Research Article
MASLD and Alcohol-Related Liver Diseases

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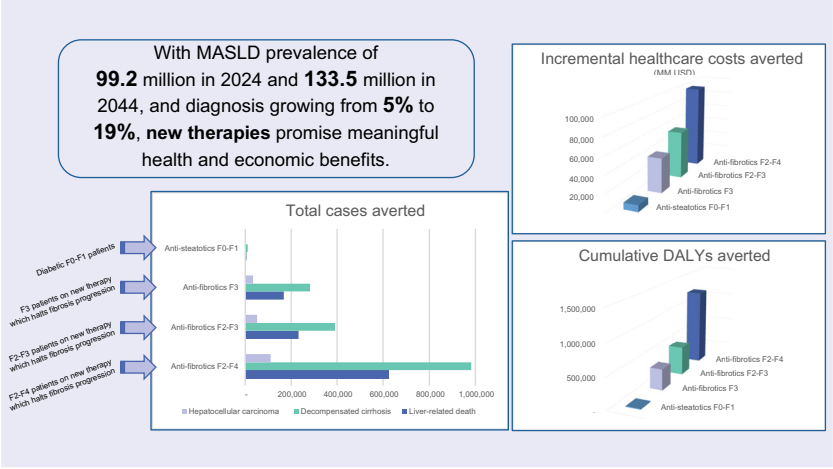
Authors

Carolyn Wallace, Ivane Gamkrelidze, Chris Estes, Homie Razavi, Arun J. Sanyal

Correspondence

hrazavi@cdafound.org (H. Razavi).

Graphical abstract



Highlights

- Therapy that halts fibrosis will avert advanced liver disease and mortality.
- Therapy that halts fibrosis will reduce direct health-care costs.
- Reversing steatosis alone is not enough to reduce MASLD disease burden and costs.
- Increasing diagnosis of MASLD is imperative to reduce disease and economic burden.

Impact and implications

Metabolic dysfunction-associated steatotic liver disease (MASLD), the most rapidly increasing and prevalent cause of chronic liver disease, is associated with substantial healthcare costs. As disease burden and costs mount, pharmacologic therapy which halts MASLD fibrosis progression is coming to fruition. Modeling the impact on disease progression of a hypothetical pharmacologic therapy which halts MASLD fibrosis progression through multiple scenarios provides insights into the key drivers of the disease and costs associated with it. This should help to facilitate best policies and practices to mitigate the burden of MASLD.

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Modeling the health and economic impact of pharmacologic therapies for MASLD in the United States

Carolyn Wallace[1], Ivane Gamkrelidze[1], Chris Estes[1], Homie Razavi[1]*, Arun J. Sanyal[2]

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Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common condition leading to chronic liver disease which generates substantial healthcare costs. Our aim was to model the impact of a hypothetical pharmacologic therapy which halts MASLD fibrosis progression on disease and economic burden.

Methods: The US MASLD disease burden model is a Markov model which forecasts disease progression and the impact of diagnosis and treatment. Diagnostic costs for all patients and direct costs for patients with MASLD-related liver disease were also incorporated. MASLD disease burden and economic impacts were modeled for five scenarios: a no treatment case and four interventions incorporating the impact of gradually increasing awareness, screening, and diagnosis, and treatment with anti-steatotic therapy and a future, hypothetical therapy that halts fibrosis progression.

Results: Treatment with therapy which only reverses steatosis had minimal (<1 to 2%) effect on cumulative chronic liver disease cases and healthcare costs averted. The scenarios in which a hypothetical therapy halts fibrosis progression resulted in reductions in cases of decompensated cirrhosis (11-39%), hepatocellular carcinoma (10-34%), and liver-related deaths (8-31%), a 9-31% reduction in cumulative DALYs, and $40.5 to $99.1B incremental healthcare costs averted.

Conclusions: Increasing diagnosis and treatment for the MASLD population with moderate-to-advanced fibrosis will prevent advanced liver disease and death and will result in reducing the associated direct healthcare costs. Increasing awareness, screening and diagnosis along with introducing pharmacologic therapies that halt fibrosis progression are necessary to realize health and economic benefits for the MASLD population.

Introduction

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in adults in the United States and globally is substantial, with worldwide estimates of over 30% and increasing.[1,2] Over 15% of individuals with MASLD have significant fibrosis (METAVIR score F2-F4),[3] which can lead to serious health consequences, including cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and liver-related deaths. As MASLD prevalence increases, so does its sequelae; MASLD is the fastest growing cause of liver cancer.[4]

Healthcare costs in patients with MASLD are nearly two times higher than matched controls without the disease.[5] Hospitalization rates for patients with MASLD-related decompensated cirrhosis (DCC) and HCC are increasing.[6] Additionally, in liver transplant candidates, the proportion of HCC cases attributable to metabolic dysfunction-associated steatohepatitis (MASH) has increased more drastically than for any other etiology.[7] Not surprisingly, substantial and disproportionate costs are associated with end-stage liver disease. In one European study, patients with end-stage liver disease represented 7.4% of the total prevalent MASH population but incurred 68% of total economic costs.[8] These trends accentuate the importance of understanding the health and economic impact of this disease.

Currently there is a dearth of treatments which halt MASLD fibrosis progression. Multiple studies have shown that GLP-1 receptor agonists and SGLT2 inhibitors used to treat type 2 diabetes and obesity have a positive effect on reducing liver fat content; fewer studies have shown their ability to halt fibrosis progression.[9] There are, however, numerous ongoing clinical trials, many in late-stage development,[10] and one drug (resmetirom) was recently approved by the FDA for the treatment of MASH with moderate-to-advanced fibrosis.[11]

The objective of the analysis was to determine the impact of hypothetical new pharmacologic therapies on MASH disease burden and healthcare costs, as well as the impact of anti-

* Corresponding author. Address: Center for Disease Analysis Foundation, 1120 W. Boulder Road, #102, Lafayette, CO 80026, USA. Tel.: 720-890-4848, fax: 720-890-3817.
E-mail address: hrazavi@cdafound.org (H. Razavi).
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steatotic agents on patients with MASLD and type 2 diabetes in the United States. The use of modeling provides insights into the key drivers of the disease and costs associated with it to facilitate best policies and practices.

