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## Editorial: Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways

Jorge Quarleri, M Victoria Delpino

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### Abstract

In the management of the growing population of hepatitis C virus-infected patients, a significant clinical challenge exists in determining the most effective methods for assessing liver impairment. The prognosis and treatment of chronic hepatitis C depend, in part, on the evaluation of histological activity, specifically cell necrosis and inflammation, and the extent of liver fibrosis. These parameters are traditionally obtained through a liver biopsy. However, liver biopsy presents both invasiveness and potential sampling errors, primarily due to inadequate biopsy size. To circumvent these issues, several non-invasive markers have been proposed as alternatives for diagnosing liver damage. Different imaging techniques and blood parameters as single markers or combined with clinical information are included. This Editorial discusses the identification of a set of six distinctive lipid metabolites in every fibrosis grade that appear to show a pronounced propensity to create clusters among patients who share the same fibrosis grade, thereby demonstrating enhanced efficacy in distinguishing between the different grades.

**Key Words:** Hepatitis C virus; Chronic hepatitis C; Liver fibrosis; Biomarker; Liquid biopsy

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**Core Tip:** Accurate diagnosis of liver damage in chronic hepatitis C is pivotal for decision-making. Liver biopsy, the traditional "gold standard" for assessing tissue damage, offers valuable insights but is invasive, with potential complications and sampling errors. Non-invasive methods have made progress in the last decade, but challenges remain. Various non-invasive techniques are in development, including serum biomarker assays and advanced imaging. They often struggle to distinguish intermediate fibrosis stages and are affected by hepatic and extrahepatic factors. This Editorial discusses which identified potential biomarkers in plasma samples linked to each fibrosis grade and hepatitis C virus-induced pathogenesis.

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## INTRODUCTION

The natural evolution of chronic hepatitis C (CHC) involves a continuous inflammatory response triggered by recurring liver injuries. This is subsequently accompanied by the activation of hepatic stellate cells, the accumulation of fibrillar collagen within the extracellular matrix (ECM), and the gradual development of fibrosis. These sequential events can potentially lead to ECM degradation, which in turn may result in vascular and architectural modifications, ultimately culminating in the occurrence of cirrhosis or hepatocellular carcinoma (HCC)[1].

Timely diagnosis and intervention are pivotal in preventing the progression to liver cirrhosis and HCC, particularly in light of the advent of direct-acting antiviral therapy, which has revolutionized the treatment of CHC. Nevertheless, effectively reducing the morbidity and mortality associated with this condition necessitates a more comprehensive understanding of liver involvement, improved prognostication, and rigorous monitoring[2]. In this context, accurate determination of the degree of liver fibrosis assumes paramount significance in the clinical management of HCC, as it not only informs treatment decisions but also aids in predicting patient outcomes. However, this endeavor is fraught with challenges, as the methods employed for fibrosis staging encompass both histological assessment through liver biopsies and various imaging modalities. The Metavir classification system, which employs a 0-4 scale, is commonly utilized for staging the various grades of fibrosis in biopsied liver tissue[3]. While liver biopsy remains the acknowledged "gold standard" for diagnosing and staging liver fibrosis, its invasiveness and associated discomfort, coupled with the risk of complications, subject to sampling errors and subjectivity between observers make it a less-than-ideal option[4-6].

Conventional imaging modalities (ultrasonography, computed tomography, and magnetic resonance imaging) are valuable but their sensitivity is limited when it comes to detecting moderate or advanced fibrosis[7]. Besides, advanced acoustic technologies (hepatic elastography) enhance the precision of imaging approaches but the cost of the equipment is a limitation, among others[8].

In the present issue of the JWH, the Ferrasi *et al*[9] study aims to investigate the plasma metabolome using mass spectrometry on samples obtained from individuals with CHC and varying degrees of fibrosis with the goal of identifying prospective biomarkers for categorizing these fibrotic conditions.

The potential clinical utility of these markers presents a compelling avenue for not only staging liver fibrosis but also evaluating the rate and progression of liver fibrogenesis. This assessment, in turn, translates into valuable prognostic insights and serves as a tool for assessing treatment response and monitoring the effectiveness of antifibrotic medications. Nevertheless, the available data regarding their performance in defining the stage of liver fibrosis is variable, and their routine availability may be limited in certain hospital settings[10]. These markers encompass various glycoproteins (such as hyaluronan and laminin), members of the collagen family (including procollagen III, type IV collagen, and type IV collagen 7s domain), collagenases and their inhibitors (metalloproteinases and tissue inhibitors of metalloproteinases), along with numerous cytokines implicated in the fibrogenic process, notably transforming growth factor- $\beta$ 1. These markers have been individually and collectively assessed to gauge the severity and progression of hepatic fibrosis and to monitor changes associated with viral treatment[2] or, even HCC[11-18].

