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Liver Fibrosis Scores (FIB-4) Outperform Metabolic Indices in Predicting All-Cause Mortality and CVD Mortality Among Patients with MASLD: A Nationally Representative Cohort Study Based on NHANES 2011-2018

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Liver Fibrosis Scores (FIB-4) Outperform Metabolic Indices in Predicting All-Cause Mortality and CVD Mortality Among Patients with MASLD: A Nationally Representative Cohort Study Based on NHANES 2011-2018

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Abstract

Background：In metabolic dysfunction–associated steatotic liver disease (MASLD), both fibrosis burden and cardiometabolic dysregulation may contribute to adverse outcomes. However, the comparative prognostic value of a fibrosis-based index versus lipid- and insulin-resistance–related indices for near-term mortality risk stratification remains unclear.

Methods：We analysed adults with MASLD from the National Health and Nutrition Examination Survey (NHANES) 2011–2018. MASLD was defined by hepatic steatosis (Fatty Liver Index ≥60) plus at least one cardiometabolic risk factor. Mortality outcomes (all-cause mortality [ACM] and cardiovascular disease mortality [CVDM]) were ascertained via linkage to the National Death Index through 31 December 2019. Baseline fibrosis-4 index (FIB-4), atherogenic index of plasma (AIP), and triglyceride–glucose (TyG) index were evaluated as continuous (per 1-SD) and categorical measures (FIB-4 risk categories; tertiles for AIP and TyG). Associations with ACM and CVDM were assessed using survey-weighted multivariable Cox proportional hazards models. Restricted cubic splines examined potential non-linear relationships. Predictive discrimination at 5 years was evaluated using time-dependent ROC analyses (with

competing-risk methods for CVDM).

Results：The analytic sample included 4,037 participants with MASLD (median follow-up ≈4.5 years), during which 222 ACM events and 66 CVDM events occurred. In fully adjusted, age-stratified Cox models, higher FIB-4 was consistently associated with increased ACM risk (per 1-SD: HR 1.24, 95% CI 1.09–1.41 for <65 years; HR 1.34, 95% CI 1.20–1.50 for ≥65 years). Participants with high FIB-4 had markedly elevated ACM risk compared with low-risk counterparts (HR=9.46, 95% CI=2.58–34.60 for <65 years; HR=3.35, 95% CI=2.14–5.26 for ≥65 years). For CVDM, FIB-4 was strongly associated with risk among participants aged ≥65 years (per 1-SD: HR=1.37, 95% CI=1.19–1.59; high-risk vs low-risk: HR=5.59, 95% CI=2.29–13.68), whereas AIP and TyG were not significant in this age stratum. FIB-4 demonstrated superior discrimination for 5-year mortality (ACM-AUC 0.763; CVDM-AUC 0.785) compared with AIP (ACM AUC 0.494; CVDM AUC 0.505) and TyG (ACM-AUC 0.522; CVDM-AUC 0.557).

Conclusions： In a contemporary, nationally representative US MASLD cohort with relatively short-term follow-up, baseline FIB-4 substantially outperformed AIP and TyG in stratifying and discriminating both all-cause and cardiovascular mortality risk, supporting fibrosis-oriented prognostic assessment for near-term risk evaluation in MASLD.

Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD) is an inclusion-based nomenclature that has replaced non-alcoholic fatty liver disease (NAFLD),

explicitly foregrounding metabolic dysfunction as the defining substrate of steatotic liver disease.[1] In parallel with the global epidemics of obesity and type 2 diabetes, MASLD has emerged as one of the most common chronic liver conditions, affecting roughly one-third of adults worldwide and imposing a rapidly escalating clinical and public-health burden.[2] Beyond semantic refinement, the MASLD framework consolidates a large body of evidence indicating that hepatic steatosis is tightly coupled to insulin resistance, atherogenic dyslipidaemia, and systemic inflammation—pathways that jointly shape both liver-related progression and extrahepatic outcomes.[2] Consequently, MASLD is increasingly conceptualized as a multisystem disorder closely associated not only with the pathological process of liver fibrosis but also with systemic insulin resistance and atherosclerosis, with cardiovascular disease (CVD) being the leading driver of morbidity and mortality. [2]

Clinically, MASLD spans a heterogeneous spectrum—from isolated steatosis to metabolic dysfunction–associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma.[3] Importantly, across the fatty liver disease continuum, fibrosis severity—rather than steatosis or necroinflammatory activity alone—has been repeatedly identified as the dominant prognostic determinant.[4,5] Landmark longitudinal evidence and meta-analytic syntheses demonstrate a stepwise increase in all-cause and liver-related mortality with advancing fibrosis stage, supporting fibrosis as the key biological “final common pathway” linking MASLD to adverse outcomes.[4,5] However, liver biopsy is neither scalable nor suitable for population-level risk stratification, given its invasiveness, sampling variability, and

limited acceptability.[3] In response, contemporary clinical pathways prioritise non-invasive tests (NITs) to triage individuals at low risk while efficiently identifying those with probable advanced fibrosis who warrant second-line evaluation and intensified management. [3,6]

FIB-4 (Fibrosis-4) is a widely recognized and extensively studied index among non-invasive tests (NITs) for liver fibrosis risk stratification. Among first-line NITs, the fibrosis-4 (FIB-4) index—derived from age, aminotransferases, and platelet count—has been widely adopted because it is inexpensive, reproducible, and immediately implementable in routine care.[7] The original derivation study established FIB-4 as a pragmatic alternative to biopsy for identifying clinically meaningful fibrosis using routinely available laboratory variables.[7] Subsequent comparative studies in NAFLD/MASLD populations further corroborated its utility and helped define commonly used cut-points for front-line risk stratification.[8] Crucially, major society guidance now endorses stepwise algorithms in which blood-based scores such as FIB-4 serve as the gateway test, followed—when indicated—by elastography or specialist referral to confirm or rule in advanced fibrosis.[3,6] Because fibrosis captures the cumulative burden of chronic hepatometabolic injury, a fibrosis-centred index such as FIB-4 is biologically positioned to integrate long-standing metabolic insult into a clinically actionable estimate of near- and long-term mortality risk.[3-6]

In parallel, there has been substantial interest in simple metabolic indices intended to operationalise insulin resistance and atherogenic lipid phenotypes—pathways that are central to both MASLD fundamental pathogenesis and CVD risk.[2] The atherogenic

index of plasma (AIP), defined as $\log_{10}$(triglycerides/HDL-cholesterol), was proposed to summarise an atherogenic lipoprotein milieu and has been repeatedly investigated as an accessible cardiometabolic marker.[9] The triglyceride–glucose (TyG) index, calculated from fasting triglycerides and glucose, was developed as a pragmatic surrogate for insulin resistance when direct insulin-based methods are unavailable or impractical.[10] Given the metabolic underpinnings of MASLD, AIP and TyG offer intuitive appeal for large-scale risk profiling. Yet, these indices largely reflect contemporaneous dyslipidaemia or glycaemic–lipid perturbation, and their impact on pathological processes requires longitudinal dynamic assessment over extended periods, therefore they may incompletely capture the accumulated fibrotic burden that most consistently governs prognosis across the MASLD spectrum.[3-6]

Recent NHANES-linked cohort analyses have reinforced that AIP- and TyG-related metrics are statistically associated with adverse outcomes among individuals with steatotic liver disease, supporting their potential prognostic relevance.[11-13] For example, a large MASLD cohort based on NHANES 1999–2018 reported that higher AIP levels were associated with increased all-cause and cardiovascular mortality.[11] In a separate NHANES-based analysis, AIP was likewise associated with both mortality and prevalent CVD among individuals meeting NAFLD or MASLD definitions.[12] TyG and derived TyG–obesity indices have also been linked to mortality and cardiovascular endpoints among adults with NAFLD in NHANES follow-up.[13] Beyond lipid and glucose composites, other routinely measured biomarkers—such as urinary albumin-to-creatinine ratio—have been associated with mortality in MASLD,

reflecting an expanding effort to develop scalable, low-cost prognostic tools in population settings.[14] Collectively, these studies underscore the promise of parsimonious indices and increasingly focus on the metabolic index domain, but they also leave a clinically salient question unresolved: when indices emphasise different biological axes (fibrosis burden vs atherogenic dyslipidaemia vs insulin resistance), which most effectively discriminates mortality risk in contemporary MASLD populations?

This gap is particularly pertinent in NHANES 2011–2018, which reflects contemporary cardiometabolic epidemiology and laboratory standardisation, and can be linked to the National Death Index through NCHS public-use linked mortality files (with mortality follow-up available through December 31, 2019).[15,16] Importantly, within this framework the observation window for 2011–2018 participants is relatively short; in our analytic cohort, median follow-up was approximately 4.5 years, creating a pragmatic test of whether commonly used indices can meaningfully stratify near-term mortality risk. Against this background, we conducted a nationally representative, survey-weighted investigation to directly compare the prognostic performance of FIB-4 against AIP and TyG for predicting all-cause mortality and CVD mortality among adults with MASLD in NHANES 2011–2018.[11-16] We postulated that—even over a comparatively short follow-up horizon—FIB-4 would provide superior mortality risk discrimination because it more directly indexes the fibrotic substrate that anchors prognosis across the MASLD spectrum.[3-6]

Methods

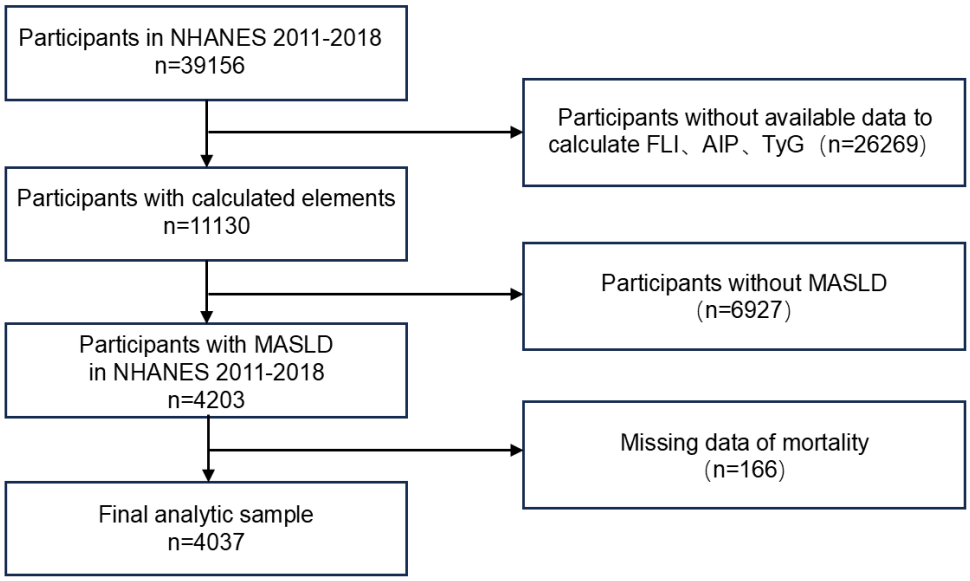


Figure 1. Flowchart depicting the selection of participants

Study design and participants

The NHANES is a nationwide study designed to assess the health status of the US population using a nationally representative sample. The original survey protocol was approved by the Institutional Review Board of the National Center for Health Statistics (NCHS). The study protocol was designed and conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.[17] The NHANES data were collected in biennial cycles, encompassing generally 500 health indicators. The analysis utilized data collected across four survey cycles between 2011 and 2018. We excluded specific groups from our analysis to ensure a focused study population: (1) Age <20 years; (2) individuals with liver cancer; (3) individuals with high alcohol intake, defined as more than three alcoholic beverages per day for men and more than two per day for women; (4) individuals diagnosed with hepatitis B or C, identified by positive hepatitis B surface antigen or hepatitis C antibody/HCV RNA tests;(5) Lack of information to

evaluate MASLD;(6) Lack of information to evaluate AIP index and TyG index and (7) those with missing mortality data or clinical information. Figure 1 provides a visual representation of the patient selection process.

Baseline indicators measurement assessment

Demographic information, physical examination findings, laboratory blood test results, and medical history were collected from the participants. Demographic data included age, sex, race, smoking status, alcohol consumption. Race was categorized into five groups: Mexican American, non-Hispanic white, non-Hispanic Black, other Hispanic, and other Race. Smoking status was assessed using the question 'Have you ever smoked at least 100 cigarettes in your lifetime?' Participants who responded 'no' were classified as 'never smokers'. Excessive alcohol use of alcohol assumption: more than 350 g/wk for females and more than 420 g/wk for males. Physical examination included measurements of body mass index (BMI, kg/m2) , weight (kg), height (cm), and waist circumference (WC, cm). BMI was calculated as weight (kg) divided by height (m2). Biochemical blood markers comprised aspartate aminotransferase (ALT, U/L), alanine aminotransferase (AST, U/L), γ-glutamyl transferase (γ-GGT, U/L), triglycerides (TG, mmol/L), total cholesterol (TC, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), fasting blood glucose (FBG, mmol/L) and platelets(109/L).

Medical history data included diabetes mellitus (DM) and hypertension diagnoses. DM was defined by any of the following criteria: self-reported diagnosis, use of insulin or oral hypoglycaemic agents, fasting blood glucose ≥ 7 mmol/L, or HbA1c ≥ 6.5%. Hypertension was defined as a self-reported diagnosis or an average SBP ≥ 140 mmHg

or average DBP ≥ 90 mmHg, or the administration of antihypertensive medication.

