



# What will happen in patients with advanced nonalcoholic fatty liver disease?

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Non-alcoholic fatty liver disease (NAFLD) and advanced form non-alcoholic steatohepatitis (NASH) have been become globally major chronic liver diseases (1,2). NAFLD is one of the leading causes of liver cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC) (3). A large number of retrospective studies reported the importance of hepatic fibrosis with NAFLD patients as the strongest factor of liver-related mortality (4,5). On the other hand, NAFLD patients with advanced hepatic fibrosis are thought to have higher risk of developing vascular events and extrahepatic cancers because of the high prevalence of coexisting cardiometabolic risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and obesity (6). However, since former literatures included only few NAFLD patients with advanced hepatic fibrosis, it is hard to estimate the accurate risk on the whole spectrum of these complications.

Vilar-Gomez *et al.* reported a multinational prospective study to clarify predictive factors for outcomes in large numbers of biopsy-confirmed NAFLD patients with advanced fibrosis, which investigated the long period overall liver transplantation free survival and cumulative incidences of major clinical events such as hepatic failure, HCC, vascular event (ischemic heart disease or stroke), and extrahepatic cancer (7,8). In the mean follow-up time of 5.5 years (range, 2.7–8.2 years), 37 NAFLD patients passed away, 37 underwent liver transplantation, 88 developed first

hepatic failure events, 41 developed HCC, 14 occurred vascular events, and 30 had extrahepatic cancers. The authors reported that death/transplantation, hepatic failure, and HCC were significantly related with baseline cirrhosis and mild steatosis (<33%). Less hepatic fat was thought to be associated with ‘burned-out NASH’ status in NAFLD patients with cirrhosis (9), and these results were quite consistent with previous reports.

What impressed us in this manuscript was mainly following three points. Firstly, the cumulative incidence rate of vascular events was higher in NAFLD patients with F3 grade fibrosis (7%; 95% CI: 3–18%) than NAFLD patients with cirrhosis (2%; 95% CI: 0–6%). It was generally well known that there are many vascular events in patients with liver cirrhosis (10). According to author’s results, it turned out that NAFLD patients with F3 grade fibrosis should be paid more attention to the occurrence of vascular events compared to NAFLD patients with cirrhosis. As shown in Table 1, blood pressure, cholesterol values, and body mass index in NAFLD patients with cirrhosis were lower than those of patients with F3 grade fibrosis, which may at least partially describe the lower rates of vascular events in NAFLD patients with cirrhosis.

Secondly, the cumulative incidence of extrahepatic cancers was higher in patients with F3 fibrosis (14%; 95% CI: 7–23%) than patients with cirrhosis (6%; 95% CI:

2–15%). The most frequent cancer was colorectal cancer (n=15, 50%), followed by skin cancer (n=6, 20%), breast cancer (n=3, 10%), and uterine cancer (n=2, 7%). Many literatures reported a higher prevalence of colorectal cancer in NAFLD cohort compared to healthy control, while the relation of NAFLD with other extrahepatic cancers was not fully proven (6). Although higher liver-related mortality in NAFLD cirrhotic patients may have possibility to preclude the development of extrahepatic cancers, they could not accurately describe the mechanism at this moment.

Thirdly, which we felt most impressive, the authors reported that mild alcohol consumption was associated with higher risk of death/transplantation (HR, 2.3; 95% CI: 1.32–4.02), liver failure (HR, 1.65; 95% CI: 1.01–2.61) and HCC (HR, 3.22; 95% CI: 1.64–6.32) among NAFLD cirrhotic. Although heavy alcohol consumption is clearly damaging with the liver, mild drinking habit reported improved insulin sensitivity and lowered cardiovascular mortality in the general population (11). Whether mild alcohol consumption is equally valuable for NAFLD patients or not has been controversial. Ascha *et al.* showed that mild drinking habit was related with higher risk of HCC in NASH cirrhotic patients cohort (12). Recently, our multivariate survival analysis in NAFLD patients with advanced fibrosis (F3 and cirrhosis) showed mild drinking habit was one of the factors significantly associated with HCC (13). We need to discuss and investigate more the impact of mild drinking habit on HCC development in NAFLD patients with F3 (or lower) grade fibrosis. Even in study of Vilar-Gomez *et al.*, HCC development rate in mild drinking-NAFLD patients with F3 grade fibrosis was not significantly different, but close to significantly higher than in patients without drinking [P=0.15, 1 case (7%) and 1 case (1%) without drinking, respectively] (shown in Supplementary Table 8 in their article). Additionally, we should take into consideration about sampling error by liver biopsy on decision of fibrosis grade. Data of Vilar-Gomez *et al.* actually showed 7 patients (4%) with F3 fibrosis had gastroesophageal varices, suggesting there could be some lower misclassification cases by liver biopsy in this study. A bigger cohort and longer observation period are needed to precisely evaluate the risk of mild drinking in patients with F3 grade, since the frequency of HCC development from patients with F3 grade is relatively low. Collectively, we propose the abstinence of ethanol in cirrhotic NAFLD patients.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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