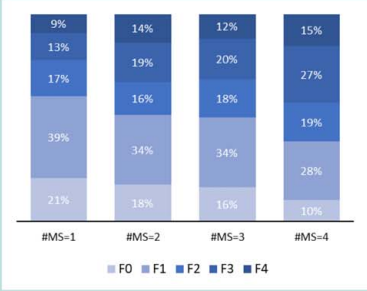
Predictors of fibrosis, clinical events, and mortality in MASLD: Data from the Global-MASLD study

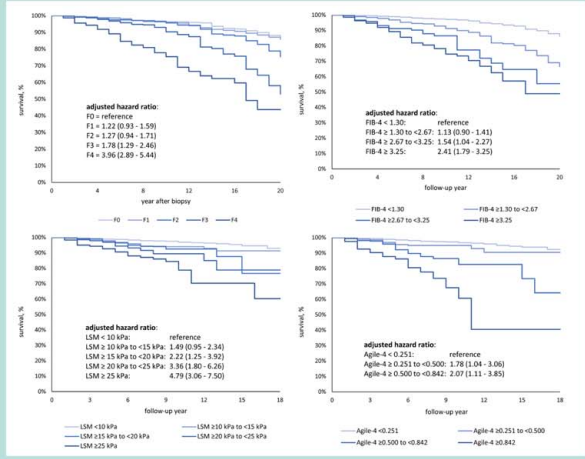
VISUAL ABSTRACT

Predictors of fibrosis, clinical events, and mortality in MASLD: Data from the Global-MASLD study

- Patients with more metabolic syndrome (MS) components have more advanced fibrosis.



- All-cause mortality in MASLD is strongly linked to histologic fibrosis and elevated NIT scores.



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ORIGINAL ARTICLE

Predictors of fibrosis, clinical events, and mortality in MASLD: Data from the Global-MASLD study

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Abstract

Background and Aims: Advanced histologic fibrosis is a major predictor of mortality in metabolic dysfunction–associated steatotic liver disease (MASLD). We aimed to identify advanced fibrosis clinical determinants across diverse MASLD populations and to assess the prognostic value of noninvasive markers (NITs) of fibrosis for adverse outcomes.

Approach and Results: The Global MASLD (G-MASLD) enrolled biopsy-confirmed MASLD patients with clinical, histologic, and noninvasive test (NIT) data. Factors associated with the presence of advanced histologic fibrosis (F3-F4) in MASLD and clinical outcomes were assessed. There were 17,792 patients with MASLD. Advanced fibrosis ($\geq$F3) was present in 35%. The prevalence of type 2 diabetes (T2D) increased stepwise with fibrosis stage, from 28% in F0 to 70% in F4 (trend $p < 0.0001$). Independent predictors of advanced fibrosis included older age, T2D, and obesity, although the association with obesity varied by region. Among patients with follow-up (mean 6.6 y), 6.5% died and 10.1% experienced a clinical event. Older age, male sex, T2D, and obesity were independent predictors of both mortality and clinical events ($p < 0.05$). Fibrosis severity, whether defined histologically or by NITs, was strongly associated with higher risks of death and liver-related outcomes (all adjusted HR > 1.0, $p < 0.001$). Five-year mortality was 2.1% overall, rising to 8.3% in patients with cirrhosis, and exceeded 10% among those with high-risk NIT score values.

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; FIB-4, fibrosis-4 index; GNC, Global NASH/MASH Council; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MS, metabolic syndrome; NAS, NAFLD Activity Score; NITs, noninvasive tests; T2D, type 2 diabetes.

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Conclusions: In this large global biopsy-based MASLD cohort, advanced fibrosis was highly prevalent and strongly linked to T2D. Both histologic fibrosis and NITs were independent predictors of mortality and clinical outcomes, underscoring the prognostic value of fibrosis assessment with NITs.

Keywords: biomarkers, chronic liver disease, diagnostic thresholds, metabolic syndrome, noncommunicable diseases, steatohepatitis, outcomes, steatotic liver disease

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) has emerged as highly prevalent across the globe.[1–3] The spectrum of MASLD ranges from isolated steatosis to steatohepatitis with progressive fibrosis, culminating in cirrhosis, liver failure, and HCC.[4] In patients with MASLD, the presence of advanced histologic fibrosis, in particular, is a predictor of liver-related and all-cause mortality.[4–6]

Despite its growing public health impact, comprehensive global data on MASLD outcomes remain limited. While metabolic risk factors such as obesity and type 2 diabetes (T2D) are well-established contributors to disease progression, most existing evidence comes from single-center or region-specific studies, limiting the generalizability and consistency of these associations across diverse global populations.[6–12] Moreover, prior outcome studies have often relied on limited histologic data or noninvasive tests (NITs), restricting the ability to fully assess disease severity and prognosis.