Materials and methods

Disease burden model

The MASLD disease burden model is a Markov model that incorporates MASLD prevalence, disease progression, mortality, and the impact of potential therapies (Fig. 1), with incidence as a function of changes in obesity. Details of the modeling were previously published.[12] Data for model inputs were based on literature review, national data reports, and expert consensus through a Delphi process. Population, mortality, and historical data inputs were entered in the model, including MASLD prevalence by age and sex, fibrosis progression rates, and the annual number of MASLD-related liver transplants (Table 1). Progression rates were assumed to be the sum of forward progression minus the rate of regression, as is common among studies of consecutive liver biopsies. Although liver transplants have increased, it was assumed that this trend cannot continue indefinitely due to the finite number of livers available for transplant and concerns related to MASH recurrence as well as other obesity-related comorbidities impacting long-term outcomes.[13] Therefore, it was conservatively assumed that the number of liver transplants in the future would not exceed the current level. The model calculates the annual number of individuals with MASLD by disease stage, age, sex, and treatment response.

Economic analysis

The model incorporated diagnostic costs for all patients and healthcare costs for patients with moderate-to-advanced MASLD-related liver disease. Diagnostic costs per patient included a complete blood count and hepatic function panel for screening, and non-invasive imaging for confirmation and staging using Medicare Procedure Prices (Table 1).[14] Annual imaging for monitoring progression within the treated patient population was also included. Healthcare costs by disease stage were based on published estimates and were inflated to 2024 US dollars.[15] The cost of pharmacologic therapy specifically to reduce steatosis or fibrosis was not included. An annual discount rate of 3% was applied to all costs. Disability-adjusted life years (DALYs)[16] were calculated based on years of life lost as a result of premature mortality and years lived with disability among chronically infected individuals in DCC, HCC, and liver transplant disease stages using the Global Burden of Disease disability weights.[17] Economic measures and measures of health outcomes were analyzed to 2044 (20 years).

Scenario development

MASLD disease burden and economic impacts were assessed from 2024-2044 for five scenarios – a no treatment scenario and four treatment scenarios (Table 2). Beginning with a historical diagnosis rate,[18] the scenarios incorporated a linear increase in diagnosis rate as reported in Table 3, assuming increasing awareness and screening will contribute to an increase in diagnosis over the model horizon.

Anti-steatotic therapy scenario

The percent usage of anti-steatotic therapy among the diabetic population was held constant.[19,20] Usage of this treatment was based upon the fibrosis distribution for individuals with diabetes, with a greater proportion of this population being in advanced fibrosis stages compared to the general MASLD population.[21] The ability of these agents to reverse steatosis was modeled for the F0-F1 population with no impact on fibrosis in F2-F4.[22,23]

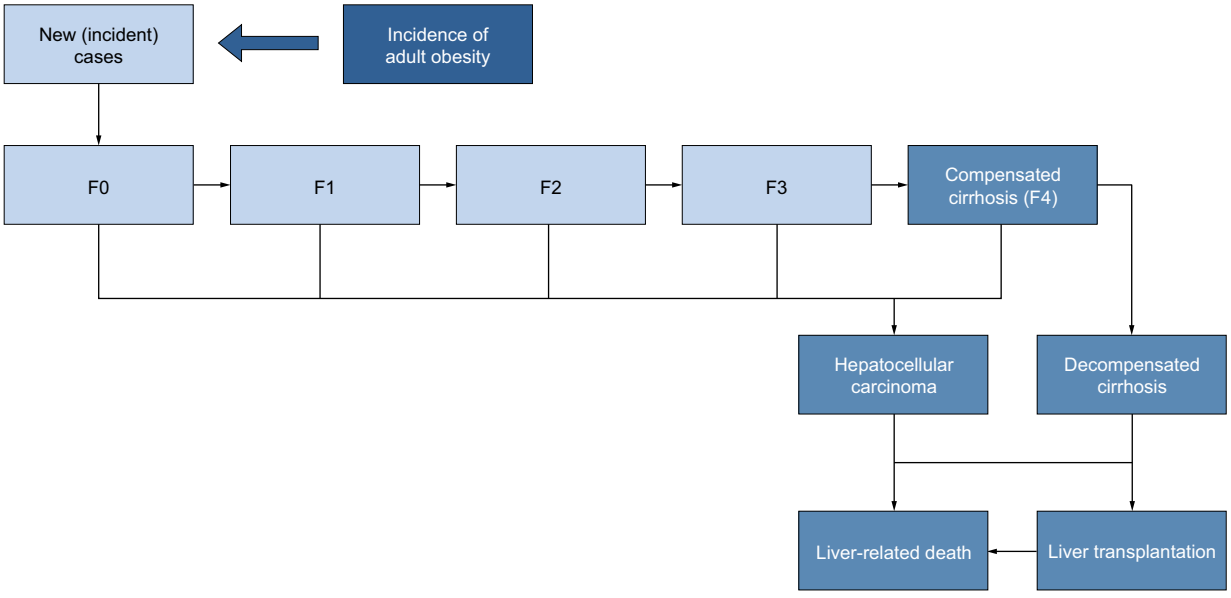

Fig. 1. MASLD model disease progression flowchart. MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 1. Model inputs and sources.

Category	Item	Value	Source
Disease burden	Adult obesity prevalence	30.5% in 1999 42.4% in 2018	45–47
	MASLD prevalence by age and gender	-	48
	Fibrosis progression rates	-	49–52
	HCC incidence	43,500 in 2015	53–55
	% HCC MASLD/MASH related	14.1–31%	49,50,56
	Total liver transplants	-	57
	% MASLD related	Reported + 41.7% cryptogenic obese	58
	Type 2 diabetes and MASLD	-	21,59
Annual healthcare costs (2024 USD)	F2 (diagnosed)	$528	60
	F3 (diagnosed)	$651	60
	Compensated cirrhosis (prevalent)	$3,431	61
	Decompensated cirrhosis (prevalent)	$40,638	61
	Hepatocellular carcinoma (prevalent)	$64,822	61
	Liver transplant (incident)	$257,338	61
	Post-liver transplant (prevalent)	$56,046	61
Diagnostic costs (2024 USD)	CBC (CPT 85025)	$7	62
	Hepatic function panel (CPT 80076)	$8	62
	Ultrasound, elastography (CPT 76981)	$131	14

CBC, complete blood count; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

Table 2. Model scenario descriptions.

Scenario	Description
No treatment	No treatment is available.
Anti-steatotic therapy	Diabetic MASLD F0-F1 patients are treated with these therapies. Assumed these therapies reduce steatosis with no worsening of fibrosis progression in 50% of patients.
F3 treatment	F3 patients are treated with a novel therapy which has been shown clinically to halt fibrosis progression in 70% of patients.
F2-F3 treatment	F2-F3 patients are treated with a novel therapy which has been shown clinically to halt fibrosis progression in 70% of patients.
F2-F4 treatment	F2-F4 patients are treated with a novel therapy which has been shown clinically to halt fibrosis progression in 70% of patients.

