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Severe obesity is associated with worse outcomes than lean metabolic dysfunction–associated steatotic liver disease

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Abstract

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent in people with obesity. We aimed to study the association of body mass index (BMI) with clinical outcomes in patients with MASLD.

Methods: A retrospective cohort of 32,900 patients with MASLD, identified through the International Classification of Diseases-9 and 10 codes within the electronic health records of a large US-based health system, with a mean follow-up of 5.5 years (range: 1–15 y), was stratified into 6 BMI categories, <25, 25–<30, 30–<40, 40–<50, and ≥50 kg/m^2.

Results: The risk of liver decompensation and extrahepatic obesity–associated cancers had a J-shaped profile (both *p*s for linear and quadratic terms <0.05). Compared to patients with BMI 25–<30 kg/m^2, the adjusted HRs (95% CIs) for liver decompensation of patients with BMI <25 and BMI ≥50 kg/m^2 were 1.44 (1.17–1.77) and 2.27 (1.66–3.00), respectively. The corresponding figures for obesity-associated extrahepatic cancer were 1.15 (0.97–1.36) and 1.29 (1.00–1.76). There was an inverse association for BMI with liver transplantation and non-obesity–associated cancer (both *p*s for linear terms <0.05), but no association with HCC or all types of cancers combined. A similar J-shaped association between BMI and all-cause mortality was observed; adjusted HRs (95% CIs) for BMI <25 and ≥50 kg/m^2 were 1.51 (1.32–1.72) and 3.24 (2.67–3.83), respectively, compared with BMI 25–<30 kg/m^2 (both *p*s for linear and quadratic terms <0.001).

Conclusions: Patients with MASLD and very severe obesity (BMI ≥ 50 kg/m^2) had the highest risk, exceeding that of patients with lean

Abbreviations: BMI, body mass index; EHR, electronic health records; ICD-9/10, International Classification of Diseases versions 9 and 10; MASLD, metabolic dysfunction–associated steatotic liver disease.

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MASLD, for developing liver decompensation, obesity-associated extrahepatic cancers, or dying from any cause.

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD; previously called NAFLD)[1] and obesity are closely associated disorders.[2] Obesity is an independent predictor of hepatic steatosis and increasing the severity of obesity is associated with a higher prevalence of MASLD.[3,4] In people with obesity, MASLD is a marker of metabolically unhealthy obesity.[5] Treatment of obesity resulting in weight loss, either through dietary, pharmacologic, or surgical intervention, is associated with improvement in MASLD.[6–9] However, MASLD can also occur in people who are in the "normal" BMI category (18.5–25 kg/m^2), an entity called "lean MASLD," which is associated with worse outcomes compared with non-lean MASLD.[10]

While imperfect as a biomarker of health, body mass index (BMI) is a widely used metric to stratify the severity of obesity, including in patients with MASLD.[11,12] The prevalence of obesity has steadily increased in the United States, with the prevalence of severe obesity rising faster than other BMI categories.[13] There is a nonlinear relationship between BMI category and risk of mortality, with the lowest mortality risk associated with the overweight category (BMI: 25–30 kg/m^2) and rising with progressively lower or higher BMI categories.[14] Consistent with the overall lower mortality observed in people in the overweight category, even among hospitalized patients with liver cirrhosis, obesity is associated with better survival than in lean patients.[15]

Both obesity and MASLD are independently associated with other metabolic complications. Obesity is associated with an increased risk of specific cancers, called obesity-associated cancers, cardiovascular disease, and type 2 diabetes.[16–18] MASLD is also associated with cardiovascular disease, incident type 2 diabetes, and extrahepatic cancers, in addition to liver-related complications.[19–21] However, the impact of the severity of obesity on the risk of developing liver-related complications (hepatic decompensation), HCC, extrahepatic cancers, liver transplantation, and death is unclear. While BMI is calculated in most clinical settings, and targeted screening for MASLD with liver fibrosis has recently been recommended in certain high-risk subgroups,[22] lack of systematic screening in the general population makes it difficult to completely elucidate the relationship between the severity of obesity and MASLD. In this study, we aimed to study the association of the severity of obesity, as measured by BMI, with liver-related complications, extrahepatic cancers, and mortality risk in patients diagnosed with MASLD. We hypothesized that patients with severe obesity have worse clinical outcomes compared with patients with nonsevere obesity or lean MASLD.

METHODS

Ethics statement

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. This study was approved by the University of Pittsburgh Human Research Protections Office with a waiver of informed consent (STUDY19010189).

Clinical setting and study subjects

Deidentified subject data were obtained from the University of Pittsburgh Department of Biomedical Informatics. We used a retrospective cohort study design. Since the study period preceded the adoption of the MASLD nomenclature in 2023, we included all patients with associated International Classification of Diseases codes versions 9 and 10 (ICD-9/10) for NAFLD/NASH/nonalcoholic cirrhosis seen between January 2004 and December 2018 at any facility within the UPMC Health System, a large, integrated health care network serving the mid-Atlantic and Midwest United States. To identify patients with MASLD, cirrhosis, HCC, and liver failure, we used the 2021 expert panel consensus guidelines on administrative coding in electronic health record (EHR)-based research of MASLD (Supplemental Table S1, http://links.lww.com/HC9/A938).[23] A patient master index at the institutional level ensured that each patient had a unique identifier despite having multiple medical records in the system. The time of entry into the study was defined as the date of the encounter at which MASLD was initially coded in either outpatient or inpatient settings. The follow-up duration was defined by the interval between entry into the study and the date of last contact within the EHRs.