All laboratory measurements, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet counts required for FIB-4 calculation, were conducted following highly standardized protocols. Throughout the 2011–2018 survey cycles, the NCHS implemented rigorous quality assurance and quality control (QA/QC) procedures, including periodic crossover studies, to monitor and adjust for potential equipment or assay shifts over time. Consequently, the inter-cycle variability of these biochemical components is minimal and is appropriately accounted for by utilizing the NHANES multi-year sample weights and variance estimation techniques.

Definitions of the exposure and outcome variables

Definition of FIB-4

FIB-4 was calculated by the following formula: FIB-4 = Age (years) × AST (U/L) / [platelet (109/L) × ALT1/2 (U/L)]. FIB-4 serves as a noninvasive tool for risk stratification of advanced liver fibrosis, with values < 1.45 indicating a low likelihood of fibrosis, scores between 1.45 and 2.67 denoting an indeterminate zone, and values >2.67 signifying a high probability of advanced fibrosis or cirrhosis.[8]

Definition of TyG

TyG was calculated as log[TG (mmol/L) × Glucose (mmol/L)/2]. $\mathbf{log}\,(\boldsymbol{TG} \times \boldsymbol{Glucose}/\mathbf{2})$.

Definition of AIP

AIP was calculated as the logarithm of the ratio of TG to HDL-C, as expressed by the formula: AIP = log10[TG (mmol/L)/HDL-C (mmol/L)].

Definition of MASLD

The specific adult cardiometabolic criteria are defined as follows: (1) BMI ≥ 25 kg/m2 (23 kg/m2 for Asians) or WC > 94 cm in men, >80 cm in women; (2) FBG≥ 5.6 mmol/L (100 mg/dL) or 2-h post-load blood glucose ≥ 7.8 mmol/L (140 mg/dL) or HbA1c≥ 5.7% (39 mmol/L) or a diagnosis of type 2 diabetes or type 2 diabetes treatment; (3) Blood pressure ≥ 130/85 mmHg or specific antihypertensive treatment; (4) Plasma TG ≥ 1.70 mmol/L (150 mg/ dL) or lipid-lowering therapy; (5) Plasma HDL-C ≤ 1.0 mmol/L (40 mg/dL) in men, ≤1.3 mmol/L (50 mg/dL) in women, or lipid-lowering therapy.

Due to the lack of consistent imaging (e.g., ultrasound or vibration-controlled transient elastography) or histological data across all included NHANES cycles, hepatic steatosis was identified using the Fatty Liver Index (FLI). An FLI⩾ 60 is a well-validated and widely accepted surrogate marker for hepatic steatosis in large-scale epidemiological studies. Previous validation studies have demonstrated that an FLI ⩾ 60 possesses high diagnostic accuracy (area under the receiver operating characteristic curve ≈ 0.84) for detecting ultrasound-diagnosed fatty liver [18]. The Fatty Liver Index (FLI) was calculated using an algorithm incorporating gamma-glutamyl transferase (GGT). Ranging from 0 to 100, the FLI serves as an indicator of fatty liver risk: scores below 30 denote low risk, while those above 60 signify high risk. An FLI score ≥ 60 has been validated as a robust marker for the presence of fatty liver and a reliable predictor of insulin resistance.[18] Therefore, MASLD was operationally defined as an FLI ⩾ 60 coupled with the presence of at least one cardiometabolic risk factor, strictly following the international consensus criteria[1].

Mortality outcomes of the study population

The outcome variables included all-cause mortality and CVD mortality. Mortality data

for the follow-up population were sourced from the NHANES Public-use link mortality files, with updates extending through December 31, 2019. These records were matched to the National Center for Health Statistics and the National Death Index using probabilistic algorithms. Mortality outcomes were coded using the standardized International Classification of Diseases, Tenth Revision (ICD-10) system. The observation time was defined as the duration between baseline assessment (initial interview) and the subsequent occurrence of either mortality or study completion[19,20]. All-cause mortality encompasses deaths from any cause, including heart disease, malignant neoplasms, unintentional injuries, cerebrovascular diseases, diabetes mellitus, and other causes. Cardiovascular disease (CVD) mortality was specifically defined based on the underlying cause of death using the International Classification of Diseases, Tenth Revision (ICD-10) codes I00–I78. This broad coding range encompasses active rheumatic fever, hypertensive diseases, ischemic heart diseases, pulmonary heart disease, and cerebrovascular diseases, ensuring a comprehensive capture of cardiovascular-related fatalities in accordance with NCHS analytical guidelines [21,22].

Statistical analysis

All statistical analyses accounted for the complex multistage stratified cluster sampling design of the NHANES. Appropriate sample weights (WTMEC2YR) were applied to produce nationally representative estimates, following the analytical guidelines provided by the National Center for Health Statistics (NCHS). New multi-year sample weights were constructed by dividing the 2-year weights by 4 to combine data from the 2011–2018 survey cycles.

Baseline characteristics of the study population were stratified by FIB-4 index categories or tertiles of metabolic indices (AIP and TyG). Continuous variables were expressed as weighted means ± standard errors (SE) or medians with interquartile ranges (IQR) depending on their distribution, and were compared using weighted linear regression or the design-adjusted Kruskal-Wallis test. Categorical variables were presented as unweighted counts (n) and weighted percentages (%) and were compared using the Rao-Scott $\chi 2$ test.

To minimize potential selection bias and maximize statistical power, missing covariate data (primarily encompassing smoking status and diabetes history) were addressed using multiple imputation by chained equations (MICE). Assuming the data were missing at random (MAR), we generated five imputed datasets. Predictive mean matching was utilized for continuous variables, while logistic regression models were applied for categorical variables. Primary survival analyses were performed across all imputed datasets, and the results were pooled using Rubin's rules. A sensitivity analysis comparing baseline characteristics and primary outcome estimates before and after imputation was conducted to ensure the imputation procedure did not introduce systematic changes to the data distribution.

To investigate the association between the three indices (FIB-4, AIP, TyG) and mortality outcomes (all-cause and cardiovascular), weighted Kaplan-Meier survival curves were generated, and the Log-rank test was used to assess differences in survival probabilities among groups. Multivariable Cox proportional hazards regression models were employed to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs). Three

sequential models were constructed to control for potential confounders: Model 1: Unadjusted.Model 2: Adjusted for age, sex, and race/ethnicity. Model 3: Further adjusted for body mass index (BMI), smoking status, hypertension, and diabetes mellitus. The proportional hazards assumption was verified using Schoenfeld residuals. To address the potential non-linear dose-response relationships between continuous indices and mortality risks, restricted cubic spline (RCS) analyses were performed with four knots located at the 5th, 35th, 65th, and 95th percentiles of the distribution. The median value of each index served as the reference point (HR = 1).

Given that cardiovascular death is often subject to competing events (e.g., cancer or liver-related death), we further evaluated the prognostic performance using time-dependent Receiver Operating Characteristic (ROC) curves adapted for competing risks. The cumulative sensitivity and dynamic specificity were calculated, and the Area Under the Curve (AUC) at 5 years was used to compare the predictive accuracy of FIB-4, AIP, and TyG. The differences between AUCs were tested for statistical significance. Time-dependent ROC curves at 5 years were estimated with marginal weighting (weighting="marginal") , and ACM and CVD death as the event of interest. The 5-year AUC for each marker was calculated from the estimated ROC coordinates. Uncertainty was quantified using paired nonparametric bootstrap resampling (1,000 replicates), in which the same resampled indices were applied simultaneously to all three markers to preserve within-sample correlation. Percentile-based 95% confidence intervals (CIs) were derived from the bootstrap distribution. Time-dependent ROC analyses were conducted as single-marker discrimination assessments; inference regarding

associations was based on multivariable Cox models as described elsewhere. Time-dependent ROC analyses were performed without incorporation of NHANES survey weights due to methodological limitations in available competing-risk ROC implementations; survey design was accounted for in regression analyses. The rationale for selecting a 5-year prediction horizon was primarily data-driven and clinically relevant , because of the median follow-up time for our study population was approximately 5 to 6 years. Therefore, evaluating discrimination at 5 years maximizes statistical power while representing a highly relevant mid-term prognostic window for chronic liver disease progression.

Subgroup analyses were conducted to evaluate the consistency of associations across strata defined by sex, BMI, and metabolic comorbidities. The heterogeneity of effects across subgroups was assessed by including interaction terms (e.g., index× covariate) in the final models. Specifically, to address the concern of mathematical coupling between age and the FIB-4 score, sensitivity analyses were performed within strict age strata (<65 vs. ≥65 years),.

Data preparation and statistical analyses were conducted using R software (Version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). Key packages included survey for weighting operations, survival and survminer for survival analysis, rms for spline modeling, and timeROC for predictive accuracy assessment. A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants according to Survival Status

Table 1. Baseline Characteristics of MASLD Patients Stratified by Survival Status

Characteristic	Overall N = 44,398,952[1]	Survivors N = 42,278,121[1]	Non-survivors N = 2,120,831[1]	p-value[2]
Age (years)	49.55 (15.77)	48.80 (15.50)	64.53 (13.51)	**<0.001**
Gender				0.051
Male	2,109.0 (54.2%)	1,971.0 (53.7%)	138.0 (62.2%)	
Female	1,931.0 (45.8%)	1,847.0 (46.3%)	84.0 (37.8%)	
Race/Ethnicity				**<0.001**
Mexican American	689.0 (10.6%)	668.0 (10.9%)	21.0 (4.2%)	
Other Hispanic	470.0 (6.4%)	451.0 (6.6%)	19.0 (3.3%)	
Non-Hispanic White	1,597.0 (66.7%)	1,470.0 (66.2%)	127.0 (77.2%)	
Non-Hispanic Black	891.0 (10.4%)	852.0 (10.5%)	39.0 (7.7%)	
Other Race - Including Multi-Racial	393.0 (5.9%)	377.0 (5.8%)	16.0 (7.6%)	
BMI (kg/m²)	34.72 (6.39)	34.80 (6.42)	33.24 (5.55)	0.050
Smoking Status	1,909.0 (48.2%)	1,763.0 (47.1%)	146.0 (68.7%)	**<0.001**
Diabetes Mellitus	583.0 (16.1%)	504.0 (15.0%)	79.0 (33.3%)	**<0.001**
Hypertension	1,946.0 (45.6%)	1,788.0 (44.7%)	158.0 (63.0%)	**<0.001**
FIB-4 Index	0.96 (0.64, 1.38)	0.95 (0.63, 1.36)	1.52 (1.09, 2.31)	**<0.001**
AIP Index	0.11 (-0.10, 0.30)	0.10 (-0.10, 0.30)	0.14 (0.01, 0.30)	**0.035**
TyG Index	8.91 (8.51, 9.31)	8.91 (8.51, 9.30)	8.99 (8.69, 9.38)	**0.024**
Triglycerides (mg/dL)	136.00 (94.00, 192.00)	135.00 (94.00, 192.00)	148.00 (105.00, 188.00)	0.063
Fasting Glucose (mg/dL)	105.00 (97.00, 118.00)	105.00 (97.00, 118.00)	110.00 (99.00, 129.00)	**0.028**
HDL-C (mg/dL)	45.00 (39.00, 54.00)	45.00 (39.00, 54.00)	46.00 (36.00, 52.00)	0.5
ALT (U/L)	25.00 (18.00, 34.00)	25.00 (18.00, 35.00)	20.00 (16.00, 27.00)	**<0.001**
AST (U/L)	23.00 (19.00, 28.00)	23.00 (19.00, 28.00)	23.00 (19.00, 28.00)	0.6

[1] Mean (SD); n (unweighted) (%); Median (Q1, Q3)

[2] Design-based KruskalWallis test; Pearson's X^2: Rao & Scott adjustment

Table 1. Baseline Characteristics of MASLD patients

The analytic sample included 4,037 participants with MASLD (3,815 survivors and 222 non-survivors), representing an estimated 44.4 million U.S. adults with MASLD in weighted analyses.During follow-up, 222 participants died, corresponding to an estimated 2.12 million individuals in the weighted population. Compared with survivors, non-survivors were substantially older (64.53±13.51 vs 48.80±15.50 years, P<0.001) and showed a higher proportion of men (62.2% vs 53.7%), although this difference did not reach conventional statistical significance (P=0.051). Race/ethnicity distributions differed significantly across groups (P<0.001), with non-survivors having

a higher proportion of non-Hispanic White participants (77.2% vs 66.2%). Non-survivors had a higher prevalence of smoking (68.7% vs 47.1%), diabetes mellitus (33.3% vs 15.0%), and hypertension (63.0% vs 44.7%) (all P<0.001)(Table1).

With respect to the studied indices, non-survivors had markedly higher FIB-4 values (median 1.52 [IQR 1.09–2.31] vs 0.95 [0.63–1.36], P<0.001). AIP and TyG indices were slightly higher among non-survivors (AIP: 0.14 [0.01–0.30] vs 0.10 [−0.10–0.30], P=0.035; TyG: 8.99 [8.69–9.38] vs 8.91 [8.51–9.30], P=0.024). Non-survivors also had higher fasting glucose levels (110 [99–129] vs 105 [97–118] mg/dL, P=0.028) and lower ALT levels (20 [16–27] vs 25 [18–35] U/L, P<0.001), whereas triglycerides, HDL-C, and AST did not differ significantly between groups.