To address the knowledge gaps, the Global MASLD (G-MASLD) initiative was established as a collaborative effort involving over 40 countries. This study represents a large-scale analysis of liver biopsy-confirmed patients with MASLD with harmonized clinical, histological, and noninvasive data, including long-term follow-up for mortality and clinical outcomes. Our objectives were (1) to characterize global patterns of advanced fibrosis in MASLD and its association with metabolic comorbidities, (2) to identify independent predictors of fibrosis severity across world regions, and (3) to assess the impact of histologic and noninvasive markers of fibrosis on long-term outcomes, including mortality and liver-related events.

METHODS

Study sample

The Global MASLD (G-MASLD) initiative was launched in 2023 by the Global NASH/MASH Council (GNC) as a collaborative effort involving investigators from >40 countries. Each participating site obtained approval from its local Institutional Review Board or equivalent authority for the collection of clinical and histological data. Deidentified data were transferred to the GNC following execution of a data use agreement and subsequently curated in a secure central database for pooled analysis.

Per study protocol, exclusion criteria included age below 18 years at biopsy, pregnancy, absence of core demographic information (age, sex, country), lack of biopsy data, absence of hepatic steatosis (defined as NAS steatosis score $=0$ and controlled attenuation parameter <238 dB/m), failure to meet MASLD diagnostic criteria (at least one cardio-metabolic risk factor), and the presence of other causes of chronic liver disease (including but not limited to viral hepatitis, autoimmune liver disease, or alcohol-associated liver disease (alcohol use >60 g/d in male, >50 g/d in female).

Data collection and definitions

Standardized forms captured demographic information (age, sex, country), anthropometric data (height, weight, body mass index [BMI], waist circumference), alcohol use frequency and amount, and liver histology features (fibrosis stage [F0-F4] and NAFLD Activity Score [NAS]). Four studied components of metabolic syndrome (MS) included obesity (defined as BMI >30 or >25 kg/m^2 in patients of East Asian origin), along with a history of T2D, hypertension, and hyperlipidemia. Advanced fibrosis was defined as histologic fibrosis stage F3-F4. NITs included vibration-controlled transient elastography with liver stiffness measurement (LSM) and controlled attenuation parameter, along with laboratory assessments. Laboratory and vibration-controlled transient elastography data obtained within 1 year of biopsy were used to calculate established biomarker-based NIT scores. FIB-4 was derived from liver enzymes and platelet counts. FibroScan-AST, Agile-3+, and Agile-4 scores

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were computed using published algorithms and available clinical data.[13–15]

Most sites also provided mortality follow-up data for their subjects. For these subjects, time to event (mortality or censoring) was calculated from the time of biopsy.

Statistical analysis

All collected demographic and clinical parameters, as well as NIT scores, were summarized as n (%) or mean ± SD. In case of missing data, only observed data were used for any analysis.

Comparisons between groups were conducted using the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test for categorical variables. Factors associated with advanced fibrosis were assessed using logistic regression models, and the independent association of fibrosis severity (defined by histology or NITs) with the risk of all-cause mortality and of clinical events (decompensation, HCC, liver transplantation, death) was evaluated using Cox proportional hazards models.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

The study received approval from the Western Institutional Review Board and from the respective Institutional Review Boards or equivalent supervisory institutions at each participating site. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul, and all subjects had provided informed consent prior to enrollment in research studies in their respective sites.

RESULTS

There were 17,792 eligible patients with liver biopsy data from 41 countries (Supplemental Table S1, Supplemental Figure S1, http://links.lww.com/HEP/K323). The mean ± SD age was 51 ± 13 years, 48% were male, 70% obese, 47% T2D, 53% hypertension, and 53% hyperlipidemia. In addition, 35% had advanced histologic fibrosis (≥F3) and 13% had F4 (cirrhosis).

Advanced fibrosis and MS in MASLD

Patients with MASLD with advanced fibrosis were older, more commonly female, and had more components of MS in comparison to those with early to moderate fibrosis (F0-F2) ($p < 0.01$) (Table 1). Subjects with more advanced fibrosis had more components of MS, especially T2D: F0-28%, F1-35%, F2-46%, F3-62%, F4-70.0% (trend $p < 0.0001$) (Figure 1, Supplemental Figure S2, http://links.lww.com/HEP/K323).

