# The 20% Rule of NASH Progression: The Natural History of Advanced Fibrosis and Cirrhosis Caused by NASH

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The global epidemic of obesity has led to the rise of nonalcoholic fatty liver disease (NAFLD) as a significant cause of cirrhosis, end-stage liver disease, and need for liver transplantation.[1] NAFLD is common, with a global estimate of 25% of adults[2]; however, only a small proportion will progress to cirrhosis and develop liver-related morbidity. As with other chronic liver diseases, the severity of underlying liver fibrosis aids prediction of outcome, with patients with bridging fibrosis or cirrhosis being at greatest risk of future liver-related morbidity.[3] Nonetheless, key questions remain largely unanswered, including what proportion of subjects develop progressive disease, how fast this occurs, and how to identify and monitor these individuals. These questions are becoming increasingly relevant given that efficacious drug treatments are likely to become available within the next few years and will need to be targeted at those with greatest risk of disease-related morbidity.

In this context, Sanyal and colleagues explore in this issue of Hepatology the progression of liver disease and predictors of fibrosis progression and decompensation, as well as potential monitoring strategies in 475 patients with nonalcoholic steatohepatitis (NASH) and bridging fibrosis or compensated cirrhosis.[4] Notably, 68% of patients with cirrhosis had a baseline hepatic venous pressure gradient (HPVG) measurement of 10 mm Hg, demonstrating that the majority had clinically significant portal hypertension at study entry. The cohort originated from two phase 2 randomized clinical trials of simtuzumab, a humanized monoclonal antibody targeting lysyl oxidase-like 2 (LOXL2), which had negative results.[5] Patients were assessed with paired liver biopsies and HPVG measurements (if cirrhotic at baseline) and were followed for outcomes. The study has a number of strengths, including a relatively large number of well-defined patients with standardized follow-up and protocol biopsies that have been centrally scored by a single liver pathologist, thereby limiting

selection bias and observer variability. Additional strengths include the use of HPVG to measure changes in portal hypertension and image morphometry to quantify liver fibrosis. The study design, however, also has some intrinsic limitations, with strict inclusion and exclusion criteria limiting generalizability, limited length of follow-up, and the possibility of altered lifestyle behavior of participants within the trial thereby changing the "natural history" of the disease.

## The 20% Rule (Fig. 1)

Although the study was relatively short (96 weeks), a surprisingly high proportion of patients progressed or developed liver-related complications: 22% (48/217) patients with baseline F3 fibrosis progressed to cirrhosis. Although sampling error cannot be excluded as a reason for apparent fibrosis progression, those patients with F3 fibrosis who progressed had lower NAFLD fibrosis scores and Fibrosis-4 score (FIB-4) and aspartate aminotransferase-to-platelet ratio index (APRI) levels than patients with cirrhosis at baseline, suggesting that these were different groups. In addition, 19% of patients with cirrhosis (50/258) had a liver-related event. Similarly, Hui et al. found a 23% incidence of decompensation at 3 years in a small cohort of patients with NASH cirrhosis.[6] Although NASH is thought to be a relatively indolent and slowly progressive disease, this suggests heterogeneity in disease progression with a subset of patients having an accelerated disease course. This is supported by a meta-analysis of patients with NAFLD undergoing paired liver biopsies that found a similar proportion (21%) of patients were "rapid progressors" who developed F3/4 fibrosis from a baseline of no/minimal fibrosis over a mean of 5.9 years.[7]

Can we predict progression to cirrhosis or future decompensation? In the Sanyal study, simple demographics, such as age, sex, and body mass index, did not predict progression, although a trend was detected regarding type 2 diabetes mellitus and liver decompensation (hazard ratio 1.90; $P = 0.07$). Liver biopsy added limited guidance: although severe hepatocellular ballooning was associated with fibrosis progression, supporting its inclusion within the histological definition of NASH, neither baseline or change in steatosis, lobular inflammation, or the NAFLD activity score were predictive of disease progression or regression in patients with advanced fibrosis. Thus, as pointed out by the study authors, treatment endpoints for patients with advanced fibrosis/cirrhosis should focus on fibrosis and clinical outcomes.

