Perspective of the risk and molecular mechanisms of hepatocellular carcinoma after HCV eradication in the post-DAA era

**short running title:** Unmet need of HCV related HCC

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We acknowledged the Editorial regarding the challenges of hepatocellular carcinoma (HCC) surveillance after hepatitis C virus (HCV) eradication. One of the hurdles is the provider-barrier regarding cost-effectiveness, which largely depends on the proportion of medical expense of GDP per capita in each region. The stakeholders or healthcare system may not be able to provide the medical service even though the incidence of HCC is deemed to be risky and providing surveillance would be cost-effective (i.e. fibrotic stage 3 with diabetes). On the other hand, the patient-barrier of poor adherence for surveillance due to unavailability or unawareness after achieving sustained virological response (SVR) may add insult to injury.\(^1\) This is a critical issue in the direct-acting antivirals (DAAs) era since more marginalized patients have been treated with the strategy of decentralization and are left behind after HCV cure.

Suboptimal visualization of the liver has a diagnostic limitation for sonography in detecting early HCC. AASLD and APASL have advocated the complementary use of tumor markers to increase the sensitivity though the false positivity would result in a clinical dilemma. CHC patients are at a greater risk of metabolic dysfunction-associated steatotic liver disease (MASLD).\(^2\) Either pre-treatment\(^3\) or post-treatment\(^4\) steatotic liver disease (SLD) has been associated with HCC development in SVR patients irrespective of the presence of diabetes. As patients with SLD are prone to have late-stage HCC at the time of diagnosis due to poor window of sonography, a
holistic care of both liver and non-liver related outcomes is of importance in CHC patients with MASLD in the post-SVR era.

The authors mentioned another risk of HCC, hepatitis B virus (HBV) dual infection. HBV dual infection might aggravate liver disease severity in the natural course. Regarding HCC risk after HCV eradication, a nationwide study in Taiwan has demonstrated that the achievement of SVR significantly reduces the risks of liver-related outcomes including HCC in HBV and HCV dually infected patients. However, the incidence of HCC did not increase in HBV coinfected patients compared to those with HCV monoinfection after adjusting the factor of HBV antivirals prescription. While HBV reactivation remains a critical concern after HCV eradication, this special population warrants long-term monitoring after HCV eradication.

On the other hand, while we are talking about the chemoprevention, a recent study has shown that both statins and metformin reduce the risk of HCC in CHC patients who failed interferon-based therapy. With the accumulation of the CHC patients who are refractory or contraindicated to DAAs, reinfection without retreatment, or living in DAA-restrained areas, the data might shed light on managing persistently viremic patients who are in need of oral hypoglycemic agents and dyslipidemia.

As the authors described recent research has advanced our understanding of the molecular features of HCC and their influence on the persistent risk of HCC in HCV
patients post-SVR. These features include genetic mutations, epigenetic modifications, gene expression changes, and variations in innate and adaptive immune responses. The authors emphasize the importance of elucidating these mechanisms, as it is pivotal for stratifying individuals at risk. This stratification is essential for the development of personalized surveillance programs, enabling customized monitoring based on individual risk levels. Furthermore, identifying these individuals allows for targeted interventions to prevent HCC, potentially reducing liver disease mortality.

Specific gene expression and epigenetic markers associated with post-SVR HCC risk have been identified\cite{7-11}, opening new research avenues for novel therapeutic targets. Since epigenetic changes are potentially reversible, unlike permanent genetic mutations, targeting these changes offers a promising strategy for preventing HCC even after HCV-induced liver damage. This approach could mitigate the persistent oncogenic effects of HCV post-treatment. Further research is needed to pinpoint actionable targets within the molecular pathways affected by HCV to develop personalized preventive treatments for HCC. In addition, our current understanding of genetic changes in post-SVR HCC is developing. Emerging insights reveal decreased ARID2 mutations, increased KEAP1 and PREX2 mutations, and distinct TP53 alterations in DAA-treated patients.\cite{12} Genome-wide association studies identifying risk alleles for HCC post-SVR are in progress. These findings have prognostic significance and
underscore the need for more research to provide comprehensive genomic profiles associated with cancer risk post-SVR, aiding in patient risk stratification. Further investigation integrating Multi-Omics studies, which include genomics, epigenomics, transcriptomics, proteomics, and metabolomics, is necessary for understanding the complex interplay between genetic and epigenetic factors in post cure HCC.

Markers for predicting post-SVR HCC risk have been identified recently, including cirrhosis, liver and spleen stiffness measurements, and serum molecular markers. Combining these markers with developing analytical tools to identify the persistent molecular pathways post-cure will enhance prognostic models, including artificial intelligence-based approaches, to improve HCC surveillance and patient outcomes.
References


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