MASLD after hepatitis C virus eradication: Do not overlook the cardiometabolic risk factors

RUNNING TITLE
MASLD care after HCV treatment

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ABBREVIATIONS

BMI: Body mass index
CHC: Chronic hepatitis C
CMRF: Cardiometabolic risk factor
DAA: Direct-acting antiviral
EASL: European Association for the Study of the Liver
HCVL: Hepatitis C virus
MASLD: Metabolic dysfunction-associated steatotic liver disease
SLD: Steatotic liver disease
SVR: Sustained virological response

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Oral direct-acting antivirals (DAAs) can effectively induce sustained virological response (SVR) in over 95% of patients, revolutionizing the care of chronic hepatitis C (CHC). As we stand in the midst of the DAA era, the focus on CHC care has gradually shifted from attaining SVR to post-treatment follow-up and management of co-morbid conditions.\(^1\) One major co-morbid condition in CHC is steatotic liver disease (SLD). Unlike the interaction between hepatitis B and steatosis – which involves interaction of distinct disease entities,\(^2,3\) the hepatitis C virus (HCV) is known to have steatogenic properties.\(^4\) HCV can induce steatosis through alteration of lipid metabolism by the HCV core protein,\(^5\) or through induction of insulin resistance (in HCV genotype 3).\(^6\) HCV eradication may reverse cardiometabolic risk factors (CMRFs) and SLD, potentially reducing risks of long-term cardiovascular adverse events.\(^7-9\) Conversely, pre-SVR or post-SVR SLD can increase risks of both liver-related and cardiovascular adverse outcomes.\(^10-12\) The impact of HCV eradication on SLD evolution has important implications on patient management, yet the data in this area remains limited.

In this issue, Huang et al. presented data from a large Taiwan cohort of 5,840 CHC patients (mean age 62.7, 33.7% cirrhotic at baseline) who achieved SVR with DAAs.\(^13\) The patients received comprehensive SLD and CMRF workup at baseline (pre-treatment) and at six months after HCV cure. The proportion of patients with CMRFs, SLD, and metabolic-associated SLD (MASLD) at baseline were 87.8%, 36.8%, and 34.0% respectively, and these numbers were 87.4%, 37.5%, and 34.8% at six months after SVR respectively. The proportion of patients with CMRFs, SLD and MASLD remained comparable at baseline and at
follow-up. Nonetheless, a dynamic shift in CMRF and SLD status was noted. Among patients with CMRFs at baseline, 3.4% had resolved CMRFs after SVR; whereas among patients without CMRFs at baseline, 20.6% had de-novo CMRF development after SVR. Among baseline MASLD patients, 27.6% became MASLD-free at follow-up; whereas 15.4% of baseline non-MASLD patients developed MASLD after SVR. Importantly, resolution of SLD after achieving SVR was more common in those without baseline CMRF than those with baseline CMRF (41.6% vs 26.4%), with the cardiometabolic profile maintained even with resolution of SLD. These results remained robust after stratifying patients by HCV genotype (genotype 3 or other genotypes), diabetes status, body mass index (BMI) and cirrhosis status. In multivariate analysis, higher baseline BMI, glycated hemoglobin and low-density lipoprotein were the independent predictors of MASLD development respectively. In contrast, lower baseline BMI was the only factor independently associated with MASLD resolution. Other patient factors including age, sex, cirrhosis status, liver function, HCV viral load and HCV genotype were not associated with MASLD evolution after HCV cure. Overall, Huang’s study provided important data on the dynamic metabolic alterations after HCV cure.

The European Association for the Study of the Liver (EASL) published a position paper in 2024 describing post-HCV treatment care. EASL recommends that patients without advanced fibrosis at baseline can be discharged to primary care, and patients with liver stiffness ≥ 10 kPa or FIB-4 > 3.25 should continue follow-up by hepatologists. For patients with liver stiffness between 8 – 10 kPa or FIB-4
between 1.45 – 3.25, assessment of MASLD or alcohol status is required, with subsequent recommendations of lifestyle changes and reassessment by non-invasive tests. Nonetheless, the position paper highlighted that post-HCV follow-up protocols for MASLD has not been well-established. The prognostic implications of fibrosis evolution after SVR, as measured by serial non-invasive testing, is also unclear.\(^\text{14}\)

The 2024 EASL MASLD guidelines suggest that MASLD screening in the general population is not recommended, yet screening in specific high-risk populations can be considered.\(^\text{15}\) As Huang’s study demonstrated high prevalence of CMRFs (87.8% at baseline, 87.4% at follow-up) and MASLD (34.0% at baseline, 34.8% at follow-up) in CHC patients,\(^\text{14}\) solely assessing MASLD status in CHC patients with borderline fibrosis at baseline may not suffice, and universal MASLD screening in HCV patients may be warranted. We hence propose an updated algorithm with comprehensive metabolic assessment before and after HCV cure in all CHC patients (Figure 1).

With our proposed algorithm of metabolic assessment, we will be able to assess the dynamic shifts of CMRFs and MASLD status with HCV eradication. More importantly, we can document post-treatment CMRF and MASLD in all patients, ensuring that patients will be appropriately managed and not lost to follow-up. For patients with MASLD, smooth transition to MASLD care pathways can also be initiated. With fibrosis assessment already performed in HCV management, the transition to MASLD care should be streamlined and would require minimal
additional resources. While the cost-effectiveness and long-term benefits of our proposed algorithm remains to be determined, our integrated algorithm will likely improve risk stratification and enable personalization of follow-up after HCV cure.

With enhanced efforts in HCV eradication and the growing obesity pandemic, the number of patients with MASLD after HCV eradication is anticipated to increase. The paper by Huang et al. provided important data on the dynamic shift of MASLD status after HCV cure. Furthermore, the paper highlighted that CMRFs remain as the key drivers of MASLD resolution and development respectively. CMRFs and MASLD should not be overlooked in CHC, and actions must be taken to improve patient care pathways after HCV cure.
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Figure 1. Proposed algorithm to incorporate metabolic assessment in hepatitis C care.