Towards a more comprehensive evaluation of liver fibrosis in patients with chronic hepatitis C

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With the recent advances in the prevention, screening, and development of highly potent direct-acting antivirals for hepatitis C virus (HCV) infection, the World Health Organization (WHO) had set a target to eliminate HCV infection globally by 2030.[1] Nevertheless, chronic hepatitis C is still one of the major etiology of liver cirrhosis and hepatocellular carcinoma (HCC) in the world currently.[2–3] It is estimated that around 71 million subjects had chronic HCV infection in the world, with a global prevalence rate of 1.0%.[2] In Taiwan, one recent survey disclosed that the national prevalence of viremic HCV was 2.44%, corresponding to 554 361 individuals with HCV viremic infections.[4]

Patients with chronic HCV infection have wide clinical manifestations, such as inactive carrier status, chronic hepatitis, compensated advanced chronic liver disease, portal hypertension, liver decompensation, and HCC. Active ongoing HCV replication, chronic persistent inflammation, and advanced hepatic fibrosis are regarded as the major determinants of developing adverse outcomes in patients with chronic hepatitis C.[5–7] For those with advanced stage liver fibrosis or cirrhosis, they still bear a high risk of developing HCC or portal hypertension even after eradication of the virus.[6] As most of the patients with chronic HCV infection are asymptomatic, or have nonspecific symptoms even in the setting of liver cirrhosis, how to identify patients with advanced stage liver fibrosis earlier is crucial to help to adopt adequate strategy for surveilling the high-risk group of patients who will develop end-stage liver diseases.

Currently, liver biopsy is still the gold standard for assessing the stage of liver fibrosis for patients with chronic HCV infection. However, this procedure is costly and carries a small risk of complications such as pain, bleeding, bile duct injury, penetration of abdominal viscera, or mortality. Moreover, sampling errors and interobserver variation might decrease the reliability of liver biopsy as well. Thus, several noninvasive markers have been applied for investigating the stage of fibrosis in patients with chronic hepatitis C, including aspartate aminotransferase (AST) to alanine aminotransferase ratio (AAR), AST to platelet ratio index (APRI), and fibrosis-4 index (FIB-4), etc.[8] However, the area under the receiver-operating characteristic curve for diagnosing cirrhosis and advanced stage fibrosis for these markers were 0.80 to 0.91 and 0.71 to 0.86, respectively.[8] It suggests that the diagnostic ability of these noninvasive markers for discriminating early vs advanced stage liver fibrosis is not ideal for patients with chronic hepatitis C.

During the natural history of chronic hepatitis C, chronic persistent necroinflammation and lasting immune response would induce the activation of several important cytokines, such as interleukins (ILs), tumor necrosis factor α, and interferon-γ, which in turns activate human stellate cells, myofibroblasts, and fibroblasts.[9] They would result in the deposition of extracellular matrix, fibrillar collagen, and the formation of liver fibrosis and cirrhosis. Several previous studies have confirmed that serum IL-4 levels were significantly higher in patients with chronic HCV infection compared with healthy controls.[10] It suggests that IL-4 activity might play a role in determining the pathogenesis and fibrosis progression in patients with chronic HCV infection.

Metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) have now become an important health threat. However, the interplay between NAFLD and chronic HCV infection seems very complex.[11] Hence, there is an unmet need to develop a reliable marker to predict the grade of hepatic steatosis in patients with chronic hepatitis C. Previous studies demonstrated that an elevated serum ferritin level was correlated to the progression of hepatic fibrosis, treatment responses as well as prognoses in patients with NAFLD or chronic HCV infection.[12–13] Consequently, it is reasonable to enroll serum ferritin levels to predict the stage of hepatic fibrosis and steatosis in patients with chronic hepatitis. However, there are very limited data to comprehensively investigate the diagnostic value of a combination of serum ferritin and IL-4 levels into the conventional noninvasive markers in predicting the stage of hepatic fibrosis in patients with chronic hepatitis C till now.

In the two recent articles published in the *Journal of the Chinese Medical Association*, Batsaikhan and colleagues investigated the diagnostic value of serum IL-4 and ferritin levels in predicting the stage of liver fibrosis in patients with chronic hepatitis C.[14–15] They disclosed that there was a positive correlation between the stage of fibrosis and the levels of serum IL-4 or ferritin levels. Moreover, an elevated serum ferritin level was observed in 40.8% of patients with chronic HCV infection, and it was correlated to not only the progression of hepatic fibrosis

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but also the development of liver steatosis.[15] It might provide an important reference for clinical physicians to stratify the patients with chronic hepatitis C into different prognostic groups and to select them into the adequate surveillance programs.

Of note, the authors proposed a fibrosis and IL-4 score (FIL4), which was composed of age, serum AST, ferritin, and IL-4 levels.[14] They demonstrated that FIL4 had a better discriminative ability to predict advanced liver fibrosis in patients with chronic hepatitis C when compared with other well-validated markers, such as AAR, APRI, and FIB-4. It had been further confirmed by subgroup analysis stratified by different HCV genotypes. It indicated that the combination of IL-4 and ferritin would increase the predicting ability for advanced stage liver fibrosis than the conventional serum markers.

Interestingly, the levels of serum IL-4 were extremely high in patients with advanced liver fibrosis in the setting of high HCV viral loads, genotype Ib, and higher serum ferritin levels, which have been confirmed to be associated with a higher risk of developing HCC.[5] It implied that serum IL-4 level could be served as a potential ancillary marker to predict the risk of HCC in patients with chronic HCV infection. However, further prospective studies are warranted to validate this concept.

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