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Editorials

For fatty liver diseases, it is time to utilize non-invasive fibrosis tests to predict liver related events rather than just histological stages of hepatic fibrosis!

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In the current issue of the Annals of Hepatology, R. Zambrano-Huailla and colleagues, compare several non-invasive scoring systems to predict the risk of liver fibrosis amongst Latin Americans with fatty liver disease. Like other groups from around the world who evaluated these and other non-invasive tests (NITs) of hepatic inflammation, steatosis, and fibrosis, they arrived to the same conclusion: NITs correlate with the histological stages of fibrosis but the thresholds of Hepamet, FIB-4 and NFS need modification to maximize diagnostic accuracy [1].

The background literature review of the EASL-ALEH clinical practice guideline [2] on NITs, cite many studies with different cut-offs based on population, diagnosis, and stage of liver disease. Previous studies have been attempting to compare and fit NITs to the histological parameters from percutaneous liver biopsies. Liver histology is the "gold standard" for diagnosis of fatty liver disease including simple steatosis, steatohepatitis and cryptogenic cirrhosis, but is percutaneous liver biopsy the "gold standard" for staging of hepatic fibrosis?

Over 60 years ago, Menghini described his "one-second" percutaneous suction liver biopsy. This revolutionized the practice of hepatology [3]. The technique has changed little since then but quickly liver biopsy became the "gold standard" for histological diagnosis of liver diseases including acute liver injury, acute on chronic liver failure, autoimmune hepatitis, drug induced liver disease, post-transplantation liver injury, alcohol-related hepatitis requiring steroids and infiltrative diseases including malignancy. This biopsy process requires liver core specimens to be at least 20 mm in length, 1.4 mm wide, containing more than 11 portal tracts. Unfortunately, in practice, only 20% of cores are adequate with 56% suboptimal and 24% inadequate [4].

Even when carried out optimally, percutaneous liver biopsy was never meant to accurately stage fibrosis in all liver diseases. Considering that an adult biopsy sample corresponds to a fraction of 1/50,000th of the entire liver, a liver biopsy specimen is insufficient in assessment of macronodular cirrhosis and quantification of fibrosis in liver diseases with patchy involvement.

Fifteen years ago, in an elaborate study, the French LIDO Study Group assessed the sampling error of liver biopsy and its impact on the diagnosis and staging of non-alcohol related steatohepatitis (NASH). No features displayed high agreement; substantial agreement was only seen for steatosis grade; moderate agreement for hepatocyte ballooning and perisinusoidal fibrosis; fair agreement for Mallory-Denk bodies; lobular inflammation displayed only slight agreement. The negative predictive value of a single biopsy for the diagnosis of NASH was at best 0.74. More concerning was the 41%, discordance in fibrosis staging between the two samples from the same liver. They concluded that histological characteristics for NASH were unevenly distributed and due to sampling error of percutaneous liver biopsies, there would be substantial misdiagnosis and staging inaccuracies [5].

If percutaneous liver biopsy in fatty liver disease staging is inaccurate, trying to correlate NITs to inaccurate "gold standard" as an end by itself will not advance the science of hepatology for diagnosis and management of fatty liver diseases.

Recent publications summarize advances in NITs [6] and its limitations [7]. There are different NITs including simple serum-based tests, more "complex" serum tests which incorporate measures of fibrogenesis or fibrolysis, and elastography methods quantify liver stiffness as a marker of fibrosis. All these NITs may have clinical roles in patients with fatty liver disease potentially helping predict future liver-related events and identifying high-risk patients for progressive hepatic fibrosis.

Fatty liver disease is a major problem affecting more than 25% of the general population especially in the Western world. Fibrosis is the main histological prognostic criteria for this disease. Percutaneous liver biopsy cannot be realistically performed in such a huge population. Primary care providers would love to utilize NITs that assist them in pinpointing patients with more rapidly progressive fatty liver disease such as those with components of metabolic syndrome. Maybe more aggressive interventions in patients with metabolic syndrome is the first step to halt the progression of fibrosis and control the burden of fatty liver diseases.

Percutaneous liver biopsy will still be needed for diagnosis of liver disease but hepatologists must move away from liver biopsy

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as the "gold standard" for staging liver fibrosis just like other disciplines have done. For example, cardiac catheterization, a "gold standard", is not performed in every patient suspected with coronary artery disease. Cardiologists and General Internists have many other surrogate but accurate markers to quantify risk for cardiovascular related events. Hepatologists need NITs to quantify risk for liver related events too. Trying to correlate NITs to histological stages of fibrosis as end by itself should stop.

There are already examples in hepatology for good NITs. The Baveno VI consensus has been ahead with this process recommending that patients with compensated advanced chronic liver disease, with liver stiffness less than 20 kPa and platelet counts greater than 150,000 /μL, are at very low risk for having varices requiring treatment; starting their screening endoscopy can be delayed. These recommendations have been validated recently in a systematic review and meta-analysis confirming its high diagnostic accuracy as "triage" test for screening of high-risk varices in patients with compensated advanced chronic liver disease [8].

There are also preliminary studies trying to identify high risk patients for development of hepatocellular carcinoma (HCC). One recent real-world study involving 18 million patients from four European cohorts [9], showed that diagnosis of fatty liver disease increased risk of liver related events including HCC. The strongest independent predictor for HCC was baseline diagnosis of diabetes but the hazard ratio was higher in patients with high-risk Fib-4 scores.

The global burden of fatty liver disease is huge due to increased prevalence of obesity, diabetes, hyperlipidemia and hypertension (components of metabolic syndrome). The health care system cannot depend on percutaneous liver biopsy to diagnose and stage fatty liver disease. There is an urgent need for NITs that can identify patients with higher risk for liver related events. Fibrosis is the major long-term histological prognostic criteria but the "gold standard" percutaneous liver biopsy is inaccurate in fatty liver disease. Given the improved accuracy for diagnosing advanced fibrosis, NITs are starting to be widely used in routine practice especially when used repeatedly or serially. Let's stop fitting NITs into hepatic fibrosis stages, instead let's use NITs to predict risk for liver related events.

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