Association between the FIB-4,AIP,TyG index and All-cause and CVD mortality

	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Panel A. Age <65 years (n=3,110; deaths=82)						
Continuous analysis						
AIP (per 1 SD)	1.04 (0.84–1.30)	0.696	0.99 (0.77–1.28)	0.933	0.91 (0.70–1.18)	0.478
FIB-4 (per 1 SD)	1.25 (1.11–1.41)	<0.001	1.23 (1.07–1.43)	0.004	1.24 (1.09–1.41)	0.001
TyG (per 1 SD)	1.09 (0.82–1.45)	0.559	1.06 (0.76–1.46)	0.737	0.84 (0.60–1.18)	0.309
Categorical analysis						
AIP tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	1.28 (0.69–2.38)	0.433	1.27 (0.66–2.46)	0.473	1.30 (0.67–2.52)	0.433
T3	1.46 (0.72–2.94)	0.290	1.32 (0.61–2.87)	0.483	1.03 (0.46–2.29)	0.937
P for trend		0.319		0.522		0.961
FIB-4 categories						
Low (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Intermediate	1.60 (0.79–3.24)	0.189	1.42 (0.69–2.94)	0.340	1.31 (0.61–2.82)	0.493
High	8.39 (2.48–28.32)	<0.001	8.00 (2.08–30.78)	0.003	9.46 (2.58–34.60)	<0.001
P for trend		0.008		0.028		0.029
TyG tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	1.29 (0.69–2.41)	0.418	1.23 (0.65–2.35)	0.526	1.25 (0.63–2.48)	0.526
T3	1.00 (0.45–2.21)	0.991	0.90 (0.39–2.09)	0.814	0.55 (0.25–1.21)	0.138
P for trend		0.960		0.759		0.058
Panel B. Age ≥65 years (n=927; deaths=140)						
Continuous analysis						
AIP (per 1 SD)	1.14 (0.88–1.48)	0.324	1.10 (0.83–1.46)	0.522	1.05 (0.79–1.39)	0.733
FIB-4 (per 1 SD)	1.35 (1.26–1.46)	<0.001	1.38 (1.26–1.50)	<0.001	1.34 (1.20–1.50)	<0.001
TyG (per 1 SD)	1.09 (0.78–1.52)	0.604	1.08 (0.77–1.51)	0.653	1.01 (0.71–1.44)	0.956
Categorical analysis						
AIP tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	1.16 (0.65–2.06)	0.614	1.13 (0.64–1.99)	0.665	1.05 (0.57–1.93)	0.886
T3	1.29 (0.76–2.21)	0.346	1.19 (0.69–2.07)	0.528	1.12 (0.65–1.91)	0.684
P for trend		0.358		0.552		0.677
FIB-4 categories						
Low (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Intermediate	1.66 (0.94–2.94)	0.084	1.64 (0.96–2.78)	0.068	1.63 (0.94–2.85)	0.084
High	3.50 (2.21–5.55)	<0.001	3.47 (2.23–5.41)	<0.001	3.35 (2.14–5.26)	<0.001
P for trend		<0.001		<0.001		<0.001
TyG tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	1.15 (0.71–1.88)	0.570	1.14 (0.71–1.84)	0.587	1.11 (0.69–1.78)	0.680
T3	0.99 (0.48–2.05)	0.981	0.97 (0.48–1.98)	0.937	0.84 (0.43–1.67)	0.625
P for trend		0.943		0.891		0.559

Model 1: unadjusted.

Model 2: adjusted for sex and race/ethnicity.

Model 3: additionally adjusted for BMI, smoking, diabetes, and hypertension.

Age-specific FIB-4 cutoffs: <65 years 1.3/2.67; ≥65 years 2.0/2.67.

P for trend was calculated by modeling tertile/category as an ordinal variable (1–3).

Table 2. (A) Association between the FIB-4,AIP,TyG index and All-cause mortality

In survey-weighted age-stratified multivariable Cox regression analyses (Table 2), FIB-4 was consistently associated with all-cause mortality in both age strata, whereas metabolic indices (AIP and TyG) were not. Among participants aged <65 years (n=3,110; deaths=82), each 1-SD increase in FIB-4 was associated with a 24% higher risk of death after full adjustment (Model 3: HR 1.24, 95% CI 1.09–1.41; P=0.001). Similarly, in participants aged ≥65 years (n=927; deaths=140), higher FIB-4 remained independently associated with all-cause mortality (Model 3: HR 1.34, 95% CI 1.20–1.50; P<0.001). In contrast, neither AIP nor TyG showed significant associations with

all-cause mortality in either age group in the fully adjusted models (all P>0.30).

When analyzed categorically, elevated FIB-4 identified markedly higher-risk subgroups. Using age-specific FIB-4 cutoffs (<65 years: 1.3/2.67; ≥65 years: 2.0/2.67), participants with high FIB-4 had substantially increased mortality risk compared with the low FIB-4 reference group in both strata (Model 3: <65 years, HR 9.46, 95% CI 2.58–34.60; P<0.001; ≥65 years, HR 3.35, 95% CI 2.14–5.26; P<0.001). A significant dose–response relationship across FIB-4 categories was observed, as indicated by the trend tests (Model 3: P for trend=0.029 for <65 years; P for trend<0.001 for ≥65 years). By contrast, AIP tertiles were not associated with all-cause mortality and showed no trend in either age stratum (Model 3 P for trend=0.961 for <65 years and 0.677 for ≥65 years). TyG tertiles were also not significantly associated with all-cause mortality, although a borderline trend was observed in younger participants (Model 3 P for trend=0.058)(Table 2A).

	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Panel A. Age <65 years						
Continuous analysis						
AIP (per 1 SD)	1.10 (0.79–1.53)	0.592	0.95 (0.66–1.37)	0.793	0.87 (0.61–1.25)	0.449
FIB-4 (per 1 SD)	1.05 (0.89–1.23)	0.587	0.98 (0.80–1.20)	0.833	0.86 (0.57–1.28)	0.448
TyG (per 1 SD)	1.47 (0.92–2.35)	0.104	1.39 (0.85–2.27)	0.188	1.12 (0.69–1.84)	0.645
Categorical analysis						
AIP tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	1.76 (0.26–11.85)	0.561	1.68 (0.24–11.72)	0.603	1.57 (0.23–10.57)	0.642
T3	2.90 (0.36–23.64)	0.320	2.27 (0.24–21.40)	0.475	1.95 (0.22–17.18)	0.548
P for trend		0.293		0.463		0.546
FIB-4 categories						
Low (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Intermediate	0.94 (0.29–3.08)	0.916	0.78 (0.22–2.80)	0.709	0.62 (0.17–2.29)	0.474
High	0.00 (0.00–0.00)	<0.001	0.00 (0.00–0.00)	<0.001	0.00 (0.00–0.00)	<0.001
P for trend		0.705		0.541		0.340
TyG tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	0.77 (0.19–3.06)	0.708	0.73 (0.17–3.19)	0.671	0.61 (0.13–2.81)	0.525
T3	2.82 (0.48–16.58)	0.252	2.37 (0.38–14.87)	0.357	1.59 (0.22–11.75)	0.647
P for trend		0.236		0.308		0.532
Panel B. Age ≥65 years						
Continuous analysis						
AIP (per 1 SD)	0.97 (0.68–1.39)	0.883	0.98 (0.68–1.40)	0.893	0.92 (0.63–1.34)	0.652
FIB-4 (per 1 SD)	1.37 (1.20–1.57)	<0.001	1.38 (1.18–1.61)	<0.001	1.37 (1.19–1.59)	<0.001
TyG (per 1 SD)	0.91 (0.62–1.33)	0.613	0.93 (0.63–1.36)	0.705	0.80 (0.55–1.18)	0.267
Categorical analysis						
AIP tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	0.74 (0.31–1.76)	0.490	0.75 (0.30–1.88)	0.543	0.62 (0.26–1.49)	0.284
T3	0.70 (0.36–1.36)	0.295	0.70 (0.35–1.41)	0.321	0.61 (0.29–1.28)	0.192
P for trend		0.315		0.336		0.223
FIB-4 categories						
Low (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Intermediate	1.25 (0.54–2.90)	0.607	1.22 (0.51–2.90)	0.660	1.31 (0.56–3.07)	0.539
High	5.46 (2.42–12.31)	<0.001	5.33 (2.25–12.61)	<0.001	5.59 (2.29–13.68)	<0.001
P for trend		0.001		0.002		0.002
TyG tertiles						
T1 (Ref)	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
T2	0.95 (0.41–2.20)	0.898	1.01 (0.42–2.43)	0.988	0.90 (0.40–2.01)	0.797
T3	0.57 (0.23–1.36)	0.205	0.60 (0.25–1.43)	0.248	0.46 (0.19–1.09)	0.077
P for trend		0.194		0.234		0.063

Model 1: unadjusted.

Model 2: adjusted for sex and race/ethnicity.

Model 3: additionally adjusted for BMI, smoking, diabetes, and hypertension.

Age-specific FIB-4 cutoffs: <65 years 1.3/2.67; ≥65 years 2.0/2.67.

P for trend was calculated by modeling tertile/category as an ordinal variable (1–3).

CVD mortality was defined as underlying cause of death due to diseases of heart or cerebrovascular disease (UCOD_LEADING=001 or 005).

Table 2. (B) Association between the FIB-4,AIP,TyG index and CVD mortality

In age-stratified Cox proportional hazards models for cardiovascular disease (CVD) mortality, no significant associations were observed for AIP, FIB-4, or TyG (per 1-SD increment) among participants aged <65 years after multivariable adjustment (Model 3: AIP HR 0.87, 95% CI 0.61–1.25; P=0.449; FIB-4 HR 0.86, 95% CI 0.57–1.28; P=0.448; TyG HR 1.12, 95% CI 0.69–1.84; P=0.645). Similarly, analyses using tertiles of AIP and TyG did not demonstrate significant dose–response trends in this age stratum (all P for trend >0.05). Estimates for the high FIB-4 category in participants aged <65 years

were unstable due to sparse CVD events, precluding reliable inference.

Among participants aged ≥65 years, FIB-4 showed a robust and consistent association with CVD mortality across all models. In the fully adjusted model (Model 3), each 1-SD increase in FIB-4 was associated with a 37% higher risk of CVD mortality (HR 1.37, 95% CI 1.19–1.59; P<0.001). In categorical analyses using age-specific FIB-4 cutoffs, the high-risk group had substantially higher CVD mortality compared with the low-risk group (Model 3: HR 5.59, 95% CI 2.29–13.68; P<0.001), with a significant trend across categories (P for trend=0.002). In contrast, neither AIP nor TyG was significantly associated with CVD mortality in the ≥65-year stratum (Model 3: AIP HR 0.92, 95% CI 0.63–1.34; P=0.652; TyG HR 0.80, 95% CI 0.55–1.18; P=0.267), although a borderline inverse trend was suggested for TyG tertiles (P for trend=0.063). In participants aged <65 years, the estimate for the high FIB-4 category was not reliably estimable due to sparse CVD events (complete separation), and therefore should be interpreted with caution(Table 2B).