In the pooled sample, adjusted for the region of enrollment, independent predictors of advanced fibrosis in MASLD included older age (OR = 1.056 [1.052–1.059] per year), obesity (OR = 1.16 [1.06–1.26]), and T2D (OR = 2.42 [2.24–2.61]) only ($p < 0.01$) (Table 2). In addition, a higher cumulative number of MS components was associated with a greater risk of advanced fibrosis (trend $p < 0.0001$) (Figure 1). In a subgroup with alcohol use data (n = 8740, 26% with advanced fibrosis), the relationship of advanced fibrosis with MS remained (trend $p < 0.0001$) and was not affected by the self-reported amount of alcohol use beyond very low levels (Supplemental Table S2, http://links.lww.com/HEP/K323).

In the region-based subgroups, the presence of advanced fibrosis was strongly associated with older age and T2D for all global regions (all adjusted $p < 0.01$); adjusted for these factors, the association of advanced fibrosis with obesity was only observed in Europe and East/Southeast Asia regions ($p < 0.01$) (Table 2).

Predictors of mortality and clinical events in MASLD

There were 8411 subjects who had follow-up data (mean [SD] duration 6.6 [6.9] years), with cumulative 6.5% deaths and 10.1% of patients with a clinical event (decompensation, HCC, transplantation, or death) (Supplemental Figure S1, http://links.lww.com/HEP/K323).

The 5-year mortality rate in the study sample was 2.1%; this rate was 8.3% in patients with cirrhosis ($p < 0.01$). With reference to NITs, the 5-year mortality of at least 10% was observed among patients with FIB-4 ≥ 3.62 or LSM ≥ 28.6 kPa. The respective annualized mortality rate is 2.5%.

In a multivariate Cox proportional hazards model that included only demographic and clinical parameters, independent predictors of all-cause mortality in MASLD included older age, male sex, obesity, and T2D (all adjusted HR > 1.0, $p < 0.05$); the same factors were also associated with a higher risk of clinical events (Table 3).

In Cox proportional hazards models which assessed the association of severity of liver disease with patient outcomes (adjusted for country of enrollment, age, sex, obesity, T2D, and hypertension), fibrosis severity by histology or NITs was associated with higher all-cause mortality and higher risks of clinical or liver events: all adjusted HR > 1.0, $p < 0.001$ (Figure 2, Supplemental Figure S3, http://links.lww.com/HEP/K323). All observed associations were most pronounced in patients with more severe fibrosis as determined by greater fibrosis stage or higher NIT score values (Figure 3).

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TABLE 1 Demographic and clinical parameters of included patients with MASLD by the presence of advanced fibrosis

	MASLD F0-F2	MASLD F3-F4	*p*	All MASLD
N	11,518	6274	—	17,792
Region of enrollment, n (%)				
Europe	3358 (29.2)	1825 (29.1)	—	5183 (29.1)
Middle East and North Africa (MENA)	996 (8.6)	280 (4.5)	< 0.0001	1276 (7.2)
Latin America	633 (5.5)	253 (4.0)	—	886 (5.0)
South Asia	923 (8.0)	219 (3.5)	—	1142 (6.4)
East or Southeast Asia	2937 (25.5)	1113 (17.7)	—	4050 (22.8)
USA/Canada	2672 (23.2)	2584 (41.2)	—	5256 (29.5)
Age, y	47.3 ± 13.2	56.6 ± 10.8	< 0.0001	50.6 ± 13.2
Male sex, n (%)	5799 (50.3)	2706 (43.1)	< 0.0001	8505 (47.8)
College degree, n (%)	737 (34.0)	150 (29.0)	0.0315	887 (33.0)
Any alcohol use (> 0 g/d), n (%)	1071 (15.5)	329 (14.4)	0.21	1400 (15.2)
Significant alcohol use (M/F > 30/20 g/d), n (%)	111 (1.7)	58 (2.6)	0.0088	169 (1.9)[a]
BMI, kg/m^2	33.8 ± 9.2	33.1 ± 6.7	0.0007	33.5 ± 8.4
Obesity (BMI > 30 or 25), n (%)	7735 (68.8)	4423 (72.3)	< 0.0001	12,158 (70.0)
Type 2 diabetes, n (%)	4123 (36.5)	4013 (65.1)	< 0.0001	8136 (46.6)
Hypertension, n (%)	5105 (46.3)	3617 (64.5)	< 0.0001	8722 (52.5)
Hyperlipidemia, n (%)	5396 (50.5)	3136 (56.9)	< 0.0001	8532 (52.7)
Cardiovascular disease, n (%)	318 (5.1)	151 (8.6)	< 0.0001	469 (5.8)
NAS score	3.90 ± 1.70	4.90 ± 1.45	< 0.0001	4.27 ± 1.68
NAS ≥ 5, n (%)	3543 (38.0)	3522 (63.8)	< 0.0001	7065 (47.6)
Noninvasive tests, n (%)				
FIB-4	1.15 ± 0.96	2.34 ± 1.89	< 0.0001	1.57 ± 1.48
CAP, dB/m	314.1 ± 48.9	318.1 ± 51.6	< 0.0001	315.6 ± 50.0[a]
LSM, kPa	8.70 ± 5.31	18.2 ± 12.1	< 0.0001	12.4 ± 9.8[a]
FAST	0.422 ± 0.231	0.638 ± 0.215	< 0.0001	0.504 ± 0.248[a]
Agile-3+	0.429 ± 0.282	0.822 ± 0.209	< 0.0001	0.583 ± 0.320[a]
Agile-4	0.067 ± 0.117	0.359 ± 0.293	< 0.0001	0.181 ± 0.249[a]
Died in follow-up	343 (5.5)	200 (9.2)	< 0.0001	543 (6.5)
Had a clinical event in follow-up	399 (6.9)	398 (19.3)	< 0.0001	797 (10.1)

