A Retrospective Cohort Study Evaluating the Association Between Fibrosis-4 Index and Major Adverse Cardiovascular Events in Patients With Metabolic Dysfunction-Associated Steatohepatitis

RWD29

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Plain Language Summary

Why does it matter? Metabolic dysfunction-associated steatohepatitis (MASH) is a serious liver disease that involves fat buildup and inflammation and may lead to fibrosis, which is scarring of tissue.

What did we do? Deidentified data from patients who were newly diagnosed with MASH were used to analyze the association between amounts of fibrosis and the risk of poor cardiovascular-related outcomes.

What did we find? Patients with more fibrosis in their liver had a higher risk for developing negative cardiovascular-related outcomes.

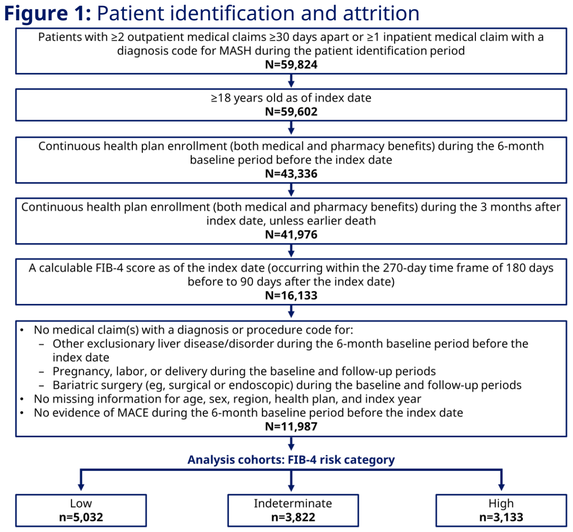
Introduction

- The cardiovascular burden in patients with metabolic dysfunction-associated steatohepatitis (MASH) is significant, particularly in patients with advanced fibrosis[1]
- Fibrosis-4 (FIB-4) index is a noninvasive test (NIT) that is used to estimate the risk of advanced fibrosis[2]
- This study aimed to quantify the relationship between FIB-4 score and the risk for developing major adverse cardiovascular events (MACE) among patients with MASH in a real-world setting in the United States

Methods

- The data set included patients (aged ≥18 years) who were newly diagnosed with MASH (index date) between October 1, 2016, and September 30, 2022, according to deidentified data from the Optum Clinformatics® Data Mart database (**Figure 1**)
- FIB-4 score within ±90 days of the index date was calculated, and patients were categorized into low- (<1.30), indeterminate- (1.30-2.67), or high-risk (>2.67) groups
- Outcomes assessed were:
  - Modified 3-point MACE, defined as any occurrence of nonfatal stroke, nonfatal acute myocardial infarction (MI), or all-cause mortality
  - Expanded MACE, defined as any occurrence of nonfatal acute MI, nonfatal stroke, coronary revascularization, heart failure (HF) hospitalization, or all-cause mortality

Figure 1: Patient identification and attrition



FIB-4, Fibrosis-4; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis.

Methods (cont'd)

- Using robust Poisson regression models, we estimated crude risk ratios and 95% CIs to evaluate the association between FIB-4 scores and MACE outcomes (both composite and individual components) during the 2-year follow-up period

Results

- Among 11,987 patients with MASH, 42%, 31.9%, and 26.1% had low-, indeterminate-, and high-risk FIB-4 scores, respectively
- The mean follow-up time was significantly lower in the high-risk group compared with that in the low-risk group (**Table 1**)
- Patients in the high-risk group were older compared with patients in the low-risk group (**Table 1**)
- Significantly more females were in the high- compared with the low-risk group, while significantly more males were in the low- compared with the high-risk group (**Table 1**)

Table 1: Baseline sociodemographic and clinical characteristics of patients with MASH by FIB-4 risk categories