The metabolome comprises the entirety of metabolites that are internally generated within a particular physiological state and can be considered as the ultimate outcome of gene expression. This approach enhances the biomarker identification in human plasma as an invaluable tool in clinical practice and research. They facilitate early detection, accurate diagnosis, personalized treatment, and improved patient outcomes, ultimately contributing to more effective healthcare and better public health.

For every stage of fibrosis, the researchers identified a distinct metabolite profile, and the significance of each molecule varies based on the fibrosis stage, potentially intensifying or diminishing over the course of the disease. Hence, the employment of metabolomics techniques in liquid biopsies exhibits potential as diagnostic, prognostic, and therapeutic monitoring tools.

The pro-viral implications of lipid metabolic reprogramming during virus infection encompass four distinct functions. Firstly, lipids play crucial roles in virus entry and trafficking, serving as attachment factors, internalization receptors, or transportation shuttles during the initial stages of viral entry. Secondly, lipids contribute to virus replication and assembly by providing subcellular spaces essential for key events in the viral life cycle. Thirdly, lipids are indispensable for the generation of energy and essential nutrients required for viral replication. Lastly, lipids serve as pivotal

components in viral envelopment and fulfill diverse functions in the process of virus egress[19]. The study from Ferrasi *et al*[9] analyzes the link between hepatitis C virus (HCV)-induced lipid metabolism abnormalities with the fibrosis grade score, at first with an emphasis on those involved in cholesterol biosynthesis[9].

In the case of grade F1, certain biomarkers that appeared to be more associated with HCV infection rather than fibrosis progression were noticed when compared to individuals with more advanced fibrosis stages. Consequently, the initial molecule detected in grade F1 belonged to the sterol category, featuring distinct characteristics related to cholesterol ester, already recognized as a critical component of HCV lipoviral particles[20]. Furthermore, a diacylglycerol was also identified in grade F1, and its elevated levels were associated with a less advanced state of fibrosis, specifically.

When considering lipid metabolism and the accrual of lipids, it became feasible to pinpoint the presence of the sphingolipid class in the intermediate-grade F2, specifically represented by ceramide. Their accumulation potentially leads to steatosis, which, in turn, may contribute to the progression of liver fibrosis[21]. Furthermore, the authors identified in F2 grade a molecule from the eicosanoid class. This particular molecule is a bioactive lipid that serves as a potent mediator of inflammation in infectious diseases and HCC.

In the case of intermediate-grade F3 and advanced-grade F4, another lipid class (glycerophospholipids) was identified, with the specific biomarkers recognized as phosphoethanolamines. Besides, in F3 grade samples the authors identified the farnesylcysteine, a prenol lipid, as a plausible biomarker for assessing the risk of tumor development, that was previously linked to liver carcinogenesis.

As mentioned above, several studies indicate the potential disruption of fatty acid lipid metabolic pathways during HCV infection. This disruption leads to the accumulation of acyl-coenzyme A (CoA) and intermediary products in fatty acid metabolism belonging to the CoA class. Among them, the authors identified the *cis*, *cis*-3,6-dodecadienoyl-CoA among those patients exhibiting F1 grade, while in those with F3 the S-2-octenoyl CoA was found.

Finally, in the advanced grade (F4), a metabolite associated with CoA was detected, along with malonyl carnitine. The presence of malonyl carnitine is noteworthy as it is intricately tied to disease progression and the development of HCC, primarily due to the dysregulation of energy-supplying metabolic pathways.

In addition to the lipid-based biomarkers, the authors identified other plausible markers such as polypeptide angiotensin III [Ang III, also called Ang-(2-8), is generated from Ang II by aminopeptidase A] in grade F1 which may augment collagen production, methyladenosine in F2 and (S)-2,3,4,5-tetrahydropiperidine-2-carboxylate in F3 grade.

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## CONCLUSION

In conclusion, despite a limited number of samples, Ferrasi *et al*[9] analysis found potential biomarkers specific to each grade of liver fibrosis. These biomarkers showed a propensity to group patients with similar fibrosis grades, although there were instances of overlap such as those proposed for grades F2 and F3. The score plot analysis showed greater efficiency in discriminating between the extreme grades (F1 and F4). This study represents an advancement in the quest for non-invasive serum markers that reflect the progression of liver damage.

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## FOOTNOTES

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