[a]The amount of daily alcohol use was available for 8745 subjects (49% of the sample); LSM was available for 10,769 subjects (61% of the sample); CAP was available for 8956 subjects (50%); FAST was available for 8656 subjects (49%); Agile-3+ and Agile-4 were available for 10,197 subjects (57%); and post-baseline follow-up was available for 8411 subjects (47% of the sample); clinical event defined as death or decompensation or HCC or liver transplantation.
Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; FAST, FibroScan-AST; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MENA, Middle East and North Africa; NAS, NAFLD Activity Score.

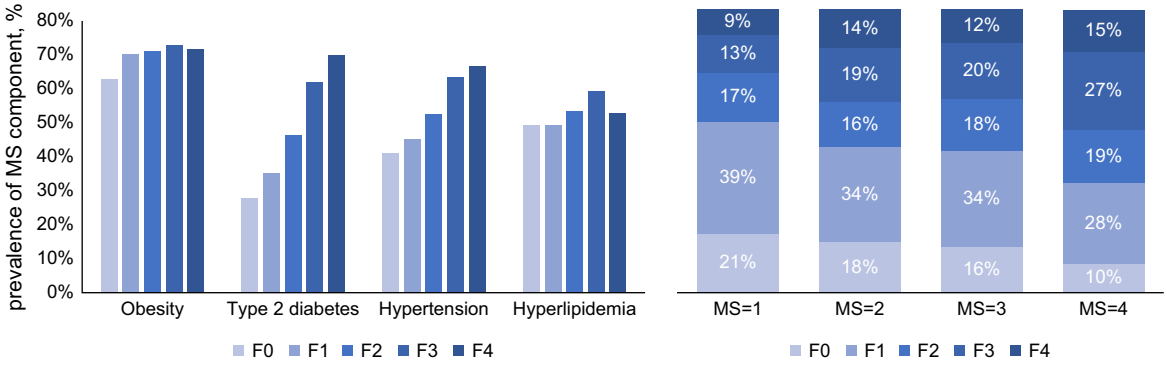


FIGURE 1 Cross-sectional association of histologic fibrosis with individual MS components and the number of MS components in patients with MASLD. Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; MS, metabolic syndrome.

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TABLE 2 Factors associated with the presence of advanced fibrosis (F3-F4) in MASLD (returned by logistic regression models,* OR adjusted for the region of enrollment)