We excluded patients with associated diagnostic codes for other chronic liver diseases (Supplemental Table S2, http://links.lww.com/HC9/A938), such as viral hepatitis, unspecified chronic hepatitis, autoimmune liver disease, secondary or unspecified biliary cirrhosis, Wilson disease, alph-1-antitrypsin deficiency, hemochromatosis, Budd-

Chiari syndrome, drug use disorder except nicotine/caffeine, alcohol-associated liver disease, alcohol use disorder, and somatic consequences of alcohol.

Data collection

The BMI recorded during the initial visit within the study period was the primary exposure. The primary exposure was the earliest recorded BMI measurement in the EHR for each patient as the precise date of initial MASLD diagnosis was unavailable for a majority of the patients in the cohort. Patients were subsequently categorized into 1 of the following BMI categories: <25, 25–<30, 30–<40, 40–<50, and ≥50 kg/m^2. Age at the earliest BMI measurement, sex, race, and smoking status closest to the earliest BMI measurement date were used in the statistical modeling. Prevalence of metabolic comorbid conditions, diabetes, hypertension, and dyslipidemia were recorded as being present if coded at least once from the time of initial BMI measurement. Available laboratory data were extracted from the date closest to BMI measurement (±6 mo). The Fibrosis-4 index, a validated noninvasive test of liver fibrosis predictive of MASLD-related outcomes, was calculated based on values closest to the date of inclusion in the study.[24]

We recorded the following outcome variables in the follow-up period: hepatic decompensation (defined as ascites, HE, and variceal hemorrhage), HCC, liver transplant, all liver-related outcomes (all outcomes included in hepatic decompensation + HCC + liver transplant), total cancers, extrahepatic obesity–associated cancers as defined by the National Cancer Institute (endometrial, esophageal adenocarcinoma, gastric cardia, liver, kidney, multiple myeloma, meningioma, pancreatic, colorectal, gallbladder, breast, ovarian, and thyroid), non-obesity–associated cancers (all other cancers not included in obesity-associated cancers), and death from any cause. Fifty-nine patients were diagnosed with extrahepatic obesity–associated as well as non-obesity–associated cancers within 30 days of each other and counted in both categories.

Statistical analysis

Categorical variables were described with frequency and continuous variables with mean and SD. The ANOVA and χ^2 statistics were used to compare the distributions of continuous and categorical variables, respectively, between BMI groups. Person-years at risk were calculated from the date of the first BMI measurement to the first clinical outcomes, date of death, or date of the last encounter, whichever came first. HR was calculated using the Cox proportional hazards regression model with adjustments for age, sex, race, and smoking status. The incident rate of outcomes was calculated using the Poisson regression model with adjustment for age and sex. To maximize sample size, 187 subjects with missing race and 455 subjects with missing smoking information were grouped as a separate category of these variables, respectively, which were included in the model adjustment. To assess the nonlinear associations between BMI and outcome incidence, restricted cubic spline analysis was performed, where a BMI of 25 kg/m^2 was set as the reference value, and 4 knots were placed at equally spaced percentiles.[25] Statistical analyses were carried out using SAS software version 9.4 (SAS Institute). All *p* values reported were 2-sided. *p* values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study cohort

A total of 47,165 patients with NAFLD-associated diagnoses were initially identified in the EHR. We excluded 4087 patients with missing BMI data, and 162 patients with BMI <18.5 (underweight) or >75 kg/m^2 (high probability of error in recording weight or height in the EHR). We also excluded 10,016 patients, in whom any outcome of interest occurred either before or within 1 year of the initially recorded BMI. After these exclusions, 32,900 subjects remained in the cohort for final analysis (Figure 1). The mean (SD) follow-up was 5.5 (2.9) years (median 5.6 y, range 1–15 y). The number of patients with outcomes of interest was as follows: 255 with HCC, 1154 with hepatic decompensation, 201 with a liver transplant, 2064 with extrahepatic obesity–associated cancer, 2106 with non-obesity–associated cancer, and 2713 deaths.

Across the 5 BMI categories, age, sex, race, and smoking status were significantly different (Table 1). The prevalence of hypertension, hyperlipidemia, and diabetes were significantly different across the BMI groups, with hypertension and diabetes prevalence, but not hyperlipidemia, progressively increasing with BMI. Several biochemical tests, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, platelet count, triglyceride, total cholesterol, and mean hemoglobin A1c, but not total bilirubin, were significantly different across groups. However, the mean Fibrosis-4 index score was similar across the BMI categories.

Association of BMI with liver-related outcomes in patients with MASLD

Next, we determined the association of BMI with risk of liver-related adverse clinical events. The rate of HCC was lowest for BMI ≥50 kg/m^2 (77.9 per 100,000

