Imaging biomarkers of diffuse liver disease: current status

Bachir Taouli^{1,2} · Filipe Caseiro Alves³

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Abstract

We are happy to introduce this special issue of Abdominal Radiology on “diffuse liver disease”. We have invited imaging experts to discuss various topics pertaining to diffuse liver disease, covering a vast array of imaging techniques including ultrasound (US), CT, MRI and new molecular imaging agents. Below, we briefly discussed the current status, limitations, and future directions of imaging biomarkers of diffuse liver disease.

Chronic liver disease (CLD) is highly prevalent worldwide, with high morbidity and mortality. Globally, it was estimated that 1.5 billion persons had CLD in 2017, most commonly resulting from NAFLD (nonalcoholic fatty liver disease), chronic hepatitis B (CHB) and C (CHC) viral infections and alcoholic liver disease [1]. CLD and liver cirrhosis are responsible for approximately 44,000 deaths in the USA and 2 million deaths worldwide each year, in addition to a high rate of morbidity and healthcare costs [2]. The epidemiology of CLD is changing, with the implementation of large-scale CHB vaccination and efficient CHC treatment with direct acting antivirals, the increasing prevalence of obesity and metabolic syndrome, and alcohol use disorder [2]. Indeed, approximately 2 billion adults are obese or overweight and over 400 million have diabetes worldwide; both of which are risk factors for NAFLD, nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) [3].

Liver biopsy is the historical gold standard method to evaluate the degree of liver fibrosis, necroinflammation, fat and iron deposition, and to characterize unexplained etiologies of CLD (such as cholestatic disease) [4]. However, liver biopsy has major limitations, including invasiveness, risk of

sampling and observer variability, and is difficult to repeat (for example in the context of drug trials) [5–7].

Over the last 15 years, the successful implementation of noninvasive tests such as transient elastography (TE) [8–11], more recently ARFI (Acoustic Radiation Force Impulse) methods [12–15] and magnetic resonance elastography (MRE) [16–18], as well as simple and proprietary serum markers [19–21] have significantly reduced the need for liver biopsy for fibrosis staging. Liver stiffness measured with elastography techniques is now considered a reliable imaging biomarker of liver fibrosis in a wide range of etiologies. It is used to predict the degree of liver fibrosis (moderate vs advanced fibrosis and cirrhosis), predict the present of esophageal varices and portal hypertension, assess response to antiviral therapy in CHC [22, 23], and provide prognostic information. TE is the most validated elastographic technique, with more recently implemented ARFI methods having overall equivalent performance to TE, while being integrated into clinical US systems allowing elastography to be performed in routine clinical examinations. MRE provides excellent diagnostic performance for fibrosis detection, superior than that of other techniques such as diffusion-weighted imaging and dynamic contrast-enhanced MRI [24, 25]. However, MRE is less well validated in single etiology cohorts, and less available than US elastography methods.

There are several limitations of these noninvasive tests for detection of liver fibrosis as follows: liver stiffness is an indirect measure of fibrosis and is prone to confounders such as hepatic inflammation, congestion, cholestasis (for all elastographic methods), and steatosis (particularly for TE). Another limitation is the risk of inaccurate or failed measurement of liver stiffness, in patients with overweight/obesity and ascites with TE/ARFI. The

✉ Bachir Taouli
bachir.taouli@mountsinai.org

¹ Department of Diagnostic, Molecular and Interventional Radiology, Icahn School of Medicine At Mount Sinai, 1470 Madison Avenue, New York, NY 10029, USA

² BioMedical Engineering and Imaging Institute, Icahn School of Medicine At Mount Sinai, New York, NY, USA

³ Department of Radiology, University Hospital of Coimbra, Coimbra, Portugal

development of the XL probe has improved the percentage of failed TE exams, while providing different liver stiffness values compared to the standard M probe [26]. MRE can also fail in patients with hepatic iron overload, ascites and obesity when using the GRE sequence [27, 28]. New EPI sequences are more immune to susceptibility artifacts from iron deposition [29].

As mentioned above, one of the urgent health issues in many countries around the world is the increasing number of patients with NAFLD and NASH. Liver fat quantification using MR spectroscopy and more recently proton density fat-fraction (PDFF) methods are now accepted as the reference, obviating the need for liver biopsy for diagnosis and quantification of steatosis [30, 31]. However, markers of disease activity and severity based on elastography [32] and other methods are essential for establishing endpoints for ongoing active drug development efforts in NASH [33, 34]. Another component of liver disease is iron deposition quantified with T2* relaxometry, which is considered the reference for iron tissue concentration [35–38].

There are areas of active research that pertain to imaging of CLD that are also worth mentioning: MR relaxometry using native T1 or corrected T1 measurements used to measure the degree of hepatic inflammation which is an important component of disease activity, especially in NASH [39–42]; T1 relaxometry or relative enhancement post-gadoxetate injection which can inform not only about degree of liver fibrosis but also about the degree of severity of cirrhosis [43–47]; MR fingerprinting applied to liver disease providing a quick quantitative assessment [48]; new DCE-MRI acquisition and quantification methods [49–52]; improved 4D flow acquisition to quantify hemodynamic parameters that may be altered in CLD and portal hypertension [53–56]; texture analysis for fibrosis characterization [57–59]; deep learning models for detection of liver fibrosis [60–63]; and last but not least, MRI contrast agents with high collagen specificity for staging liver fibrosis (still in preclinical stage) [64, 65]. Finally, there has been recent interest in implementing abbreviated MRI protocols for diffuse liver disease (combining PDFF, T2* and MRE) [66] or for HCC screening [67–69]. These abbreviated protocols may improve MRI access and provide valuable information in a short amount of time.

In summary, the future of imaging in CLD is bright, and radiologists will continue with their mission of helping clinicians and patients make informed decisions regarding diagnosis, surveillance, therapy and prognosis. Some techniques still need clinical validation and/or need to be clinically translated. Considerations such as local expertise, cost and cost-effectiveness should be considered when choosing the appropriate test in CLD.

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