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Reply: Cystic Fibrosis Liver Disease in Adults: limits of non-invasive tests of fibrosis

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We appreciate the interest in our work by Hillaire et al. While we proposed a new diagnostic criterion incorporating non-invasive fibrosis markers that led to greater numbers of patients diagnosed with adult cystic fibrosis liver disease (CFLD), Hillaire et al. have drawn attention to the growing recognition of non-cirrhotic portal hypertensive (NCPH) liver diseases playing a larger role in CFLD. In recent publications, there appears to be a growing identification of NCPH in CFLD^{1, 2}. Obviously, larger studies are needed to elucidate the true prevalence of NCPH in CFLD and we agree with our colleagues that this may just be the tip of the iceberg.

In our study, the incorporation of non-invasive fibrosis markers and vibration controlled transient elastography (VCTE) yielded seemingly higher diagnostic value in adult CFLD. It should be noted that APRI and FIB-4 have been described to be significantly elevated in CFLD patients with esophageal varices³. Additionally, elevated VCTE measurements have also predicted the presence of esophageal varices in CFLD⁴. However, if NCPH is truly more prevalent in CFLD, or is increasing, the utility of these non-invasive markers will need to be studied further given the suggestion of performance differences between cirrhotic and non-cirrhotic chronic liver diseases⁵.

Secondly, we suggest that our case of nodular regenerative hyperplasia (NRH), not focal nodular hyperplasia (FNH), may be related to chronic antibiotic use. This clinical association is well described in primary immunodeficiency patients where chronic antibiotic use is typical. However, we and others agree that venopathy, first described in the 1980's by Wanless et al., continues to be a potential causative factor of NRH.

Finally, we agree that there is a need in identifying clinically useful diagnostic tests and biomarkers that can identify subjects with end-stage CFLD who may be candidates for multiple organ transplants (including liver). These tools would ideally take into account the potential existence of NCPH. The current use of the MELD allocation policy often makes it

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difficult for NCPH patient to meet MELD criteria for listing since synthetic function is often preserved for longer periods compared to cirrhosis related end-stage liver disease.

Abbreviations

CFLD	cystic fibrosis liver disease
NCPH	non-cirrhotic portal hypertension
APRI	ast-to-platelet ratio index
FIB-4	fibrosis-4 index
VCTE	vibration controlled transient elastography
CSPH	clinical significant portal hypertension
MELD	model for end-stage liver disease

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