MASLD, metabolic dysfunction-associated steatotic liver disease.

New therapies for F2 and above

These scenarios assumed the introduction of pharmacological therapies indicated for MASLD that successfully halt the progression of fibrosis with a response rate of 70%.[23–26] This would also apply to anti-steatotic agents if trial data demonstrates halting fibrosis. The three scenarios assumed usage within F3, F2-F3, and F2-F4 patients with a treatment rate of 80% among those diagnosed. All scenarios assumed that patients with advanced liver disease (DCC, HCC, and liver transplantation) maintained the current treatment course and were not treated with the hypothetical new therapies.

Uncertainty and sensitivity analysis

Uncertainty intervals were generated using Beta-PERT distributions around model inputs (Table 4) using Oracle Crystal Ball (Oracle Corp., Redwood City, CA, Release 11.1.3708.0). Inputs for uncertainty included low and high estimates for MASLD prevalence (NHANES [National Health and Nutrition Examination Survey] and pooled prevalence studies), transition rates, treatment response rates, and direct healthcare costs by disease state. Transition rates ranges were based on published literature analysis.[27–29] Ranges around the response rate for the hypothetical new therapy were based on clinical trial results of

Table 3. Diagnosis and treatment rate assumptions.

	2022-2024	2025-2029	2030-2034	2035-2039	2040-2044
Diagnosis rate (anti-steatotic therapy)					
F0–F4*	22%	22%	22%	22%	22%
Treatment rate (anti-steatotic therapy)					
Impact on steatosis in F0-F1	10%	10%	10%	10%	10%
Diagnosis rate (hypothetical new therapies)					
F0–F1	3%	6%	9%	12%	15%
F2–F3	5%	14%	23%	31%	40%
F4	10%	20%	30%	40%	50%
DCC/HCC/LT	100%	100%	100%	100%	100%
Treatment rate (hypothetical new therapies)					
Hypothetical new therapy (when applicable)	-	80%	80%	80%	80%
DCC/HCC/LT	0%	0%	0%	0%	0%

DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation.
*Represents diagnosed population with comorbid metabolic dysfunction-associated steatotic liver disease and diabetes.

Table 4. Uncertainty analysis parameters.

Key model inputs assumptions	Base	Low	High
2015 prevalence	25%	19%	25.3%
F0 to F1 transition probability	1.43%	0.84%	2.19%
F1 to F2 transition probability	9.54%	5.63%	14.59%
F2 to F3 transition probability	9.90%	5.84%	15.15%
F3 to F4 transition probability	7.52%	4.29%	14.29%
F4 to DCC transition probability	3.71%	2.60%	5.05%
F0 to HCC transition probability	0.0004%	0.0003%	0.001%
F1 to HCC transition probability	0.009%	0.006%	0.011%
F2 to HCC transition probability	0.02%	0.01%	0.02%
F3 to HCC transition probability	0.03%	0.03%	0.05%
F4 to HCC transition probability	0.38%	0.28%	0.51%
DCC to LRD transition probability	20.00%	16.00%	24.00%
HCC to LRD (sub years) transition probability	61.00%	37.21%	66.49%
HCC to LRD (year 1) transition probability	16.20%	11.02%	23.00%
Anti-steatotic treatment response rates	50%	30%	60%
Hypothetical new treatment response rates	70%	30%	83%
Annual healthcare costs by disease state	See Table 1	-20%	+20%

DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LRD, liver-related death.

products in development for MASLD including THR-β agonists, FGF21 analogs, and GIP receptor/GLP-1 receptor agonists. Annual healthcare costs by disease state were varied by 20%. These inputs were used to generate 95% uncertainty intervals. Sensitivity analysis was conducted to identify the key drivers of uncertainty.

Results

Disease burden

The model estimated 3.62 million incident cases of MASLD in 2024, rising to 3.73 million incident cases in 2034 before gradually declining to 3.68 incident cases in 2044, as the historical obesity rate in the US levels off. MASLD prevalence was estimated to grow from 99.2 million people in 2024 to 133.5 million in 2044, an increase of 35%. Incorporating assumptions of gradually (linearly) increasing awareness, screening, and diagnosis, the diagnosed patient population grew from 5 million to 26 million over the 20-year study period corresponding to a diagnosis rate increase of 5% to 19%. Treatment responders by scenario can be found in Table 5. In the no treatment scenario, annual liver-related deaths grew from 63,300 in 2024 to 130,100 in 2044. Total liver-related deaths during the study period were estimated at 2.02 million deaths (Table 6).

The anti-steatotic therapy-only scenario resulted in a treated population in 2024 of 2.6 million, which grew to 3.8 million in 2044. The increase in the diagnosed population was the impetus for the growth. This scenario resulted in 10,000 DCC cases and 1,800 HCC cases averted (Table 6).

The hypothetical new therapy scenarios resulted in a treated population of 2.6 million in 2024, coming entirely from anti-steatotic therapy usage since new therapies were assumed to launch in 2025. By 2044, between 2.4 million and 6.8 million incremental treated patients were forecasted, driven by the increase in size of the diagnosed population paired with the likely assumption that most diagnosed patients will be treated once effective therapies are available, with the difference due to which fibrosis stages received treatment (see Table 2). These scenarios demonstrated the greatest impact on disease progression and mortality since patients had advanced fibrosis (F2-F4) and hypothetical new therapies were assumed to halt fibrosis.

Under all treatment scenarios, annual liver-related deaths grew during the study period; however, the rate of annual growth dropped sooner and more precipitously in the hypothetical new therapy scenarios than in the no treatment scenario. Annual liver-related deaths peaked in 2033 and then began to decline in the scenario in which the hypothetical new therapy halted fibrosis progression in F2-F4 patients. Cumulative liver-related deaths during 2024-2044 decreased by 6,000 deaths, a <1% change, for the anti-steatotic treatment scenario. In contrast during the same period, the hypothetical new therapy scenarios resulted in cumulative liver-related deaths decreasing by 167,800–621,700, an 8-31% reduction from the no treatment scenario. Similar trends were observed with DCC and HCC cases. The hypothetical new therapy scenarios resulted in 281,000–982,700 DCC cases averted and 34,000–110,200 HCC cases averted (Table 6). Fig. 2 depicts total prevalent cases of DCC, HCC, and liver-related deaths for each scenario. Treating the F4 patient population was the greatest determinant for reducing disease burden and mortality.

Economic analysis

Direct costs included healthcare costs by disease stage. Both annual costs and cumulative costs (2024-2044) were compared between scenarios (Table 6).