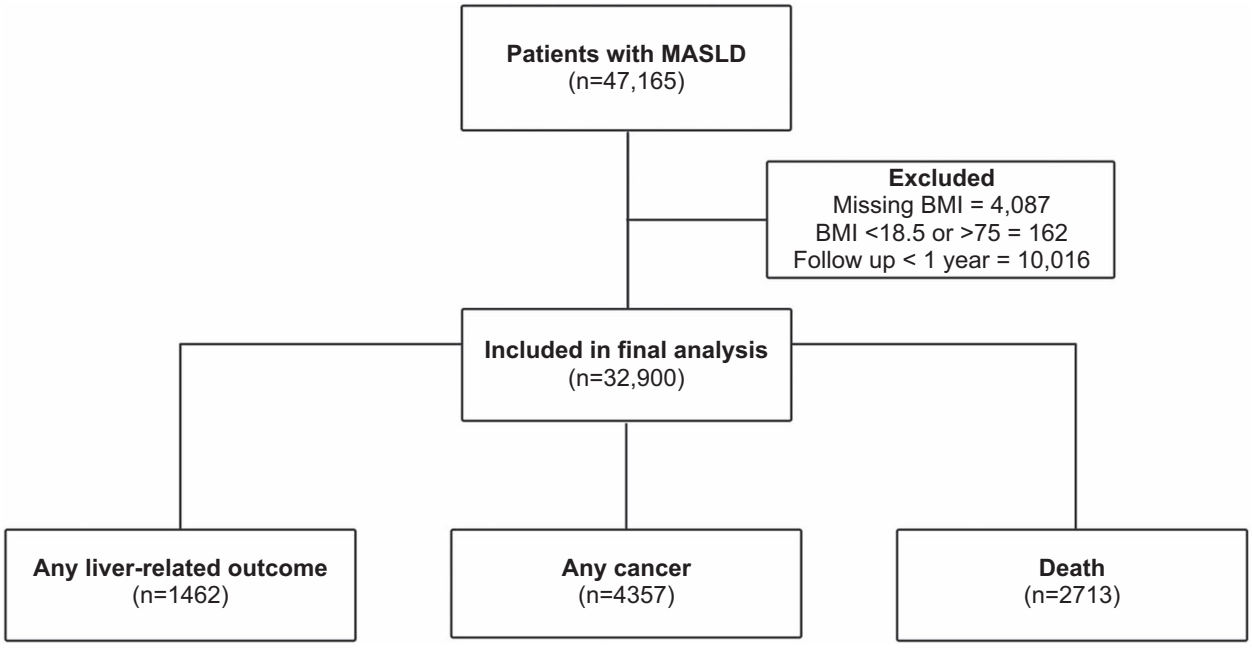

FIGURE 1 Flow chart of the study population. The entire cohort of patients diagnosed with MASLD-related codes was 47,165. Patients with missing BMI, extreme BMI ranges, and short follow-up intervals were excluded from the final analysis. Any liver-related outcome (defined as ascites, HE, variceal hemorrhage, or hepatorenal syndrome), any hepatic or extrahepatic cancer, and all-cause mortality were recorded in the cohort included in the final analysis. Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease.

person-years) and highest for the BMI <25 kg/m^2 group (106.9 per 100,000 person-years). However, neither the linear nor quadratic trends for HCC incidence were significant across BMI categories (Table 2).

For liver decompensation, the lowest rate was observed in the BMI category 25–<30 kg/m^2 (419.2/100,000 person-years) and highest in BMI ≥50 kg/m^2 (930.6/100,000 person-years). The association between BMI and liver decompensation was in a J-shape with significant p values for both linear term ($p = 0.03$) and quadratic term ($p < 0.001$). Compared to the reference BMI category 25–<30 kg/m^2, BMI categories <25, 40–<50, and ≥50 kg/m^2 all demonstrated a higher risk of hepatic decompensation (Table 2).

Ascites is one of the decompensating events in patients with cirrhosis. Since ascites may be due to hepatic decompensation or malignant ascites, we further evaluated the association of BMI with liver decompensation with or without ascites. There were 821 cases of ascites in the cohort, of which 94 were concurrently diagnosed with HCC. There was insufficient data in the EHR to distinguish malignant ascites from cirrhosis-associated ascites. However, we found a similar association for BMI with liver decompensation including ascites, and decompensating after excluding ascites (Supplemental Table S3, http://links.lww.com/HC9/A938).

In contrast to liver decompensation, the BMI category <25 kg/m^2 demonstrated the highest (254/100,000 person-years), and the ≥50 kg/m^2 category had the lowest rate (32.7/100,000 person-years) of liver transplantation (Table 2). Compared to the reference BMI 25–<30 kg/m^2 category, the <25 kg/m^2 category had a significantly higher likelihood (HR: 1.89, 95% CI: 1.27, 2.82) of liver transplantation, and this likelihood of liver transplantation progressively decreased with increasing BMI levels. There was a highly significant negative linear trend for the likelihood of liver transplantation with increasing BMI ($p < 0.001$).

We then determined the risk of combined liver-related outcomes (HCC, liver decompensation, or liver transplant) across BMI groups. There was a U-shaped association between BMI and the risk of combined liver-related outcomes (p for quadratic term <0.001 but not significant for linear term) Compared to the reference BMI category 25–<30 kg/m^2, HRs (95% CIs) for liver-related outcomes were 1.52 (1.27–1.81) for BMI <25 kg/m^2 and 1.72 (1.28–2.30) for BMI ≥50 kg/m^2 (Table 2).

We also performed sensitivity analysis by limiting the cohort to patients with a diagnosis of cirrhosis and found similar results, with no association with HCC, increased risk of liver-related outcomes in patients with severe obesity, and negative linear trend for the likelihood of liver transplantation with increasing BMI ($p < 0.001$; Supplemental Table S4, http://links.lww.com/HC9/A938).