Region	Predictor	OR (95% CI)	*p*
Europe	Age, per year	1.051 (1.044–1.058)	< 0.0001
	Male (ref: female)	0.962 (0.844–1.097)	0.57
	Obesity	1.383 (1.209–1.583)	< 0.0001
	Type 2 diabetes	2.283 (1.986–2.624)	< 0.0001
	Hypertension	0.980 (0.850–1.129)	0.78
	Hyperlipidemia	1.024 (0.894–1.174)	0.73
Middle East and North Africa (MENA)	Age, per year	1.072 (1.053–1.091)	< 0.0001
	Male (ref: female)	1.263 (0.911–1.750)	0.16
	Obesity	0.796 (0.561–1.130)	0.20
	Type 2 diabetes	2.179 (1.525–3.112)	< 0.0001
	Hypertension	1.230 (0.867–1.746)	0.25
	Hyperlipidemia	0.986 (0.704–1.381)	0.94
Latin America	Age, per year	1.056 (1.039–1.073)	< 0.0001
	Male (ref: female)	0.846 (0.598–1.198)	0.35
	Obesity	1.113 (0.796–1.557)	0.53
	Type 2 diabetes	1.451 (1.047–2.010)	0.0252
	Hypertension	1.090 (0.786–1.513)	0.60
	Hyperlipidemia	0.719 (0.520–0.994)	0.0457
South Asia	Age, per year	1.047 (1.030–1.065)	< 0.0001
	Male (ref: female)	0.972 (0.697–1.357)	0.87
	Obesity	1.156 (0.800–1.672)	0.44
	Type 2 diabetes	2.065 (1.475–2.891)	< 0.0001
	Hypertension	1.088 (0.756–1.566)	0.65
	Hyperlipidemia	0.344 (0.243–0.486)	< 0.0001
East or Southeast Asia	Age, per year	1.058 (1.051–1.066)	< 0.0001
	Male (ref: female)	0.935 (0.793–1.101)	0.42
	Obesity	1.531 (1.240–1.891)	< 0.0001
	Type 2 diabetes	2.189 (1.846–2.595)	< 0.0001
	Hypertension	1.241 (1.048–1.469)	0.0122
	Hyperlipidemia	0.691 (0.586–0.815)	< 0.0001
USA/Canada	Age, per year	1.053 (1.047–1.060)	< 0.0001
	Male (ref: female)	1.209 (1.054–1.388)	0.0068
	Obesity	0.803 (0.675–0.956)	0.0135
	Type 2 diabetes	2.946 (2.567–3.383)	< 0.0001
	Hypertension	0.947 (0.817–1.099)	0.48
	Hyperlipidemia	0.866 (0.752–0.999)	0.0476
All*	Age, per year	1.056 (1.052–1.059)	< 0.0001
	Male (ref: female)	1.047 (0.972-1.129)	0.23
	Obesity	1.159 (1.065–1.262)	0.0006
	Type 2 diabetes	2.417 (2.237–2.612)	< 0.0001
	Hypertension	1.048 (0.968–1.135)	0.24
	Hyperlipidemia	0.837 (0.775–0.903)	< 0.0001

To further explore heterogeneity in the prognostic performance of NITs, we examined effect modification by age, BMI, T2D, and alcohol use for the association of fibrosis severity (by histology or NITs) with the risk of clinical events.

Age was found to be a significant effect modifier for FIB-4 (p for interaction = 0.0187). Indeed, among patients younger

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TABLE 3 Clinico-demographic factors associated with all-cause mortality and clinical events in MASLD (adjusted for the country of enrollment)

Predictor	aHR (95% CI)	*p*
All-cause mortality		
Age, per year	1.091 (1.081–1.101)	< 0.0001
Male sex	1.32 (1.11–1.58)	0.0022
Obesity	1.28 (1.06–1.54)	0.0089
Type 2 diabetes	1.25 (1.02–1.53)	0.0324
Hypertension	1.21 (0.98–1.49)	0.07
Hyperlipidemia	0.89 (0.72–1.11)	0.30
Clinical events		
Age, per year	1.077 (1.069–1.085)	< 0.0001
Male sex	1.25 (1.08–1.46)	0.0039
Obesity	1.21 (1.03–1.41)	0.0197
Type 2 diabetes	1.40 (1.18–1.66)	0.0001
Hypertension	1.10 (0.93–1.30)	0.28
Hyperlipidemia	0.91 (0.76–1.08)	0.27

Additional association of histologic fibrosis and NITs with the outcomes is shown in Figure 2.
Abbreviation: aHR, adjusted hazard ratio.

than 65 years, those with FIB-4 ≥ 3.25 had a cumulative incidence of clinical events of 26.8% versus 6.7% in those with lower FIB-4 (risk ratio = 3.99). In contrast, among patients aged 65 and older, the cumulative incidence was 33.2% versus 17.0%, respectively (risk ratio = 1.95). In time-to-event models, the adjusted HR for FIB-4 ≥ 3.25 was 3.54 (2.71–4.63) in patients < 65 years, compared to 2.56 (1.90–3.45) in those ≥ 65 years (Supplemental Table S3, http://links.lww.com/HEP/K323). There was no significant effect modification by age for the association of outcomes with histologic fibrosis or LSM (all $p > 0.05$).

Elevated LSM was consistently associated with increased risk of clinical events across all BMI categories; however, the magnitude of this risk varied substantially by BMI. Specifically, the adjusted hazard of clinical events associated with LSM ≥ 15 kPa was highest among lean individuals and progressively lower in those with higher BMI (p for interaction = 0.0003) (Supplemental Table S3, http://links.lww.com/HEP/K323). There was no significant effect modification by BMI for the association of outcomes with histologic fibrosis or FIB-4 (all $p > 0.05$). Finally, there was no significant effect modification by T2D or alcohol use for the association of outcomes with fibrosis severity defined by histology or NITs (all $p > 0.05$).