Under the no treatment scenario, annual direct costs increased from $22.0B in 2024 to a peak of $25.9B in 2039, then declined slightly to $25.4 in 2044. Cumulative direct costs were estimated at $520.3B during this period.

Under the anti-steatotic treatment scenario, annual direct costs were $22.8B in 2024 and $24.4B in 2044, with peak costs occurring at $25.1B in 2037. This scenario resulted in cumulative direct costs of $512.8B, with $7.6B of incremental healthcare costs averted due to their impact on reducing steatosis.

Among the hypothetical new therapy scenarios, the scenario in which only F3 patients were treated generated the highest

Table 5. Hypothetical treatment responders by scenario.

Scenario	2024	2034	2044
No treatment	0	0	0
Anti-steatotic therapy (F0-F1)	1,443,200 (1,131,900-1,544,600)	1,794,900 (1,475,900-1,891,500)	2,014,800 (1,659,000-2,129,800)
F3 treatment		1,164,400 (688,100-1,532,200)	2,213,500 (1,353,400-2,856,300)
F2-F3 treatment		2,652,100 (1,567,400-3,489,900)	4,790,400 (2,929,100-6,181,800)
F2-F4 treatment		3,526,600 (2,084,200-4,640,600)	6,172,900 (3,774,400-7,965,700)

NB: All scenarios assume 50% response rate (reduction in steatosis) in patients treated with anti-steatotics and 70% response rate (halting of fibrosis) in patients treated with hypothetical new therapies.

Table 6. Advanced liver disease cases and direct healthcare costs by scenario – United States, 2024-2044.

Scenario	Cumulative liver-related deaths (millions)	Cumulative liver-related deaths averted	Cumulative HCC cases	Cumulative HCC cases averted	Cumulative DCC cases (millions)	Cumulative DCC cases averted	Cumulative direct costs (USD billions)	Cumulative costs averted (USD billions)	Cumulative DALYs averted
No treatment	2.023	-	325,100	-	2.506	-	$520.3	-	-
Anti-steatotic therapy (F0-F1)	2.017 (0.912-3.731)	6,000 (2,700-11,100)	323,400 (179,600-576,800)	1,800 (1,000-3,200)	2.496 (1.060-4.630)	10,000 (4,200-18,500)	$512.8 ($266.9-$881.3)	$7.6 ($3.9-$13.0)	12,900 (5,400-30,400)
F3 treatment	1.855 (0.836-3.525)	167,800 (75,600-318,900)	291,100 (160,400-533,400)	34,000 (18,800-62,400)	2.225 (0.951-4.206)	281,000 (120,200-531,300)	$479.9 ($254.6-$829.3)	$40.5 ($21.5-$69.9)	339,100 (154,900-574,900)
F2-F3 treatment	1.790 (0.807-3.402)	232,600 (104,800-441,900)	273,900 (150,900-501,800)	51,300 (28,300-94,000)	2.115 (0.904-3.998)	390,900 (167,200-739,100)	$464.6 ($246.5-$802.9)	$55.8 ($29.6-$96.4)	470,300 (214,800-797,400)
F2-F4 treatment	1.401 (0.631-2.662)	621,700 (280,100-1,181,500)	215,000 (118,400-393,900)	110,200 (60,700-201,900)	1.523 (0.651-2.880)	982,700 (420,100-1,857,700)	$421.2 ($223.5-$728.0)	$99.1 ($52.6-$171.3)	1,247,300 (569,700-2,114,600)

DALYs, disability-adjusted life years; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

annual direct costs, and the scenario in which F2-F4 patients were treated generated the lowest annual direct costs. Annual direct costs in 2024 were $22.0B. The F3 treatment scenario annual direct costs were $21.4B in 2044, a 3% decline. The F2-F3 treatment scenario annual direct costs were $19.5B in 2044, a 12% decline. The F2-F4 treatment scenario resulted in an 24% decline in annual direct costs to $16.8B in 2044. F3 treatment annual healthcare costs peaked in 2032, while F2-F3 treatment annual costs peaked in 2031; however, with the F2-F4 treatment scenario, annual costs peaked in 2025, the year of pharmaceutical therapy introduction. Due to the disease's slow progression, the impact of treating patients in earlier stages will be realized later than treating patients in later stages; however, these results indicate that treatment that halts fibrosis progression across moderate-to-advanced fibrosis and cirrhosis will curb the rise in healthcare costs associated with late-stage disease that is imminent without treatment (no treatment scenario). Compared with the no treatment scenario, treatment of the F2-F3 patient groups provided an 8-11% decrease in cumulative healthcare costs, while treatment of F2-F4 patient groups provided a 19% decrease in cumulative healthcare costs. Cumulative direct costs were between $421.2B and $479.9, resulting in $40.5 to $99.1B incremental healthcare costs averted.

The economic impact analysis also looked at cumulative DALYs averted for the different scenarios. The anti-steatotic treatment scenario yielded 12,900 cumulative DALYs averted, compared with the hypothetical new therapy scenarios, which yielded more than 339,100 cumulative DALYs averted. Treatment of F2-F3 patients yielded 470,300 cumulative DALYs averted, while the F2-F4 treatment scenario resulted in 1.2 million DALYs averted, a near one-third reduction from the no treatment scenario.

Uncertainty and sensitivity analysis

Results from the uncertainty analysis are listed as confidence intervals in Tables 5 and 6. Sensitivity analysis of 2044 prevalence showed that the largest driver of uncertainty was the prevalence in 2015 which accounted for 99% of the total variance in our analysis. On the other hand, the largest drivers of uncertainty for total MASLD healthcare costs were F3 to F4, F0 to F1, F2 to F3, and F4 to DCC transition rates, in that order. These uncertainties accounted for 87% of the total variance in the healthcare cost analysis. The results of the sensitivity analysis are summarized in tornado diagrams in Fig. 3.

Discussion

This study highlights the large burden of MASLD in the United States if untreated. Over a 20-year period, no action will lead to $520.3 billion (Table 6) in healthcare costs and four million cumulative DALYs that can be averted. However, gradually increased rates of screening and diagnosis partnered with hypothetical treatment that halts fibrosis progression resulted in an estimated 8-19% reduction in direct healthcare costs, 8-31% reduction in liver-related deaths, and 9-31% reduction in cumulative DALYs over the next 20 years.