Another sensitivity analysis was conducted on the data set with the exclusion of patients with missing data on smoking status (455 patients or 1.4% of the overall cohort) or race (187 patients or 0.6% of the cohort), and the results remained the same as those based on the entire data set (data not shown). Since the cohort

TABLE 1 Baseline characteristics of patients with MASLD by BMI groups

Characteristics	BMI groups (kg/m^2)					p
	< 25 (N = 2426)	25– < 30 (N = 8027)	30– < 40 (N = 16,512)	40– < 50 (N = 4867)	50–75 (N = 1068)	
BMI						
Mean (SD)	23.01 (1.58)	27.78 (1.40)	34.33 (2.76)	43.70 (2.70)	55.64 (5.19)	< 0.001
Age						
Mean (SD)	58.28 (12.64)	57.62 (11.68)	55.90 (10.79)	53.83 (10.32)	51.72 (9.59)	< 0.001
Sex						
Men, n (%)	790 (32.56)	3723 (46.38)	7505 (45.45)	1568 (32.22)	290 (27.15)	< 0.001
Women, n (%)	1636 (67.44)	4304 (53.62)	9007 (54.55)	3299 (67.78)	778 (72.85)	
Race[a]						
White, n (%)	2154 (88.79)	7409 (92.30)	15,502 (93.88)	4497 (92.40)	963 (90.17)	< 0.001
Non-White, n (%)	246 (10.14)	569 (07.09)	923 (05.59)	348 (07.15)	102 (09.55)	
Ever smoking[b]						
No, n (%)	1245 (51.32)	4482 (55.84)	9149 (55.41)	2722 (55.93)	592 (55.43)	< 0.001
Yes, n (%)	1126 (46.41)	3429 (42.72)	7174 (43.45)	2078 (42.70)	448 (41.95)	
Hypertension						
No, n (%)	1497 (61.71)	4388 (54.67)	7738 (46.86)	1958 (40.23)	415 (38.86)	< 0.001
Yes, n (%)	929 (38.29)	3639 (45.33)	8774 (53.14)	2909 (59.77)	653 (61.14)	
Hyperlipidemia						
No, n (%)	1664 (68.59)	4778 (59.52)	9625 (58.29)	2930 (60.20)	716 (67.04)	< 0.001
Yes, n (%)	762 (31.41)	3249 (40.48)	6887 (41.71)	1937 (39.80)	352 (32.96)	
History of diabetes						
No, n (%)	2046 (84.34)	6490 (80.85)	11,911 (72.14)	3092 (63.53)	643 (60.21)	< 0.001
Yes, n (%)	380 (15.66)	1537 (19.15)	4601 (27.86)	1775 (36.47)	425 (39.79)	
Cirrhosis						
No, n (%)	1975 (81.41)	6916 (86.16)	14,462 (87.58)	4244 (87.20)	899 (84.18)	< 0.001
Yes, n (%)	451 (18.59)	1111 (13.84)	2050 (12.42)	623 (12.80)	169 (15.82)	
ALT						
N	1402	4483	9413	2806	627	
Mean (SD)	40.97 (96.79)	42.59 (43.69)	46.65 (45.96)	47.48 (65.59)	43.49 (39.50)	< 0.001
AST						
N	1396	4430	9301	2780	619	
Mean (SD)	33.47 (60.86)	31.76 (34.57)	32.67 (37.44)	36.32 (79.84)	33.67 (40.77)	0.002
ALP						
N	1359	4278	8984	2692	588	
Mean (SD)	94.35 (84.59)	84.26 (44.32)	84.45 (39.33)	87.53 (37.17)	95.30 (56.82)	< 0.001
Albumin						
N	1362	4291	9067	2713	602	
Mean (SD)	3.94 (0.61)	4.04 (0.53)	4.00 (0.50)	3.85 (0.87)	3.63 (0.53)	< 0.001
Platelet						
N	1225	3664	7621	2425	585	
Mean (SD)	241.87 (87.60)	234.45 (75.72)	233.96 (72.21)	240.36 (75.92)	235.16 (70.16)	< 0.001
Triglycerides						
N	999	3526	7452	2250	466	
Mean (SD)	146.36 (107.48)	178.50 (196.23)	195.13 (191.89)	183.64 (120.50)	175.64 (221.91)	< 0.001
Cholesterol						
N	990	3545	7490	2258	470	
Mean (SD)	193.10 (46.76)	192.15 (47.42)	189.78 (47.77)	183.97 (42.55)	179.14 (38.50)	< 0.001

TABLE 1. (*continued*)

Characteristics	BMI groups (kg/m²)					*p*
	< 25 (N = 2426)	25– < 30 (N = 8027)	30– < 40 (N = 16,512)	40– < 50 (N = 4867)	50–75 (N = 1068)	
Total bilirubin						
N	1342	4240	8928	2674	587	
Mean (SD)	0.69 (0.65)	0.73 (4.22)	0.65 (0.62)	0.62 (0.48)	0.64 (0.77)	0.170
A1C						
N	432	1671	4704	1738	397	
Mean (SD)	6.76 (1.92)	6.81 (2.64)	6.99 (1.66)	7.19 (1.71)	7.25 (1.72)	< 0.001
FIB-4 score						
N	1020	3010	6320	1976	472	
Mean (SD)	1.57 (1.48)	1.46 (1.44)	1.40 (1.53)	1.46 (3.59)	1.46 (1.86)	0.120

[a]One hundred eighty-seven patients with missing data were excluded from the analysis.
[b]Four hundred fifty-five patients with missing data were excluded from the analysis.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 index.

