White Paper

Insights into Clinical Trial Enrollment for MASH with Compensated Cirrhosis

MARK DELEGGE, MD, Senior Medical Director, Head, Gastroenterology Center of Excellence
MARGARETH TERADA, PharmD, Associate Director, Therapeutic Analytics Lead

Table of contents

Executive summary

Metabolic dysfunction-associated steatohepatitis (MASH) remains underdiagnosed.

To date, two drugs (resmetirom and semaglutide) have been conditionally approved for the treatment of MASH with moderate (F2) to advanced (F3) fibrosis (scarring). Full drug approval is pending results of longer-term studies demonstrating improvements in liver-related clinical outcomes and all-cause mortality.

Clinical trial enrollment criteria for MASH almost always require that participants treated with glucagon-like peptide-1 (GLP-1) agonists be on a stable dose over a prolonged period before randomization. In 2024, IQVIA published the white paper *Insights into MASH Clinical Research: Enrollment Amid Increasing access to GLP-1 Agonists*, which evaluated enrollment trends in Phase IIb and III clinical trials for F2 and F3 MASH. The analysis showed declining enrollment rates concurrent with a rapid increase in GLP-1 agonist use for the treatment of type-2 diabetes mellitus (T2DM) and obesity.

More recently, clinical trials are being conducted in patients with MASH with compensated cirrhosis (F4 MASH), in which liver function is relatively preserved despite fibrotic scarring. Strategic operational planning for clinical trials in this population presents many challenges.

The size of the target population is unclear both because MASH and cirrhosis are underdiagnosed and because randomization rates for completed F4 MASH clinical trials are unpublished. Patients' ability to participate is affected by the common requirement that GLP-1 agonist or sodium-glucose cotransporter 2 (SGLT2) inhibitor dose must be stable for a prolonged period before randomization.

The purpose of this white paper is to:

- Estimate MASH and cirrhosis prevalences in the United States, taking underdiagnosis into account.
- Evaluate the impact of common exclusion criteria for F4 MASH clinical trials accounting for:
  - » Decompensated cirrhosis.
  - » Other liver diseases.
  - » Alcohol use disorder.
  - » Use of GLP-1 agonists and SGLT2 inhibitors.
- Develop recommendations for how to identify and engage undiagnosed patients to consider enrolling in F4 MASH clinical trials.

Estimating F4 MASH prevalences in the United States

To estimate MASH and cirrhosis prevalences in the U.S., we interrogated the TriNetX database, which contains health records for 179 million adults (baseline population) from 87 U.S. healthcare organizations. The database was queried for de-identified data including diagnostic codes, medication use and lab values. Patient counts were rounded to the nearest ten.

Four separate analyses of 14 cohorts of patients with and without a MASH or cirrhosis diagnosis were used to estimate prevalence (Table 1). Risk factors were defined to identify patients who may have MASH or cirrhosis without a formal diagnosis.

- **Analysis 1a** was performed to identify people with a diagnosis of MASH and a diagnosis of cirrhosis (1 patient funnel).
- **Analysis 1b** was performed to identify groups of people with risk factors for MASH and a diagnosis of cirrhosis (6 patient funnels).

- **Analysis 2a** was performed to identify people with a diagnosis of MASH and risk factors for cirrhosis (1 patient funnel).
- **Analysis 2b** was performed to identify groups of people with risk factors for MASH and risk factors for cirrhosis (6 patient funnels).

Table 1: Patient cohorts included in analyses of TriNetX database queries

	MASH	Cirrhosis
Analysis 1a	Diagnosis	Diagnosis
Analysis 1b	Risk factors	Diagnosis
Analysis 2a	Diagnosis	Risk factors
Analysis 2b	Risk factors	Risk factors

Abbreviation: MASH, metabolic dysfunction-associated steatohepatitis.

Inclusion and exclusion criteria for estimation (Table 2)

The American Association for the Study of Liver Disease replaced the term nonalcoholic steatohepatitis (NASH) with MASH in June 2023, and this new terminology has been accepted by the National Institutes of Health and the U.S. Food and Drug Administration. The term has not yet been updated in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification* (ICD-10-CM), which is used to record formal diagnoses in health records. Thus, the code K75.81 for NASH was used to identify adult men and women (age 18 years or more) diagnosed with MASH.

ICD-10-CM codes K74.60 for unspecified cirrhosis of liver and K74.69 for other cirrhosis of liver were used to identify adult men and women with a diagnosis of cirrhosis. Because there is no specific ICD-10 code for compensated cirrhosis, we also excluded patients with decompensating liver events including portal hypertension, ascites, hepatic encephalopathy, jaundice and esophageal varices without bleeding.