Survival analysis

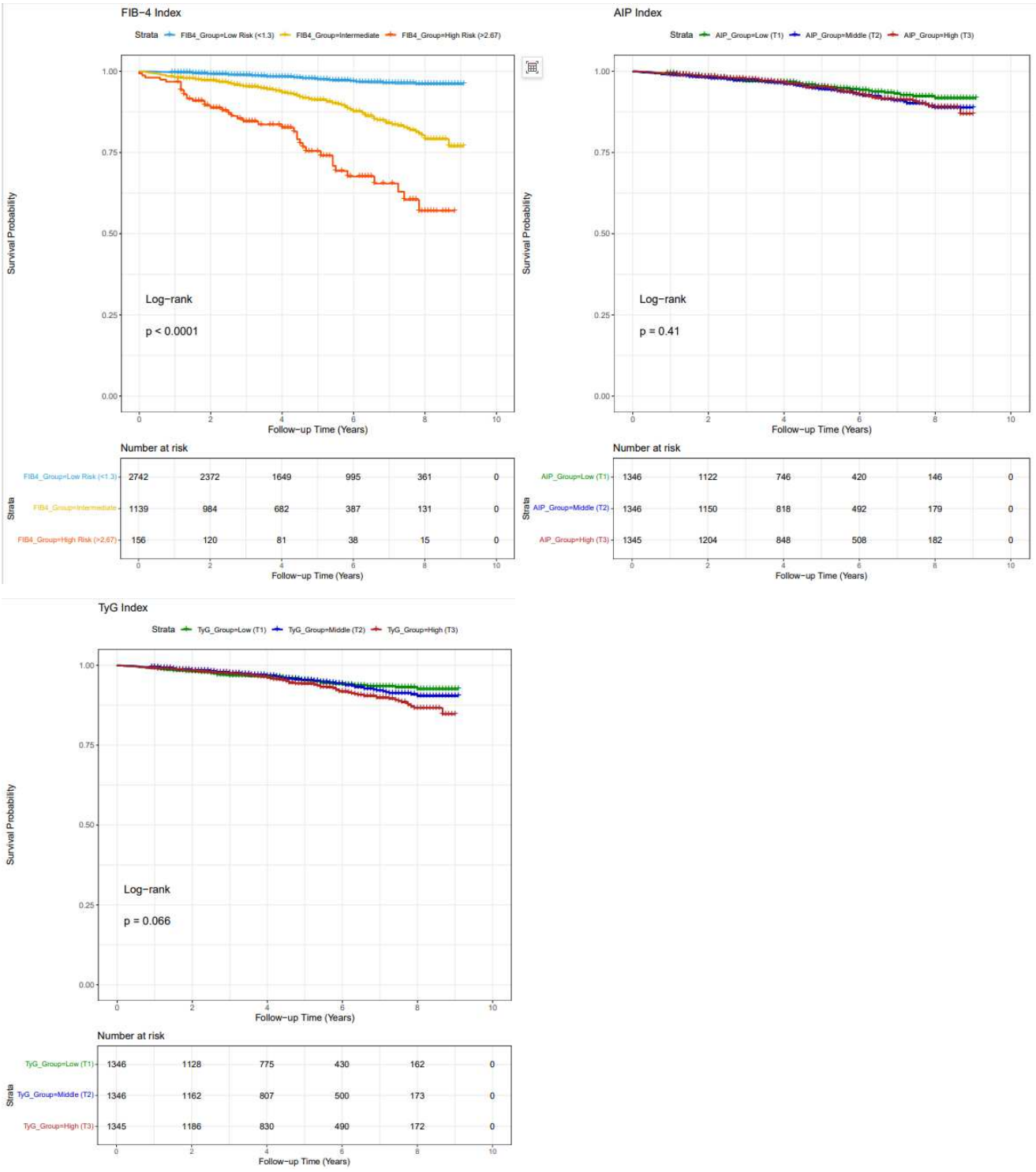
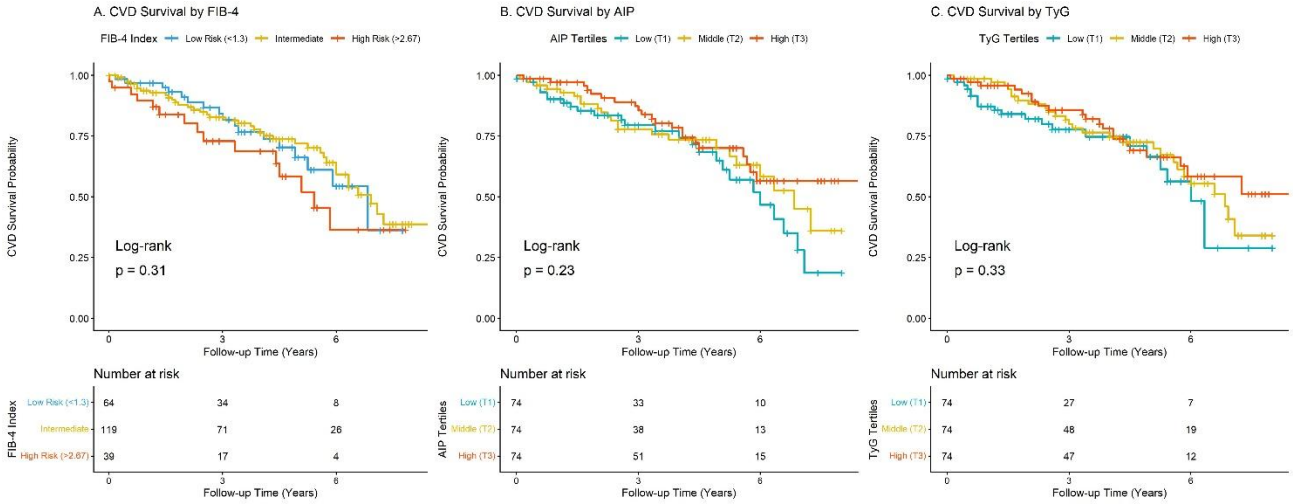


Figure 2. Kaplan–Meier curves for all-cause mortality among participants with MASLD stratified by baseline (A) FIB-4 categories, (B) AIP tertiles, and (C) TyG tertiles.

Kaplan–Meier survival analyses were performed to compare all-cause mortality across baseline categories of FIB-4, AIP, and TyG (Figure 2). Survival curves stratified by FIB-4 categories (low risk <1.3, intermediate, and high risk >2.67) showed clear and

progressive separation over follow-up, with the high FIB-4 group demonstrating the lowest survival probability throughout the study period (log-rank p<0.0001). In contrast, Kaplan–Meier curves across AIP tertiles largely overlapped, indicating no significant survival differences (log-rank p=0.41). For TyG tertiles, survival curves showed only modest divergence, with a borderline difference that did not reach statistical significance (log-rank p=0.066). Numbers at risk over time are shown beneath each panel.(Figure 2)



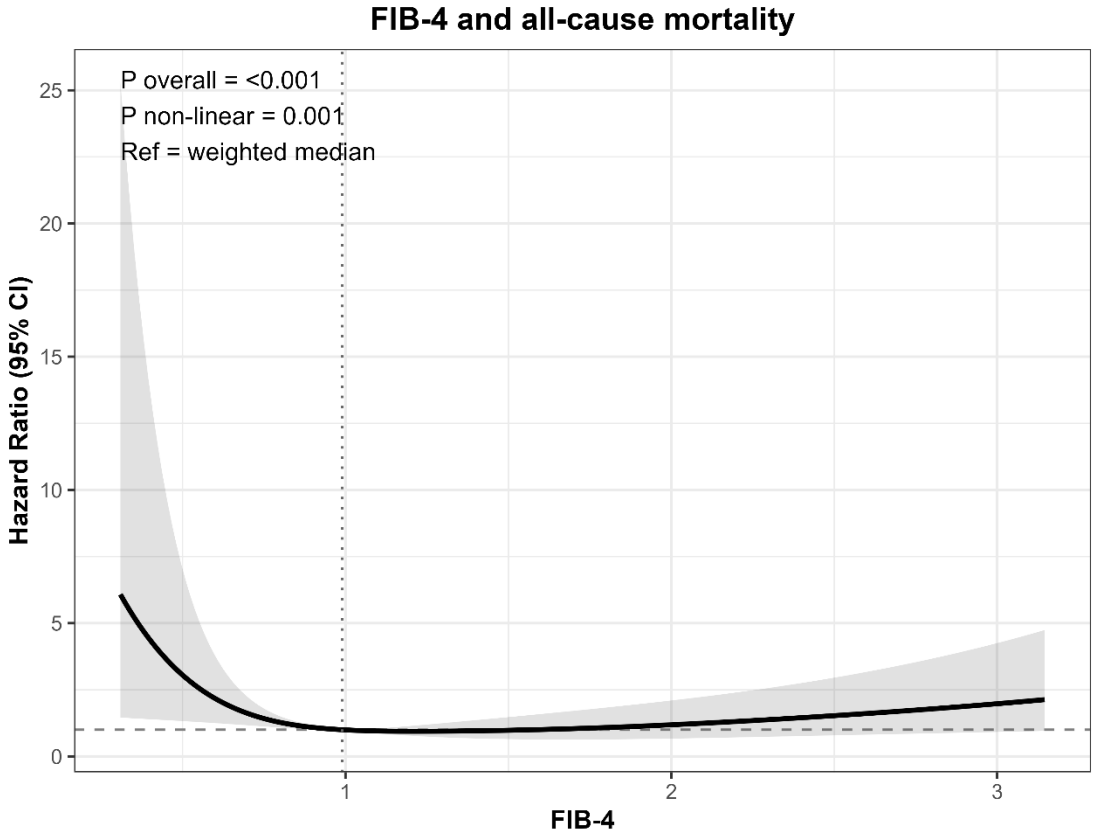
Supplementary Figure S1. Kaplan–Meier curves for CVD survival by (A) FIB-4 risk categories, (B) AIP tertiles, and (C) TyG tertiles among participants with MASLD. P values were derived from the log-rank test; numbers at risk are shown below each panel.

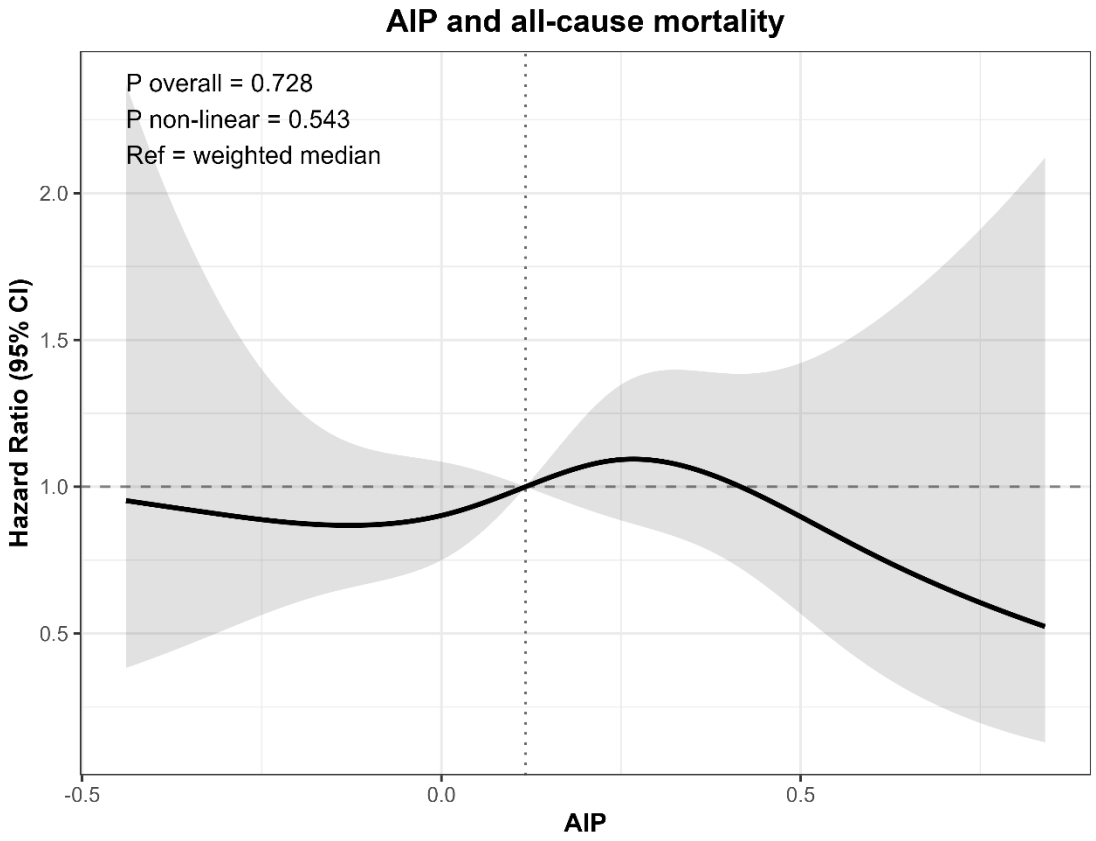
Kaplan–Meier curves were constructed to compare cardiovascular disease (CVD) survival across categories/tertiles of FIB-4, AIP, and TyG (Supplementary Figure S1). Overall, no statistically significant differences in CVD survival were observed across FIB-4 risk categories (log-rank P=0.31), AIP tertiles (log-rank P=0.23), or TyG tertiles (log-rank P=0.33). (Supplementary Figure S1)

Visually, participants in the high-risk FIB-4 category tended to show lower CVD

survival probabilities during follow-up compared with the low- and intermediate-risk groups; however, separation was modest and became less stable at later time points due to the small number at risk in the high-risk group. For AIP and TyG, the lowest tertile showed a numerically lower CVD survival probability than the higher tertiles, particularly after approximately 5 years of follow-up, yet these differences did not reach statistical significance by the log-rank test. Given the limited numbers at risk at longer follow-up times, these KM comparisons should be interpreted as descriptive and were complemented by multivariable Cox models. (Supplementary Figure S1)

Nonlinear association between FIB-4,AIP,TyG index and All-cause and CVD mortality





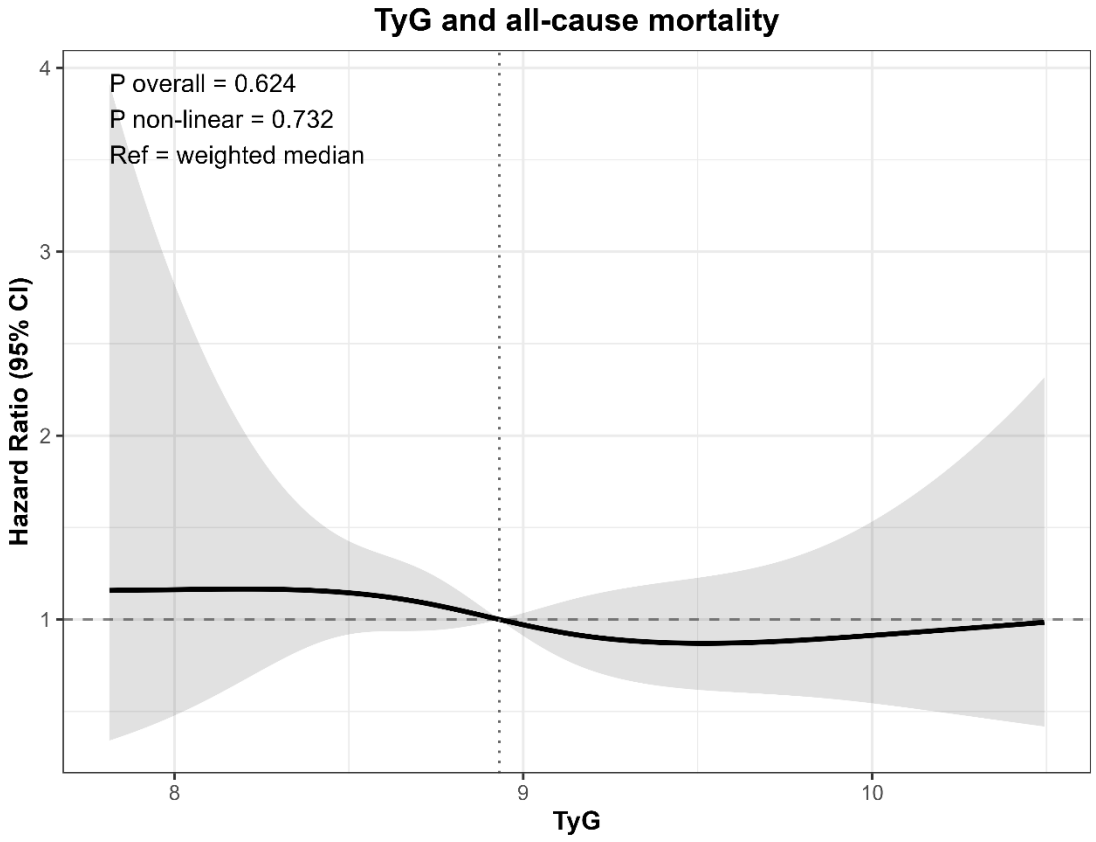


Figure 3. (A) Restricted cubic spline analyses of FIB-4, AIP, and TyG in relation to all-cause mortality among

participants with MASLD. Models were adjusted for age, sex, race/ethnicity, body mass index, smoking status, diabetes, and hypertension. The solid line indicates the adjusted HR, and the shaded area represents the 95% confidence interval.