TABLE 2 Association of BMI with incidence of liver-related outcomes in patients with MASLD

	BMI (kg/m²)					*p* for linear trend	*p* for quadratic trend
	< 25.0	25.0– < 30.0	30.0– < 40.0	40.0– < 50.0	≥ 50.0		
HCC							
Person-years	15,445	51,875	103,598	29,973	6206		
Cases	28	83	114	26	4		
Rate[a]	106.9	96.0	78.1	80.6	77.9		
HR (95% CI)[b]	1.10 (0.72, 1.70)	1.00 (Reference)	0.81 (0.61, 1.08)	0.84 (0.54, 1.31)	0.83 (0.30, 2.28)	0.114	0.529
Liver decompensation							
Person-years	15,302	51,563	102,853	29,673	6133		
Cases	129	288	515	174	48		
Rate[a]	610.6	419.2	422.9	584.9	930.6		
HR (95% CI)[b]	1.44 (1.17, 1.77)	1.00 (Reference)	1.02 (0.88, 1.18)	1.42 (1.17, 1.72)	2.27 (1.66, 3.09)	0.037	< 0.001
Liver transplant							
Person-years	15,384	51,763	103,543	29,961	6205		
Cases	38	70	77	14	2		
Rate[a]	254.1	128.4	70.6	46.9	32.7		
HR (95% CI)[b]	1.89 (1.27, 2.82)	1.00 (Reference)	0.58 (0.42, 0.80)	0.38 (0.21, 0.67)	0.26 (0.06, 1.05)	< 0.001	0.478
Combined outcomes[c]							
Person-years	15,137	51,229	102,528	29,620	6126		
Cases	182	393	639	196	52		
Rate[a]	930.2	602.9	544.2	678.4	1022.6		
HR (95% CI)[b]	1.52 (1.27, 1.81)	1.00 (Reference)	0.91 (0.81, 1.04)	1.14 (0.96, 1.36)	1.72 (1.28, 2.30)	0.178	< 0.001

[a]Rate per 100,000 person-years, adjusted for age and sex.
[b]Adjusted for age, sex, race, and smoking status.
[c]Includes HCC, liver decompensation, and liver transplant.
Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease.

included only 233 Asian Americans, representing 0.7% of the total, this small sample size did not allow us to perform a subgroup analysis for Asian Americans only, who have lower BMI cutoff values for obesity.

Association of BMI with extrahepatic cancers in MASLD

Obesity is associated with an increased risk of 13 extrahepatic cancers, called obesity-associated cancers (Supplemental Table S5, http://links.lww.com/HC9/A938). BMI category 25–<30 kg/m^2 had the lowest rate of obesity-associated extrahepatic cancers at 875.7/100,000 person-years, which was not statistically significantly different from BMI categories <25 and 30–<40 kg/m^2 (Table 3). However, BMI categories 40–<50 and ≥50 kg/m^2 were associated with significantly higher HRs for obesity-associated extrahepatic cancers (HR: 1.23, 95% CI:1.07–1.42, and HR: 1.29, 95% CI: 1.00–1.76, respectively). Both linear and quadratic trends for obesity-associated extrahepatic cancers were statistically significant across BMI categories (All *p*s <0.05).

Next, we grouped all cancers not associated with obesity into extrahepatic non-obesity–associated cancers (Supplemental Table S5, http://links.lww.com/HC9/A938). The highest rate of these cancers was observed in the BMI <25 kg/m^2 category (1048.1/100,000 person-years), which progressively decreased with increasing BMI levels (Table 3). The linear trend for BMI with decreasing risk of non-obesity–associated extrahepatic cancers was significant ($p = 0.049$).

We then calculated the rate of any extrahepatic cancer (obesity-associated and non-obesity–associated cancers combined) across BMI categories. The BMI ≥50 kg/m^2 category had the lowest rate (2038.1/100,000 person-years) and BMI <25 kg/m^2 the highest rate (2310.4/100,000 person-years) of all cancers (Table 3). Compared to the reference category 25–<30 kg/m^2, only the BMI group <25 kg/m^2 had a significantly higher risk of all cancers (HR: 1.12, 95% CI: 1.00, 1.26). Neither the linear nor quadratic trend for the incidence of any cancer was significant across BMI categories.

Association of BMI with all-cause mortality in MASLD

After adjustment for age, sex, race/ethnicity, and smoking status, patients with MASLD with BMI

TABLE 3 Association of BMI with cancer incidence in patients with MASLD

	BMI (kg/m^2)						
	<25.0	25.0–<30.0	30.0–<40.0	40.0–<50.0	≥50.0	*p* for linear trend	*p* for quadratic trend
Extrahepatic obesity–associated cancers[a]							
Person-years	14,832	50,203	100,234	28,995	6025		
Cases	183	495	993	327	66		
Rate[b]	994.9	875.7	925.9	1065.9	1096.6		
HR (95% CI)[c]	1.15 (0.97, 1.36)	1.00 (Reference)	1.06 (0.95, 1.18)	1.23 (1.07, 1.42)	1.29 (1.00, 1.76)	0.049	0.023
Non-obesity–associated cancers							
Person-years	14,997	50,358	100,808	29,366	6120		
Cases	182	591	1055	244	34		
Rate[b]	1048.1	969.9	941.5	884.8	680.4		
HR (95% CI)[c]	1.09 (0.92, 1.29)	1.00 (Reference)	0.98 (0.88, 1.08)	0.93 (0.80, 1.09)	0.74 (0.52, 1.05)	0.040	0.634
Any cancer[d]							
Person-years	14,267	48,463	97,143	28,313	5933		
Cases	386	1148	2130	589	104		
Rate[b]	2310.4	2077.7	2074.1	2175.1	2038.1		
HR (95% CI)[c]	1.12 (1.00, 1.26)	1.00 (Reference)	1.01 (0.94, 1.08)	1.07 (0.97, 1.18)	1.03 (0.84, 1.26)	0.747	0.072

[a]Obesity-associated extrahepatic cancers: endometrial, esophageal adenocarcinoma, gastric cardia, kidney, multiple myeloma, meningioma, pancreatic, gallbladder, breast, ovarian, and thyroid.
[b]Rate per 100,000 person-years, adjusted for age and sex.
[c]Adjusted for age, sex, race, and smoking status.
[d]Includes HCC, extrahepatic obesity–associated cancers, and non-obesity–associated cancers.
Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease.

