DOI: 10.1111/apt.17453

INVITED EDITORIAL

AP&T Alimentary Pharmacology & Therapeutics WILEY

Editorial: clinical outcomes in lean NAFLD – the devil is in the details. Authors' reply

We read with great interest the editorial by Tan et al[1] on our recent study on clinical outcomes in patients with lean non-alcoholic fatty liver disease (NAFLD), where we found that lean patients with NAFLD experienced higher mortality than patients with overweight or obesity, despite lower prevalence of baseline metabolic disease and lower incidence of cirrhosis and diabetes.

We would like to clarify how our cohort was generated and the rationale for this approach.[2] We identified patients with hepatic steatosis based on simple natural language processing algorithms applied to imaging, biopsy, and vibration-controlled transient elastography reports. We used this approach with the aim of identifying consecutive patients with objective evidence of hepatic steatosis and to avoid referral biases inherent in cohorts based in subspecialty clinics who typically have more advanced disease.[3,4] This approach inevitably includes a high proportion of patients with incidental diagnoses of NAFLD: we previously found that the most common indication for abdominal imaging in our centre was abdominal pain or other abdominal symptoms (44%) which are unlikely to be caused by NAFLD.[5]

Tan et al correctly point out several limitations of our study. First, our study was based out of a single medical centre, though we included the entire spectrum of care from primary care through subspecialty care. Fewer than 10% of the patients in our cohort were followed in hepatology clinic.[6] Second, our cohort included patients with incidental and early-stage NAFLD not severe enough to warrant biopsy or even elastography. As detailed above, we consider our approach to be more reflective of "real-world" NAFLD in that patients not seen in subspecialty clinic could nonetheless be included. We conducted a sensitivity analysis stratified based on Fibrosis-4 scores to account for baseline disease severity. There was no overall change in our findings with this analysis.

Third, Tan et al point out that some lean patients with NAFLD may have died of unrelated diseases due to a higher burden of comorbidities. We agree with this point, which is especially relevant since patients with comorbidities may have been more likely to undergo imaging resulting in a NAFLD diagnosis.[5] We addressed this question via a sensitivity analysis adjusting for Charlson comorbidity index, a commonly used score to quantify disease burden, and lean body mass index remained associated with higher mortality. However, we acknowledge the risk of residual confounding, especially with diseases that are not included in the Charlson comorbidity index.

Lean NAFLD is a growing health concern worldwide which affects over 5% of the general population and up to 20% of patients with NAFLD.[7] Our study along with others found that lean patients with NAFLD may have higher mortality than their overweight/obese counterparts,[8] but we acknowledge the limitations in our study outlined in the editorial and stress that our findings should be interpreted with caution in light of them. Further research into the impact of lean NAFLD and mechanisms of disease is crucial to understanding and treating lean NAFLD.

ACKNOWLEDGEMENTS

Karn Wijarnpreecha was a recipient of the American Association for the Study of Liver Diseases (AASLD) Advanced/Transplant Hepatology Fellowship Award. Vincent L. Chen was supported in part by an AASLD Clinical, Translational and Outcomes Research Award and an NIDDK K08 DK132312.

CONFLICT OF INTEREST STATEMENT

The authors' declarations of personal conflicts of interest are unchanged from those in the original article.[2]

AUTHOR CONTRIBUTIONS

Karn Wijarnpreecha: Writing – review and editing (equal). **Anna S. Lok:** Writing – review and editing (equal). **Vincent Lingzhi Chen:** Writing – original draft (equal).

LINKED CONTENT

This article is linked to Wijarnpreecha et al papers. To view these articles, visit https://doi.org/10.1111/apt.17424 and https://doi.org/10.1111/apt.17449

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