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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 5123 NAFLD patients 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 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 without imaging confirmation of steatosis still a substantial number of patients were included while only a minority was individually reviewed by the authors (1101/1171 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, 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 betablockers and/or statins) that lower portal pressure and hence likely impact on the disease course (particularly variceal bleeding) were not investigated.

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