

Disease Progression Overview of Metabolic Dysfunction-Associated Steatohepatitis (MASH)

STAGE

THE LIVER AT EACH STAGE

OVERVIEW

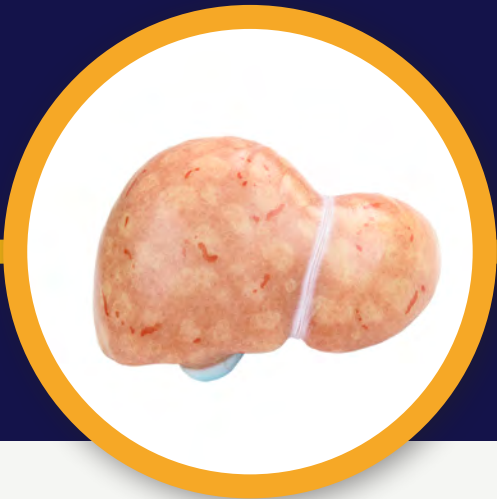
Normal Liver



The liver is located in the upper right of the abdominal cavity, is a dark reddish-brown colour and weighs about 1500 grams.¹

The liver regulates many metabolite levels in the blood. Functions include production of bile, production of cholesterol, glucose homeostasis and production of certain proteins for blood plasma.¹

Steatotic Liver



The presence of excess triglycerides in the liver is called hepatic steatosis.²⁻⁴

MASLD



MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor and no other discernible cause.²⁻⁴

38% of all adults and 7-14% of children and adolescents currently have MASLD worldwide.⁵

MASH



Some patients progress from simple steatosis to **MASH**, a condition characterised by histological features of liver injury, hepatocellular ballooning and lobular inflammation in the presence of hepatic steatosis, which can lead to liver fibrosis.^{3,6}

Why some patients progress from simple steatosis to **MASH** with inflammation and increased fibrogenesis is complex and not fully understood.⁶

Prevalent MASH cases are forecasted to increase 45%, from 12.6 million (2015) to 18.2 million (2030) in the EU.⁷

MASH with Fibrosis



Fibrosis



As fibrosis accumulates, the risk of all-cause and liver-related mortality increases substantially.⁸

A study with a mean follow-up period of 20 years found that decompensated liver disease occurred in:

- 3.7% of patients with fibrosis stage (F) 0
- 4.3% in patients with F1
- 8.7% in patients with F2
- 12.1% in patients with F3
- 45% of patients with cirrhosis (compared with 1.8% in controls)⁹

Cirrhosis



Cirrhosis



Cirrhosis is the most important risk factor for progression to liver transplant, development of HCC, and death.⁶

Transition to cirrhosis involves inflammatory, hormonal, and structural changes that lead to portal hypertension.⁶

A meta-analysis found that cirrhosis was associated with an approximately:

- 13x higher rate of liver-related events
- 11x higher rate of liver-related mortality
- 4x higher rate of all-cause mortality (compared with patients without fibrosis)¹⁰

Major Adverse Liver Outcomes (MALO)



MASH can progress to MASH with fibrosis, cirrhosis, or liver cancer and may ultimately lead to liver transplantation or death.¹¹

MALO



Liver cancer remains a global health challenge, with an estimated incidence of >1 million cases by 2025.¹²

MASLD is becoming the second leading cause of HCC behind alcohol-related liver disease.¹³

Progression from compensated cirrhosis to decompensation events, liver transplant, or death may be rapid compared with progression at earlier stages of MASH.¹⁴



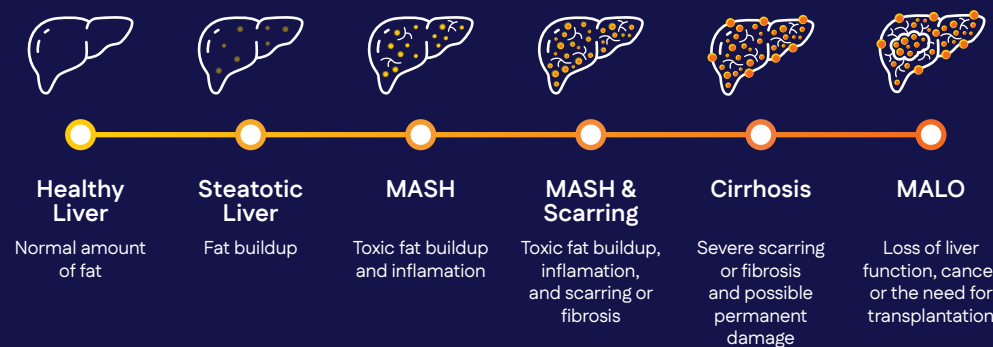
What is the process of MASH progression?



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Progression of MASH from steatosis to cirrhosis and MALO

The natural history of MASLD is complex and variable. A minority of patients develop inflammation and risk progressive fibrosis that can result in cirrhosis. Progression to cirrhosis occurs in 3–5% of patients and it takes 7 years on average to progress by 1 stage of fibrosis.^{6,15} A subset of patients can progress to cirrhosis in as little as 3 years from the date of diagnosis.¹⁶



Optimise patient outcomes
Early risk stratification for advanced fibrosis in patients with MASLD/MASH is critical for optimisation of patient outcomes.³

EU5, France, Germany, Italy, Spain, United Kingdom; **F**, fibrosis stage; **HCC**, hepatocellular carcinoma; **MALO**, major adverse liver outcomes; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **MASH**, metabolic dysfunction-associated steatohepatitis.

1. Hopkins Medicine: <https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions>. Accessed January 2025; **2**, Rinella et al. J Hepatol. 2023;79:1542–1556; **3**, Tacke et al. J Hepatol. 2024;81:492–542; **4**, Qadri S, Yki-Järvinen. Diabetologia. 2024;67:961–973; **5**, Younossi et al. Clin Mol Hepatol. 2024;doi:10.3350/cmh.2024.0431; **6**, Hagström et al. Lancet Gastroenterol Hepatol. 2024;9:944–56; **7**, Estes C, et al. J Hepatol. 2018;69(4):896–904; **8**, Ng et al. Clin Gastro Hep. 2024;21:931–939; **9**, Hagström et al. J Hepatol. 2017;67:1265–1273; **10**, Taylor. Gastroenterology. 2020;158:1611–1625; **11**, Diehl, Day. N Engl J Med. 2017;377:3063–3072; **12**, Llovet et al. Nat Rev Dis Primers. 2021;7:6; **13**, Qiu et al. JAMA Netw Open. 2024;7:e2445525; **14**, Allen et al. J Hepatol. 2022;77(5):1237–1245; **15**, Singh et al. Clin Gastroenterol Hepatol. 2015;13(4):643–e40; **16**, Schattenberg et al. Gastro Hep Adv. 2024;3(1):191–108.

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