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EDITORIAL

Individualization of HCC and Portal Hypertension Surveillance in Patients with Compensated Advanced Chronic Liver Disease and SVR

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Interferon (IFN)-free therapies for chronic hepatitis C (HCV) infection achieve sustained virologic response (SVR) in almost all patients with advanced chronic liver disease (ACLD) [1]. Viral eradication ameliorates portal hypertension (PH)—as evidenced by a decrease in hepatic venous pressure gradient (HVPG) [2, 3]—thereby mitigating or even removing the primary driver of first hepatic decompensation [2, 4]. Importantly, patients with compensated ACLD (cACLD) in whom clinically significant PH (CSPH) can be excluded post-treatment do not require continued PH surveillance if no cofactors are present. Based on the Baveno VII [5] recommendations for the management of patients in whom the primary etiological factor has been removed, non-invasive tests (NIT)-based criteria (such as elastographic liver stiffness measurement [LSM] < 12 kPa and a normal platelet count [PLT]) are recommended for identifying the latter group, which accounts for approximately half of patients with cACLD. On the contrary, non-selective beta blocker therapy should be maintained in those with LSM > 25 kPa, due to the high likelihood of CSPH and an ongoing risk of hepatic decompensation. Accordingly, Baveno VII has paved the way for the individualization of post SVR PH surveillance using NIT, thereby reducing the need for endoscopy.

In addition to preventing complications of PH, achieving SVR decreases, but does not eliminate the risk of hepatocellular carcinoma (HCC). Importantly, there are currently no recommendations for deescalating/discontinuing surveillance for de novo HCC, primarily due to the limitations of available risk prediction models.

In this issue of *Digestive Diseases and Sciences*, Liu and colleagues [6] from Taiwan propose a simple risk stratification approach for de novo HCC based on LSM by vibration-controlled transient elastography and the fibrosis-4 (FIB-4)—a score calculated from age and routine blood tests initially developed for staging liver fibrosis in patients with HIV/HCV co-infection. The authors found that cACLD patients with pre-treatment LSM < 12 kPa and post-treatment FIB-4 < 3.7 had the lowest risk of de novo HCC (1.1/100 person-years) post SVR, whereas patients not meeting one or two of these criteria were assigned to the intermediate- (3.6/100 person-years) or high-risk (5/100 person-years) groups, respectively. Accordingly, the incidence of HCC in the low-risk group was below the cost-effectiveness threshold (at $50,000/quality-adjusted life year [QALY]) for HCC surveillance, which has been estimated at 1.32%/year [7]. Thus, while the authors suggested a prolongation of ultrasound intervals in the low-risk group, even a discontinuation of HCC surveillance may be conceivable, particularly in resource-limited settings. Nevertheless, owing to the profound implications of a delayed diagnosis of HCC that may result from an unwarranted termination of surveillance due to an underestimation of HCC risk, there is a clear need for exhaustive validation of potential surveillance discontinuation criteria before they may be applied in the clinic. Therefore, future studies of HCC risk stratification post SVR should not only aim at establishing novel algorithms/methods, but also at evaluating—and potentially validating—previously established approaches.

Notably, the present study [6] also provides relevant information on predictors of post SVR hepatic decompensation. Important lessons can be learned by comparing these data to the findings regarding HCC: First, HCC was nearly twice as common as hepatic decompensation, indicating that HCC might be the most important liver-related complication post

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SVR. Second, the areas under the receiver operating characteristic curves of LSM and FIB-4 for hepatic decompensation were ~ 0.9, although those for HCC only attained ~ 0.65. This suggests that more comprehensive predictive models using readily available information, novel parameters, or a combination of both are required to obtain a similarly high accuracy for HCC prediction, as compared with hepatic decompensation. In a recent study by Semmler et al. [8], a simple scoring system for de novo HCC occurrence based on age, alcohol consumption, LSM, and serum albumin as well as α-fetoprotein (AFP) level identified more than two thirds of cACLD patients as being at low risk (i.e., < 1/100 patient-years) for HCC. This number compares favorably to the approach proposed by Liu et al. [6], in which only ~ 1/3 of patients were assigned to the low-risk group. Notably, Semmler et al. [8] showed a consistent prognostic utility within the derivation and validation cohorts, which both were comprised primarily of patients of European descent. Although direct comparisons are limited by differences in ethnicity and other patient characteristics, it appears that despite the theoretical concern of overfitting, more comprehensive predictive models provide superior prognostic accuracy. However, this comes at the cost of increasing complexity, which may in turn compromise clinical implementation.

Seen from a different perspective, 6-monthly surveillance for HCC in patients who achieved SVR was cost-effective (willingness-to-pay threshold of $150,000 USD/QALY) only until the age of 70 for patients with compensated cirrhosis (F4) and until the age of 60 for patients with advanced fibrosis (F3) [9]. Although this approach neglects substantial interindividual variability in HCC risk within F3/F4 stages (as indicated by fibrosis-unrelated risk factors established by Semmler et al. [8]) it highlights that not only HCC risk, but also the individual benefit of an early diagnosis, which largely depends on age and comorbidities, should be taken into account when deciding on HCC surveillance.

Finally, Liu and colleagues [6] as well as other studies not only identified patients at low risk but also patients at high risk. Although it remains to be elucidated whether screening strategies should be modified in these patients (e.g., shortening imaging intervals as proposed by Liu et al. [6]), the overall adherence to HCC surveillance was only ~ 50% according to a meta-analysis of published studies [10], underscoring the urgent need for quality improvement and patient education initiatives targeting high-risk patients, following the credo: "Whatever is worth doing at all is worth doing well."[1]

Though post SVR PH surveillance has entered the era of personalized medicine [5], there is still no guidance governing the individualization of HCC surveillance. This may be explained by the observation that HCC occurrence remains less predictable as compared to hepatic decompensation, although studies such the one by Liu and co-workers (6) suggest that NIT and other parameters are capable of identifying low-risk populations in whom screening is not cost-effective.

[1] Stanhope, P (4.th Earl of Chesterfield) Letters to his son, 1746.

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Declarations

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