Review Article

Incidence rates of hepatocellular carcinoma in relation to dynamic changes of liver fibrosis following viral clearance

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Abstract: Chronic hepatitis C (CHC) infection is a major public health problem with an estimated 71 million people chronically infected with hepatitis C worldwide. Hepatitis C virus (HCV) is the most common cause of hepatocellular carcinoma (HCC), with an annual incidence of almost 3–8% in patients with cirrhosis. HCC remains a major health problem, as it is one of the most prevalent cancers globally, with a poor prognosis and a leading cause of cancer-related death. Nowadays, the availability of highly effective all-oral antiviral drugs scaled up the continuum of care and has increased access to HCV treatment especially in patients with compensated advanced liver diseases. It is proved that viral clearance either by pegylated interferon (IFN) or direct-acting antivirals (DAAs) reduced liver related complications and mortality. Also, viral clearance reduced the incidence of HCC in post-sustained virologic response (post-SVR) patients but did not eliminate. Liver fibrosis stage is the most important determinant of HCC occurrence. The degree of liver fibrosis does not remain constant and was reported to change following sustained virological response. It is uncertain whether the prediction of HCC development based on liver fibrosis at baseline is effective. Furthermore, the risk of HCC after SVR may correlate with changes in liver fibrosis caused by the eradication of HCV. Several studies highlighted the dynamics of liver fibrosis following viral clearance by IFN or DAAs. However, none of these studies investigated thoroughly the risk of HCC in relation to dynamic changes of liver fibrosis. Therefore, in this review we highlighted the incidence rates of HCC in relation to dynamic changes of liver fibrosis following viral clearance.

Keywords: Hepatitis C virus (HCV); sustained virologic response (SVR); fibrosis stages; hepatocellular carcinoma (HCC)

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Introduction

WHO estimates about 71 million are chronically infected with hepatitis C virus (HCV) worldwide (1). HCV is the most common cause of hepatocellular carcinoma (HCC), with an annual incidence of almost 3–8% in patients with cirrhosis (2). Nowadays, the availability of highly effective all-oral antiviral drugs scaled up the continuum of care and has increased access to HCV treatment especially in patients with compensated advanced liver diseases (3,4).

Several studies reported that viral clearance following direct-acting antivirals (DAAs) prevents the progression of liver fibrosis and the development of HCC although the risk is not eliminated particularly in those with advanced fibrosis

(5,6). Liver fibrosis stage is one of the most important factors in stratifying the risk of HCC development even after achieving sustained virologic response (SVR) (7,8). However, the degree of liver fibrosis does not remain constant after SVR and was reported to change following SVR (9-11).

It is uncertain whether the prediction of HCC development based on liver fibrosis at baseline is effective. Furthermore, the risk of HCC after SVR may correlate with changes in liver fibrosis caused by the eradication of HCV. Therefore, in this review we highlighted the incidence rates of HCC in relation to dynamic changes of liver fibrosis following viral clearance.

Interferon (IFN) based therapy

During the era of IFN based therapy several studies previously reported regression of liver fibrosis; Shiratori *et al.* reported reversal of liver cirrhosis proved by paired liver biopsies among 11 chronic hepatitis C (CHC) patients who achieved SVR after IFN therapy where stage of fibrosis changed from F4 to F2 in seven patients and from F4 to F3 among four patients (11). Poynard *et al.* also reported reversal or regression of HCV related cirrhosis occurred in 49% of patients where 15% regressed to stage 3, as well as 16% reversed to stage 2, 15% reversed to stage 1 and 2% reversed to stage zero (12).

Moreover Maylin *et al.*, showed long standing benefits of IFN-based therapy including regression of cirrhosis among 64% of CHC patients (13). Correspondingly, D'Ambrosio *et al.* reported that achievement of SVR leads to regression of cirrhosis in 61% and reversal of cirrhosis in 23.6% of the patients, in addition, regression of fibrosis among 36% of the patients following viral clearance by IFN-based therapy as evident by paired liver biopsies (14).

Other studies assessed the outcome of IFN-based therapy using non-invasive tools; Poynard *et al.*, stated regression of cirrhosis among 56% of CHC patients who achieved SVR using fibro test and transient elastography (TE) (15), also, Lu *et al.*, reported a significant decrease (P<0.0001) of fibrosis stage evaluated by fibrosis 4 (FIB-4) in 48% patients who had SVR after 10-year follow up (16).