Currently, only a small portion of the MASLD population is diagnosed. Many individuals are not diagnosed even when imaging indicates steatosis.[30,31] Learning from hepatitis C, treating patients with early disease stages is more effective and

Modeling the health and economic impact

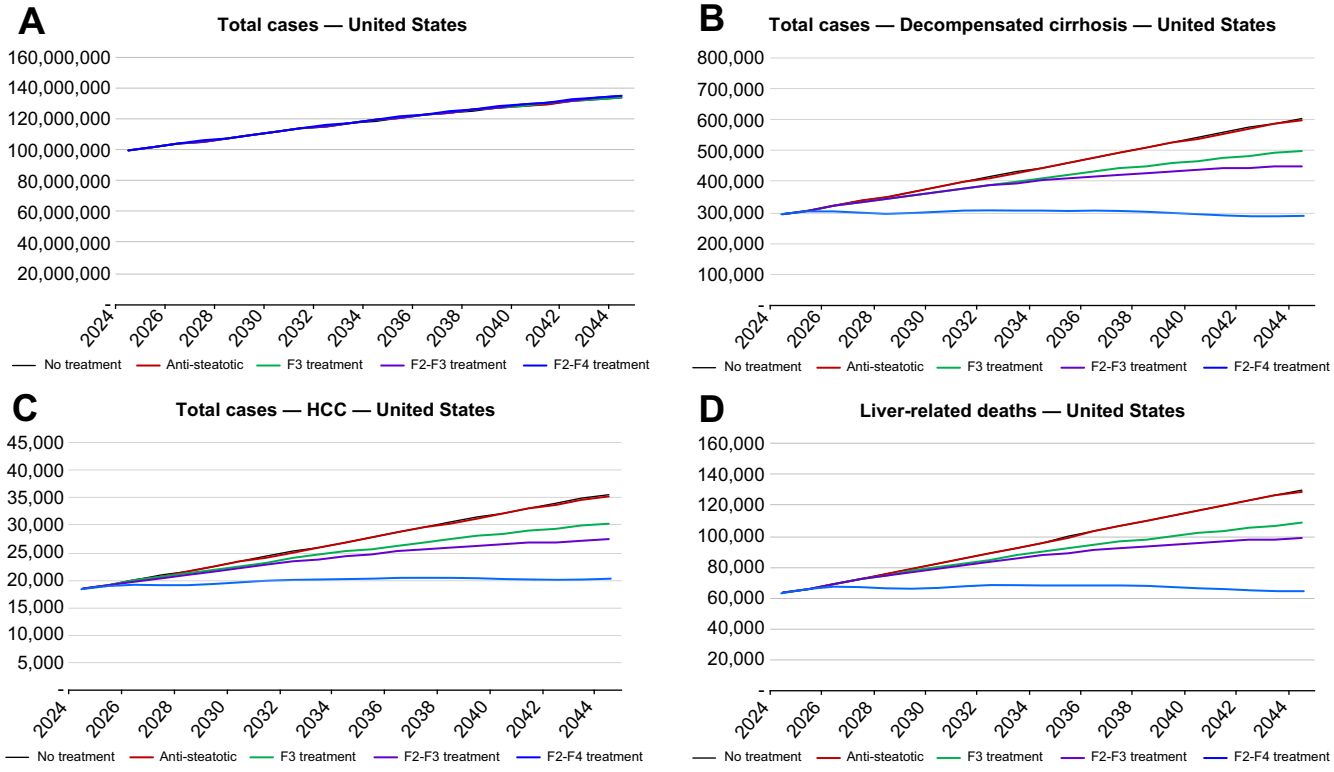

Fig. 2. Disease burden by scenario – United States, 2024-2044. (A) Total MASLD cases. (B) Total decompensated cirrhosis cases. (C) Total hepatocellular carcinoma cases. (D) Total liver-related deaths. HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

less expensive than delaying treatment initiation until more advanced disease stages occur.[32,33] Although MASLD may not correlate directly with hepatitis C, end-stage liver disease is costly regardless of the etiology. This analysis demonstrated that therapy that halts disease progression in patients with moderate-to-advanced fibrosis will prevent the high burden and economic cost associated with end-stage liver disease. It is imperative to establish and implement standardized, cost-effective screening and diagnostic measures, so care can be offered sooner to those at the greatest risk of progressing to advanced liver disease and to lessen the long-term deleterious effects of the disease.

Imaging – necessary for treatment initiation and monitoring – accounts for a notable portion of overall direct healthcare costs. Therefore, the application of reliable, cost-effective, non-invasive diagnostic and monitoring tools is essential. Reducing annual imaging to a less frequent schedule for most patients will produce cost savings without impacting quality of care due to the relatively slow progression of the disease, particularly in earlier stages (F0-F2). Identification of the subset of patients who are more likely to rapidly progress to advanced disease (approximately 20%)[27] and those with known risk factors of progression (*e.g.* type 2 diabetes, obesity, hypertension)[27,34,35] will be important to ensure those who may require more frequent monitoring receive it. Alternatively, less costly diagnostic and monitoring tests will improve the cost effectiveness of MASLD diagnosis, monitoring, and treatment.

Disease burden and economic impact were reduced most with the addition of a hypothetical pharmacological therapy that is effective in halting fibrosis progression, particularly when widely prescribed to a population with diagnosed cirrhosis (80% of the F4 population). Additional reductions in disease burden and costs were shown with treatment of the F2-F3 population. Smaller incremental reductions were shown when treating the F2 population compared to the F3 population; this was primarily an effect of the relatively short (20 year) window of analysis and the relatively slow progression of the disease from moderate fibrosis to cirrhosis and end-stage liver disease. This analysis emphasizes the unmet need for effective treatments which definitively halt fibrosis progression, as reversing steatohepatitis without halting fibrosis progression in patients with moderate-to-advanced fibrosis will have minimal impact on disease burden prior to 2044.

