

MASH Advanced Fibrosis: Experts Detail Unique Challenges at EASL 2026

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Managing metabolic dysfunction-associated steatohepatitis (MASH) with advanced fibrosis presents a significant clinical dilemma due to its progressive nature and increased risk of liver-related morbidity and mortality. Discussions at EASL 2026 underscored the urgent need for refined diagnostic strategies and targeted therapeutic interventions for this specific patient population. Data supporting this approach is available in the peer-reviewed literature.

KEY TAKEAWAYS

- **The Pivot:** Advanced fibrosis in MASH requires a distinct management approach compared to earlier stages, given its higher risk of progression to cirrhosis and hepatocellular carcinoma.
- **The Data:** While no specific trial data was presented, expert consensus emphasized that patients with F3-F4 fibrosis face a 2-3 fold increased risk of liver-related events compared to F0-F2.
- **The Action:** Clinicians should prioritize early and accurate fibrosis staging in MASH patients to identify those at highest risk and consider enrollment in trials for novel antifibrotic agents.

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), is characterized by hepatic steatosis, inflammation, and hepatocellular ballooning, with or without fibrosis.¹ The progression of fibrosis is a primary determinant of clinical outcomes, with advanced fibrosis (stages F3 and F4) being associated with an increased risk of cirrhosis, liver decompensation, hepatocellular carcinoma (HCC), and liver-related mortality.² At EASL 2026, experts convened to address the specific challenges inherent in the diagnosis and management of MASH patients who have already developed advanced fibrosis.

Patients with advanced fibrosis represent a distinct subgroup requiring tailored approaches. Unlike earlier stages of MASH, where lifestyle modifications and metabolic control may suffice, advanced fibrosis often necessitates more aggressive interventions.³ The natural history of MASH with advanced fibrosis indicates a higher annual incidence of liver-related events, estimated to be between 2% and 5%, compared to less than 1% in patients with mild or moderate fibrosis.⁴ This elevated risk emphasizes the need for precise risk stratification and timely therapeutic decisions. The global prevalence of MASH is rising, mirroring the increasing rates of obesity and type 2 diabetes, which are major risk factors. Patients with advanced fibrosis often present with more severe metabolic derangements, including higher rates of insulin resistance and dyslipidemia, further complicating their clinical management. Clinicians must understand these specific metabolic profiles to develop targeted interventions.

Non-Invasive Staging Cannot Reliably Separate F3 from F4 Fibrosis

Accurate staging of fibrosis dictates whether a MASH patient requires immediate intervention for impending liver failure or routine metabolic management. Advanced fibrosis, specifically F3 and F4, carries a significantly higher risk of cirrhosis, liver decompensation, hepatocellular carcinoma (HCC), and liver-related mortality compared to earlier stages.² Liver biopsy remains the gold standard for assessing fibrosis, offering detailed histological information. But its invasiveness, the potential for sampling variability, and patient discomfort limit its widespread application in routine clinical practice.⁵

Non-invasive methods, including transient elastography (FibroScan), magnetic resonance elastography (MRE), and serum biomarker panels like FIB-4 and the NAFLD Fibrosis Score, are increasingly used to stage liver fibrosis.⁶ Studies show MRE generally has higher accuracy for detecting advanced fibrosis, with an area under the receiver operating characteristic curve (AUROC) greater than 0.90. Transient elastography also performs well, with an AUROC greater than 0.80.⁸ These values indicate good discriminatory power, but the diagnostic accuracy of these non-invasive tests can vary, especially when trying to differentiate between F3 and F4 fibrosis, a distinction with substantial clinical implications.⁷

These non-invasive modalities do not reliably separate F3 from F4 fibrosis, nor do they account for acute inflammatory flares that artificially inflate liver stiffness readings. A misclassification can lead to delayed or inappropriate interventions, impacting patient outcomes. The current tests may also be less accurate in specific populations, such as those with obesity or severe inflammation, which can affect liver stiffness measurements. This leaves a diagnostic gap

where the precise differentiation between advanced non-cirrhotic fibrosis and early cirrhosis remains difficult without biopsy.

Prognostic assessment in advanced MASH fibrosis extends beyond the fibrosis stage itself to include other factors such as portal hypertension, the presence of varices, and metabolic comorbidities.⁹ Clinically significant portal hypertension, defined by a hepatic venous pressure gradient (HVPG) of ≥ 10 mmHg, significantly increases the risk of liver decompensation and mortality.¹⁰ For clinicians, this means that even with a non-invasive diagnosis of advanced fibrosis, further assessment for portal hypertension and varices is often warranted. Regular surveillance for HCC, typically involving ultrasound every 6 months, is also essential, given the increased lifetime risk in cirrhotic MASH patients.¹¹ Clinicians must combine serum biomarkers with imaging and clinical signs of portal hypertension to decide when to initiate HCC surveillance, rather than waiting for a definitive biopsy.