Table 2: Diagnostic codes used to identify people in the TriNetX database with a MASH or compensating cirrhosis diagnosis or related risk factors within the last ten years

	Diagnostic codes*
MASH Diagnosis	ICD-10-CM K75.81 NASH
MASH Risk Factors	
Fatty liver	ICD-10-CM K76.0 Fatty (change of) liver, not elsewhere classified
T2DM	ICD-10-CM E11 T2DM
Dyslipidemia	ICD-10-CM E78.0 Pure hypercholesterolemia
	ICD-10-CM E78.1 Pure hyperglyceridemia
	ICD-10-CM E78.2 Mixed hyperlipidemia
	ICD-10-CM E78.4 Other hyperlipidemia
	ICD-10-CM E78.5 Hyperlipidemia, unspecified
	ICD-10-CM E78.6 Lipoprotein deficiency

	Diagnostic codes*
Obesity	ICD-10-CM E66.0 Obesity due to excess calories
	ICD-10-CM E66.1 Drug-induced obesity
	ICD-10-CM E66.2 Morbid (severe) obesity with alveolar hypoventilation
	ICD-10-CM E66.8 Other obesity
	ICD-10-CM E66.9 Obesity, unspecified
	ICD-10-CM Z68.3 BMI 30-39, adult
	ICD-10-CM Z68.4 BMI 40 or greater, adult
Cirrhosis diagnosis	ICD-10-CM K74.60 Unspecified cirrhosis of liver
	ICD-10-CM K74.69 Other cirrhosis of liver
Cirrhosis risk factors	TNX Curated 9020 platelets [volume] in blood [≤ $150x10^3$/μL, ever]
Decompensating liver events	ICD-10-CM K76.6 Portal hypertension
	ICD-10-CM R18 Ascites
	ICD-10-CM K76.82 Hepatic encephalopathy
	ICD-10-CM R17 Unspecified jaundice
	ICD-10-CM I85.10 Secondary esophageal varices without bleeding

***All child codes are included in the parent codes**
Abbreviations: BMI, body mass index; ICD-10-CM, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; MASH, metabolic dysfunction-associated steatohepatitis; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; TNX, TriNetX.

Relying on ICD-10 codes to determine that a person has a diagnosis is dependent on the treating clinician having assigned that code based on laboratory, imaging or clinical data. Because MASH or cirrhosis could be present without a treating clinician recording the ICD-10-CM code, we also interrogated the TriNetX cohorts for the presence of risk factors that could indicate a person had MASH or cirrhosis.

The following six combinations of metabolic risk factors for MASH were used to identify subcohorts of adult men and women (age 18 years or more) at high risk of MASH without a formal diagnosis.

- Dyslipidemia and fatty liver.
- Obesity and dyslipidemia.
- Obesity and fatty liver.
- T2DM and dyslipidemia.
- T2DM and fatty liver.
- T2DM and obesity.

The TriNetX code TNX Curated 9020 Platelets was used to identify people with platelet counts below 150,000/μL who may have cirrhosis but lack a diagnosis. We acknowledge that conditions other than cirrhosis, such as cancer, severe immune disorders or medication reactions, could also account for these platelet values.

Estimating the impact of common exclusion criteria on F4 MASH clinical trial enrollment

Common exclusion criteria for clinical trials in MASH cirrhosis were applied to the patient funnels to evaluate how these affected the size of each subcohort, including

other liver diseases, alcohol use disorder in the last 10 years, and use of GLP-1 agonists or SGLT2 inhibitors in the last 6 months (Table 3). We considered empagliflozin as the most common SGLT2 inhibitor used in the U.S. and recognize there could be additional inclusion and exclusion criteria in an F4 MASH protocol that would further reduce the size of impacted cohorts.

Table 3: Diagnostic codes related to common exclusion criteria in clinical trials for F4 MASH

	Medical Codes
Other liver diseases	ICD-10-CM K74.3 Primary biliary cirrhosis
	ICD-10-CM K83.01 Primary sclerosing cholangitis
	ICD-10-CM K75.0 Abscess of liver
	ICD-10-CM K71.9 Toxic liver disease, unspecified
	ICD-10-CM B18.0 Chronic viral hepatitis B with delta-agent
	ICD-10-CM B18.1 Chronic viral hepatitis B without delta-agent
	ICD-10-CM B18.2 Chronic viral hepatitis C
	ICD-10-CM B17.0 Acute delta-(super) infection of hepatitis B carrier
	ICD-10-CM E83.01 Wilson's disease
	ICD-10-CM E83.10 Disorder of iron metabolism, unspecified
	ICD-10-CM E88.01 Alpha-1-antitrypsin deficiency
Alcohol use disorder	ICD-10-CM F10.20 Alcohol dependence, uncomplicated
GLP-1 agonist use	ATC A10BJ Glucagon-like peptide-1 (GLP-1) analogues
SGLT2 inhibitor use	RxNorm 1545653 empagliflozin

Note: Codes for other liver diseases and alcohol use disorder were evaluated for the prior 10 years; GLP-1 agonist and SGLT2 inhibitor use were evaluated for the prior six months.
Abbreviations: ICD-10-CM, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; SGLT2, sodium-glucose cotransporter 2.