There is a potential for therapies to have a greater impact on disease burden and costs than modeled. If the number of liver transplants exceeds the current amount, treatment may avert a larger number of liver transplants than currently modeled. Previously aggregated costs of care by fibrosis level were applied; if additional labs, diagnostics or physician fees are necessary, new therapies halting patients' transition into more advanced disease states with additional costs would increase their economic benefit. Societal costs, such as indirect economic costs, were not evaluated in this model, although patients with MASH have reported worse health-related quality of life and work productivity.[36] Including societal costs would result in additional cost savings associated with therapies indicated for MASLD. Additionally, Medicare Procedure Prices were used. Private health insurer costs on average are higher

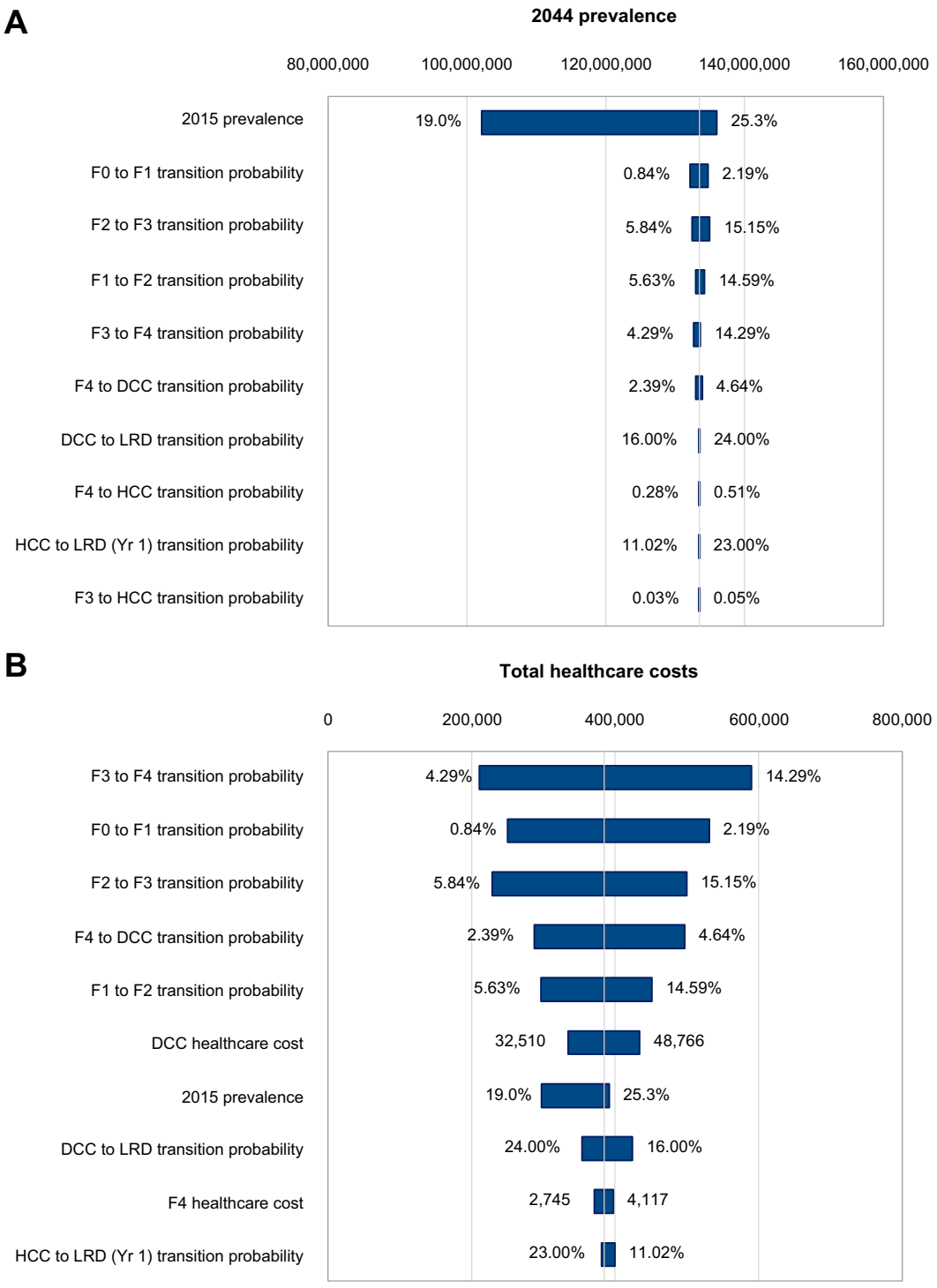

Fig. 3. Tornado diagrams summarizing sensitivity analysis. (A) 2044 prevalence. (B) Total healthcare costs (2024-2044). DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LRD, liver-related death.

than Medicare pricing,[37] so including these costs would increase the economic burden of MASLD and effect of hypothetical treatments.

Therapies that reduce steatosis were modeled to evaluate the health and economic impact independently of therapies that reduce fibrosis. To quantify only the effects of reducing steatosis, it was assumed that the treatment rate remained constant within the diabetic MASLD population and usage was limited to F0-F1 patients. However, this intentional delineation between anti-steatotics and anti-fibrotics may oversimplify the effects of anti-steatotic therapies. Given the potential for steatosis to contribute to inflammation and in turn fibrosis, these products' impact may extend beyond the anti-steatotic benefits modeled. For example, if future clinical trials

demonstrate halting of fibrosis and hence disease progression, particularly in the population with advanced fibrosis, and current issues that mitigate usage are resolved (*e.g.* persistence of usage long enough to realize benefits), these products will display an increased impact on reducing the burden of MASLD, either as monotherapy or in conjunction with other therapies which halt fibrosis. The modeled F2-F4 scenarios quantify the effects of therapies with anti-fibrotic properties on the disease and economic burden of MASLD.

Given the large uncertainty in MASLD prevalence, it was the major driver of future (2044) MASLD prevalence in the sensitivity analysis. All other uncertainties, including transition probabilities, had a less than 1% impact on the overall variance in the forecast. On the other hand, total healthcare cost was highly dependent on the transition probabilities in the model. Faster progression resulted in future populations moving to advanced liver disease more quickly and incurring higher healthcare costs. Similarly, slower progression resulted in lower overall healthcare costs. Prevalence had a relatively low impact since the majority of the MASLD population is not incurring large healthcare costs until they progress to end-stage liver disease. New therapy response rate (varying between 30-83%) had a low impact on prevalence, disease states, and healthcare costs.

There are certain limitations with this analysis. The lack of consistent diagnostic measures in MASLD epidemiologic studies hinders modeling this disease. Estimates of MASLD incidence are subject to uncertainty, as are age-specific fibrosis progression and liver cancer incidence rates. Available historical data may not accurately represent the current disease landscape, especially as the rates of comorbid conditions such as obesity and diabetes continue to rise.[38,39]

The average duration at each stage of fibrosis (F1-F4) was estimated to be 10 years.[40] Progression rates are similar to other studies; a pooled analysis showed the average duration by stage to be 7.1 years for MASH, 14.3 years for steatosis, and 7.7 years overall.[27] Analysis of placebo arms of randomized clinical trials reported progression rates of 9.0-11.6% for F3 to F4, corresponding to average durations in F3 of 8.6-11.1 years (reciprocal of incidence).[41] Shorter durations will result in larger cost savings and DALYs averted over a 20-year period. In addition, given the slow progression of MASLD, lifetime analyses would result in much larger cost savings and DALYs averted. The impact of treating patients in F2 would also become larger in lifetime economic analyses.