DISCUSSION

This global, biopsy-based study of nearly 18,000 patients with MASLD from 41 countries offers new insights into the worldwide burden of advanced fibrosis and its clinical consequences. Consistent with prior studies, our findings confirm that age and T2D are strong, independent predictors of advanced fibrosis across all regions, reinforcing their central role of T2D in the pathogenesis of fibrotic progression in MASLD.[8,16,17] Interestingly, the association of obesity with advanced fibrosis was more variable: while obesity was an independent predictor of advanced fibrosis in the pooled global sample and in regions such as Europe and East/Southeast Asia, this was not consistently observed. While this may be a reflection of the limitations of measuring obesity via BMI,[18] this may

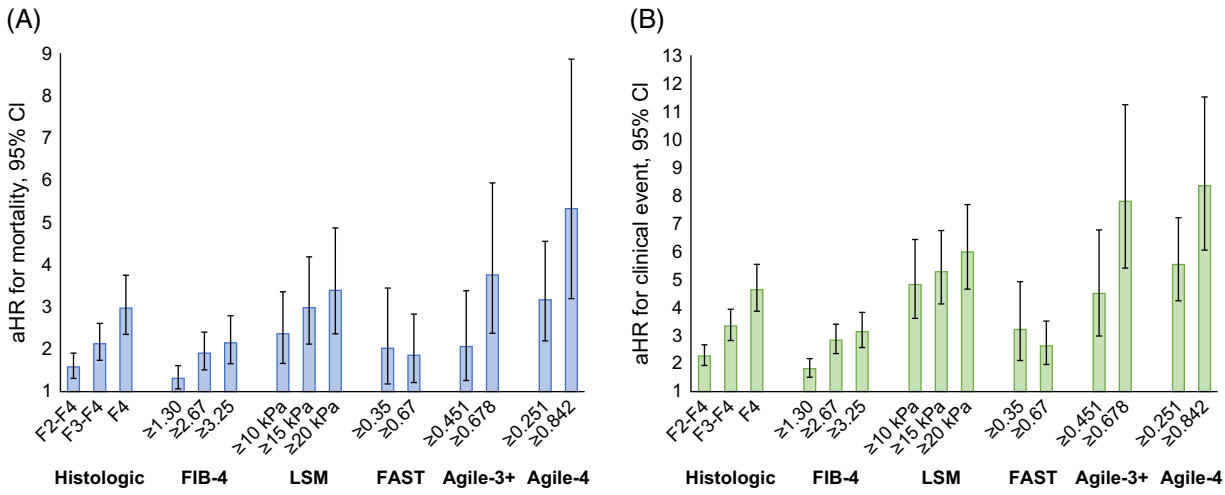


FIGURE 2 Independent association of fibrosis severity with (A) all-cause mortality and (B) clinical events (death or liver event). The aHRs with 95% CI were returned by Cox proportional hazards models adjusted for country of enrollment, age, sex, obesity, type 2 diabetes, and hypertension. A similarly assessed association of fibrosis severity with liver events only is shown in Supplemental Figure S3, http://links.lww.com/HEP/K323. For noninvasive tests, the categories are binary and not mutually exclusive. Each threshold group includes all patients meeting or exceeding that threshold, and the corresponding aHRs are shown relative to patients not meeting the threshold. Abbreviations: aHR, adjusted hazard ratios; FAST, FAST, FibroScan-AST; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement.

