



New insights on portal hypertension's screening in people with cystic fibrosis

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Cystic fibrosis-associated liver disease (CFLD) is a significant cause of morbidity and mortality affecting people with cystic fibrosis (PwCF) (1). Approximately 40% of PwCF have liver involvement, defined as the existence of any hepatic manifestation, including biochemical liver abnormalities (2). In a small percentage of these patients, liver involvement may ultimately result in the development of portal hypertension (PH) and its complications. The presence of at least two of the following variables—abnormal liver tests, abnormal liver ultrasound (US), abnormal physical examination with hepatosplenomegaly or histologic evidence of liver disease—were historically the basis for the European criteria to define CFLD (3). Nevertheless, the emergence of a new approach for liver assessment as liver elastography has led to the proposal of its inclusion in new diagnostic criteria (4).

Research on the pathogenesis of CFLD is still ongoing, however relevant hypotheses have been formulated. Cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction can lead to biliary fibrosis by causing bile obstruction and inflammation. This is due to reduced flow and increased viscosity of bile, resulting in the retention of toxic bile acids and subsequent cell damage (5). CFTR's role

in biliary innate immunity is also significant. A defective CFTR can activate inflammatory pathways, leading to liver damage (1). Additionally, gut dysbiosis in cystic fibrosis patients can increase intestinal permeability and promote the translocation of bacteria and their products, triggering liver inflammation (6). However, cholestatic and hepatocellular damage do not give the full picture of the pathological alterations of CFLD and the clinical scenario seems more complex. Porto-sinusoidal vascular disease (PSVD), a liver disorder characterized by non-cirrhotic PH given by different entities such as nodular regenerative hyperplasia, incomplete septal fibrosis or obliterative portal venopathy, has been proposed as one of the main drivers of PH in PwCF (7). This hypothesis is supported by histological (1,7), radiological (8) and, more recently, single-cell RNA sequencing data (9).

Despite the relative rarity of the disease, a recent consensus has provided guidelines for screening for CFLD and monitoring patients after the initial diagnosis (10). For initial liver involvement screening, it is recommended that annual laboratory tests and physical abdominal examinations be conducted, along with abdominal US every other year, beginning at age 3 and continuing through late

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adolescence. This recommendation is consistent with the evidence of increased prevalence of already severe CFLD after the age of 5, reaching 10% by age 30 (2). However, the optimal frequency for ultrasound imaging has yet to be fully established. Ideally, a stratified approach based on patients' relative risk of developing CFLD should be implemented. Debray *et al.* have noted that individuals with cystic fibrosis (PwCF) who carry the SERPINA1 Z allele are at a higher risk of developing CFLD and related complications compared to non-carriers (11). Additionally, Stonebraker *et al.* provided further insights into genetic risk factors for CFLD by reporting on whole-genome sequencing conducted in 4,082 individuals with CF, identifying four additional genes relevant to the pathophysiology of severe CFLD (12). While a systematic review of the literature is warranted, other risk factors that may help identify PwCF who could benefit from more frequent screening include male sex, a history of meconium ileus, and exocrine pancreatic insufficiency (5).

If hepatobiliary abnormalities are detected, a baseline liver elastography assessment is advised to identify any sign of advanced liver disease (10). Besides other chronic liver diseases, PH is a major driver of liver-related complications (8). Consequently, screening tests should focus on identifying both the direct (such as the presence of varices and portosystemic collaterals) and indirect (such as splenomegaly, thrombocytopenia, and ascites) signs of PH. Abdominal US remains a crucial diagnostic tool for the initial screening of CFLD as it provides valuable information not only on liver structure but also on the direct and indirect signs of PH (1). In CFLD, as also stated by the consensus, PH primarily seems to arise not only from advanced chronic liver disease (ACLD), but also from the presence of PSVD. Distinguishing between these two conditions is essential for the appropriate therapeutic management of patients. In fact, patients with ACLD-PH have compromised liver function, are at risk of liver cancer, and should eventually undergo liver transplant in case of end-stage disease, while patients with PSVD-PH, could, at least in the initial phases of disease, benefit from treatments aiming at the reduction of portal pressure. According to Baveno consensus (13) for adult population, non-selective beta-blockers would be treatment of choice for primary prophylaxis of PH complications, while endoscopic variceal ligation or positioning of transjugular intrahepatic portosystemic shunt (TIPS) would be reserved for secondary prophylaxes or refractory complications (i.e., ascites, variceal bleeding). However since data on primary