Analysis 1 includes all patients with confirmed cirrhosis

Analysis 1 focused on identifying the total potential MASH population, including both those with a confirmed diagnosis and those with risk factors for MASH. All patients had a confirmed diagnosis of cirrhosis.

Confirmed MASH with confirmed cirrhosis

Analysis 1a was performed to identify subcohorts with confirmed MASH and a confirmed diagnosis of cirrhosis (Table 4). Of the 179 million patients in the baseline population, 0.20% had a confirmed MASH diagnosis. Of those with confirmed MASH, 42.17% also had confirmed cirrhosis. Excluding those with decompensating liver events resulted in 45,050 people with presumed F4 MASH (12.30% of the MASH diagnosed cohort). Among those with presumed compensated cirrhosis, 9.72% had other liver diseases, 2.34% had alcohol use disorder, 22.49% of them were using GLP-1 agonists and 4.81% of them were using SGLT-2 inhibitors. Together these results suggest 8.00% patients with a confirmed MASH with cirrhosis diagnosis cohort would be reasonable candidates for enrollment in an F4 MASH clinical trial.

Table 4: Impact of inclusion and exclusion criteria on estimated population size for analysis 1a: confirmed MASH with confirmed cirrhosis

Criteria	MASH
Include	
MASH risk factors	100.00%
Cirrhosis diagnosis	-57.83%
Exclude	
Decompensating liver events	-70.84%
Other liver disease	-9.72%
Alcohol dependence	-2.34%
GLP-1 agonists	-22.49%
SGLT2 inhibitors	-4.81%
Percent of initial count	**8.00%**

Note: The largest population reductions were due to decompensating liver events (red), followed by no cirrhosis diagnosis (orange), use of GLP-1 agonists (yellow), other liver diseases (light green), and use of SGLT2 inhibitors or the presence of alcohol use disorder (dark green).
Abbreviations: GLP-1, glucagon-like peptide-1, MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium-glucose cotransporter 2.

MASH risk factors and confirmed cirrhosis

Analysis 1b was performed to identify subcohorts with at least two of four metabolic risk factors for MASH and a confirmed diagnosis of cirrhosis (Table 5). Of the baseline population of 179 million patients, 2.04% had T2DM and dyslipidemia and 1.96% had obesity and dyslipidemia. Among those with T2DM and dyslipidemia or obesity and dyslipidemia, 1.93% and 0.82% also had confirmed cirrhosis. Excluding those with decompensating liver events resulted in 0.89% people in the T2DM and dyslipidemia subcohort and 0.42% people in the obesity and dyslipidemia subcohort with presumed F4 MASH. Of these two subcohorts with presumed F4 MASH, 24.37% and 24.85% had other liver diseases, 5.03% and 7.99% had alcohol use disorder, 1.31% and 0.88% were being treated with GLP-1 agonists and 1.70%) and 1.55% were using SGLT2 inhibitors. Ultimately, 0.62% in the T2DM and dyslipidemia subcohort and 0.28% in the obesity and dyslipidemia subcohort would be reasonable candidates for enrollment in an F4 MASH clinical trial.

Table 5: Impact of inclusion and exclusion criteria on estimated population size for analysis 1b: MASH risk factors with confirmed cirrhosis

	T2DM and Obesity	T2DM and Dyslipi-demia	T2DM and Fatty Liver	Obesity and Dyslipi-demia	Obesity and Fatty Liver	Dyslipi-demia and Fatty Liver
Include						
MASH risk factors	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Cirrhosis diagnosis	-97.32%	-98.07%	-88.64%	-99.18%	-95.14%	-94.78%
Exclude						
Decompensating liver events	-61.64%	-53.60%	-59.74%	-49.13%	-59.64%	-51.47%
Other liver disease	-21.78%	-24.37%	-24.01%	-24.85%	-24.71%	-25.88%
Alcohol dependence	-4.92%	-5.03%	-13.85%	-7.99%	-14.87%	-17.26%
GLP-1 agonists	-1.48%	-1.31%	-1.01%	-0.88%	-8.13%	-0.42%
SGLT2 inhibitors	-0.75%	-1.70%	-0.51%	-1.55%	0.02%	-0.42%
Percent of initial count	**0.75%**	**0.62%**	**2.95%**	**0.28%**	**1.16%**	**1.54%**

Note: The largest population reductions were due to no cirrhosis diagnosis (red), decompensating liver events (orange), and other liver diseases (yellow), followed by alcohol use disorder and use of GLP-1 agonists or SGLT2 inhibitors (light to dark shades of green).
Abbreviations: GLP-1, glucagon-like peptide-1, MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium-glucose cotransporter 2.