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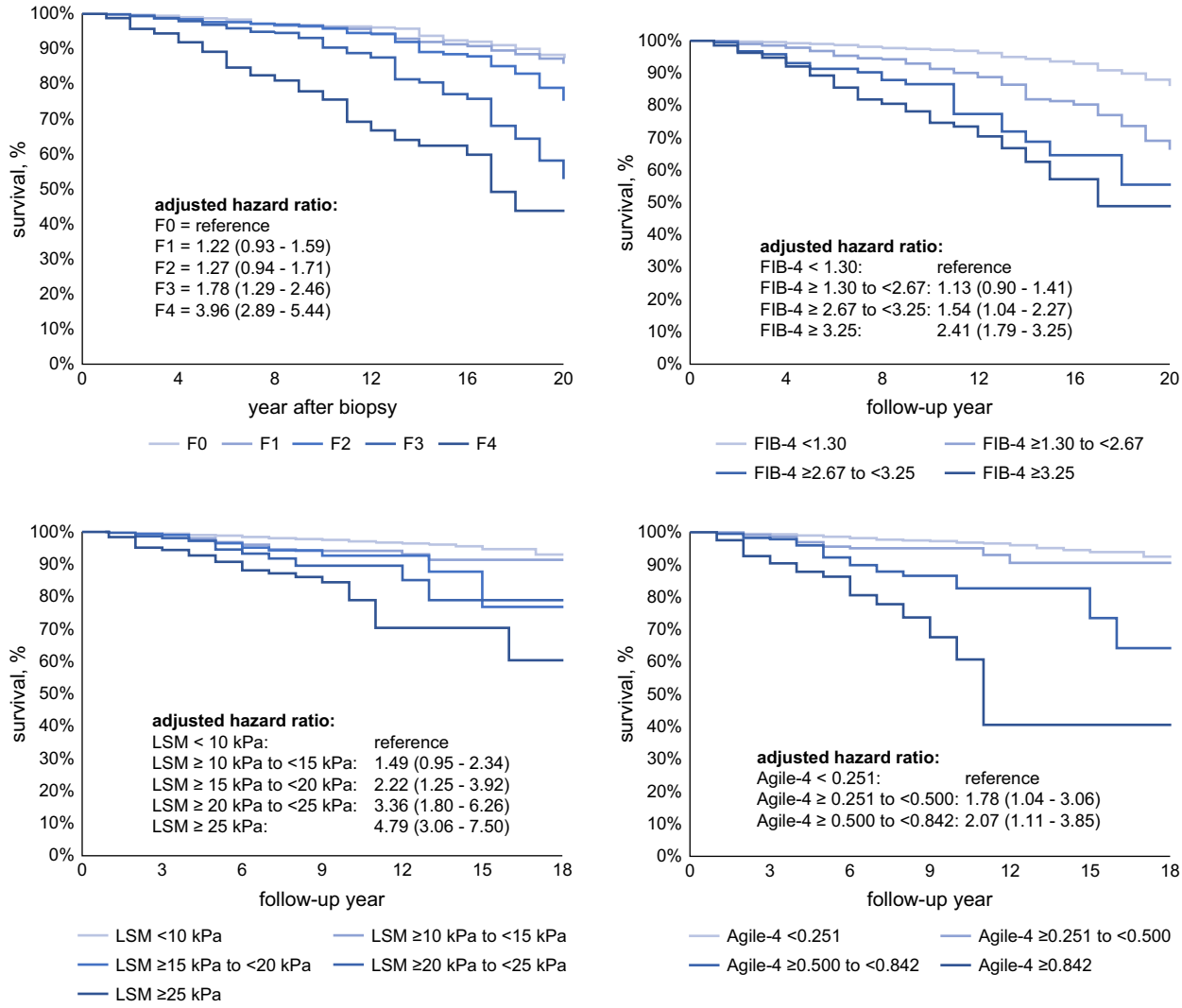


FIGURE 3 Survival in follow-up by fibrosis stage and NIT scores in patients with MASLD. Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; NIT, noninvasive test.

also be influenced by regional differences in body composition, adipose distribution, diagnostic thresholds for obesity, or unmeasured genetic and environmental factors.[19] These findings emphasize the importance of contextualizing MASLD risk assessments using region-specific data and definitions.

Our finding of a stepwise rise in the prevalence of T2D across fibrosis stages (from 28% in F0 to 70% in F4), together with the independent association of T2D with advanced fibrosis, not only supports current recommendations to prioritize fibrosis assessment among patients with T2D[20] but also carries immediate clinical implications. In particular, it underscores the need for active case-finding for those individuals with significant hepatic fibrosis among people with T2D and, conversely, proactive screening for T2D among patients with suspected MASLD. Moreover, the co-existence of T2D should influence therapeutic priorities toward regimens that address both hepatic and metabolic endpoints. Furthermore, because T2D identifies a subgroup at substantially higher risk of advanced fibrosis and adverse outcomes in our sample, it is plausible that different cutoffs for select NITs may be warranted to guide escalation of care for these higher-risk patients. Future work should assess whether systematic case-finding and earlier initiation of targeted metabolic therapies in people with T2D translate into improved clinical outcomes. Although most patients with metabolic dysfunction–associated steatohepatitis already have an established diagnosis of T2D, on rare occasions, an evaluation for T2D and insulin resistance in those with metabolic dysfunction–associated steatohepatitis should be considered.

In patients with available follow-up, our findings reinforce the prognostic significance of the stage of hepatic fibrosis. Both histologically determined fibrosis and fibrosis severity estimated using NITs were strongly associated with higher risks of all-cause mortality and liver-related events. Importantly, while NITs are typically

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validated against liver-specific outcomes, their relationship with overall mortality is less well established; our analysis, therefore, extends the evidence base by demonstrating robust associations with all-cause death. Notably, NITs such as FIB-4 and LSM by transient elastography were effective at stratifying risk, with 5-year mortality exceeding 10% among patients with high-risk NIT values. These results further support the use of NITs as clinically meaningful endpoints in both routine care and therapeutic trials.