≥50 kg/m^2 had lowest survival rate (or reversely the highest mortality rate), followed by those with BMI <25 and 40–<50 kg/m^2 (Figure 2). There was no discernable difference in the survival curves between patients with MASLD with BMI 25–<30 and BMI 30–<40 kg/m^2. On average, BMI category 25–<30 kg/m^2 had the lowest mortality rate (780.4/100,00 person-years) and BMI ≥50 kg/m^2 had the highest mortality rate (2390.5/100,000 person-years), followed by BMI <25 kg/m^2 (1194.6/100,000 person-years) (Table 4). Compared with BMI 25–<30 kg/m^2, the HRs of mortality were significantly higher for BMI <25 kg/m^2 (HR: 1.51, 95% CI: 1.32–1.72), BMI 40–<50 kg/m^2 (HR: 1.54, 95% CI: 1.36–1.75), and BMI ≥50 kg/m^2 (HR: 3.24, 95% CI: 2.67–3.93), that was statistically significant for both linear and quadratic terms (both p's <0.001).

Trends in clinical outcomes across BMI in patients with MASLD

To generate further insight into the association of BMI with trends in liver-related and extrahepatic clinical outcomes in patients with MASLD, we generated restricted cubic spline curves with BMI as a continuous variable. As shown in Figure 3, the curves for 3 liver-related clinical outcomes were very different—a flat line for HCC risk across the BMI spectrum examined, a J-shaped curve for liver decompensation, and an L-shaped curve for liver transplant. Overall, a J-shaped association was observed for the risk of liver-related outcomes combined across the BMI range from 20 to 75 kg/m^2.

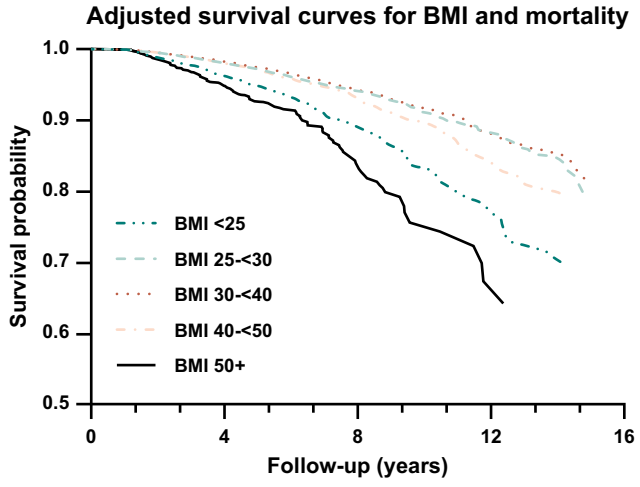

FIGURE 2 Adjusted survival curve stratified by BMI category in patients with metabolic dysfunction–associated steatotic liver disease. Patients were stratified by BMI into the following categories: <25, 25–<30, 30–<40, 40–<50, and >50 kg/m^2 category. The survival curves were adjusted for age, sex, race/ethnicity, and smoking status. Abbreviation: BMI, body mass index.

In terms of extrahepatic cancers, increasing BMI was associated with an increased risk of obesity-associated cancers and a decreased risk of non-obesity–associated cancers. When all cancers were combined, a J-shaped association was observed with the nadir at BMI between 30 and 40 kg/m^2 (Figure 3). For all-cause mortality, the risk remained flat for BMI <40 kg/m^2 and increased progressively for BMI >40 kg/m^2.

Sensitivity analyses for clinical outcomes occurring beyond 3 years

One potential concern regarding the association of BMI with clinical outcomes in MASLD is that patients with advanced liver disease may have changes in BMI either from losing weight due to sarcopenia or cachexia, or gaining weight from cirrhosis-associated volume overload in the time immediately preceding an adverse clinical event. Therefore, we performed sensitivity analyses by studying the association of BMI with liver-related outcomes after excluding incident cases observed within 3 years of the initial BMI measurement (Supplemental Table S6, http://links.lww.com/HC9/A938). The results for liver-related outcomes were similar to those in the entire cohort. Once again, no association was found between BMI and the risk of HCC. There was a J-shaped association between BMI and liver decompensation with significant linear (p = 0.026) and quadratic terms (p < 0.001). Similarly, there was a strong inverse association between BMI and liver transplantation (p_{linear} < 0.001). For all liver-related outcomes, there was a U-shaped association with higher risk at BMI <25 and ≥50 kg/m^2 (p for quadratic term <0.001).

For cancer incidence, we again observed a J-shaped association between BMI and extrahepatic obesity–associated cancers, with higher risk in BMI 40–<50 (HR: 1.26, 95% CI: 1.06, 1.50) and ≥50 kg/m^2 (HR: 1.59, 95% CI: 1.18, 2.15) categories with significant linear (p = 0.008) and quadratic terms (p = 0.001) (Supplemental Table S7, http://links.lww.com/HC9/A938). There was no association between BMI categories and non-obesity–associated cancers or overall cancer risk. However, there was a significant U-shaped association with significant quadratic terms only (p = 0.003).

For all-cause mortality, we again observed a J-shaped association with BMI (Supplemental Table 8, http://links.lww.com/HC9/A938). Compared with BMI 25–<30 kg/m^2, the mortality rate was significantly increased in BMI <25 kg/m^2 (HR: 1.52, 95% CI: 1.28, 1.80), 40–<50 (HR: 1.68, 95% CI: 1.43, 1.96), and ≥50 kg/m^2 (HR: 3.29, 95% CI: 2.57, 4.21) with significant linear and quadratic trends (both p < 0.001).