A combination of the MASH risk factors obesity and T2DM occurred in 0.45% of baseline population patients, and 2.68% of these patients had confirmed cirrhosis. Excluding those with decompensating liver events resulted in 1.03% patients in the obesity and T2DM subcohort with presumed F4 MASH. In this group, other liver diseases 21.78%, alcohol use disorder 4.92% or treatment with GLP-1 agonists 1.48% or SGLT2 inhibitors 0.75% reduced the number of patients who would be reasonable candidates for an F4 MASH clinical trial to 0.75%.

There were 0.21% of baseline population with the MASH risk factors dyslipidemia and fatty liver and 0.17% of baseline population with obesity and fatty liver. In these two subcohorts, 5.22% and 4.86% had confirmed cirrhosis. Excluding those with decompensating liver events resulted in 2.53% people with dyslipidemia and fatty liver and 1.96% of people people with obesity and fatty liver cohort having presumed F4 MASH. Within those two groups, 25.88% and 24.71% had other liver diseases, 17.26% and 14.87% had alcohol use disorder, 0.42% and 8.13% were using GLP-1 agonists and 0.42% and 0.02% were using SGLT2 inhibitors. Ultimately, 1.54% patients in the dyslipidemia and fatty liver subcohort and 1.16% in the obesity and fatty liver subcohort would be reasonable candidates for enrollment in an F4 MASH clinical trial.

The smallest subcohort with MASH risk factors included patients with T2DM and fatty liver (0.04% of baseline population). Interestingly, 11.36% patients in this subcohort had confirmed cirrhosis. Excluding those with decompensating liver events resulted in 4.57% with presumed F4 MASH. In that population, 24.01% had other liver diseases, 13.85% had alcohol use disorder, 1.01% were using GLP-1 agonists and 0.51% were using SGLT2 inhibitors reducing the number of patients in the T2DM and fatty liver subcohort who would be reasonable candidates for enrollment in an F4 MASH clinical trial to 2.95%.

Analysis 2 includes all patients with cirrhosis risk factors

Analysis 2 focused on the same MASH populations as analysis 1 — patients with confirmed MASH and MASH risk factors — but with presumed cirrhosis based on platelet counts less than 150,000/µL rather than confirmed cirrhosis. The analysis 2 MASH cohort and presumed MASH subcohorts were smaller than in analysis 1 because many patient records did not include platelet count information.

The size of cohorts for analysis 2 relative to analysis 1 were:

- **45%** for confirmed MASH.
- **18%** for T2DM and obesity.
- **25%** for T2DM and dyslipidemia.
- **30%** for T2DM and fatty liver.
- **16%** for obesity and dyslipidemia.
- **18%** for obesity and fatty liver.
- **25%** for dyslipidemia and fatty liver.

The proportion of patients in analysis 2 with presumed cirrhosis was larger than the proportion with confirmed cirrhosis in analysis 1, which could reflect overcounting because low platelets may indicate diseases other than cirrhosis.

Confirmed MASH and cirrhosis risk factors

In analysis 2a, there were 9.32% patients with confirmed MASH and platelet count information in the baseline population, and 72.07% had a cirrhosis risk factor. Excluding those with decompensating liver events resulted in 14.82% with confirmed MASH with presumed compensated cirrhosis. Among this population, 9.21% had other liver diseases, 3.12% had alcohol use disorder, and 20.64% and 6.58% were being treated with GLP-1 agonists or SGLT-2 inhibitors. After considering those common exclusion criteria, 9.66% patients had confirmed MASH with presumed compensated cirrhosis would be reasonable candidates for enrollment in an F4 MASH clinical trial (Table 6).