Surprisingly, pathologist staging (Ishak stage 4 [marked bridging] versus Ishak stage 3 [occasional bridging]) did not predict a greater risk of progression to cirrhosis, nor did stage 6 versus 5 predict future clinical decompensation. In contrast, computerized quantification of collagen using image morphometry predicted cirrhosis progression and decompensation, and alpha smooth muscle staining (a marker of hepatic stellate cell activation) was also predictive of cirrhosis progression. Nonetheless, baseline image morphometry had poor sensitivity and specificity (60% and 62%, respectively), suggesting it is not a useful in isolation.

The most notable parameters predicting cirrhosis progression and future liver-related events were serum markers (Fig. 1). These included simple noninvasive fibrosis algorithms (FIB-4, APRI, NAFLD Fibrosis Score) and proprietary algorithms (Enhanced Liver Fibrosis [ELF] score and FibroTest/FibroSure) as well as levels of serum LOXL2 (sLOXL2), a protein involved in collagen cross-linking and fibrosis matrix stabilization. On multivariable analysis, only ELF and platelet count remained predictive of progression to cirrhosis, albeit with modest accuracy (C statistic 0.76). The inclusion of liver biopsy parameters (alpha smooth muscle expression, fibrosis stage) to ELF and FIB-4 marginally increased the accuracy to 0.78. For the prediction of liver decompensation in patients with cirrhosis, Model for End-Stage Liver Disease, alkaline phosphatase, and albumin but not noninvasive fibrosis algorithms were significant on multivariable analysis. HPVG was predictive of decompensation, with 8% of patients with cirrhosis with an HVPG < 10 mm Hg developing decompensation compared with 25% with a reading 10. However, HPVG added marginal benefit over blood tests alone (C statistic 0.76 versus 0.75).

A related question is whether serum markers can be used to monitor disease progression or regression. Standard liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase) were not useful. Increasing ELF, APRI, and sLOXL2 levels correlated with fibrosis progression; however, only the latter improved with fibrosis regression. Changes in FIB-4, NAFLD fibrosis score, and FibroTest/FibroSure were not associated with change in fibrosis. Recent data from the NASH Clinical Research Network suggest that incorporation of these scores with baseline fibrosis stage (determined by liver biopsy) may be useful to predict the development of advanced fibrosis but not progression of any fibrosis stage or resolution of fibrosis.[8,9]

## Clinical Implications

The study by Sanyal suggests that 1 in 5 patients with NASH and advanced fibrosis or cirrhosis will develop cirrhosis or decompensation within a short time frame. Heightened levels of hepatic fibrogenesis, evidenced by increased hepatic stellate cell activation (alpha smooth muscle actin staining), collagen deposition on biopsy, and increased serum fibrosis markers, are associated with a greater risk of progression to cirrhosis and can aid in prioritizing patients for more intensive lifestyle management, monitoring, and clinical trials. Nonetheless, noninvasive serum markers only have modest accuracy to guide clinical management decisions (C statistic 0.76–0.78), and the optimal combination of parameters to accurately predict outcomes or reflect changes in disease state remains to be determined.

## The Future

The importance of fibrosis in predicting outcomes in NAFLD has been highlighted by several studies,[3,10] with discrete fibrosis categories dramatically influencing future liver-related outcomes. The study by Sanyal and colleagues goes beyond the pathologist fibrosis stage to highlight the biological process of fibrogenesis. Future endeavors will need to focus on how best to capture this in a noninvasive fashion to enable accurate prediction and monitoring of patients with NAFLD without the need for liver biopsy.

## Acknowledgments

## Abbreviations:

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| **APRI** | aspartate aminotransferase-to-platelet ratio index |
| **ELF** | Enhanced Liver Fibrosis |
| **HPVG** | hepatic venous pressure gradient |
| **NAFLD** | nonalcoholic fatty liver disease |
| **NASH** | nonalcoholic steatohepatitis |

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# The 20% rule for progression in F3/4 NASH



**FIG. 1.**

The natural history of disease progression in NASH with advanced fibrosis and cirrhosis: the 20% rule. Approximately 20% of patients with NASH with advanced NAFLD Fibrosis Score (NFS) (F3) fibrosis or compensated cirrhosis will progress to cirrhosis or develop decompensation, respectively, over a 2-year time period.