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Reply to: "Assessment of liver phenotype in adults with severe alpha-1 antitrypsin deficiency (Pi*ZZ genotype)"

Establishing valid cut-offs for non-invasive measures of liver fibrosis to assess liver phenotype in severe alpha-1 antitrypsin deficiency

To the Editors:
We appreciate the interest and comments by Dr. Kumpers[1] *et al.* on our recent work characterizing the clinical and histological findings in patients with severe alpha-1 antitrypsin (AAT) deficiency.[2] To that end, we reviewed how the proposed liver stiffness measurements (LSM) ≥7.1 kPa performed in our cohort. Using that cut-off, the prevalence of clinically significant fibrosis defined as stage ≥2 would be 26%, which is remarkably similar to the 23.6% reported by Hamesch *et al.*[3] in a large study that did not include biopsies. However, our population had fibrosis stage confirmed, and the actual prevalence of fibrosis ≥2 was approximately 35%. The reason for the discrepancy was that an LSM ≥7.1 kPa misclassified the fibrosis stage in a significant number of Pi*ZZ individuals (n = 8 over staged; n = 15 under staged). This highlights the importance of performing a liver biopsy in every patient when evaluating the diagnostic accuracy of non-invasive fibrosis markers. Therefore, it is not surprising that biopsies performed selectively on Pi*ZZ individuals at risk of fibrosis actually confirmed significant liver fibrosis.[1] We agree that an established and validated cut-off (for LSM) would be an important tool in evaluating patients with AAT deficiency. When used to rule in liver disease, an LSM ≥7.1 kPa may be valuable given their cohort contains a population with more advanced disease. Our concern is that this cut-off had a poor negative predictive value when applied to our cohort. The strength in our study was that everyone was biopsied; however, the few individuals with advanced fibrosis limited the ability to establish an LSM that is more in line with established clinical practice. We await better non-invasive markers of fibrosis to rule out advanced disease. Overall, the similarities between our smaller cohort from North America with biopsies and the author's large European cohort with multiple non-invasive measures of fibrosis are notable.[3] What is emerging from these studies is that liver steatosis is a common finding either on biopsy or as measured by controlled attenuation parameter (CAP). We demonstrated that steatosis alone did not predict fibrosis but that PAS + D accumulation and steatosis were significantly associated with metabolic syndrome.[2] Impaired lipid metabolism and its association with alpha-1 accumulation is an interesting hypothesis that deserves further study. The presence of steatosis may be an early sign of cellular stress and/or injury. In the future, measuring steatosis by CAP may be a valuable tool for identifying those at risk.

Conflict of interest
Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.003.

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