Table 6: Impact of inclusion and exclusion criteria on estimated population size for analysis 2a: confirmed MASH with cirrhosis risk factors

Criteria	MASH
Include	
MASH risk factors	100.00%
Cirrhosis diagnosis	-27.93%
Exclude	
Decompensating liver events	-79.43%
Other liver disease	-9.21%
Alcohol dependence	-3.12%
GLP-1 agonists	-20.64%
SGLT2 inhibitors	-6.58%
Percent of initial count	**9.66%**

Note: The largest population reductions were due to decompensating liver events (red), no cirrhosis diagnosis (dark yellow), and use of GLP-1 agonists (light yellow), followed by other liver diseases, use of SGLT2 inhibitors, and alcohol use disorder (light to dark shades of green).
Abbreviations: GLP-1, glucagon-like peptide-1, MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium-glucose cotransporter 2.

MASH and cirrhosis risk factors

In analysis 2b, the two largest subcohorts with MASH risk factors had T2DM and dyslipidemia (0.05% of baseline population) or obesity and dyslipidemia (0.03% of baseline population) (Table 7). Among these subcohorts, 5.83% and 3.84% had cirrhosis risk factors.

After excluding those with decompensating liver events, there were 2.40% with T2DM and dyslipidemia and 1.62% with obesity and dyslipidemia cohort with presumed compensated cirrhosis. Within these groups, 22.98% and 23.93% had other liver diseases, 5.92% and 9.72% had alcohol use disorder and 1.08% and 0.78% and 1.61% and 0.17% were being treated with GLP-1 agonists or SGLT2 inhibitors, respectively.

The resulting estimates are that 1.69% patients with T2DM and dyslipidemia with presumed cirrhosis and 1.10% patients with obesity and dyslipidemia with presumed cirrhosis would be reasonable candidates to consider for enrollment in an F4 MASH clinical trial.

Table 7: Impact of inclusion and exclusion criteria on estimated population size for analysis 2b: MASH risk factors and cirrhosis risk factors

	T2DM and Dyslipi-demia	Obesity and Dyslipi-demia	T2DM and Obesity	Dyslipi-demia and Fatty Liver	Obesity and Fatty Liver	T2DM and Fatty Liver
Include						
MASH risk factors						
Cirrhosis diagnosis	-94.17%	-96.16%	-88.67%	-85.35%	-81.05%	-72.29%
Exclude						
Decompensating liver events	-58.89%	-57.81%	-68.79%	-62.60%	-72.59%	-68.15%
Other liver disease	-22.98%	-23.93%	-23.11%	-24.95%	-26.53%	-25.42%
Alcohol dependence	-5.92%	-9.72%	-5.97%	-25.11%	-25,00%	-18.52%
GLP-1 agonists	-1.08%	-0.78%	-1.21%	-0.87%	-0.74%	-0.94%
SGLT2 inhibitors	-1.61%	-0.17%	-0.92%	-2.63%	0.65%	-0.95%
Percent of initial count	**1.69%**	**1.10%**	**2.50%**	**2.97%**	**2.86%**	**5.26%**

Note: The largest population reductions were due to no cirrhosis risk factors (red/orange), decompensating liver events (orange), and other liver diseases (yellow), followed by alcohol use disorder (yellow/light green) and use of GLP-1 agonists or SGLT2 inhibitors (dark green).
Abbreviations: GLP-1, glucagon-like peptide-1, MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium-glucose cotransporter 2.

The third largest subcohort with MASH risk factors had obesity and T2DM (0.08% of baseline population), and 11.33) of these patients had presumed cirrhosis. Excluding those with decompensating liver events resulted in 3.54% patients with obesity and T2DM and presumed compensated cirrhosis. In this population, 23.11% had other liver diseases, 5.97% had alcohol use disorder, 1.21% were using GLP-1 agonists and 0.92% were using SGLT2 inhibitors. Thus, a total of 2.50% patients in the obesity and T2DM cohort would be reasonable candidates to consider enrollment in an F4 MASH clinical trial.

The next two largest subcohorts with MASH risk factors had dyslipidemia and fatty liver (0.05% of baseline population) or obesity and fatty liver (0.03% of baseline population). Within these subcohorts, 14.65% and 18.95% had presumed cirrhosis. Excluding those with decompensating liver events resulted in 5.48% with dyslipidemia and fatty liver and 5.19% with obesity and fatty liver with presumed compensated cirrhosis. Among these presumed F4 MASH populations, 24.95% and 26.53% had other liver diseases, 25.11% and 25.00% had alcohol use disorder, 0.87% and 0.74% were being treated with GLP-1 agonists and 2.63% and 0.65% were using SGLT2 inhibitors. Ultimately 2.97% patients in the dyslipidemia and fatty liver subcohort and 2.86% patients in the obesity and fatty liver subcohort would be reasonable candidates to consider for F4 MASH clinical trial enrollment.