Restricted cubic spline analyses were performed to explore potential non-linear relationships between fibrosis- and metabolism-related indices and all-cause mortality (Figure 3A). After multivariable adjustment, FIB-4 showed a significant association with all-cause mortality (P overall <0.001) with evidence of non-linearity (P non-linear = 0.001). The risk was lowest around the weighted median of FIB-4 and increased at higher FIB-4 values, consistent with a fibrosis-related risk gradient. In contrast, no significant associations were observed for AIP (P overall = 0.728; P non-linear = 0.543) or TyG (P overall = 0.624; P non-linear = 0.732), with spline curves remaining largely flat around HR = 1 across most of the exposure ranges. Notably, confidence intervals widened at the extreme tails, indicating limited precision in data-sparse regions(Figure 3A).

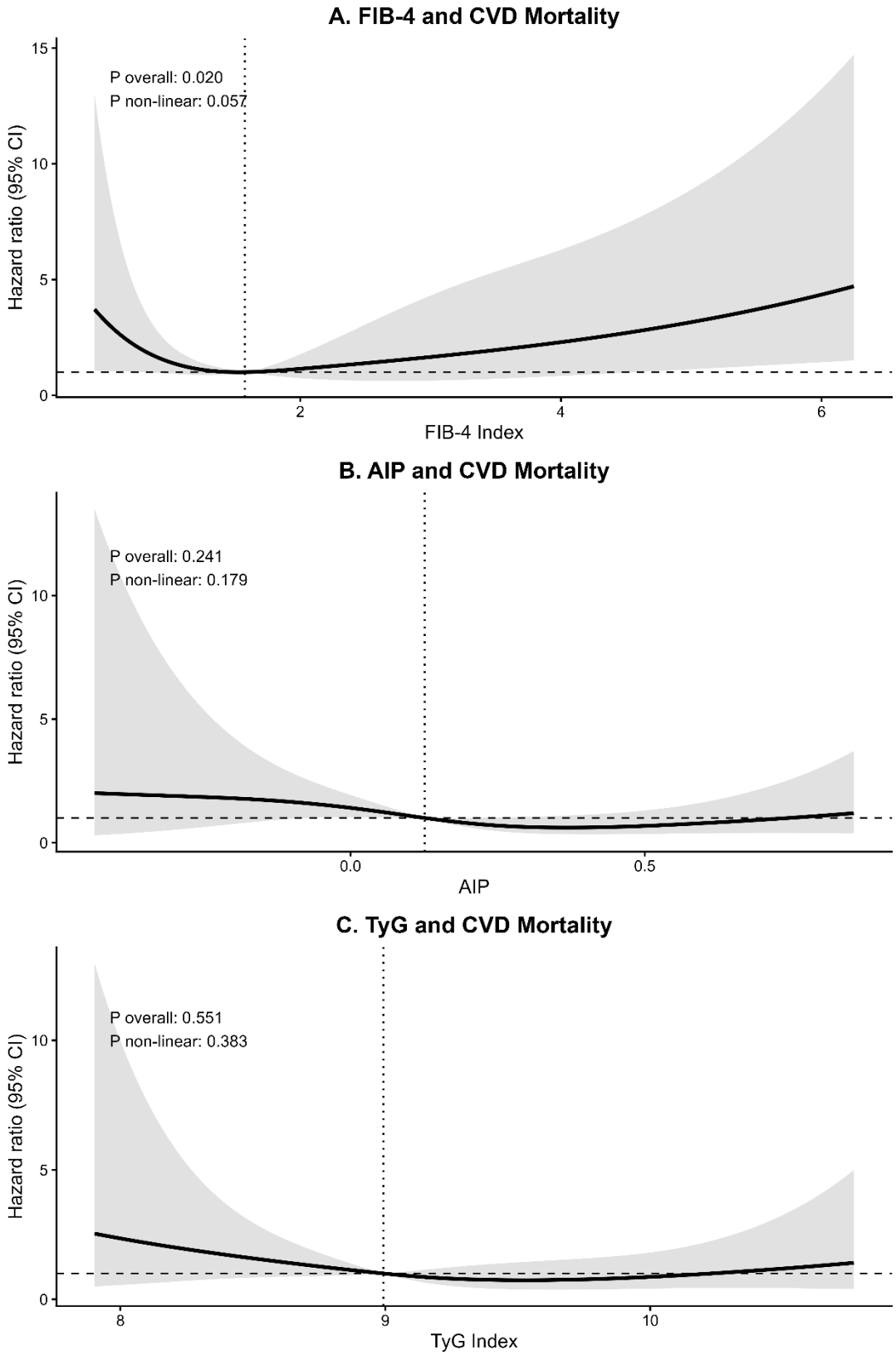


Figure 3. (B) Restricted cubic spline analyses of FIB-4, AIP, and TyG in relation to CVD-cause mortality among participants with MASLD. Models were adjusted for age, sex, race/ethnicity, body mass index, smoking status, diabetes, and hypertension. The solid line indicates the adjusted HR, and the shaded area represents the 95% confidence interval.

Restricted cubic spline analyses were performed to explore potential non-linear associations between the indices and cardiovascular disease (CVD) mortality (Figure 3B). FIB-4 demonstrated a statistically significant overall association with CVD mortality (P overall=0.020). The test for non-linearity was borderline (P non-linear=0.057), suggesting that the relationship was largely monotonic with a possible modest deviation from strict linearity. Visual inspection indicated that CVD mortality risk increased progressively with higher FIB-4 values, particularly in the upper range, whereas the confidence intervals widened at extreme values, consistent with sparse observations at the tails.

In contrast, neither AIP nor TyG showed evidence of an association with CVD mortality in spline models (AIP: P overall=0.241, P non-linear=0.179; TyG: P overall=0.551, P non-linear=0.383). The corresponding spline curves fluctuated around the null with no discernible monotonic trend(Figure 3B).

The incremental effect of FIB-4 on all-cause mortality

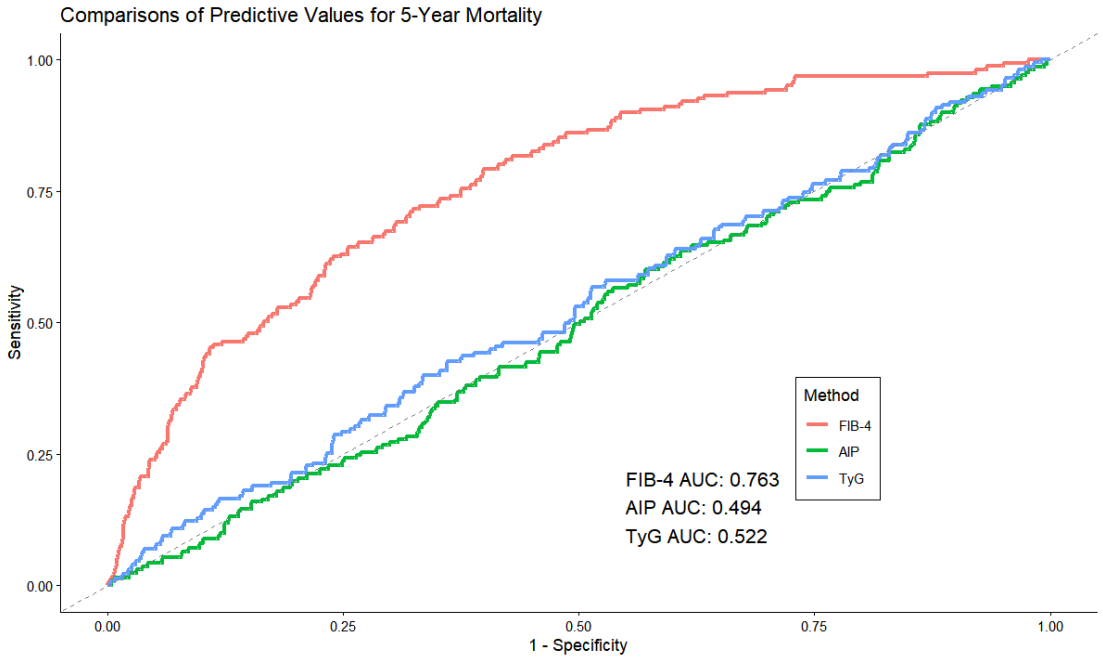


Figure 4. (A) Time-dependent ROC curves at 5 years for predicting all-cause mortality among participants with MASLD.

To evaluate the discriminative ability of liver fibrosis scores versus metabolic indices, we performed time-dependent ROC analysis at the 5-year follow-up (Figure 4A). FIB-4 demonstrated superior predictive performance, with an Area Under the Curve (AUC) of [0.763] (95% CI: 0.725-0.801), significantly outperforming both metabolic markers.

In contrast, the metabolic indices showed limited predictive value. The AUC for AIP was [0.494] （95% CI 0.446–0.542）and for TyG was [0.522] （95% CI 0.473–0.572）. Pairwise comparisons confirmed that the AUC of FIB-4 was significantly higher than that of AIP ($P < 0.001$) and TyG (P < 0.001). Although AIP showed a statistically significant difference compared to TyG (P = 0.044), both metabolic markers exhibited substantially lower discriminative ability compared to FIB-4(Figure 4A).

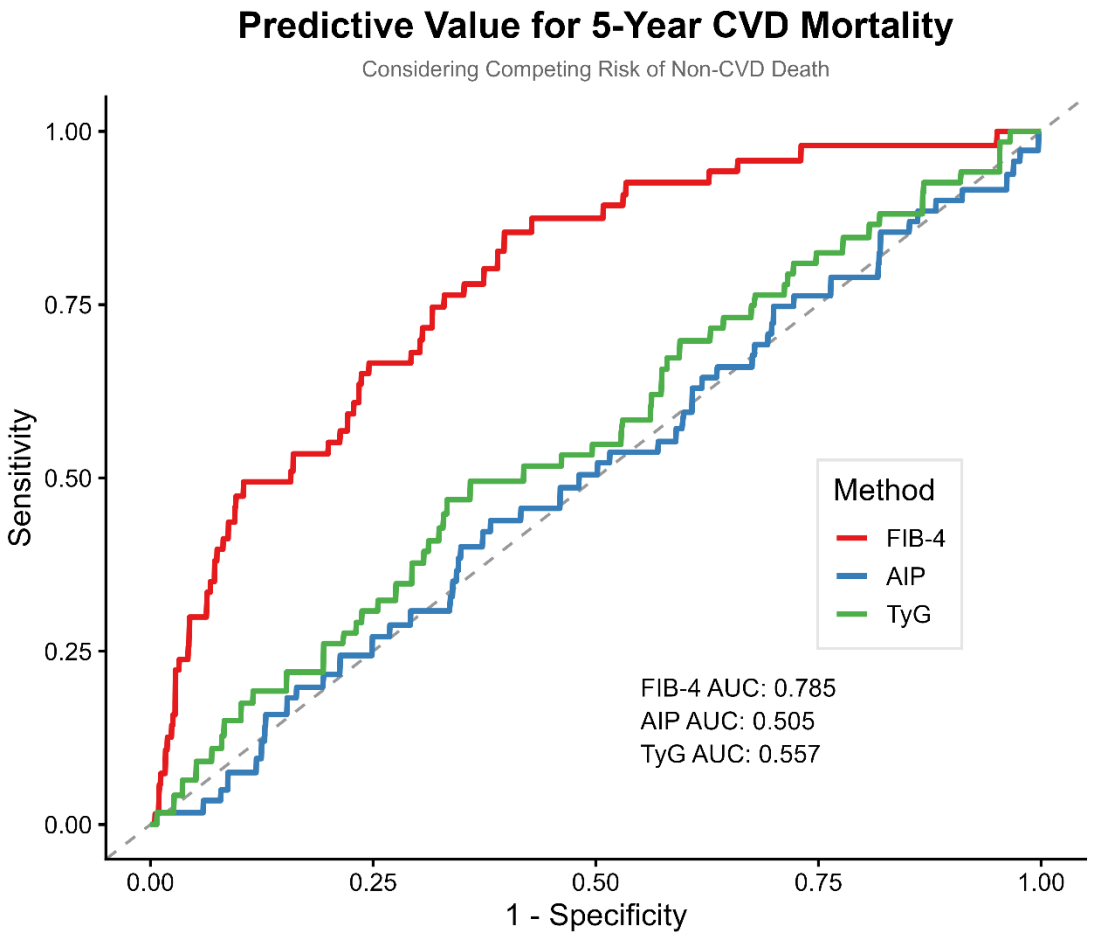


Figure 4. (B)Time-dependent ROC curves for predicting 5-year CVD mortality based on FIB-4, AIP, and TyG, accounting for the competing risk of non-CVD death using marginal weighting.