This study has several important strengths, including its large and diverse international cohort, standardized histologic and NIT assessments, and inclusion of longitudinal outcome data. However, some limitations merit discussion. First, cause-specific mortality data, such as liver-related mortality, were not available. Second, the sample may be subject to referral or selection bias, as liver biopsy is typically performed in higher-risk individuals; the resulting high prevalence of advanced fibrosis in our sample (35%) may limit the generalizability of our findings to primary care or other nonspecialty care settings. Select global regions (sub-Saharan Africa, Central Asia, Western Pacific) were not represented. Comorbid conditions were reported by participating sites based on their local clinical documentation, and although standardized definitions were recommended in the data collection guidance, centralized validation was not performed. Similarly, outcomes were recorded as part of routine clinical care and were not adjudicated by a central committee. Another limitation is the lack of information on PNPLA3 and other genetic variants associated with MASLD susceptibility and progression, which may differ across regions.

In conclusion, this global analysis of patients with biopsy-confirmed MASLD underscores the critical roles of T2D and fibrosis stage—whether determined histologically or by NITs—as key predictors of mortality and clinical outcomes. These findings highlight the importance of broad implementation of NITs in clinical practice and support targeted surveillance and intervention strategies for high-risk patients worldwide.[21]

DATA AVAILABILITY STATEMENT

Deidentified data used in this study may be available upon written request to the corresponding author.

AUTHOR CONTRIBUTIONS

Zobair M. Younossi was responsible for study design, data interpretation, manuscript writing, and critical review of the final manuscript. Maria Stepanova was responsible for data analysis, data interpretation, manuscript writing, and critical review of the final manuscript. Andrei Racila and Leyla de Avila were responsible for data management, manuscript writing and critical review of the final manuscript. Maria Stepanova was responsible for the study's oversight and critical review of the manuscript. All other authors were responsible for data collection, data management, data interpretation, manuscript writing and critical review of the final manuscript. All authors had access to the study data. Zobair M. Younossi is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

Zobair M. Younossi consults for or received grants from ~~Intercept, Cymabay,~~ Boehringer Ingelheim, Ipsen, Gilead, ~~Inventiva,~~ BMS, GSK, Novo Nordisk, Siemens, Madrigal, ~~Merck, Akero,~~ and Abbott. Javier Crespo consults for and received grants from AbbVie and Gilead. He received grants from Janssen. Laurent Castera consults for and is on the speakers' bureau for Echosens, Gilead, Madrigal, and Novo Nordisk. He consults for Boehringer Ingelheim, Boston Pharmaceutical, GSK, MSD, Pfizer, Sagimet, and Siemens. He is on the speakers' bureau for AstraZeneca and Inventiva. Naim Alkhouri consults for, is on the speakers' bureau for, and received grants from Gilead, Intercept, Ipsen, Madrigal, and Perspectum. He consults for and is on the speakers' bureau for Echosens. He consults for and received grants from 89bio, Akero, Boehringer Ingelheim, NorthSea Therapeutics, Novo Nordisk, and Pfizer. He consults for Fibronostics, HistoIndex, and Regeneron. He is on the speakers' bureau for AbbVie and AstraZeneca. He received grants from BMS, Corcept, DSM, Galectin, Genentech, Genfit, Hepagene, Healio, Inventiva, Ionis, Merck, NGM, Noom, Poxel, Viking, and Zydus. Emmanuel Tsochatzis consults for and is on the speakers' bureau for Novo Nordisk and Boehringer Ingelheim. He consults for Madrigal, MSD, and Siemens. He is on the speakers' bureau for Echosens, AbbVie, AstraZeneca, and Gilead. Vincent Wai-Sun Wong consults for, advises, is on the speakers' bureau, and received grants from Gilead. He consults for, advises, and is on the speakers' bureau for AbbVie and Novo Nordisk. He consults for and advises Boehringer Ingelheim, Echosens, Intercept, Inventiva, Pfizer, Sagimet, and TARGET PharmaSolutions. He is on the speakers' bureau for Abbott. He owns stock in Illuminatio Medical Technology. Yusuf Yilmaz consults for Zydus. He advises Novo Nordisk. Ahmed Cordie advises and is on the speakers' bureau for GSK and MSD. He advises Gilead. He is on the speakers' bureau for EVA Pharma. Ming-Lung Yu consults for, is on the speakers' bureau for, and received grants from AbbVie, BMS, Gilead, and Roche. He consults for and

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