Editorial

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NASH cirrhosis trials and major adverse liver outcomes: Big data needed

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Although non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease and cirrhosis, approved therapies for NAFLD are not yet accessible.[1,2] The NAFLD spectrum is distributed into 1) non-alcoholic fatty liver (NAFL or steatosis); 2) the progressive form, non-alcoholic steatohepatitis (NASH); and 3) NAFLD or NASH with various stages of fibrosis (F0–F4).[3,4] Natural history studies have informed us about the histological progression and regression of this disease. Studies have shown that individuals with NASH and significant fibrosis (≥F2) are more prone to develop major adverse liver outcomes (MALOs), and this risk is at its peak in individuals with F3 and F4 fibrosis.[5,6] MALOs are usually defined by the occurrence of overt ascites, overt hepatic encephalopathy, variceal bleeding, liver transplantation, or liver-related death.[7] In addition, individuals with compensated cirrhosis (F4) can be divided into those with or without portal hypertension; the former are more likely to progress to decompensated cirrhosis.[7]

Over the last two decades, phase III randomized clinical trials (RCTs) have focused on two main histological outcomes, *i.e.* resolution of NASH without worsening fibrosis and improvement of fibrosis without worsening of NASH.[1] MALOs have been proposed as primary efficacy endpoints in addition to histological outcomes; however, histological outcomes are more commonly used in trials for individuals with NASH and F2–F3 fibrosis, as they allow for faster assessment of drug efficacy with a smaller sample size. On the other hand, a recent update in regulatory guidance has been proposed, in which two parallel phase III studies can be conducted; one in F2–F3 NASH patients using histological outcomes, and another trial in well compensated NASH cirrhosis where MALOs can be used as a primary efficacy endpoint.[8] This approach can lead to faster full approval of the drug (moving forward from subpart-H), rather than waiting for patients in the F2–F3 trial to reach MALOs, which would require a much longer-duration study.[8]

Meta-analyses have informed us about the rate of resolution of NASH or improvement in fibrosis in the placebo arm[9,10] and, recently, on the rates of progression and regression histologically.[4] However, data regarding MALOs in NAFLD and NAFLD cirrhosis are lacking, as long-duration natural history trials are required. In the recent era, these data have come mainly from RCTs[11–14] and a large observational study with a median follow-up of 4 years.[5]

In a recent issue of the *Journal*, Allen *et al.* performed an important retrospective analysis in the Mayo health system that examined 5,123 individuals with NAFLD over a median follow-up of 6.4 years (range 1-23 years), which is the longest duration in which the incidence of MALOs in individuals with NAFLD has been studied.[15] The authors followed a multistep modeling approach for NAFLD transition, in which 6 states defined transitions between non-consecutive states: State 1, NAFLD without cirrhosis; State 2, compensated cirrhosis; State 3, first decompensation, hepatocellular carcinoma (HCC), or liver transplantation; State 4, two or more decompensations, HCC, or liver transplantation; and State 5, death. State 6, which is transition to another liver disease and transition to death was excluded from the analysis as it no longer represents the natural history of NAFLD. It is important to highlight that the authors have followed a rigorous methodology, going beyond the traditional methods in epidemiological studies (using ICD codes alone), and using multiple steps to confirm the diagnosis. These steps included natural-language processing, reviewing charts extensively (such as confirming the HCC diagnosis via ICD codes with chart review), and using non-invasive testing followed by chart review to confirm cirrhosis (*e.g.* using FIB-4 of >2.67 to confirm cirrhosis status). These approaches are imperative to overcome biases introduced when

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Table 1. Clinical Trials using MALO as an endpoint.

Study	Follow-up duration	Patient stages	Progression to cirrhosis	Progression to MALOs	Additional criteria for MALOs*
Randomized-controlled trials					
Simtuzumab trials	2.57 years	F3–F4	~9%/year	~7.4%/year	2-point increase in CP score and/or MELD ≥15 and development of varices and HCC
Selonsertib trials	1.375 years	F3–F4	9.5%-11.6%/year	~2.3%/year	MELD ≥15 and HCC
Galectin-3 study	1 year	F4 with HVPG ≥6	N/A	~18.1%/year	Development of MELD ≥15 or CP ≥2, development of varices or progression from small to large varices
Observational study					
The NASH CRN cohort	4 years (2.1-7.4)	F0–F4	Not mentioned	Hepatic encephalopathy in 2.39 per 100 persons a year, ascites in 1.20, variceal bleeding in 0.70, HCC in 0.14 and death form any case in 1.76.	MELD ≥15 and HCC were assessed
Real-world cohort					
Mayo Health System cohort	6.4 years (1-23)	F0–F4 including decompensated cirrhosis	n.a.	~8%/year	Bilirubin >1.5 mg/dl and HCC

MALOs, major adverse liver outcomes; CP, Child-Pugh; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; NASH-CRN, NASH-Clinical Research Network
*MALOs are usually defined as the occurrence of overt ascites, overt hepatic encephalopathy, variceal bleeding, liver transplantation, or liver-related death.