	Low risk (n=5,032)	Indeterminate risk (n=3,822)	High risk (n=3,133)	Indeterminate vs low risk *P* value	High vs low risk *P* value
Follow-up, d					
Mean (SD)	875.6 (572.7)	891.5 (587.3)	749.0 (568.5)	.20	<.001
Age at index, y					
Mean (SD)	52.3 (13.0)	64.4 (10.2)	68.0 (9.8)	<.001	<.001
Sex, n (%)					
Male	2,107 (41.9)	1,520 (39.8)	1,184 (37.8)	.05	<.001
Female	2,925 (58.1)	2,302 (60.2)	1,949 (62.2)	.05	<.001
BMI,[a] n (%)					
Normal weight: 20.0-24.9 kg/m^2	62 (1.2)	79 (2.1)	97 (3.1)	.002	<.001
Overweight: 25.0-29.9 kg/m^2	452 (9.0)	387 (10.1)	294 (9.4)	.07	.54
Obesity class 1: 30.0-34.9 kg/m^2	526 (10.5)	441 (11.5)	368 (11.8)	.11	.07
Obesity class 2: 35.0-39.9 kg/m^2	487 (9.7)	343 (9.0)	309 (9.9)	.26	.78
Obesity class 3: ≥40.0 kg/m^2	867 (17.2)	580 (15.2)	514 (16.4)	.01	.33
Unspecified	1,099 (21.8)	797 (20.9)	604 (19.3)	.26	.01
Race and ethnicity, n (%)					
Non-Hispanic White	2,885 (57.3)	2,473 (64.7)	2,103 (67.1)	<.001	<.001
Non-Hispanic African American/Black	394 (7.8)	283 (7.4)	241 (7.7)	.46	.82
Non-Hispanic Asian	264 (5.3)	126 (3.3)	77 (2.5)	<.001	<.001
Hispanic	1,188 (23.6)	762 (19.9)	536 (17.1)	<.001	<.001
Other/unknown	301 (6.0)	178 (4.7)	176 (5.6)	.006	
Region, n (%)					
Northeast	552 (11.0)	447 (11.7)	340 (10.9)	.01	<.001
Midwest	532 (10.6)	440 (11.5)	463 (14.8)	.16	<.001
South	3,166 (62.9)	2,435 (63.7)	1,963 (62.7)	.44	.81
West	780 (15.5)	500 (13.1)	367 (11.7)	.001	<.001
Other	2 (0.04)	0 (0.0)	0 (0.0)	.22	.26
Baseline comorbidities, n (%)					
T2D	1,883 (37.4)	1,990 (52.0)	2,036 (65.0)	<.001	<.001
Hypertension	2,778 (55.2)	2,711 (70.9)	2,396 (76.5)	<.001	<.001
Lipid metabolism disorder	2,881 (57.3)	2,531 (66.2)	1,989 (63.5)	<.001	<.001
Coronary heart disease	490 (9.7)	684 (17.9)	676 (21.6)	<.001	<.001
Tobacco/nicotine history	368 (7.3)	256 (6.7)	209 (6.7)	.26	.27

BMI, body mass index; FIB-4, Fibrosis-4; ICD, *International Classification of Diseases*; MASH, metabolic dysfunction-associated steatohepatitis; T2D, type 2 diabetes.
[a]Patients may have had evidence of more than 1 BMI category during the observation period, as the data include separate ICD code categories for normal weight, overweight, obesity, and unspecified BMI.

