be considered outdated since SVR is now achievable in more than 95% of cases, the study highlights that HCC risk factors and their relative contribution differ according to response to antiviral therapy. Clinical variables such as past excessive alcohol intake, HCV genotype 1, platelet count, gamma glutamyltransferase (GGT), alpha-fetoprotein and albumin were identified as predictors of HCC in patients without SVR, while prothrombin time, aspartate aminotransferase (AST) and platelet count were predictors after SVR. The decision tree analysis stratified patients into 8 different phenotypes with distinct cancer risks. The 5-year HCC incidence ranges from 7.9% in the 3 best profiles of patients with SVR to 37.3% in the worst group of viremic patients. Interestingly, patients with active HCV infection but still with the best liver function profile (high albumin and platelets, low GGT), were found to have an HCC incidence as low that of patients with SVR (9.6% incidence after 5 years).

Synthesizing all these predictors could not identify a group with zero risk of liver cancer, leading to the conclusion that patients with advanced fibrosis or established cirrhosis before SVR maintain a high enough risk to merit HCC surveillance.

Innovative biometrics will be required to overcome this issue and properly address the identification of predictors of HCC events in the future. Audureu *et al.*[8] performed an elegant study using new biometric instruments to analyse their data. Machine learning algorithms use data-driven mathematical models to make predictions or take decisions. These new methods may permit the best refinement of the individual prediction of outcomes since they are able to evaluate complex interactions between predictors. However, even if the choice of potential predictors to use in the model is established by a mathematical model and not driven by clinicians, it is necessary to explain the biological plausibility of the results and confirm their reproducibility. Moreover, although the analysis achieved interesting results for the identification of the low risk categories, HCC occurrence is underestimated by all models and we still seem to be far from tailoring screening strategies according to risk.

Since the numerous models developed to predict HCC risk have not been able to accurately identify the patients who will or will not develop cancer, despite the use of an extensive number

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* Corresponding Author. Address: Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Piazza delle Cliniche n.2, 90127 Palermo, Italy. Tel.: +39 09123890679; fax: +39 0916552156.
E-mail address: vincenza.calvaruso@unipa.it (V. Calvaruso).
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of parameters related to the evolutionary stage of chronic liver disease, we need innovation in translational research so that robust data are inputted after validation in prospective cohorts with adequate patient annotation. The underlying molecular mechanisms leading to HCC have been studied using tumorous and non-tumorous tissue from HCC specimens. Genomic profiling of such samples suggested an oncogenic signature to predict metachronic HCC after initial resection,[9] but it also reflected stellate cell activation[10] and probably a higher degree of portal hypertension. The role of portal hypertension is further supported by the Italian study of Faillaci *et al.*,[11] showing that liver angiopoietin-2 (ANGPT2) expression in the primary tumor or in cirrhotic tissue before DAAs was independently related to the risk of HCC occurrence. They also observed that vascular endothelial growth factor (VEGF) increased during DAA treatment and this favors HCC emergence in high-risk patients, defined by the presence of portal hypertension. These patients already have abnormal activation of neo-angiogenic pathways in liver tissues.

Hamdane *et al.*[12] investigated HCV-induced epigenetic alterations that might affect the risk for HCC after DAA treatment in patients and mice with humanized livers. Epigenetic alterations affect the expression of genes without changing the nucleotide sequence, as oberved in the acetylation of distinct lysine (K) residues (K27 of histone H3 - H3K27ac) which result in the elevated expression and transduction of sphingosine kinase 1 (SPHK1) and transcription factor SOX-9. These changes persisted after an SVR to DAAs or interferon-based therapies. Integrative pathway analyses of liver tissues demonstrated that HCV-induced epigenetic alterations were associated with increased cancer risk.[12] Indeed, persistence of epigenetic changes depends on the degree of fibrosis and this indicates that HCV-associated tumorigenesis may become independent from the virus and persist despite SVR.

Other studies tried to identify if the risk of HCC could be genetically determined and several single nucleotide polymorphisms (SNPs) have been identified as indicators of elevated HCC risk.[13] A recent genome-wide association study identified an SNP in the Tolloid-like protein 1 (TLL1) gene associated with HCC risk after HCV cure.[14] Other preliminary data showed that the AA allele of rs6726639 deSNP of MERTK (MER tyrosine kinase) gene, a regulator of tumor-associated macrophages involved in the modulation of inflammatory responses and angiogenesis, is associated with a higher risk of developing HCC after HCV eradication by DAAs in patients with HCV cirrhosis.[15] Finally, Liu *et al.*[16] recently demonstrated that a viral exposure signature is predictive of HCC in at-risk patients who had long-term follow-up for HCC development. These relevant data open a new approach to grade cancer risk that, combined with established parameters, could become the clue to define the absence of HCC risk.

As said, clinical predictors have been extensively validated – the time has come to incoporate molecular profiling into individualized HCC risk prediction and thereby, to personalize surveillance. At the same time, such profiling will be instrumental to identify targets for potential chemopreventive interventions, This is the optimal goal to curb the death toll of liver cancer and such efforts are eagerly awaited.

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Conflicts of interest

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Authors' contributions

VC: Study concept, writing the draft and approving the final version. JB: Study concept, writing the draft and approving the final version.

Supplementary data

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