The smallest subcohort with risk factors for MASH had T2DM and fatty liver (0.01% of baseline population) and interestingly, 27.71% had presumed cirrhosis. Excluding those with decompensating liver events resulted in 8.83% with T2DM and fatty liver and presumed compensated cirrhosis. Within this group with presumed F4 MASH, 25.42% had other liver diseases, 18.52% had alcohol use disorder, 0.94% were being treated with GLP-1 agonists and 0.95% were being treated with SGLT2 inhibitors. After applying those common F4 MASH clinical trial exclusions, 5.26% of the T2DM and fatty liver subcohort would be reasonable candidates for enrollment in an F4 MASH clinical trial.

The relative impact of common exclusion criteria for F4 MASH clinical trials among analyzed cohorts

Other liver diseases

Other liver diseases were approximately two to three times as common (21.78%-25.88% vs. 9.72%) in the subcohorts with presumed MASH versus the confirmed MASH cohort (Table 8). The T2DM and obesity subcohort had the lowest proportion with other liver diseases and the dyslipidemia and fatty liver cohort had the highest proportion. Within the cohort with presumed MASH and presumed compensated cirrhosis, other liver diseases were also approximately two to three times as common as in the cohort with confirmed MASH and presumed compensated cirrhosis (22.98%-26.53% vs. 9.21%). In those with presumed MASH and presumed compensated cirrhosis, the T2DM and dyslipidemia subcohort had the lowest proportion of other livier diseases and the obesity and fatty liver subcohort had the highest proportion.

Table 8: Proportion with common exclusion criteria that would make them ineligible to participate in F4 MASH clinical trials among those with confirmed or presumed F4 MASH

	Other liver diseases		Alcohol use disorder		GLP-1 agonist or SGLT2 inhibitor treatment	
Cohort or subcohort	Confirmed cirrhosis	Presumed cirrhosis	Confirmed cirrhosis	Presumed cirrhosis	Confirmed cirrhosis	Presumed cirrhosis
Confirmed MASH	9.72%	9.21%	2.34%	3.12%	26.22%	25.87%
T2DM and fatty liver	24.01%	25.42%	13.85%	18.52%	1.51%	1.89%
Dyslipidemia and fatty liver	25.88%	24.95%	17.26%	25.11%	0.84%	3.48%
Obesity and fatty liver	24.71%	26.53%	14.87%	25.00%	8.11%	0.09%
T2DM and obesity	21.78%	23.11%	4.92%	5.97%	2.22%	2.11%
T2DM and dyslipidemia	24.37%	22.98%	5.03%	5.92%	2.99%	2.68%
Obesity and dyslipidemia	24.85%	23.93%	7.99%	9.72%	2.42%	0.95%

Note: Alcohol use disorder proportions exclude those with other liver diseases and GLP-1 agonist or SGLT2 inhibitor treatment proportions exclude those with both other liver diseases and alcohol use disorder.
Abbreviations: GLP-1, glucagon like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Alcohol use disorder

Among subcohorts with presumed MASH and confirmed cirrhosis, alcohol use disorder (after excluding those with other liver diseases) was two to nine times more common than in those with confirmed F4 MASH (4.92%-17.26% vs. 2.34%). The lowest proportion with alcohol use disorder was in the T2DM and obesity cohort, and the highest proportion was in the dyslipidemia and fatty liver subcohort. Within the presumed cirrhosis population, alcohol dependence was more common in those with presumed MASH versus confirmed MASH (5.92%-25.11% vs. 3.12%). The lowest proportion with alcohol use disorder among those with presumed MASH and presumed cirrhosis was in the T2DM and dyslipidemia subcohort. The subcohort with presumed cirrhosis and dyslipidemia and fatty liver had the highest proportion of alcohol use disorder.

Treatment with GLP-1 agonists and SGLT-2 inhibitors

Subcohorts with presumed MASH and confirmed cirrhosis were treated with GLP-1 agonists and SGLT2 inhibitors much less commonly than those with confirmed F4 MASH (0.84%-8.11% vs. 26.22%) or confirmed MASH with presumed cirrhosis (0.09%-3.48% vs 25.87%). Within these subcohorts, the highest proportions treated with GLP-1 agonists or SGLT2 inhibitors were in the subcohorts with obesity and fatty liver with confirmed cirrhosis and dyslipidemia and fatty liver with presumed cirrhosis.

Implications for future clinical trial enrollment

Underdiagnosis

The proportion of patients in the TriNetX database who had a ICD-10-CM code representing a diagnosis (0.20%) was considerably lower than published data showing overall MASH prevalence in the U.S. is 1.5%-6.0%.[1] This discrepancy suggests either that we queried healthcare organizations with populations at low-risk of MASH, that a MASH diagnosis does not always generate an identifiable ICD-10-CM code, or that MASH remains underdiagnosed, which is most likely in our opinion. In contrast, patients with two of four MASH risk factor diagnoses represented 4.88% of the examined TriNetX database, reinforcing that MASH is likely underdiagnosed. These are patients most likely to already have or developing MASH who would benefit from transient elastography or other screening tests to determine if they should have a confirmatory liver biopsy or specialized imaging.