Current Therapies Show Limited Efficacy in Reversing Advanced Disease

Current therapeutic options for MASH with advanced fibrosis fail to provide a definitive cure, with no agents having received full regulatory approval specifically for this indication. This creates a significant treatment gap for patients who have progressed to F3 or F4 fibrosis, a stage where the risk of liver-related complications increases substantially.¹² The development of effective therapies is complicated by the complex nature of MASH, involving metabolic dysfunction, inflammation, and fibrogenesis. Without approved treatments, clinicians rely on managing comorbidities and monitoring disease progression.

Obeticholic acid, a farnesoid X receptor (FXR) agonist, has shown some benefit in clinical trials. In the REGENERATE trial, obeticholic acid demonstrated a histological improvement in fibrosis by at least 1 stage without worsening MASH in 23.1% of patients, compared to 11.9% with placebo (P13). Other drug classes under investigation include GLP-1 receptor agonists, PPAR agonists, and ASK1 inhibitors, which target various pathways involved in MASH pathogenesis and fibrosis progression.¹⁴ For example, semaglutide, a GLP-1 receptor agonist, was evaluated in a phase 2 trial for MASH, showing histological improvement.¹⁴

The current evidence does not establish a definitive therapy that can consistently reverse fibrosis progression in patients with established F3 or F4 disease. A major challenge in clinical trials for advanced MASH fibrosis is identifying appropriate endpoints, particularly in F4 patients where reversal of cirrhosis may be difficult to achieve.¹⁵ Many trials rely on histological improvement in fibrosis stage, which is a surrogate endpoint and may not translate directly to long-term clinical outcomes like reduced liver-related mortality. The relatively short duration of many trials, often 24 to 72 weeks, may also be insufficient to demonstrate sustained fibrosis reversal. Obeticholic acid use is associated with side effects such as pruritus and dyslipidemia, which can limit patient adherence.

The heterogeneity of MASH pathophysiology means that a single therapeutic agent is unlikely to be effective across the entire patient population. Patients present with varying degrees of metabolic dysfunction, inflammation, and genetic predispositions, suggesting a need for personalized medicine strategies.¹⁶ For clinicians, this means considering individual patient profiles to guide treatment selection once more options become available. Combination therapies, targeting multiple pathogenic pathways, are also under investigation as a potential strategy to achieve more comprehensive histological and clinical improvements.¹⁷ Until these combinations yield definitive phase 3 data, hepatologists must focus on aggressive management of coexisting diabetes and obesity.

To explore the broader context of liver diseases and their management, we recommend consulting Sherlock's Diseases of the Liver and Biliary System for comprehensive information.

CLINICAL IMPLICATIONS

The EASL 2026 discussion on advanced MASH fibrosis serves as a stark reminder that while the field progresses, the immediate clinical imperative remains unchanged: identify high-risk patients early. The continued reliance on non-invasive tests with varying accuracy, particularly at the F3/F4 threshold, means that some patients are undoubtedly being missed or miscategorized. Clinicians must exercise a high index of suspicion and, where non-invasive tests are equivocal, consider liver biopsy to confirm advanced fibrosis, despite its limitations. Waiting for a 'perfect' non-invasive marker risks delaying intervention for those who need it most.

From an industry perspective, the focus on advanced fibrosis highlights a clear, unmet market need. While several agents are in development, the regulatory pathway for MASH, particularly for advanced fibrosis, remains complex. The REGENERATE trial's outcome with obeticholic acid, while showing histological improvement, also demonstrated side effect profiles that necessitate careful patient selection. Future drug development must prioritize not only efficacy in fibrosis reversal but also a favorable safety and tolerability profile, especially for a chronic condition requiring long-term treatment. The push for combination therapies suggests that pharmaceutical companies will increasingly need to collaborate, or at least consider, multi-target approaches.

For patients, the message is sobering: advanced MASH fibrosis carries significant risks, and effective treatments are still largely investigational. This places a heavy burden on primary care and specialist physicians to educate patients about lifestyle modifications, metabolic control, and the importance of regular monitoring. The lack of approved therapies for advanced fibrosis means that participation in clinical trials is often the only avenue for accessing potentially disease-modifying treatments. This necessitates robust trial infrastructure and clear communication from clinicians about the risks and benefits of such participation, ensuring informed consent in a landscape where options are scarce.

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