These studies highlighted the dynamics of liver fibrosis following viral clearance by IFN. However, none of these studies investigated the risk of HCC in relation to dynamic changes of liver fibrosis.

To our knowledge only Huang *et al.* (17), investigated the association of fibrotic changes with HCC after achieving SVR following IFN therapy. The authors enrolled 265 SVR patients with mean age of 50.4 years and 52.2% were males with paired liver biopsies with 1.4 years of mean interval between the paired biopsies. About 29 % of the patient showed improvement of the liver fibrosis, 38.9% remained stationary while liver progression was detected in 31.7% (17).

The percentage of patients who had fibrosis stage (F0–2) & (F3–4) and remained stationary were 63% (n=167) and 12.5% (n=33), respectively while 11.3% (n=30) regressed from F3–4 to F0–2. However, 13.2% (n=35) of the patient progressed from F0–2 to F3–4. The 1-, 3-, 5-, and 10-year cumulative incidence rates of HCC were 0%, 1.1%, 2.3%, and 6.7%, respectively, for patients with mild liver disease *vs.* 3.2%, 3.2%, 5.0%, and 18.1%, respectively, for patients who had advanced liver fibrosis at baseline.

The HCC risk was significantly higher in patients whose fibrosis stages progressed from F0–2 to F3–4 (P=0.035) and in those whose fibrotic stages remained stationary at F3–4 pre and post treatment (P=0.001), while the HCC risk was lower in patients whose fibrotic stage remained at F0–2 pre and post treatment, and the risk did not change among patients whose fibrotic stage improved from F3–4 to F0–2 (17).

The authors demonstrated that HCC risk was lowermost among patients with persistent mild fibrosis stage. Conversely, the HCC risk was the highest among patients with stationary advanced fibrosis stage after viral clearance. In addition, HCC risk reduced mainly in patients with fibrosis regression, similarly in patients who had persistently mild liver disease after antiviral therapy. Notably, HCC risk increased in patients with deteriorating liver fibrosis (17).

DAAs

During the era of DAAs therapy, Pietsch *et al.* prospectively evaluated the long-term changes in liver fibrosis stages among 143 CHC patients (68 patients were F4 and 19 patients were F3) who achieved SVR after DAAs using TE, aspartate aminotransferase to platelet ratio index (APRI) and FIB-4. The authors observed a significant improvement of liver fibrosis stages in all patients after 96 weeks; however, they did not make clear the percentage of cirrhosis reversibility or delta change of TE (18).

Lledó *et al.* also reported considerable fibrosis regression in 40% of among 260 CHC patients following viral

clearance particularly in patients with cirrhosis and baseline advanced fibrosis (19). Furthermore, Dolmazashvili *et al.* in a study of 304 CHC patients treated with IFN-free DAA (n=151) or IFN-based (n=153) reported regression of liver fibrosis stage in patients with F4 from 56.6% to 36.5% (P<0.0001) using TE. These two studies were prospective but with short follow-up period, only 3 to 6 months post treatment (20).

Additionally, a meta-analysis about dynamic changes of liver stiffness following DAAs therapy in CHC patients reviewed 11 studies reporting paired baseline and post treatment LSM; most of these studies included small sample sizes of patients with liver cirrhosis or were retrospective. In addition, follow-up evaluation period was only 12 or 24 weeks. Only two studies had a relatively long follow-up period (48 weeks) (21); Mandorfer *et al.*, who reported improvement of liver stiffness measurements with median decrease of 3.6 KPa—nevertheless, the study comprised only 31 CHC patients (20). Martini, 2017 reported regression of fibrosis stage in almost half of hepatitis C patients with advanced fibrosis (18 F3, 21 F4) who had liver transplant (22).

The study of Bachofner *et al.* enrolled a larger cohort of 392 HCV infected patients who received DAAs, they reported a significantly decreased of the overall TE values after DAAs treatment (P<0.001), however this study was retrospective and included small number of patients with advanced hepatic fibrosis or liver cirrhosis (45 patients were F4 and 71 only were F3) (23). In this meta-analysis, the authors reported that the clinical outcome of the dynamic changes of liver stiffness could not be confirmed (21). Also, there is no mention of the incidence of HCC in relation to dynamic changes of liver fibrosis following DAAs except for few studies.