Among patients with a MASH diagnosis, 42.17% also had confirmed cirrhosis, which is higher than published data showing prevalence of cirrhosis in MASH is 10%-12%.[2] Of those with MASH and cirrhosis, 70.84% had decompensating liver events, suggesting 29.16% had compensated cirrhosis. This is lower than prior reports indicating that 34% to 50% of people with MASH and cirrhosis are decompensated.[3] This discrepancy may be a result of identifying decompensation on the basis of recorded events rather than clinical signs and symptoms, considering that many with decompensation may be asymptomatic until such an event occurs.

The two most common paths to a diagnosis of cirrhosis before compensation are incidental findings on abdominal imaging and abnormal liver function tests.

People suspected of cirrhosis are referred to gastroenterologists and hepatologists who will likely conduct further labs including liver enzyme testing (i.e., alanine transaminase [ALT] and aspartate transaminase [AST]), platelets, serum albumin, bilirubin and other confirmatory serum biomarkers of a specific liver disease diagnosis. Confirmatory specialized radiologic imaging, and sometimes liver biopsy may also be performed.

Assessing records of 8,728,850 patients with high-risk metabolic disease and compensated cirrhosis identified 0.86% who are reasonable candidates for an F4 MASH clinical trial. Although this is a very small proportion of the original queried populations, we believe it is an important population to identify and consider for F4 MASH clinical trials. When low platelet counts were used to identify presumed cirrhosis, higher proportions of patients who potentially have F4 MASH were identified, suggesting there is a population of patients with F4 MASH in whom cirrhosis goes undiagnosed cirrhosis who have MASH. Evaluating these individuals for cirrhosis could expand the pool of potential subjects for F4 MASH clinical trials.

Among the cohort with confirmed F4 MASH, after applying common exclusion criteria used in F4 MASH drug development trials, there were 29,300 potential F4 MASH clinical trial participants. Across the subcohorts with presumed MASH and confirmed cirrhosis, a total of

50,370 potential F4 MASH clinical trial participants were identified. Within the cohort with confirmed MASH and presumed cirrhosis, 16,120 potential participants were identified, and in subcohorts with presumed MASH and presumed cirrhosis, 31,330 potential participants were identified. It is important to note that not all patients identified here with presumed cirrhosis or presumed MASH will have an F4 MASH diagnosis confirmed after screening for participation in F4 MASH clinical trials.

Recommendations to improve recruitment

All cohorts and subcohorts included in this analysis would provide reasonable candidates for F4 MASH clinical trials, but the most practical approach to recruiting undiagnosed patients would be to focus on the largest cohorts (Table 9), which included patients with:

- Confirmed MASH.
- T2DM and dyslipidemia
- Obesity and dyslipidemia with or without confirmed cirrhosis.

Table 9: Reasonable candidates to consider for F4 MASH clinical trials by cohort (percentage of initial count)

	Confirmed cirrhosis	Presumed cirrhosis
MASH	8.00%	9.66%
T2DM and dyslipidemia	0.62%	1.69%
Obesity and dyslipidemia	0.28%	1.10%
T2DM and obesity	0.75%	2.50%
Dyslipidemia and fatty liver	1.54%	2.97%
Obesity and fatty liver	1.16%	2.86%
T2DM and fatty liver	2.95%	5.26%

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; T2DM, type 2 diabetes mellitus.

The ideal investigator profile for an F4 MASH clinical trial is a gastroenterologist or hepatologist who treats people with advanced liver disease. Considering the global underdiagnosis of both MASH and cirrhosis, sites may consider a prioritized recruitment approach prioritizing the identification of patients within their database in the following order:

- Diagnosis of cirrhosis and MASH.
- Diagnosis of cirrhosis and T2DM and dyslipidemia.
- Diagnosis of cirrhosis and obesity and dyslipidemia.

To supplement recruitment, sites may conduct a broader search of their health system targeting endocrinology and primary care practices for patients with the following risk factor combinations who have not yet been referred to a liver specialist:

- T2DM and dyslipidemia with low platelet counts.
- Obesity and dyslipidemia with low platelet counts.

In locations where transient elastography is not commonly used to identify liver fibrosis in patients with high risk for MASH, results of CT, MRI, and ultrasound scans ordered for other reasons, such as abdominal pain, could be evaluated to identify potential trial participants with evidence of steatotis and cirrhosis.