ICD codes alone are used. On the other hand, these proposed "States" fall short, as they cannot identify various degrees of fibrosis preceding cirrhosis (F0–F4). Nor can they identify cirrhosis at its first incidence, as cirrhosis is often asymptomatic, and liver biopsy or non-invasive testing are usually required to identify cirrhosis initially. Nevertheless, the study has focused on the incidence of MALOs, which manifest immediately upon incidence and are easier to detect.

In addition to MALOs, the authors included bilirubin >1.5 mg/dl as a qualifying MALO event[7] (a value lower than that used previously) but not the model for end-stage liver disease (MELD) score, as it could be affected by other conditions. The authors have also examined the incidence of death, which was high in this enriched cohort, reaching 575 deaths, 6% of which were liver related. Allen *et al.*[15] found that the rate of transition from NAFLD to cirrhosis was 3% in 15 years; compensated cirrhosis to first decompensation was 33% in 4 years (8%/year); first decompensation to two or more was 47% in 2 years (~23%/year). Not surprisingly, albumin, bilirubin, non-bleeding esophageal varices, and diabetes were independent predictors of decompensation with c-statics of ~0.75. Importantly, the authors used their data to calculate the required sample size to detect a ≥15% relative decrease in clinical liver endpoints (MALOs) in cirrhosis trials, and found it to be 2,886 individuals followed over 2 years. The current study has added to the scattered natural history that examined MALOs in the NAFLD population.

In the simtuzumab study,[10] the rate of progression from F3 (the study did not include F0-2) to cirrhosis was 22% over 29 months, or about ~9%/year. On the other hand, the rate of MALOs was 19% over 30.9 months (~7.4%/year) in individuals with compensated cirrhosis.[11] Importantly, this varied by Child-Pugh (CP) scores (overall: 8.9 per 100 person-years [95% CI 6.7-11.7]; CP-A5: 5.5 per 100 person-years [95% CI 3.7-8.1]; CP-A6: 20.7 per 100 person-years [95% CI 13.2-32.4]). The definition of MALOs included the traditional factors in addition to ≥2-point increase in CP score and/or MELD ≥15 and development of varices.[11] The most common MALO event was ascites (7%), followed by hepatic encephalopathy (5%) and esophageal variceal bleeding (3%); the prevalence of events were consistent with those reported by Allen *et al.*[15]

In the RCT with selonsertib,[11,16] histologic progression to cirrhosis (from F3) occurred in 13% of patients receiving the drug at the dose of 18 mg, 16% receiving 6 mg, and 16% receiving placebo over a duration of 16.5 months (9.5%-11.6%/year). Among MALOs in the compensated cirrhosis population, 3% (27 patients) of the population developed MALOs over 15.8 months: ascites (n = 13); hepatic encephalopathy (n = 7); portal hypertensive bleeding (n = 4); qualified for liver transplantation (n = 4); and transplantation (n = 1). HCC was diagnosed in 0.5% of patients.

Data on MALOs is also available in the RCT with galectin,[12] which included individuals with cirrhosis and evidence of portal hypertension (confirmed by portal pressure measurements). In this study, MALOs occurred at a rate of 18.1% over 1 year.[13] Development of MELD ≥15 or CP ≥2, and the development of varices or progression from small to large varices were added to the traditional MALO events. This study may reflect the inclusion of sicker patients, as they were required to have evidence of portal hypertension to enter the study while the study by Allen *et al.*[15] did not separate individuals with cirrhosis into those with or without portal hypertension. The finding of an 18.1% rate of

decompensation in those with portal hypertension in the galectin study is between the 8%/year rate of decompensation in the cirrhosis group and the 23%/year in the cirrhosis with decompensation group presented in the study by Allen *et al.*[15]

In the emricasan RCT in individuals with cirrhosis,[13] MALO events included all-cause mortality, new decompensation events, or ≥4-point MELD-Na score progression. Overall, 37.4% of individuals experienced 80 first events at the time of the primary analysis. However, most events were related to ≥4-point MELD-Na score progression, and solid conclusions cannot be made from this study.

Finally, the prospective observational study by Sanyal *et al.*[4] found that individuals with biopsy-proven cirrhosis developed hepatic encephalopathy at a rate of 2.39 per 100 persons a year, ascites in 1.20/100, variceal bleeding in 0.70/100, HCC in 0.14/100, and death from any case in 1.76/100. The median duration for this study was 4 years (interquartile range, 2.1 to 7.4). Patients were likely monitored closely in this study, with non-invasive tests, biopsies, and treatments; an earlier identification of cirrhosis and better management are expected in such an observational study. A summary of the current literature on MALOs in cirrhosis is presented in Table 1.

In summary, the current study adds to the understanding of the natural history of NAFLD and its progression to cirrhosis and decompensation. The study is the first to be conducted in a large, real-world cohort of individuals with NAFLD. It highlights the need for large sample sizes to conduct cirrhosis trials with MALOs as the primary outcome. Such trials will be impossible to conduct with biopsy as an entry criterion. Fortunately, non-invasive tests are a great alternative to liver biopsy in diagnosing cirrhosis and can be used as an inclusion criterion. Studies of pharmacological agents to assess changes in MALOs in cirrhosis are urgently needed, and it is anticipated they will enroll large numbers of patients.

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Authors' contributions

Both authors contributed to the writing of this editorial.

Supplementary data

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