In time-dependent ROC analyses accounting for the competing risk of non-CVD death, FIB-4 demonstrated substantially superior discrimination for 5-year CVD mortality compared with AIP and TyG (Figure 4B). The 5-year AUC for FIB-4 was 0.785 (95% CI 0.715–0.841), whereas AIP and TyG exhibited minimal discrimination with AUCs of 0.505 (95% CI 0.420–0.589) and 0.557 (95% CI 0.473–0.642), respectively.

Compared with AIP, FIB-4 showed a significantly higher AUC (ΔAUC 0.280, 95% CI 0.153–0.392; P<0.001). Similarly, FIB-4 outperformed TyG (ΔAUC 0.227, 95% CI 0.108–0.342; P<0.001). Collectively, these findings indicate that, as a standalone marker, FIB-4 provides markedly better 5-year CVD mortality discrimination than lipid- and insulin-resistance–related indices in MASLD(Figure 4B).

To confirm that our findings were not sensitive to the chosen 5-year timeframe, we re-evaluated the time-dependent AUCs at alternative follow-up horizons (3 years and 7 years). The discriminative superiority of FIB-4 remained remarkably robust and highly significant. For all-cause mortality at 3 years, the AUC for FIB-4 was 0.753 (95% CI: 0.704–0.802), substantially outperforming both AIP (AUC = 0.456, P < 0.001) and TyG (AUC = 0.465, P < 0.001). This outperformance was similarly maintained at the 7-year horizon (FIB-4 AUC = 0.766 vs. AIP AUC = 0.503 and TyG AUC = 0.532; both P < 0.001). Furthermore, in competing-risk analyses for CVD mortality, FIB-4 exhibited even stronger discrimination at both 3 years (AUC = 0.795, 95% CI: 0.729–0.861) and 7 years (AUC = 0.777, 95% CI: 0.712–0.842), completely surpassing the metabolic indices (all pairwise P < 0.001) (Supplementary Figure S3).

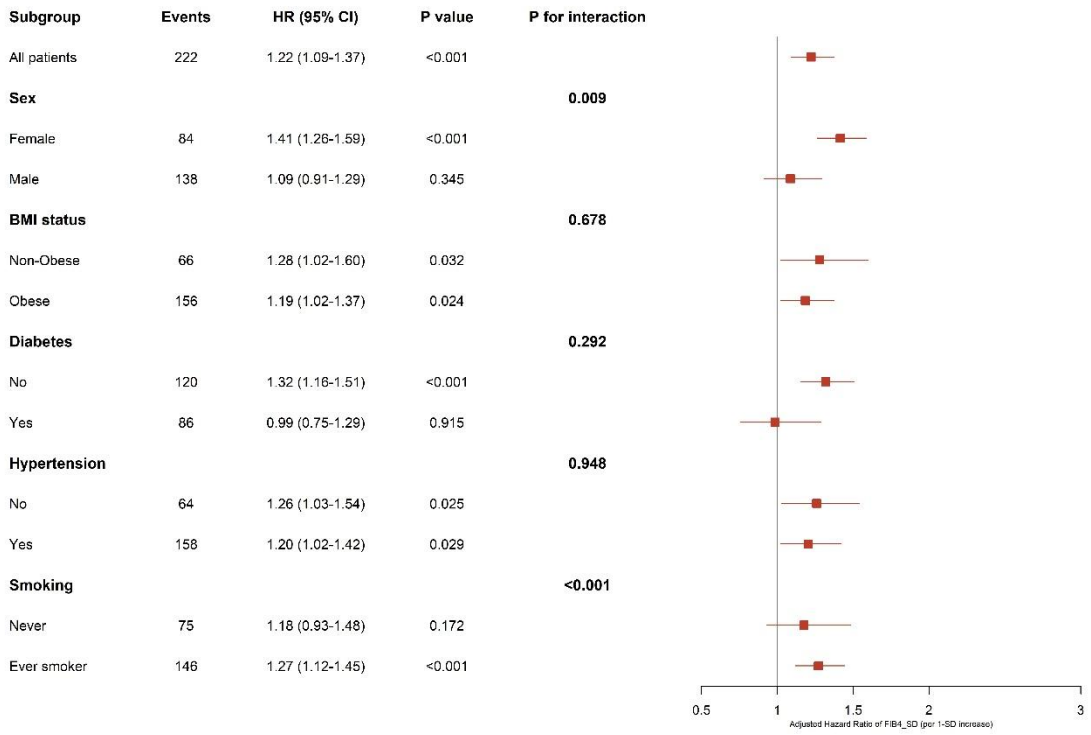


Figure 5. (A) Survey-weighted subgroup analyses of the association between FIB-4 (per 1-SD increase) and all-cause mortality among MASLD participants

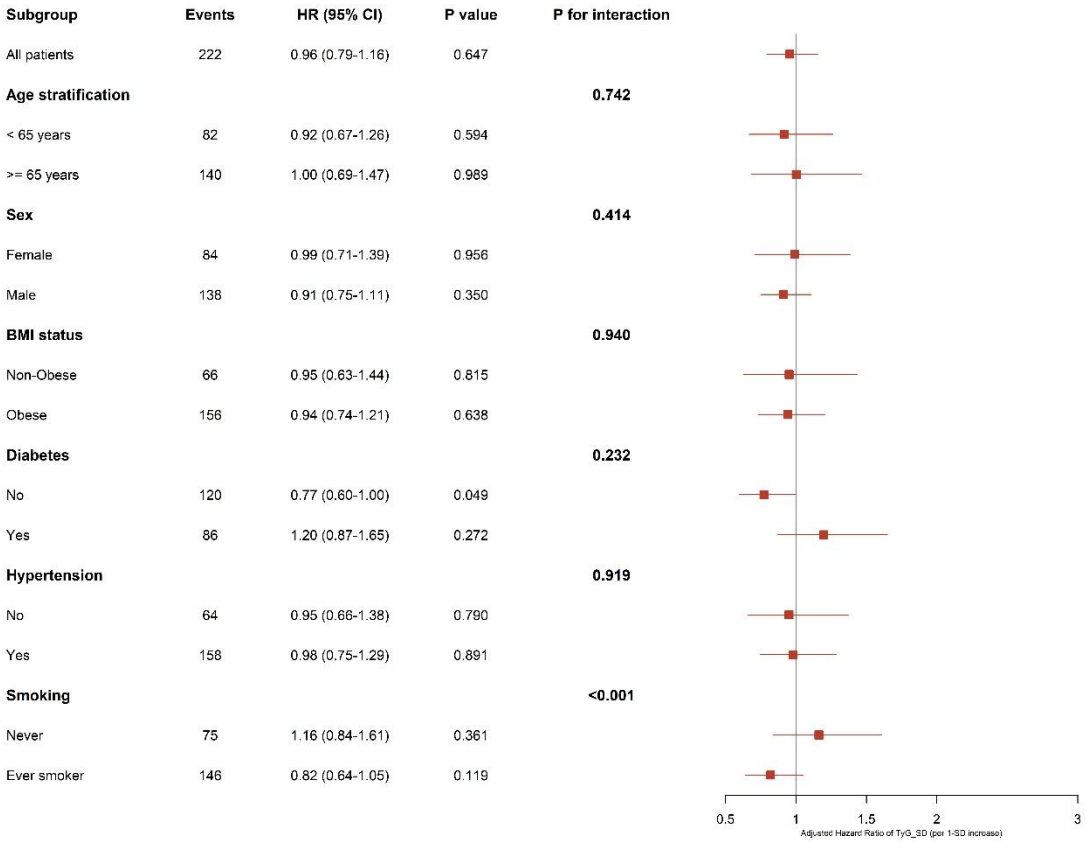


Figure 5. (B) Survey-weighted subgroup analyses of the association between TyG index (per 1-SD increase) and all-cause mortality among MASLD participants

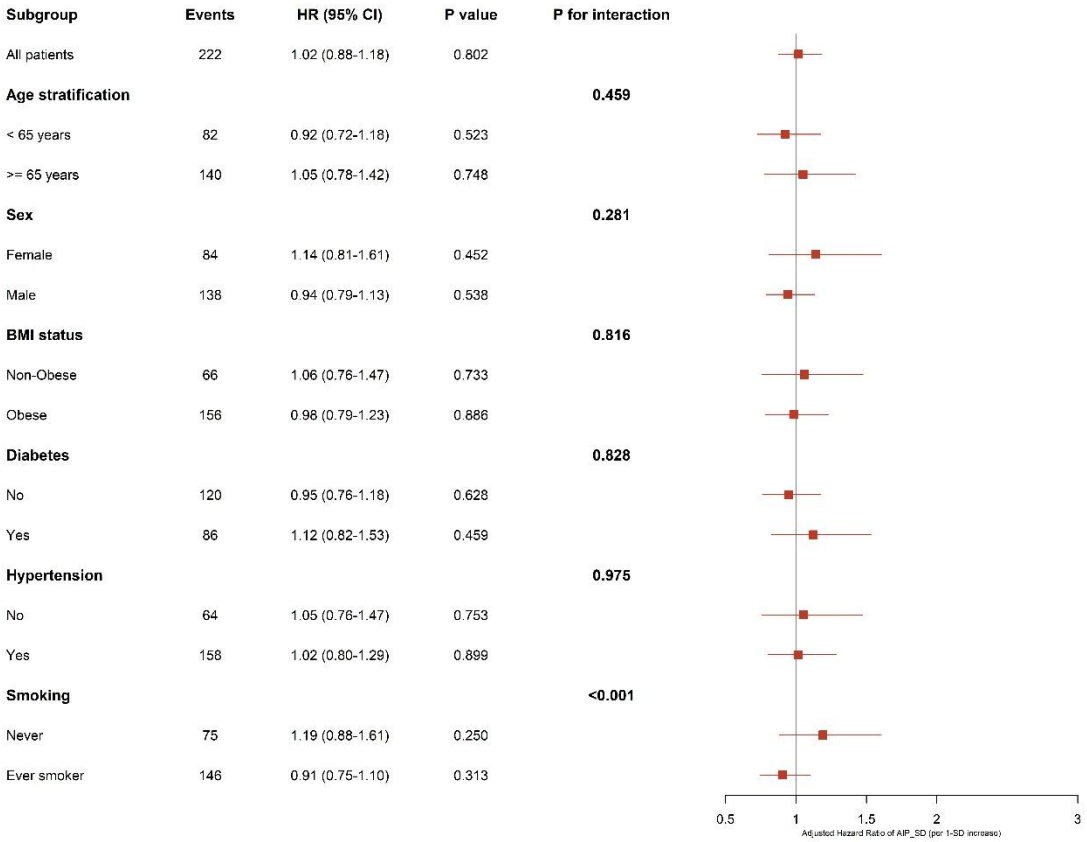


Figure 5. (C) Survey-weighted subgroup analyses of the association between the atherogenic index of plasma (AIP per 1-SD increase) and all-cause mortality among MASLD participants

In the NHANES 2011–2018 MASLD cohort, a total of 222 all-cause deaths occurred in the analytic sample. In survey-weighted multivariable Cox models, each 1-SD increase in FIB-4 was significantly associated with higher all-cause mortality (HR=1.22, 95% CI=1.09–1.37; P<0.001). In subgroup analyses, a statistically significant interaction by sex was observed (P for interaction=0.009), with a stronger association in women (HR=1.41, 95% CI=1.26–1.59; P<0.001) than in men (HR=1.09, 95% CI=0.91–1.29; P=0.345). Smoking status also modified the association (P for interaction<0.001): FIB-4 was significantly associated with higher mortality among ever smokers (HR=1.27, 95% CI=1.12–1.45; P<0.001) but not among never smokers (HR=1.18, 95% CI=0.93–1.48; P=0.172).No evidence of effect modification was found

across BMI categories (P for interaction=0.678), diabetes status (P for interaction=0.292), hypertension status (P for interaction=0.948),with generally consistent directions of association.

By contrast, neither TyG nor AIP (per 1-SD increase) was associated with all-cause mortality in the overall population (TyG: HR=0.96, 95% CI=0.79–1.16; P=0.647; AIP:=HR 1.02, 95% CI =0.88–1.18; P=0.772). Subgroup analyses for TyG and AIP did not reveal significant interactions across age strata, sex, BMI status, diabetes, or hypertension (all P for interaction >0.05). Notably, smoking status significantly modified the associations of TyG and AIP with mortality (both P for interaction<0.001), showing opposite directions between never and ever smokers; however, the stratum-specific estimates did not reach statistical significance (TyG: never smokers HR =1.16, 95% CI=0.84–1.61; P=0.361; ever smokers HR=0.82, 95% CI=0.64–1.05; P=0.119; AIP: never smokers HR=1.19, 95% CI=0.88–1.61; P=0.250; ever smokers HR=0.91, 95% CI=0.75–1.10; P=0.313). Overall, these findings indicate that FIB-4 showed more robust mortality risk stratification than TyG and AIP in this MASLD population(Figure 5 A B C).