TABLE 4 Association of BMI with death in patients with MASLD

	BMI (kg/m^2)						
	< 25.0	25.0– < 30.0	30.0– < 40.0	40.0– < 50.0	≥ 50.0	*p* for linear trend	*p* for quadratic trend
Person-years	15,509	52,010	103,782	29,999	6209		
Cases	334	684	1182	385	128		
Rate[a]	1194.6	780.4	806.0	1155.6	2390.5		
HR (95% CI)[b]	1.51 (1.32, 1.72)	1.00 (Reference)	1.06 (0.96, 1.16)	1.54 (1.36, 1.75)	3.24 (2.67, 3.93)	< 0.001	< 0.001

[a]Rate per 100,000 person-years, adjusted for age and sex.
[b]Adjusted for age, sex, race, and smoking status.
Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease.

Sensitivity analysis for clinical outcomes after excluding patients with bariatric surgery

Since bariatric surgery may change the natural history of MASLD in patients with severe obesity, we performed additional analysis after excluding 1403 (4.3%) patients who underwent bariatric surgery. This sensitivity analysis showed similar results as those derived from the entire cohort (Supplemental Table S9, http://links.lww.com/HC9/A938).

DISCUSSION

Our study provides new insights into the clinical outcomes of patients with MASLD belonging to different BMI categories. The novel finding of our study was that patients with MASLD with BMI <25 kg/m^2 and > 40 kg/m^2 are at an increased risk of adverse clinical outcomes. The former group, called "lean MASLD" is already known to be associated with worse outcomes than patients with "non-lean" MASLD.[26,27] Our study, however, highlights the importance of recognizing another important subphenotype, MASLD with very severe obesity (BMI ≥ 50 kg/m^2), which is associated with an even higher risk of liver-related complications and all-cause mortality. This subgroup of patients may require earlier intervention and management of not just liver disease but also intensive therapy for obesity. On the other hand, the risk of liver-related complications appears to be relatively similar in patients with MASLD with overweight or nonsevere obesity (BMI range 25–40 kg/m^2).

In our cohort, we found that the lowest risk for liver decompensation was observed in the overweight MASLD subgroup (25– < 30 kg/m^2), and the highest risk in MASLD with severe obesity (≥ 50 kg/m^2) subgroup. We also found a negative linear association that increasing BMI was associated with decreasing likelihood of liver transplantation. There was a J-shaped association between BMI and risk of extrahepatic obesity-associated cancer among patients with MASLD, but a lack of an association between BMI with the risk of HCC or non-obesity–associated cancer. Finally, we found that patients with MASLD with BMI <25 kg/m^2 had a 50% higher risk, and those with BMI ≥ 50 kg/m^2 had over 3-fold higher risk of all-cause mortality compared to patients in the overweight category.

Prior studies have reported an increased risk of HCC in patients with MASLD, with only a modest increase in the risk of some other cancers such as colorectal, kidney, bladder, uterine, and pancreas cancers.[28,29] Our results suggest that the relationship between MASLD, obesity, hepatic, and extrahepatic cancers is nuanced. The risk of HCC was similar in patients with MASLD across all BMI categories, consistent with prior research showing that liver fibrosis is the most important risk factor for the development of HCC.[30] However, there was an increased risk of obesity-associated but not non-obesity–associated extrahepatic cancers with increasing BMI. While current evidence does not support extrahepatic cancer screening solely based on the presence of MASLD, our results suggest that prospective studies are needed to further elucidate the impact of coexisting obesity and MASLD on specific extrahepatic cancers.

Liver transplantation is a life-saving procedure for patients with liver decompensation and studies have suggested that patients with obesity have similar survival rates compared to patients with normal BMI.[31,32] However, a liver transplant is reserved for patients after undergoing a stringent evaluation process designed to exclude those with extrahepatic comorbid conditions. We found a strong negative linear association of liver transplantation with increasing BMI among patients with MASLD overall as well as in patients with MASLD with a diagnosis of cirrhosis. Since severe obesity was associated with an increased risk of liver decompensation as well as a lower probability of liver transplant, the combination of both factors contributed to the significantly higher mortality risk in patients with severe obesity. Further research is warranted to elucidate this important gap in the care of people with severe obesity and MASLD.

We acknowledge several weaknesses in the study. Given the geographical location of the health care system that provided EHRs for the present study, our study population was not as diverse as the US general