In addition to uncertainty around epidemiologic inputs, quantifying changes in the diagnostic and treatment landscape over the model's horizon is challenging. Currently, MASLD awareness and rates of diagnosis are very low.[42] Given that approximately one-quarter of individuals with diabetes[43] and over 40% of those with hypercholesterolemia[44] go undiagnosed even with the long-standing availability of simple diagnostic blood tests, reasonable increases in diagnosis and treatment rates were included in the MASLD model (see Table 3), assuming increased awareness of MASLD, use of cost-effective screening and diagnostic tools, and availability of effective treatments. Identifying the impact of any one development (*e.g.* use of artificial intelligence in diagnosis) was beyond the scope of this project.

It was also not the intention of this analysis to forecast the effect of any one therapy or class of therapies on the disease or economic burden of MASLD. Instead, the analysis considered recently reported clinical trial data collectively to represent response rates. Modeled treatment rates assumed that approved therapies were effective and well tolerated. If newly approved therapies vary from clinical trial results in real-world usage, the impacts to disease and economic burden would be altered as well, in either direction.

The objective of this analysis was not to provide a definitive quantification of future events. Instead, the purpose of this analysis was to apply modeling to allow the exploration of scenarios to determine the important drivers of the disease and economic burden of MASLD. This analysis demonstrates that if new therapies can halt fibrosis, increasing diagnosis and treatment of the MASLD population with advanced fibrosis would avert a meaningful number of cases of advanced liver disease and related mortality, and confer the economic benefit of reducing direct healthcare costs. It also highlights that reversing steatosis alone is not sufficient to have a large impact on the disease and economic burden of MASLD. It underlines the need for systematic screening, affordable and accessible diagnostics, and effective therapies to quell the most rapidly increasing and prevalent liver disease in history.

Affiliations

[1]*Center for Disease Analysis Foundation, Lafayette, Colorado, USA;* [2]*Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA*

Abbreviations

DALY, disability-adjusted life year; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

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Conflicts of interest

CW, IG and CE have no conflicts of interest. CE is an employee of Exact Sciences Corporation. HR has no conflicts for this project. He has received research grants from Gilead, Assembly Biosciences, AbbVie, Boehringer Ingelheim, Intercept, Merck, Novartis, Pfizer, and Roche. AS has stock options in Genfit, Tiziana, Hemoshear, Rivus, Northsea, Inversago. He has served as a consultant to Gilead, Intercept, Boehringer Ingelheim, Merck, Novo Nordisk, Eli Lilly, Madrigal, Alnylam, Hanmi, LG Chem, Takeda, Regeneron, Genentech, Siemens, Surrozen, Poxel, Path AI, Histoindex, Zydus, 89 Bio, Akero, Salix. His institution has received grants from Gilead, Bristol Myers Squibb, Intercept, Novo Nordisk, Akero, Takeda, merck, Salix, Eli Lilly, Hanmi, Madrigal, Boehringer Ingelheim, Pfizer. He received royalties from Elsevier and Uptodate.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

HR and AS conceived the study. HR designed the methodology and was responsible for the project administration. HR, CW, IG and CE conducted the formal analysis. CW and CE wrote the original draft. HR, CW, IG, CE had access to the underlying data and verified the data. All authors curated and validated the data as well as reviewed and edited the manuscript. All authors had full access to the data and accepted responsibility for publication.

Data availability statement

Data is available to other researchers upon request within 12 months of publication.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.01.009.

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Supplemental information

Modeling the health and economic impact of pharmacologic therapies for MASLD in the United States

Carolyn Wallace, Ivane Gamkrelidze, Chris Estes, Homie Razavi, and Arun J. Sanyal

Modeling the health and economic impact of pharmacologic therapies for MASLD in the United States

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Markov model

The Markov model was built using Microsoft Excel® (Microsoft Corp., Redmond, WA) to track the annual MASLD population by fibrosis stage and MASH status (steatosis only [MASL] or MASH) from 1950-2050.

Beginning with the estimated annual new MASLD cases (defined as the onset of steatosis rather than newly diagnosed), fibrosis progression of all cases was modeled through 2050. Cases by stage of disease were calculated annually by age and gender, with one-year age cohorts through age 84 and cases aged ≥85 years tracked as a single cohort. Annually, the population in each age group (excluding the ≥85 year cohort) was advanced to the next age to simulate the impact of aging. Historical and medium-fertility projection population data were obtained from the United Nations' population database by gender and one year age cohort.[1]

Disease progression through fibrosis and advanced liver disease (decompensated cirrhosis and HCC) was estimated with adjustment for all-cause mortality (including general background, excess cardiovascular and liver-related mortality). New cases by disease stage (*New Cases* stage x) were calculated by multiplying progression rates and the total cases at prior stages of the disease in the previous year (*Total Cases* stage x-1, Year Y-1) as shown in Equation 1.

Equation 1

$$Total\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = \left(Total\ Cases_{Stage_x\ \&\ Year_{y-1}\ \&\ Age\ Cohort_{z-1}}\right) + New\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} - All\ Cause\ Mortality_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} - Progressed_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z}$$

where:

$$New\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = (Total\ Cases_{Stage_{x-1}\ \&\ Year_{y-1}\ \&\ Age\ Cohort_z})(Progression\ Rate_{Stage_{x-1} \rightarrow Stage_x\ \&\ Age\ Cohort_z})$$

$$Background\ Mortality_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = (Total\ Cases_{Stage_x\ \&\ Year_{y-1}\ \&\ Age\ Cohort_z})([Background\ Mortality\ Rate][CVD\ Multiplier]_{\ Age\ Cohort_z})$$

$$Progressed_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = (Total\ Cases_{Stage_{x-1}\ \&\ Year_{y-1}\ \&\ Age\ Cohort_z})(Progression\ Rate_{\ Stage_x \rightarrow Stage_{x+1}\ \&\ Age\ Cohort_z})$$

$$\text{Liver Related Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} - \text{Adjusted Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Progressed}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z}\right)\left(\text{Liver Related Mortality Rate}_{\ \text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)$$

Transition rates

The annual transition probabilities were based on published estimates and expert consensus as shown in Table S1. However, single annual transition rates resulted in poor validation of the models (i.e., comparison of modeled and reported HCC cases). Thus, age- and gender-specific fibrosis progression rates were developed based on assumptions for the distribution of cases by MASH status and fibrosis stage, as described below. Fibrosis progression rates are available from studies analyzing consecutive liver biopsies, but report highly varied rates, including negative progression (e.g. regression).[2] For the purpose of the model, progression rates were assumed to be the sum of forward progression minus the rate of regression. Where data or expert input were available for the incidence of MASLD-related HCC, decompensated cirrhosis and related mortality, progression rates were modified to align with reported data and expert consensus (Table S1). A long-term follow-up study of individuals with MASH-related cirrhosis reported that 45% experienced liver failure or decompensated cirrhosis, defined as an increase in Child-Turcotte-Pugh score by 2 points over twelve years of follow-up in patients with Child Class A Cirrhosis.[3] An annual progression rate of 3.8% decompensation among cirrhotics was calculated and applied in the model.

