FIB-4 score and hepatocellular carcinoma risk after hepatitis C virus cure: time to revise surveillance?

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Comment on: Ioannou GN, Beste LA, Green PK, *et al.* Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. Gastroenterology 2019;157:1264-78.e4.

Hepatitis C virus (HCV) is a main cause and important risk factor for hepatocellular carcinoma (HCC) in Western countries (1). Direct antiviral agents (DAAs) for HCV are highly effective and well-tolerated antiviral drugs which allow HCV cure even in patients with advanced liver disease. However, whilst HCV cure improves liver function and decreases overall HCC risk, a significant HCC risk persists in particular in patients with advanced fibrosis including cirrhosis who have the highest risk of developing HCC (2-4).

Current international guidelines suggest that HCC surveillance programs, consisting in biannual ultrasound surveillance, should be offered to all HCV patients affected by cirrhosis (5,6). Nevertheless, it is not clear whether non-cirrhotic patients, e.g., with fibrosis graded Metavir F3, should be included nor whether these programs should be offered indefinitely to cirrhotic patients after HCV cure. Even though resolution or reduction of fibrosis has been observed after viral cure, it is unknown whether this translates in a reduction of HCC risk over-time. Moreover, HCC risk can change over time because of HCV-independent risk factors such as age, alcohol intake, obesity and diabetes.

FIB-4 is a simple and easy-to-use score composed by patient's age, ALT, AST and platelet level and it has been developed and validated as non-invasive marker of liver fibrosis. An elevated FIB-4 score (≥3.25) has a high specificity (>96%) for advanced liver fibrosis (Ishak stage 4–6 or Metavir F3–F4) while a low FIB-4 score (≤1.45) is associated with low fibrosis stages (Ishak stage 1–3 or Metavir F0–F2) (7). The FIB-4 score has been already shown to correlate with HCC risk in non-cirrhotic HCV patients treated with DAA and in patients with chronic HBV, non-alcoholic fatty liver disease (NASH) and alcoholic cirrhosis (8-11).

In a recent study published in the journal *Gastroenterology*, Ioannou *et al.* analyzed patients' data from the Veterans Health Administration (VHA), one of the first US center to adopt an unrestricted access to DAAs with more than 50,000 HCV patients treated in 15 years (2000–2015) who obtained a sustained viral response (SVR) (12,13). Using individual laboratory data and ICD-9 and ICD-10 diagnosis records, Ioannou and colleagues calculated the HCC risk after SVR in cirrhotic and non-cirrhotic patients stratifying them according to anti-viral regimen (IFN or DAA) and pre-treatment and post-SVR FIB-4 score (13). Post-SVR FIB-4 changes were analyzed both as categorical variable at 1-year post-SVR and as a time-dependent factor (13). Since some studies had reported an increased HCC risk associated with DAA treatment (14,15), it is important to note that this study included only patients with no HCC diagnosis in the first 6 months post-SVR. This choice was justified by the need of excluding undiagnosed or occult HCC at the time of the antiviral treatment and clearly evaluate long-term HCC risk.

Altogether, more than 48,000 patients were included,

Table 1 HCC risk after DAA treatment according to cirrhosis status, baseline FIB-4 and FIB-4 changes at 1-year

Liver disease	HCC risk with the baseline FIB-4 (HCC % per year)	FIB-4 at 1 y post-SVR	HCC risk (HCC % per year)
Cirrhosis			
FIB-4 <3.25	1.16	<3.25	1.02
		≥3.25	2.3
FIB-4 ≥3.25	3.66	<3.25	2.45
		≥3.25	5.08
No cirrhosis			
FIB-4 <3.25	0.24	<3.25	0.24
		≥3.25	0.47
FIB-4 ≥3.25	1.22	<3.25	0.95
		≥3.25	2.39

DAA, direct antiviral agent; HCC, hepatocellular carcinoma; SVR, sustained viral response. Data from Ioannou *et al.* (13).

approximately ~20% of them had liver cirrhosis and 60% were treated by DAA. Iannou *et al.* showed that baseline FIB-4 ≥3.25 is an independent risk factor for HCC (*Table 1*). In patients with pre-treatment cirrhosis, HCC risk is more than 2-fold higher when baseline FIB-4 is ≥3.25. In patients without cirrhosis, HCC risk is higher than 1%/year in patients with baseline FIB-4 ≥3.25 with an adjusted risk 3 to 5 times higher compared to non-cirrhotic patients with baseline FIB-4 <3.25. During 10-year follow-up, the HCC risk in IFN-treated cirrhotic patients did not significantly decrease over time in patients with baseline FIB-4 ≥3.25 while remained lower than 1% in patients with baseline FIB-4 <3.25. The same findings, showing stability of HCC risk over-time in patients with FIB-4 ≥3.25 and FIB-4 <3.25, were observed in the non-cirrhotic group. Data from the DAA-treated patients showed a reduction of HCC risk over time after SVR but the short follow-up (only 4 years) cannot allow to draw any firm conclusion. Changes in HCC risk following FIB-4 drop or increase after SVR were also calculated (*Table 1*). Cirrhotic patients with baseline high FIB-4 which dropped below 3.25 following SVR halved the HCC risk but this was still higher than 1.9%/year. Cirrhotic patients with FIB-4 <3.25 which became ≥3.25 after SVR, increased their risk of 2–3 times which ranges to 1.35% to 2.75%/year. Non-cirrhotic patients with baseline FIB-4 ≥3.25 who dropped to a FIB-4 <3.25 after SVR also halved their risk to ~1%/year. Non-cirrhotic patients with baseline FIB-4 <3.25 who increased to a FIB-4 ≥3.25 after treatment increased their HCC risk from 2 to 5 times but the HCC

incidence was still lower to 1%/year.