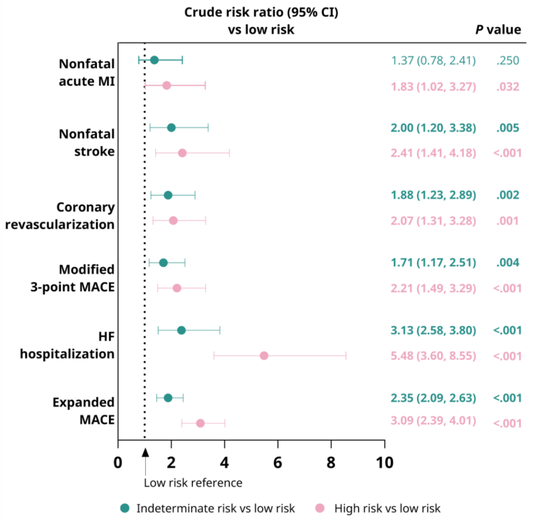
- Body mass index distributions showed significant differences between risk categories, with obesity patterns varying across groups (**Table 1**)
- Baseline comorbidities, including type 2 diabetes, hypertension, lipid metabolism disorders, and coronary heart disease, were all significantly more prevalent in patients in the high-risk group compared with the low- and indeterminate-risk groups (**Table 1**)
- In the FIB-4 risk groups, cumulative incidences progressively increased from the low- to high-risk groups across all MACE end points. The crude number of events also increased progressively for HF hospitalization and expanded MACE (**Table 2**)
- High FIB-4 risk was significantly associated with increased risk of nonfatal acute MI, nonfatal stroke, coronary revascularization, modified 3-point MACE, and specifically HF hospitalization, as well as expanded MACE, compared with low FIB-4 risk (**Figure 2**)
- Similar significant associations were observed between indeterminate- and low-risk groups for most outcomes except nonfatal acute MI (**Figure 2**)

Table 2: Cumulative incidences of MACE outcomes at 2 years in patients with MASH by FIB-4 risk categories

MACE outcome	Low risk (n=2612)			Indeterminate risk (n=1982)			High risk (n=1322)		
	Events, n	Incidence, %[a]	95% CI	Events, n	Incidence, %[a]	95% CI	Events, n	Incidence, %[a]	95% CI
Nonfatal acute MI	27	1.03	.68-1.50	28	1.41	.94-2.04	25	1.89	1.23-2.78
Nonfatal stroke	27	1.03	.68-1.50	41	2.07	1.49-2.80	33	2.50	1.72-3.49
Coronary revascularization	40	1.53	1.10-2.08	57	2.88	2.19-3.71	42	3.18	2.30-4.27
Modified 3-point MACE	51	1.95	1.46-2.56	66	3.33	2.58-4.22	57	4.31	3.28-5.55
HF hospitalization	31	1.19	.81-1.68	56	2.83	2.14-3.65	86	6.51	5.24-7.97
Expanded MACE definition	101	3.87	3.16-4.68	144	7.27	6.16-8.50	158	11.95	10.25-13.82

FIB-4, Fibrosis-4; HF, heart failure; MACE, major adverse cardiovascular event; MASH, metabolic dysfunction-associated steatohepatitis; MI, myocardial infarction.
[a]Exact 95% binomial confidence limits were used for percentages of binary measures.

Figure 2: Crude risk ratios of MACE outcomes at 2 years in patients with MASH by FIB-4 risk categories



FIB-4, Fibrosis-4; HF, heart failure; MACE, major adverse cardiovascular event; MASH, metabolic dysfunction-associated steatohepatitis; MI, myocardial infarction.

Exact binomial distribution was used to calculate 95% CIs for crude risk ratios. Z-test using robust standard errors in a Poisson regression was used for assessing significance of crude risk ratios.

Conclusions

- Patients with high FIB-4 scores had increased risks for cardiovascular events compared with patients with low FIB-4 scores, which suggests that advanced fibrosis may serve as an independent risk factor for cardiovascular morbidity
- The strong association between FIB-4 scores and MACE outcomes suggests that this NIT may be valuable for risk stratification and clinical decision-making
- Further research is needed to elucidate the mechanisms underlying the relationship between hepatic fibrosis and cardiovascular complications in patients with MASH

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References:
(**1**) Charlton M, et al. *J Med Econ*. 2024;27(1):919-930; (**2**) Sterling RK, et. al. *Hepatology*. 2006;43:1317-1325.