prophylaxis in the pediatric population with CF are scarce, the decision on the choice of treatment should be based on the best available level of evidence, the experience of physicians, and the clinical situation of each individual.

In order to reach this goal, abdominal US should always be coupled to elastography. The presence of normal liver stiffness measurement (LSM) values associated with ultrasonographic findings of PH strongly indicates the presence of a presinusoidal PH (i.e., PSVD), while the same signs associated with elevated LSM may indicate ACLD (14). In our recently published prospective monocentric cohort study assessing liver involvement in 182 PwCF, we found that signs of PH were present in 26% of the population but most (81%) had LSM <10 kPa and were therefore likely to have PSVD, while only 19% had CF-ACLD (15). Furthermore, we found how transplantation-free survival progressively worsens among the three categories: patients with CFLD but no PH, patients with likely PSVD and patients with ACLD and PH. Notably, 31% of patients with signs of PH did not meet at least two of the criteria to diagnose CFLD (4). In order to confirm the presence of PH and give a non-invasive estimate of its severity, another useful tool can be spleen stiffness measurement (SSM) (8). In fact, as proven in other liver conditions, SSM is an excellent and non-invasive surrogate of the hepatic venous pressure gradient (HVPG), with the added quality of being able to detect also the presinusoidal component of PH, overlooked by HVPG measurement (8). In our cohort (15), patients with ultrasonographic signs of PH had significantly higher absolute values of SSM. Accordingly to this evidence, we proposed the use of the SSM/LSM ratio as a reliable tool to distinguish PSVD from CF-ACLD finding that patients in the group with suspected PSVD had significantly higher ratios (5.7 *vs.* 2, $P=0.002$) (15). Recently, a European multicentric study on a cohort of patients with PSVD showed that SSM <40 kPa and serum total bilirubin <1 mg/dL can successfully predict the absence of varices, allowing to avoid 38% of screening endoscopies (16). Avoiding unnecessary upper endoscopy in patients with CFLD is crucial, as this population has an inherently higher susceptibility to respiratory infections and often requires anaesthesia during endoscopy procedures due to their young age (10).

In the recently published consensus on CFLD, there was not sufficient agreement to always recommend a diagnostic liver biopsy in PwCF who are found to have evidence of PH (10). The controversy is understandable as the need to understand the specific picture of CFLD, diagnosed with

liver biopsy, clashes with the progressive trend to reduce the number of invasive procedures in favour of non-invasive ones (13). Although the ideal scenario would be to diagnose not only the presence of PH-CFLD but also its causative agent with non-invasive tests until more evidence is available liver biopsy remains the gold standard to diagnose PSVD (17).

The field of research on liver involvement in CF is still open and many questions remain unsolved.

We believe that future research should focus on stratifying the risk of development of any type of liver involvement, useful to determine the optimal timing for screening and follow-up. Possible strategies include the characterization of a gut microbiota signature (6) along with a genetic panel (11,12) of high risk patients. Important data is missing on the effect of application of Baveno VII criteria (13) in this population. Trials on this topic should assess the rate of variceal bleeding, both in terms of development of first bleeding episode (primary prophylaxis) and re-bleeding (secondary prophylaxis), along with the overall mortality in case of conservative treatments or liver transplant.

In conclusion, the growing body of evidence on the emerging pathophysiology of cystic fibrosis-related liver disease, particularly the significant role of PSVD, necessitates a shift from traditional diagnostic methods relying solely on physical examination and ultrasonography. Instead, a combined approach using ultrasonography along with liver and SSMs should be adopted starting from the screening phase in all individuals with cystic fibrosis.

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