NAFLD

**Nonalcoholic fatty liver disease natural history: what we know**

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Although nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide, there is a paucity of good quality data on its natural history and most studies to date have reported on retrospective data. Robust data are required to inform regulatory endpoints, trial design and models of care.

Refers to Sanyal AJ et al. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. The New England journal of medicine. 2021;385(17):1559-69

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide and the main reason for referrals to secondary care services [1]. NAFLD is becoming a leading cause of cirrhosis and hepatocellular carcinoma (HCC) and a growing indication for liver transplantation worldwide [2]. However, there is a paucity of good quality data on the natural history of NAFLD and most studies to date have reported on retrospective data.

A recently published prospective observational study, by Sanyal and co-authors [3], filled some important knowledge gaps, but also inevitably generated further questions. In total, 1773 adult patients in the United States with NAFLD and a liver biopsy at baseline were followed for a median time of 4 years. The mean age was 52 years, 64% were women, 85% were white and 12% were Hispanic. From a histological point of view, 75% had borderline or conclusive nonalcoholic steatohepatitis (NASH), 21% had advanced fibrosis (fibrosis stage F3) and 9% had cirrhosis (fibrosis stage F4). All-cause and liver-related mortality was higher in the NAFLD population than the expected background age-related rates, but this difference was

mainly driven by patients with cirrhosis. In total, 37 patients (0.46 per 100 person-years) had a new-onset decompensating event, which was predominantly hepatic encephalopathy, 9 patients (0.11 per 100 person-years) developed HCC and 12 patients (0.15 per 100 person years) died from a liver-related cause. Mortality increased with increasing fibrosis stages and was significantly higher in patients with F4 than patients with fibrosis stage F0 to F2. Importantly, the incidence of cardiac events and non-hepatic cancers was similar across fibrosis stages. Incident hepatic decompensation was significantly associated with increased mortality.

There are important insights from this observational study that advance our knowledge of NAFLD. Firstly, liver disease progression and the incidence of decompensation in patients with NAFLD is relatively slow compared with other causes of liver disease, most notably hepatitis C virus (HCV), which was the leading cause of liver-related mortality before the advent of direct acting antivirals, and alcohol-related liver disease. To put this in perspective, the 5-year incidence of liver-related death was 16.3% in patients with cirrhosis

secondary to HCV infection [4], whereas 18% of patients with alcohol-related liver disease developed a clinical event within a median follow-up of 18 months [5]. This information has important implications for designing and adequately powering studies in patients with NASH-related cirrhosis but also cirrhosis in general if patients with NASH are included. It also implies that studies examining the natural history of NAFLD need to have a larger sample size and/or longer follow-up for more robust conclusions, particularly on the mortality rates of patients with significant fibrosis (fibrosis stage F2).

Secondly, the incidence of HCC in patients with NAFLD was fairly low. It is well established that HCC can develop in patients with non-cirrhotic NAFLD at a low incidence rate[1]. Sanyal et al. showed that even in patients with established cirrhosis, the incidence of HCC was low. This finding puts into question the surveillance of unselected patients with cirrhosis and NAFLD. We clearly need more data in larger cohorts of patients but also the adoption of risk stratification

in patients with NASH and cirrhosis to select for surveillance those patients that would benefit most [6].

Thirdly, the study provides important information on the currently accepted regulatory endpoints for clinical trials in NASH. At the moment, resolution of steatohepatitis and improvement of fibrosis are surrogate endpoints that could lead to provisional regulatory approvals, whereas progression to cirrhosis can be used for final drug approval. The findings support the use of progression to cirrhosis for non-cirrhotic patients and progression to decompensation for patients with established cirrhosis as valid endpoints. The data also provide a strong rationale for the use of improvement in fibrosis as a surrogate endpoint. As more than 90% of patients with advanced fibrosis or cirrhosis had NASH, the association of NASH with decompensation could not be established and therefore the validity of this endpoint could not be verified.

A puzzling finding of the study by Sanyal et al. was that hepatic encephalopathy was the most common decompensating event. Conventional knowledge dictates that encephalopathy is a late event

in patients with cirrhosis, and presents in people who have already decompensated and have markedly impaired liver function [7]. Even taking into account that 17 patients had ascites at enrolment, there were 30 patients who developed new onset hepatic encephalopathy, which means that in at least 13 of them this was the first decompensating event. Over-diagnosis is a concern and adjudication of these events, even post hoc, would be of value. Additional factors to explore would be the use of opioid analgesics in this population with various comorbidities, that could lower the threshold for the clinical manifestation of encephalopathy. Clearly further information and data are required.

The study was limited by the inclusion of a predominantly white population and the selection bias of people who had a liver biopsy at inclusion. The latter implies a higher suspicion index for the presence of fibrosis by the treating physician but also the self-selection of patients who were willing to undergo the procedure. The increasing use of non-invasive fibrosis tests will make the inception of biopsy proven cohorts of patients with NAFLD challenging, but also not

representative of the wider population. The use of non-invasive fibrosis tests has moved from surrogates of fibrosis to prognostic indicators [8]. Combinations of non-invasive fibrosis tests can be used instead of a liver biopsy with similar diagnostic accuracy [9]. The inception of large cohorts will be facilitated by the use of non-invasive fibrosis tests instead of a liver biopsy, with the additional benefit of repeated measurements that can further refine prognosis.

In conclusion, the study by Sanyal is the first prospective observational study in patients with NAFLD and provided important information on the natural history of the disease. Going forward, we need larger studies and longer follow-ups with a wider inclusion of patients. These studies will adequately inform the clinical trial design, but also the models of care for this multimorbid disease.

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