The screen failure in MASH clinical trials that require a liver biopsy for diagnostic confirmation is high. Thus, it may be beneficial to have standardized prescreening processes and tools that give sites sufficient information about potential participants to avoid unnecessary invasive procedures. Such prescreening could include evaluating patients for a proscribed set of risk factors for both MASH and cirrhosis, as well as other eligibility criteria that should be known to the treating physicians. Sites that do not have access to or do not use detailed medical records have a higher risk of screen failure.

IQVIA has implemented this type of structured prescreening program in a Phase III imaging study for MASH, which reduced the study timeline by 45%.

Prescreening during site startup enabled visibility into each site's enrollment potential and prepared them for rapid recruitment.

Conclusions

This analysis suggests the prevalence of F4 MASH is higher than previously reported, particularly when including patients with MASH risk factors and undiagnosed cirrhosis. Additionally, the results suggest there are more patients with decompensated cirrhosis among the newly diagnosed MASH with cirrhosis population, who are not being identified. The population of underdiagnosed F4 MASH patients may be receiving care in diverse clinical practice settings including, but not limited to, general practice, endocrinology, obesity, and nonhepatology-focused gastroenterologists. Once a person develops decompensating features they are largely managed by hepatologists.

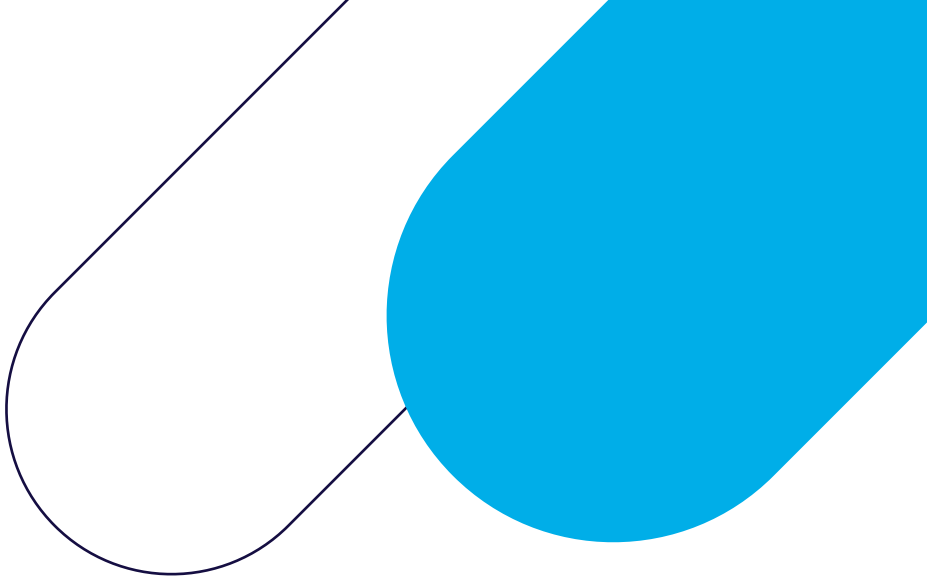
To efficiently run an F4 MASH clinical trial, it is important to select sites willing to identify people outside their own practice who are at risk of F4 MASH and prescreen them with a standardized process. Establishing enrollment potential before site activation and prescreening patients before obtaining informed consent to screen them for participation may help accelerate recruitment and reduce screen failure. Targeting an underdiagnosed population is challenging for sites, patients, and sponsors, but defining a path to identify people at highest risk for both diseases may increase the probability of enrollment, reduce the risk of unnecessary biopsies, and provide sponsors with greater confidence in meeting their timelines.

References

1. Le P, Tator M, Dasarthy S, Alkhour N, Herman WH, Taksler MB, et al. Estimated burden of metabolic dysfunction associated steatotic liver disease in US adults, 2020 – 2050. JAMA Netw Open. 2025 Jan17;8(1):e2454707. doi:10.1001/jamanetworkopen.2024.54707

2. Eskridge W, Cryer DR, Schattenberg JM, Gastaldelli A, Malhi H, Allen AM, et al. Metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis: the physician and patient perspective. J Clin Med 2023. 26;12(19):6216. doi:10:3390/jcm12196216

3. Guillot J, Williams CYK, Azzam S, Bhasuran B, Fernades G, Ru B, et al. Risk prediction in patients with metabolic dysfunction-associated steatohepatitis using natural language processing. Gastro Hep Adv. 20-25 May 14;4(9):100701.doi: 10.1016/j.gastha.2025.100701



CONTACT US

iqvia.com

07.2026.RDS.26-CRS-1824-05MAY