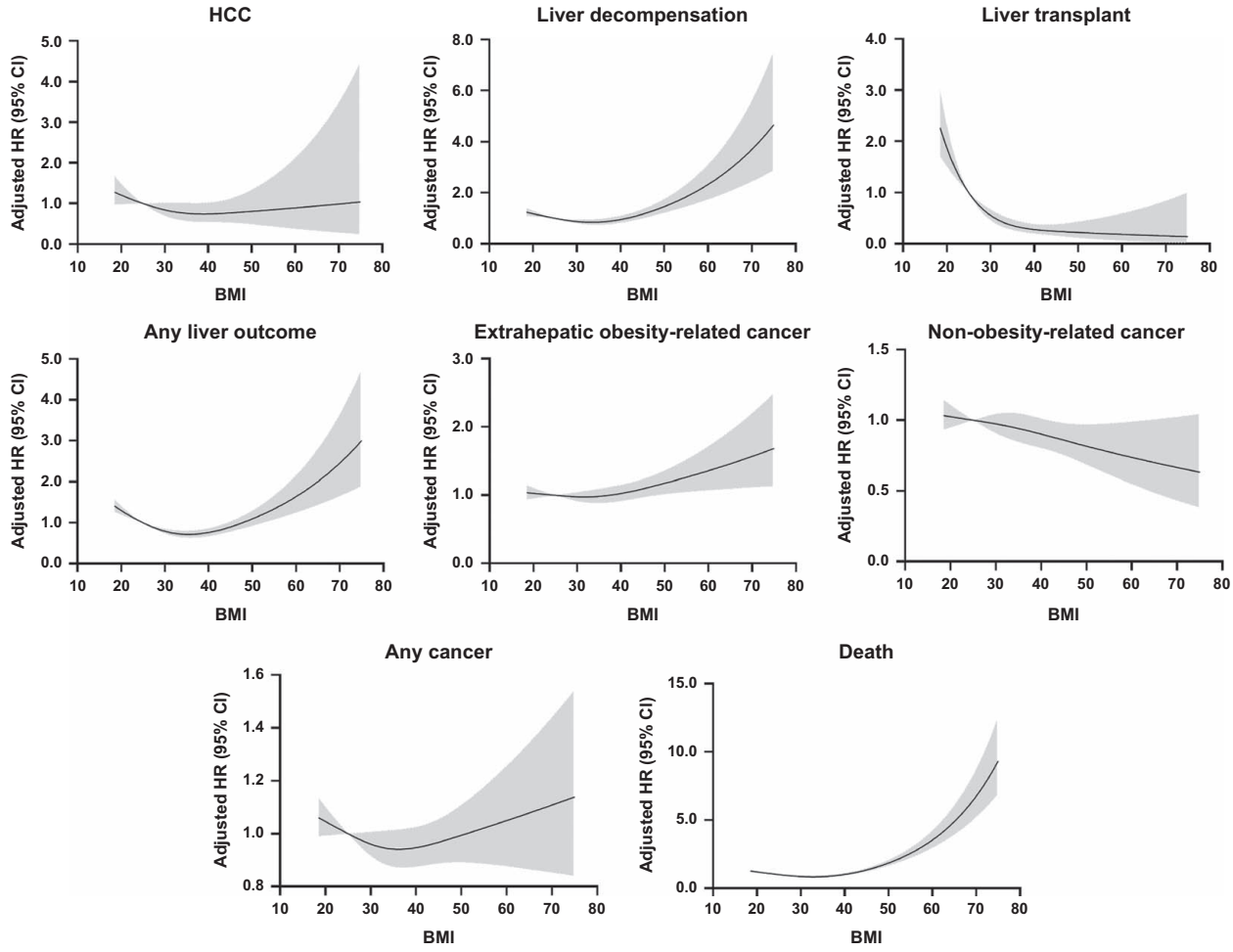

FIGURE 3 Risk of adverse clinical outcomes in patients with MASLD stratified by BMI. Restricted cubic spline curves for liver-related and extrahepatic adverse clinical outcomes in patients with MASLD stratified by BMI. The solid lines indicate HRs and the shaded areas indicate 95% CIs. Liver decompensation was defined as the presence of ascites, HE, variceal hemorrhage, or hepatorenal syndrome. Any liver outcome was a composite of HCC, liver decompensation, and liver transplant. Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease.

population. The natural history of MASLD with obesity in our study population may be different from other populations in the United States. Furthermore, the outcomes ascertained using ICD codes in the EHR may be higher in our study population than those present in the US general population. We assigned patients to the initial BMI category recorded on entry into the study and, due to limitations in the data set, could not adjust for changes in the BMI category over time, such as in patients who may have undergone bariatric surgery or treatment with antiobesity pharmacotherapy. We had insufficient data to control for the initial liver fibrosis stage determined either through liver biopsy or noninvasive tests of liver fibrosis. Cardiovascular disease is a common cause of death in patients with MASLD, but our data set did not include information on specific causes of death including cardiovascular death which precluded our analysis of cardiovascular outcomes. Since this retrospective study cohort included patients identified through administrative diagnostic codes, it also had the limitations inherent in studies that use this experimental design, particularly the difficulty in controlling for patients misclassified as having MASLD, who in reality had underlying alcohol-associated liver disease (ALD). The new multisociety consensus nomenclature for steatotic liver disease introduces the new term met-ALD (MASLD with increased alcohol intake).[1] However, we could not exclude such patients from sensitivity analysis since there have been no associated ICD-9/10 codes for this new diagnosis. Nonetheless, we excluded any patients diagnosed with ALD or other alcohol-associated health outcomes at any time during their entire period of receiving health care from this health care system, which would exclude the potential confounding effect of ALD on the BMI and outcomes studied among patients with MASLD in the present study.

Our study also has several strengths. We studied a large cohort of patients with MASLD, distributed across a wide BMI range with a relatively long-term follow-up at various clinical settings. Importantly, our study

population included a large population of patients with MASLD in the highest BMI category, which is growing faster than other BMI categories in the United States. The ICD-9/10 codes for the identification of MASLD used are recommended by an expert panel for EHR data, which would be consistent and comparable across different studies. To minimize the concern that liver-related complications may affect body weight in end-stage liver disease, we performed sensitivity analyses after excluding patients with adverse clinical outcomes within 3 years of study entry and obtained similar results.

In conclusion, patients with MASLD and very severe obesity (BMI $\geq$50 kg/m^2) represent the highest-risk subgroup, with significantly elevated risk of liver decompensation, obesity-associated cancer, and all-cause mortality. On the other hand, patients with MASLD with increasing BMI above 30 kg/m^2 are less likely to be considered for liver transplantation.

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CONFLICTS OF INTEREST

Jaideep Behari has research grant support from Gilead, Pfizer, and AstraZeneca. His institution has research contracts with Intercept, Pfizer, Inventiva, Galection, Madrigal, and Rhythm. The remaining authors have no conflicts to report.

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