We prospectively investigated the incidence of HCC among 2,372 chronic HCV patients with advanced liver fibrosis (n=638) or cirrhosis (n=1,734) receiving DAAs and the association between fibrotic changes following DAAs and the incidence of HCC. Our results showed for patients with advanced fibrosis (F3) at base line, 26.0% (166/638) showed reversal of fibrosis to F0 or F1, 30.0% (197/638) patients showed fibrosis regression to F2, and 31.2% (199/638) patients remained stationary at F3 while 76 patients (11.9%) progressed to F4 (4).

Moreover, our results showed 375 patients (21.6%) who had F4 before treatment showed reversal of liver fibrosis to ≤ F2, 470 patients (27.1%) showed fibrosis regression to only one stage (F3) while 889 patients (51.3%) remained stationary at F4. Among F4 patients who developed HCC (101 patients), 15 patients regressed to ≤ F2, 16 regressed to F3, while 70 remained stationary at F4 at the end of follow-up period.

We concluded that regression of fibrosis is associated with decreased HCC incident which is obvious in patients with liver cirrhosis (F4) who regressed to < F2 following DAAs (2.052/100 py) compared to those who remained stationary at F4 (3.931/100 py). However, patients with advanced hepatic fibrosis (F3) who progressed to (F4) showed higher incidence of HCC compared to those who regressed to F2 (2.05 *vs.* 0.44/100 py) (4).

Several studies have reported various cutoff values for determining the degree of fibrosis and for predicting HCC development using magnetic resonance elastography (MRE) (24-26). Lee *et al.*, enrolled 217 patients with compensated chronic liver disease who underwent MRE with mean follow-up of 45.0±17.6 months and concluded that the cutoff stiffness values that predicted the occurrence of HCC, overall survival, and the development of hepatic decompensation were 5.53, 4.44, and 4.46 kPa, respectively (26).

Another multicenter study in Japan using MRE and non-invasive fibrosis marker FIB-4 measure the changes in the liver stiffness among 537 CHC patients who achieved SVR following DAAs. The authors reported that the cumulative incidence rates of HCC occurrence in patients with MRE values of <4.5 and ≥4.5 kPa were 0.0% and 4.6% at 2 years, respectively, and 0.6% and 14.2% at 4 years, respectively, (P<0.0001). In addition, they reported the HCC incidence rate among patients with FIB-4 score >3.25 and MRE values <4.5 and ≥4.5 kPa were 0.0% and 6.1% at 2 years, respectively, and 1.0% and 16.7% at 4 years, respectively (P<0.005). However, there was no significant difference in cumulative incidence rates of HCC development in patients with an FIB-4 score <3.25 and MRE values <4.5 and ≥4.5 kPa (27). In contrast, Anaparthy *et al.*, did not observe association between liver stiffness assessed by MRE and the presence of HCC among patients with compensated cirrhosis (28).

Many studies reported that the risk of HCC is a positive association with baseline FIB-4 scores in CHC patients (29-31) and CHB (32,33). Moreover, the change of FIB-4 after achieving SVR and the association with HCC risk has been investigated among 3823 CHC where FIB-4 was measured at SVR 24 and 1, 2, 3 years. The authors concluded that in patients with FIB-4 >3.25 at post treatment 24 weeks and 1, 2, and 3 years, the incidence of HCC was significantly

higher than in those with FIB-4 score ≤3.25 at each visit. The HCC incidence rates at 1, 2, 3, and 4 years post SVR24 were significantly higher in patients with sustained FIB-4 >3.25 than in those whose FIB-4 decreased to ≤3.25 (5.4%, 9.2%, 11.7%, and 16.0%, respectively, *vs.* 2.2%, 3.1%, 3.7%, and 4.4%; P<0.001) (34).

Conclusions

Post-treatment fibrotic changes overwhelmed pretreatment status in terms of prediction of HCC in CHC patients following viral clearance. Dynamic assessment of liver fibrosis stages after achieving SVR could be useful in prediction of the risk of HCC.

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Footnote

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