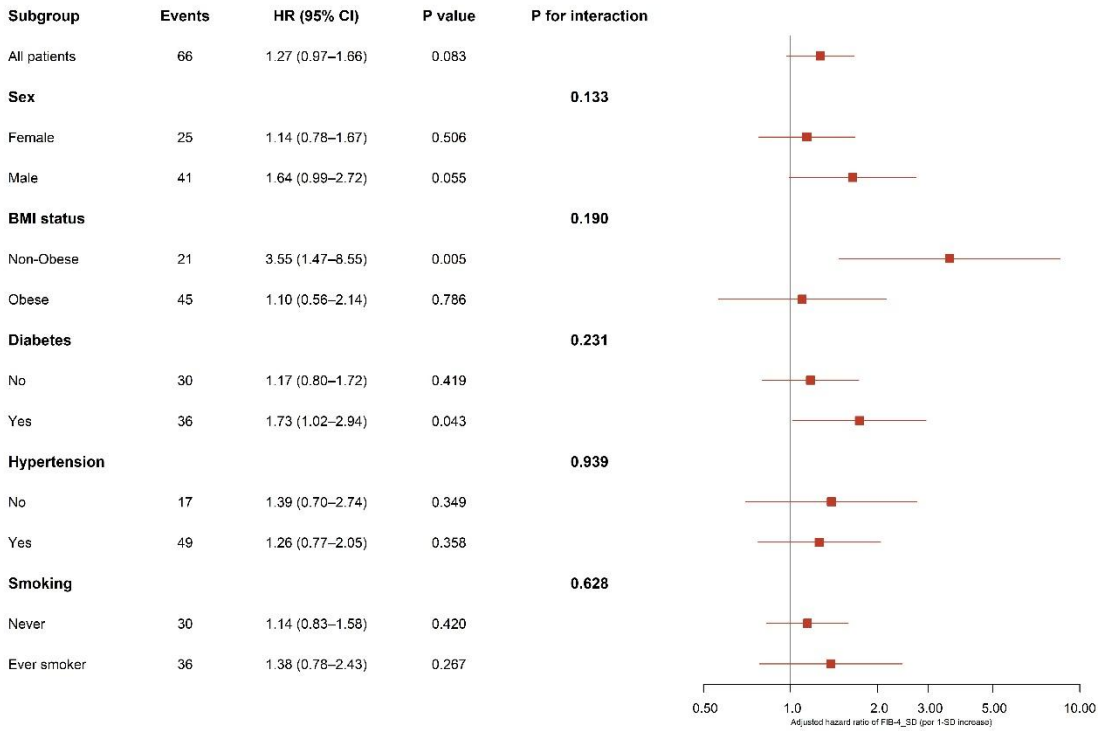


Figure 5. (D) Survey-weighted subgroup analyses of the association between FIB-4 (per 1-SD increase) and CVD mortality among MASLD participants

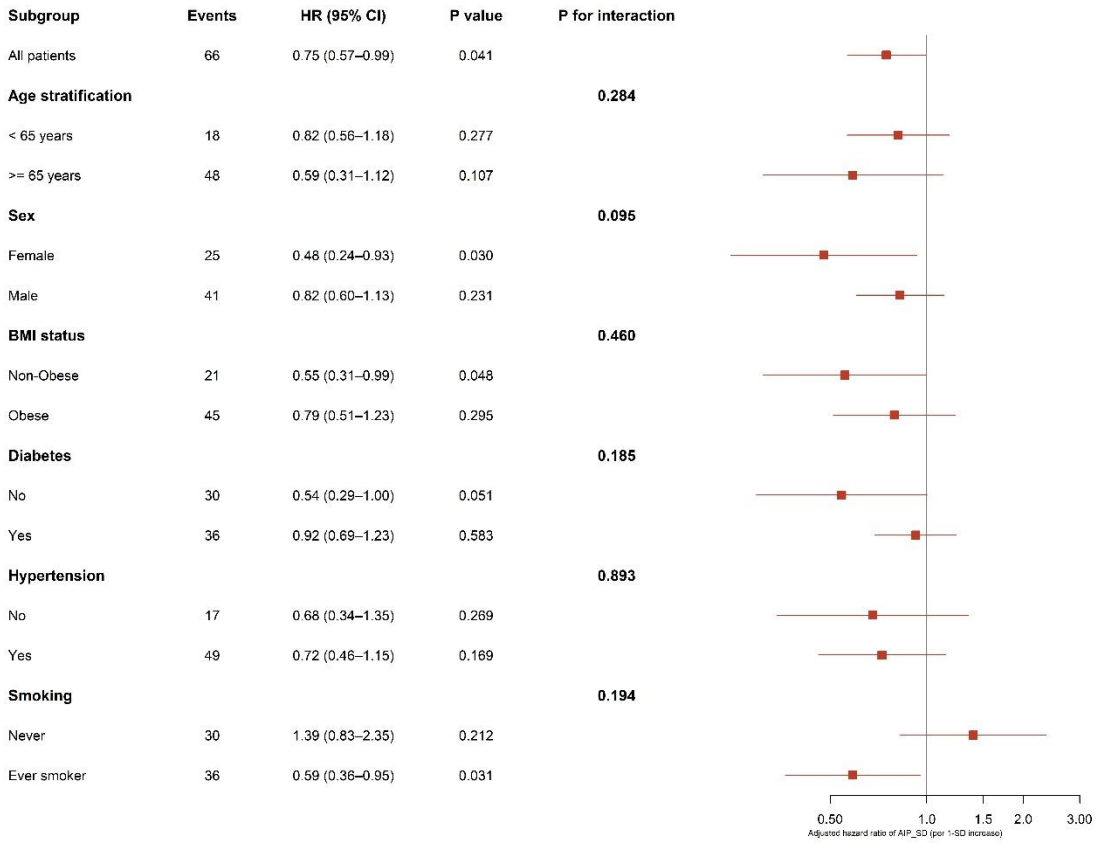


Figure 5. (E) Survey-weighted subgroup analyses of the association between AIP index (per 1-SD increase)

and CVD mortality among MASLD participants

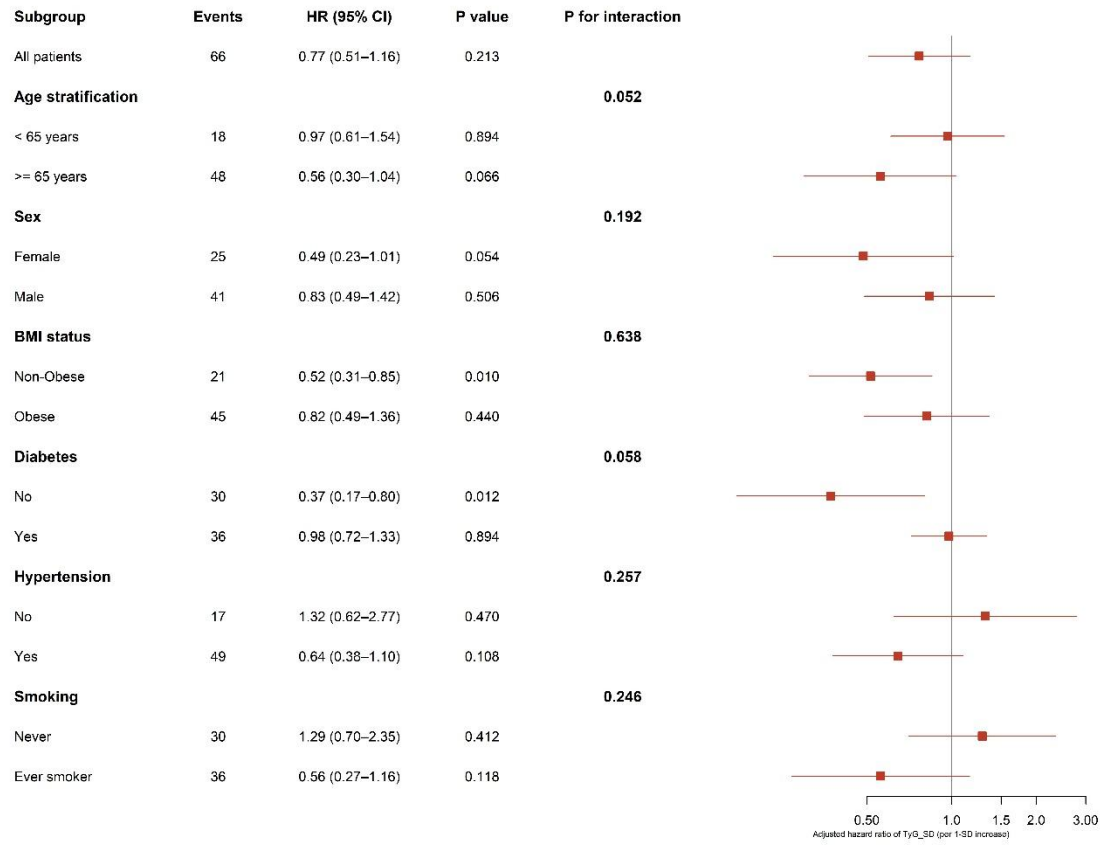


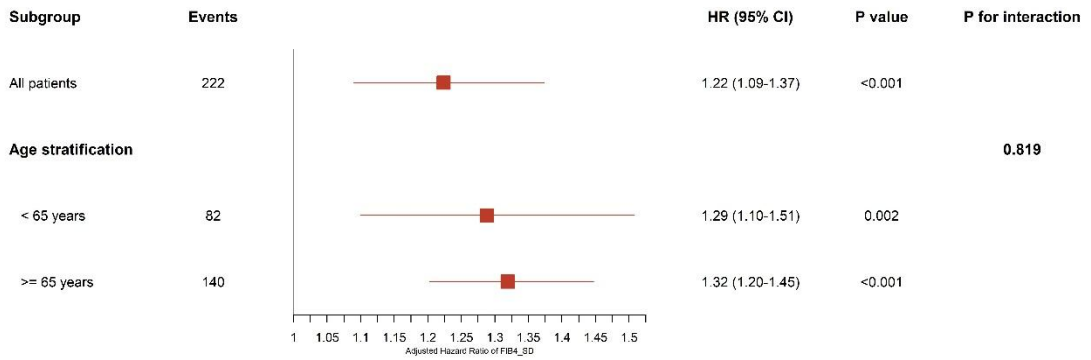
Figure 5. (F) Survey-weighted subgroup analyses of the association between TyG index (per 1-SD increase) and CVD mortality among MASLD participants

Across 66 CVD deaths, the association between FIB-4 (per 1-SD increase) and CVD mortality was directionally positive but did not reach conventional statistical significance in the overall population (HR 1.27, 95% CI 0.97–1.66; P=0.083). Associations were generally consistent across prespecified subgroups, with no evidence of effect modification by sex (P_interaction=0.133), BMI status (P_interaction=0.190), diabetes (P_interaction=0.231), hypertension (P_interaction=0.939), or smoking (P_interaction=0.628). Notably, the association appeared stronger among non-obese participants (HR 3.55, 95% CI 1.47–8.55; P=0.005) and among those with diabetes (HR 1.73, 95% CI 1.02–2.94; P=0.043), although interaction tests were not statistically significant.

For AIP, a higher AIP (per 1-SD increase) was associated with a lower risk of CVD mortality in the overall population (HR 0.75, 95% CI 0.57–0.99; P=0.041). Subgroup-specific estimates varied in magnitude, with significant inverse associations observed in females (HR 0.48, 95% CI 0.24–0.93; P=0.030), in non-obese participants (HR 0.55, 95% CI 0.31–0.99; P=0.048), and in ever smokers (HR 0.59, 95% CI 0.36–0.95; P=0.031). However, formal interaction tests did not support effect modification (all P_interaction>0.05), including by age (P_interaction=0.284) and smoking status (P_interaction=0.194).

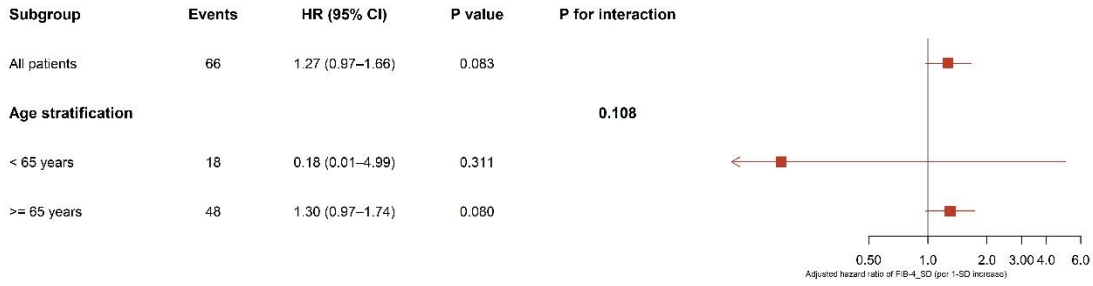
TyG was not significantly associated with CVD mortality in the overall population (HR 0.77, 95% CI 0.51–1.16; P=0.213). In subgroup analyses, TyG showed significant inverse associations among non-obese participants (HR 0.52, 95% CI 0.31–0.85; P=0.010) and among participants without diabetes (HR 0.37, 95% CI 0.17–0.80; P=0.012), whereas no association was observed among obese participants or those with diabetes. Interaction tests suggested potential heterogeneity by age (P_interaction=0.052) and diabetes status (P_interaction=0.058), although these did not meet the prespecified threshold for statistical significance(Figure 5 D E F).

Sensitivity analysis



Supplementary Figure S2 . (A) Age-stratified sensitivity analysis of the association between FIB-4 (per 1-SD increase) and all-cause mortality in MASLD participants.