Fibrosis progression rates were further adjusted with overweight individuals (BMI 25 to <30kg/m^2) having 2.35 greater odds and obese individuals (BMI ≥30kg/m^2) having 5.70 greater odds of advanced fibrosis (Table S2).[4] It was assumed that relative differences in the proportion of overweight and obese individuals would be reflective of the country's MASLD population.

It was assumed that 64% of incident HCC cases would occur among cirrhotics.[5] Using U.S. data, the annual transition rate from F4 to HCC was estimated at 0.38%. The remaining 36% of incident HCC cases occurred among F0-F3 cases. The incidence rate among F3 cases was back calculated and progression decreased exponentially with each decreasing level of fibrosis from 0.03% (F3 to HCC) to 0.0004% (F0 to HCC) (Table S1). MASLD-related HCC cases may experience greater mortality as compared to HCV-related HCC; first year mortality (61%) was applied to new HCC cases, with subsequent years mortality rates based on long-term survival data.[6,7] The annual calculated transition rates are shown in Table S2.

Table S1. Disease Stage Annual Transitions Rates

Disease Stage Transition	Annual Rate	Source
F0 to F1	0.3-2.2%	Back-calculated
F0 to HCC	0.0004%	[5,6]
F1 to F2	2.8-13.3%	Back-calculated
F1 to HCC	0.009%	[5,6]
F2 to F3	2.8-13.3%	Back-calculated
F2 to HCC	0.02%	[5,6]
F3 to F4 (Cirrhosis)	3.8-9.9%	Back-calculated
F3 to HCC	0.03%	[5,6]
Cirrhosis to Decomp Cirrhosis	3.80%	[3]
Cirrhosis to HCC	0.38%	[5,6]
Decomp Cirrhosis to Liver Rel. Death	20.0%	[3]
HCC to Liver Rel. Death (Yr 1)	61.0%	[6]
HCC to L.R. Death (Sub Yrs)	16.2%	[7]

Table S2. Fibrosis Transition Probabilities by Disease Stage, Sex and Age Group – United States

F0-F1	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Males	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%
Low	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%
High	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	1.1%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%
Females	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	1.6%	1.6%	1.6%	1.6%	1.6%	1.6%	1.6%	1.6%	1.6%	1.6%
Low	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%
High	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	2.4%	2.4%	2.4%	2.4%	2.4%	2.4%	2.4%	2.4%	2.4%	2.4%
F1 to F2	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**	**25–29**	**30–34**	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**85+**
Males	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%
Low	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%
High	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%
Females	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%
Low	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%
High	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%
F2 to F3	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**	**25–29**	**30–34**	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**85+**
Males	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%	11.7%
Low	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%	6.9%
High	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	6.8%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%	17.9%
Females	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	3.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%
Low	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%	5.7%
High	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%	14.9%
F3 to F4	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**	**25–29**	**30–34**	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**85+**
Males	5.3%	5.3%	5.3%	5.3%	5.3%	5.3%	5.3%	5.3%	8.7%	8.7%	8.7%	8.7%	8.7%	8.7%	8.7%	8.7%	8.7%	8.7%
Low	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%
High	10.2%	10.2%	10.2%	10.2%	10.2%	10.2%	10.2%	10.2%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%
Females	4.5%	4.5%	4.5%	4.5%	4.5%	4.5%	4.5%	4.5%	7.3%	7.3%	7.3%	7.3%	7.3%	7.3%	7.3%	7.3%	7.3%	7.3%
Low	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%
High	8.5%	8.5%	8.5%	8.5%	8.5%	8.5%	8.5%	8.5%	13.8%	13.8%	13.8%	13.8%	13.8%	13.8%	13.8%	13.8%	13.8%	13.8%

Incidence (new cases) calculations

Recent and accurate estimates of MASLD incidence and prevalence were either unavailable, had limitations that precluded application to the general population, or were subject to varied diagnostic techniques. Therefore, annual changes in the number of new cases were back calculated using the change in obesity as a surrogate for the change in new MASLD cases. Total prevalent cases were assumed to be the sum of existing and new MASLD cases after accounting for mortality and were calibrated to the estimated prevalence of MASLD in 2015. Incidence was used to describe new MASLD cases (onset of steatosis) and not the time of first diagnosis.

The reported rates of adult obesity and diagnosed diabetes have increased over time.[8,9] Unlike obesity, T2DM data are less readily available due to changes in awareness, screening, and diagnosis levels. Reliable estimates of true T2DM prevalence (diagnosed and undiagnosed) were unavailable until recent decades. Long term changes in adult obesity were plotted.[8,10-12] The growth in MASLD new cases was assumed to follow the growth in obesity. Future trends in adult obesity were forecasted using best-fit sigmoidal functions.

Published data suggest that males have a higher MASLD prevalence than females and prevalence rates increase with age.[13-15] Relative incidence values describe changes in the annual number of new MASLD cases. A curve was fitted from 1950 to the estimated peak and a second curve followed the decline in relative incidence. Relative changes in the number of total MASLD cases and the distribution of MASL versus MASH within the

population were imputed from data related to trends for obesity for which more robust data existed.

Annual relative incidence values were used to describe changes in the annual number of new MASLD cases over time. The Excel® Solver add-in was used to solve for the constant, which when multiplied by the annual relative incidence, resulted in the known prevalence after adjusting for mortality. This constant multiplied by the relative incidence provided the number of new MASLD cases per year. Data related to the distribution of MASL vs. MASH in these populations were used to impute the trends for these histological phenotypes.[15-17]

Next, annual incident cases were distributed by age and gender to fit the adjusted MASLD prevalence. A weighting factor was applied to reported prevalence by age and gender to reach estimated MASLD prevalence in the adult age groups in 2015. The percentage of the incident population allocated to each age and gender cohort in years 1950-1965 was set equal to 1966 and trended linearly in five-year increments until 2011, at which point the percent of incident cases allocated to each age and gender cohort were held constant until 2050. The relative impact of incident MASLD cases occurring prior to 1950 was negligible and not included.

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