The current international recommendations for HCC surveillance are based on cost-effectiveness analysis considering the costs per quality-adjusted life year (QALY) gained with the intervention. When the traditional cost-effectiveness benchmark of $50,000/QALY is used, HCC surveillance in HCV patients is cost-effective in population with an HCC risk ≥1.5%/year. Using exclusively the presence of cirrhosis as discriminating factor, HCC surveillance in HCV could be strongly recommended only in cirrhotic patients. The data from Ioannou *et al.* suggest, however, that using FIB-4, it may be possible to stratify cirrhotic and non-cirrhotic patients into different groups of HCC risk to personalize post-SVR follow-up (*Figure 1*). Surveillance could be recommended for cirrhotic patients with FIB-4 ≥3.25 (any time before and after SVR) and non-cirrhotic patients with FIB-4 ≥3.25 that do not drop to <3.25 at 1-year post-SVR. Non-cirrhotic patients with baseline FIB-4 <3.25 and cirrhotic patients with FIB-4 constantly <3.25 could avoid surveillance. With the actual cost-effectiveness benchmark, this approach would change the follow-up of approximately 27% of cirrhotic patients (no surveillance recommended) and 4% of non-cirrhotic patients (surveillance recommended) in the cohort of Ioannou and colleagues.

FIB-4 ≥3.25 could help in refining the actual dichotomous assessment of HCC risk based on the diagnosis of liver cirrhosis because it has high specificity for advanced liver fibrosis (Metavir F3–F4) and it is higher in patients
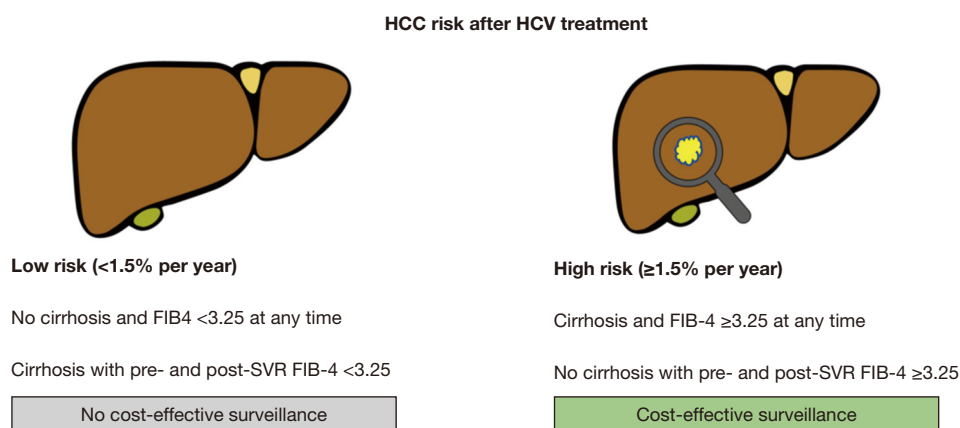
HCC risk after HCV treatment

Low risk (<1.5% per year)

No cirrhosis and FIB4 <3.25 at any time

Cirrhosis with pre- and post-SVR FIB-4 <3.25

No cost-effective surveillance

High risk (≥1.5% per year)

Cirrhosis and FIB-4 ≥3.25 at any time

No cirrhosis with pre- and post-SVR FIB-4 ≥3.25

Cost-effective surveillance

Figure 1 HCC risk after DAA treatment according to cirrhosis status and FIB-4. Cost-effectiveness is based on the traditional threshold of $50,000/quality-adjusted life year gained. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; DAA, direct antiviral agent; SVR, sustained viral response. Data from Ioannou *et al.* (13).

who are older, with portal hypertension and have higher transaminases. After SVR, the latter could be an indirect indicator of other concomitant liver diseases (e.g., NASH or alcohol abuse). Assessing the data by type of treatment, it appeared that HCC risk in DAA-treated patients with liver cirrhosis seemed to be higher than in IFN-treated cirrhotic patient. This could partly be explained by the inclusion of more advanced patients in the DAA group but a direct comparison of the HCC risk in the two groups was not the primary endpoint of the study and was not performed.

The need for HCC surveillance in F3 patients is uncertain and there are no strong recommendations for these patients (5,6). Ioannou *et al.* showed that non-cirrhotic patients with pre- and post-treatment FIB-4 ≥3.25 have high risk of HCC and may benefit from surveillance. Considering that the category FIB-4 ≥3.25 includes F3–F4 patients, these high-risk non-cirrhotic patients might have F3 fibrosis, indirectly suggesting that F3 patients can benefit from HCC surveillance. However, it is impossible to confirm this hypothesis and draw any conclusions on F3 patients since in this study FIB-4 was the only tool used to stratify patients for fibrosis level.

This study has some limitations that should be taken into account. Definition of cirrhosis is based on the ICD diagnosis record and not on pre-specified clinical criteria. Then, it is possible that some patients in the non-cirrhotic FIB-4 high group had unrecognized cirrhosis and conversely some patients in cirrhotic low FIB-4 group did not have cirrhosis. Moreover, no data on transient elastography or other non-invasive fibrosis biomarkers were available to confirm ICD

diagnosis of cirrhosis, possibly further stratify patients and/or verify the hypothesis that HCV F3 patients should be included in surveillance programs. Lastly, the follow-up of DAA treated patients is still short and confirmation from other cohorts, ideally with prospective data, are needed before change recommendations for HCC surveillance.

The data from Ioannou *et al.* reveal the complexity of the HCC risk in HCV patients after SVR and support the need for a better stratification that should not be based only on the presence of liver cirrhosis. The combination of cirrhosis, pre-treatment and post-SVR FIB-4 appears a promising strategy and more data are needed to confirm this approach.

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Footnote

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