Title

Reply to: “Screening for NAFLD and its severity in type 2 diabetic patients: Value of magnetic resonance imaging and outstanding issues”



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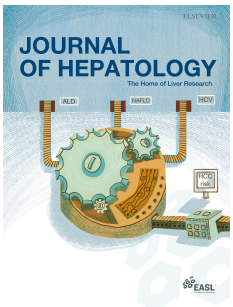


# Response to Letter to the Editor Written by Binet

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# Response to Letter to the Editor Written by Binet

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RL serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

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**AUTHOR CONTRIBUTIONS**

Drafting of manuscript VA, critical revision and approval VA, RL

We thank Dr. Binet for his comments regarding our recently published manuscript characterizing the prevalence of NAFLD, advanced fibrosis and cirrhosis in a prospectively recruited cohort of older adults with type II diabetes mellitus (T2DM) [1]. Dr. Binet and colleagues raise a few points, which we seek to clarify. First, recruitment occurred through primary care and endocrinology clinics as well as IRB approved advertisements directly to the patients. Collaborators in primary care and endocrinology throughout the greater San Diego area were contacted and educated about the study. However, referral to our study was dependent on patient referrals from these collaborating clinicians, as required by the IRB, and therefore it is not feasible to ensure that the study was offered to all patients with T2DM during the study period. Furthermore, the COVID-19 global pandemic further impacted recruitment, and together this highlights the significant effort required to recruit patients for prospective studies.

The second point of clarification is that T2DM was not newly diagnosed in the study population. Rather, patients had an established diagnosis of diabetes based on the American Diabetes Association clinical practice recommendations. While patients with a prior diagnosis of NAFLD were not excluded from the study, the study was conducted over a time period prior to the recommendation of systematic screening of NAFLD in the United States in this high-risk population. The number of new diagnoses will likely vary based on the environment and evolving practice guidance.

In the letter, the authors comment on the prevalence of NAFLD being lower than expected and that this may be related to the hepatic steatosis “burning out” [2] in patients with advanced fibrosis and cirrhosis. While our findings (NAFLD prevalence 65%) were consistent with a prior meta-analysis [3], we agree, and explicitly included in the manuscript that our strict definition of NAFLD may be a conservative estimate because of burnout of liver fat. We also, specifically did not include liver fat in the definition of advanced fibrosis secondary to NAFLD for this reason. However, we do contend that the accurate

quantification of liver fat is requisite to quantify the burden of NAFLD, and N=449, 91%, of the analytic population underwent MRI-PDFF, which is an accurate, precise biomarker of liver fat [4]and has emerging data regarding its utility as a prognostic marker in cross-sectional and longitudinal studies [5-7]. The cut-point of 288 dB/m on controlled attenuation parameter (CAP) is based on recent data with MRI-PDFF as the reference and utilization of M and XL probes in a population at risk for NAFLD [8], whereas prior studies supporting lower cut-points were performed in heterogeneous populations and without utilization of the XL probe. We recommend clinicians incorporate both liver fat and liver stiffness into decision making and support defining advanced fibrosis based on liver stiffness irrespective of liver fat as done in the manuscript and other publications using magnetic resonance elastography [9].

Finally, we agree with the observation that alcohol intake is an important co-factor and even moderate amounts of alcohol may impact disease severity in patients with metabolic syndrome and NAFLD[10]. The UCSD NAFLD Research Center is actively evaluating the spectrum of alcohol use, including in excess of the strict definition of NAFLD, in patients with obesity and metabolic syndrome in ongoing prospective studies using advanced MRI assessment and look forward to better characterizing the burden of liver disease in this important population.

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