Letter to the Editor

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Portal hypertension is a key determinant of the risk for liver-related events in non-alcoholic fatty liver disease

To the Editor:

Studies on the natural history of non-alcoholic fatty liver disease (NAFLD) are crucial for the understanding of the specific risk of developing NAFLD-related complications. Hence, the study by Allen AM *et al.*[1] describing the clinical course of 5,123 patients with NAFLD over a median follow-up time of 6.4 years is a valuable contribution to the field. When drawing conclusions, especially on the expected disease course, it is, however, important to reflect on the specific characteristics of the respective patient cohort from which results have been obtained. After insightful discussions with Prof. Dr. Sven Francque, who also contributed his expertise on the topic of portal hypertension in NAFLD,[2,3] we would like to emphasise some important issues:

First, the selection of any patient cohort (and especially of NAFLD aetiology) by using codes/key words may be problematic and prone to selection bias. In their study[1] the authors state that within 20 years after initial NAFLD diagnosis "other liver disease(s)" were diagnosed in 26% of patients. Since fatty liver disease may be multifactorial and can co-exist with other aetiologies, fuelling the current debate on metabolic dysfunction-associated liver disease (MAFLD), NAFLD still could be a concomitant driver of liver disease progression in these patients with other aetiologies. Also, while NAFLD diagnosis can be suspected by a combination of clinical and radiological markers, it is interesting to see that a substantial number of patients were included without imaging confirmation of steatosis, while only a minority were individually reviewed by the authors (1,101/1,171 patients with no liver images available were included, with only 442 (37.7%) reviewed; 370/453 patients with no mention of steatosis or cirrhosis on the available imaging were included, with only 223 (50%) reviewed).

Secondly, the authors present interesting data on the progression from compensated NAFLD cirrhosis to decompensation/death. However, portal hypertension (PH) – the main driver of hepatic decompensation[4] – should have been characterised in more detail. Splenomegaly and portosystemic collaterals, two parameters defining PH, and thus reflecting cirrhosis severity, were apparently not assessed as potential predictors of decompensation, whereas platelet count and non-bleeding varices representing two other surrogates for PH were. Importantly, benefits of therapies (*e.g.* non-selective beta blockers and/or statins) that lower portal pressure and hence likely impact on the disease course (particularly variceal bleeding) were not investigated.

These aspects call for further research to comprehensively characterise the severity of PH as a potential driving and predicting factor for decompensation in patients with compensated NAFLD.

It has been shown that the prevalence of PH-related decompensation is higher in patients with NAFLD and advanced chronic liver disease (ACLD) at any hepatic venous pressure gradient (HVPG) value when compared to patients with HCV-ACLD.[5] Also, it has been demonstrated that PH can occur in early non-cirrhotic NAFLD.[2] These particularities of PH in the setting of NAFLD may be caused by an effect of steatosis on the hepatic microcirculation[3] or by distinct structural and dynamic components of PH in NAFLD-cirrhosis.[6,7] Furthermore, we also have evidence that the severity of PH impacts the risk of hepatic decompensation in patients with compensated NAFLD-ACLD[8] and those with NASH-cirrhosis and varices.[9] Our own data[8] suggest that the cumulative incidence of hepatic decompensation in patients with compensated NAFLD-ACLD after 2 years of follow-up is only 3.1% in those with subclinical PH (HVPG <10 mmHg), but rises to 15% in those with clinically significant portal hypertension (CSPH, HVPG ≥10 mmHg). After 5 years of follow-up, the cumulative incidence rates of hepatic decompensation in patients with compensated NAFLD-ACLD increased to 24.3% (subclinical PH), 39.3% (CSPH) and 50.4% (severe PH, *i.e.* HVPG ≥16 mmHg). As in the study by Allen and colleagues,[1] the most frequent decompensating event was ascites. These results underline the importance of the characterisation of the severity of PH in patients with NAFLD-ACLD to improve the prediction of their specific risk of hepatic decompensation, which is especially relevant for selecting and comparing the appropriate patient groups for clinical trials aimed at preventing hepatic decompensation.

To conclude, we need further large-scale studies that define the specific risk for liver-related events in patients with NAFLD-ACLD, similar to the study of Allen AM *et al.*[1] We would like to advocate for studies that include a well-characterised cohort of patients with verified ACLD due to NAFLD, and even more importantly, a detailed characterisation of the severity of PH, best by means of HVPG. The results of these trials will allow for the characterisation and subsequent selection of patients with NAFLD-ACLD at particularly high risk of hepatic decompensation for clinical trials with a sufficiently high expected event rate, evading the need to include >500-1,000 patients, as suggested by Allen AM *et al.*,[1] to be sufficiently powered to detect therapeutically relevant differences.[10]

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Conflicts of interests

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Authors' contributions

RP drafted the manuscript which was then critically revised by WJK and TR.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.031.

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Author names in bold designate shared co-first authorship

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