Given that age is a component of the FIB-4 formula, age-stratified analyses were conducted as a sensitivity analysis to assess the robustness of the findings and to minimize mathematical coupling in the primary subgroup analyses. Higher FIB-4 (per 1-SD increase) was significantly associated with increased risk of all-cause mortality. Overall, 222 all-cause deaths occurred during follow-up, and each 1-SD increment in FIB-4 was associated with a 22% higher hazard of all-cause death (HR=1.22, 95% CI=1.09–1.37; P < 0.001).The association between FIB-4 and all-cause mortality remained directionally consistent across age groups, and no significant interaction by age group was detected (P for interaction >0.05), supporting the robustness of the primary findings (Supplementary Figure S2).



Supplementary Figure S2 . (B) Age-stratified sensitivity analysis of the association between FIB-4 (per 1-SD

increase) and CVD-cause mortality in MASLD participants.

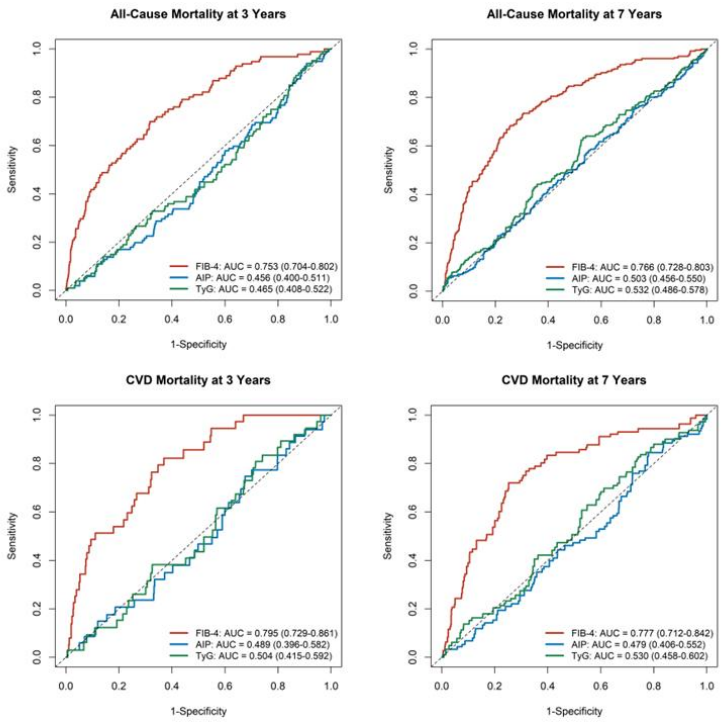
In sensitivity analyses incorporating age stratification for FIB-4, there was no evidence of statistically significant interaction by age (P_interaction=0.108). Estimates among participants aged <65 years were imprecise with wide confidence intervals (HR 0.18, 95% CI 0.01–4.99; P=0.311), consistent with limited event counts, whereas the association in those aged ≥65 years remained directionally similar to the primary analysis (HR 1.30, 95% CI 0.97–1.74; P=0.080) (Supplementary Figure S2).

Characteristics		Survivors	Non-survivors	P Value
Estimated Population (Weighted N)		30,564,724	1,949,347	
Age..mean..SD..		48.64 (15.14)	64.80 (13.63)	**<0.001**
Gender....	Male	53.8%	62.1%	0.069
X	Female	46.2%	37.9%	
Race....	Mexican American	10.6%	4.3%	**0.002**
X.1	Non-Hispanic Black	10.2%	7.7%	
X.2	Non-Hispanic White	67.6%	76.9%	
X.3	Other Hispanic	6.7%	3.4%	
X.4	Other Race - Including Multi-Racial	4.8%	7.6%	
BMI..mean..SD..		34.71 (6.46)	33.33 (5.71)	0.052
Smoking....	Never	52.7%	30.4%	**<0.001**
X.5	Ever smoker	47.3%	69.6%	
Diabetes....	No	81.5%	64.7%	**<0.001**
X.6	Yes	18.5%	35.3%	
Hypertension....	No	54.4%	33.9%	**<0.001**
X.7	Yes	45.6%	66.1%	
FIB4..median..IQR..		0.97 [0.66, 1.39]	1.57 [1.14, 2.30]	**<0.001**
AIP..median..IQR..		0.11 [-0.09, 0.32]	0.13 [0.02, 0.30]	0.090
TyG..median..IQR..		8.93 [8.53, 9.34]	8.99 [8.70, 9.37]	0.063
Fasting_Glucose..median..IQR..		104.00 [96.00, 117.00]	110.47 [99.00, 132.00]	**0.008**
ALT..median..IQR..		24.00 [20.00, 29.00]	23.00 [20.00, 28.00]	0.596
AST..median..IQR..		26.00 [19.00, 35.00]	20.00 [16.00, 28.00]	**<0.001**
TG_mmol..median..IQR..		1.57 [1.09, 2.24]	1.66 [1.21, 2.09]	0.312
HDL_mmol..median..IQR..		1.16 [1.01, 1.40]	1.19 [0.93, 1.32]	0.194

Note: Data are presented as weighted mean (SD) for normally distributed continuous variables, median [IQR] for non-normally distributed variables, and weighted percentages (%) for categorical variables.

Supplementary Table S1. The baseline characteristics before multiple imputation

The baseline characteristics before and after multiple imputation are largely consistent, indicating that the imputation process did not introduce significant changes to the overall distribution of the variables. This suggests that the imputation was conducted appropriately, maintaining the integrity of the dataset(Supplementary Table S1).



Supplementary Figure S3. Time-dependent ROC curves for predicting 3-year and 7-year all-cause and CVD mortality based on FIB-4, AIP, and TyG

Discussion

The escalating global burden of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) underscores the urgent need for non-invasive biomarkers capable of reliably stratifying long-term mortality risk. In this large-scale prospective cohort study utilizing NHANES 2011–2018 data, we conducted a comprehensive head-to-head comparison of a structural fibrosis marker (FIB-4) against two dynamic lipid-metabolic indices (AIP and TyG). Our findings provide compelling evidence for a definitive hierarchy in near or mid-term prognostication within the MASLD population: the extent of liver fibrosis, as approximated by the FIB-4 index, is a significantly more potent predictor of both all-cause and cardiovascular survival than purely metabolic parameters. While metabolic dysfunction acts as the initiator of hepatic steatosis, our data suggest that once MASLD is established, the severity of structural liver damage

(fibrosis) surpasses metabolic dysregulation to become the primary driver of adverse outcomes.[4,35]

The most salient finding of our study is the robust, independent predictive value of the FIB-4 index for all-cause mortality across all statistical models. In our time-dependent ROC analysis, FIB-4 achieved an AUC of 0.763 for 5-year all-cause mortality, vastly outperforming AIP (AUC 0.494) and TyG (AUC 0.522), whose predictive abilities were akin to chance. This was further corroborated by Kaplan-Meier curves, where the high-risk FIB-4 group (>2.67) demonstrated a precipitous decline in survival probability ($P < 0.0001$), a trend notably absent for the AIP and TyG tertiles.

This pattern suggests that fibrosis burden—approximated by a simple index integrating age, AST, ALT, and platelet count—captures a more proximate “risk state” for near- to mid-term mortality than metabolic surrogates of dyslipidaemia or insulin resistance in a MASLD population. These results align with a paradigm shift in hepatology, positing that fibrosis stage—rather than the grade of steatosis or inflammatory activity (MASH)—is the single most critical histological determinant of mortality.[4,36] While AIP and TyG serve as excellent surrogates for insulin resistance and dyslipidemia, which drive the onset of MASLD, our data indicate they likely represent the "exposure" risk factors rather than the "outcome-determining" pathology in this specific cohort. Consistent with findings from Unulpathuarana et al., who showed fibrosis scores outperform metabolic syndrome components in predicting mortality[23], our study specifically extends this conclusion to the increasingly popular lipid-glucose indices, definitively establishing their inferiority to FIB-4 in the prognostic context of MASLD.

This reinforces the utility of FIB-4 not just as a screening tool, as recommended by AASLD guidelines[33], but as a robust prognostic marker for near-term survival.

A nuanced and critical insight from our study emerges from the cardiovascular mortality analysis. In our time-dependent ROC analysis, FIB-4 achieved an AUC of 0.785 for 5-year CVD mortality, which is far superior to AIP (AUC 0.505) and TyG (AUC 0.557), the latter of which has almost no predictive ability. In unadjusted Kaplan-Meier analyses, none of the indices (FIB-4, AIP, TyG) showed significant separation for CVD survival ($P > 0.05$). However, after rigorous adjustment for confounding variables and competing risks using Restricted Cubic Spline (RCS) modeling, FIB-4 emerged as a significant, non-linear predictor of CVD mortality ($P_{overall} = 0.020$), exhibiting a J-shaped dose-response relationship. Conversely, the relationships for AIP and TyG remained flat and non-significant ($P_{overall} > 0.05$). We acknowledge that the exclusion of survey weights may introduce a degree of bias when estimating precise national population-level absolute performance metrics. However, the primary objective of the ROC analysis was to evaluate the comparative discriminative ability between FIB-4 and metabolic indices. Given that our fully survey-weighted multivariable Cox models and Restricted Cubic Splines yielded highly concordant results—consistently demonstrating the predictive superiority of FIB-4—we believe this methodological inconsistency did not meaningfully alter our comparative conclusions.

This revealment of the FIB-4 effect in multivariate analysis highlights the intricate "Liver-Heart Axis."[24] The lack of significance in unadjusted analysis is likely

attributable to the "competing risk" of non-CVD deaths (e.g., malignancy, liver failure) in this older, multimorbid population. Once these competing risks were accounted for, the specific contribution of fibrosis to cardiovascular death became evident. Mechanistically, advanced hepatic fibrosis is not merely a bystander but an active contributor to systemic endothelial dysfunction.[31] The fibrotic liver acts as a source of systemic inflammation, releasing pro-inflammatory cytokines (IL-6, TNF-α), pro-coagulant factors (PAI-1), and dysregulated hepatokines (e.g., elevated Fetuin-A, resistant FGF21), which collectively accelerate atherosclerosis and myocardial remodeling.[24,32] Our results may challenge the traditional view that metabolic markers are the superior predictors of cardiac death in MASLD; instead, In short-term cohort studies with a median follow-up of 4.5 years， they suggest that the consequence of metabolic toxicity on the liver (i.e., fibrosis) serves as a more integrated and potent summary of cumulative cardiovascular stress.

A frequent critique of the FIB-4 index is its reliance on age in its formula.[27] Raising concerns of "mathematical coupling"—that its predictive power merely reflects the patient's age. Our study rigorously addressed this through age-stratified sensitivity analyses. We demonstrated that FIB-4 remained a significant predictor of mortality in both younger (<60 years) and older (> 60 years) subgroups, with hazard ratios remaining elevated even when age was strictly controlled. This confirms that the prognostic value of FIB-4 is derived from its liver-specific components (aminotransferases and platelets), reflecting true pathology such as portal hypertension-induced thrombocytopenia, rather than being an artifact of aging.[25]

Furthermore, our subgroup analysis revealed a significant interaction by sex (P_interaction = 0.011 for all-cause mortality), where FIB-4 showed stronger predictive value in females (HR 1.42) compared to males (HR 1.09, non-significant). This sex dimorphism is likely driven by the protective anti-fibrotic effects of estrogen.[26] The "high risk" females in our cohort were predominantly post-menopausal, suggesting that the loss of estrogenic protection may trigger a more rapid and lethal fibrotic progression. Additionally, higher baseline ALT levels and muscle mass in males might inflate FIB-4 scores artificially in the absence of severe disease, potentially diluting its specificity in men. This finding supports the growing call for sex-specific cut-offs in fibrosis biomarkers to enhance prognostic precision.

The inability of AIP and TyG to predict mortality in our adjusted models contrasts with their established utility in the general population.[28,29,37] However, within a MASLD-specific cohort which had a median follow-up of 4.5 years, this "failure" is biologically plausible.

Like so-called The "Burn-out" Effect, in advanced MASLD (cirrhosis), metabolic profiles often paradoxically "improve."[30] As hepatic synthetic function declines, the liver's ability to produce glucose, cholesterol, and triglycerides diminishes. Consequently, a patient dying of end-stage liver disease or severe heart failure might present with low or normal TyG/AIP levels due to malnutrition (cachexia) or hepatic failure. This reverse causality renders metabolic indices unreliable markers in advanced disease stages.

Secondary, in a cohort defined by the presence of steatosis (MASLD), the baseline

metabolic risk is universally elevated. While AIP and TyG are excellent for diagnosing MASLD vs. non-MASLD[34], they lack the dynamic range to distinguish "severe" MASLD from "moderate" MASLD outcomes. Fibrosis, representing the cumulative end-organ damage from years of metabolic stress, offers a more distinct stratification of terminal risk.

Furthermore, metabolic indices such as the AIP index and TyG index do not clearly demonstrate the cumulative risk of all-cause and cardiovascular mortality from lipid metabolism disorders and insulin resistance during short-term follow-up periods. Because metabolic indices such as AIP and TyG are dynamic markers reflecting a cross-sectional state, which may fluctuate over time. In contrast, liver fibrosis (FIB-4) represents the cumulative, structural end-result of long-standing metabolic stress.[38] Recent studies suggest that the cumulative burden of high TyG index over time, rather than a single baseline measurement, is a stronger predictor of CVD events.[39] Therefore, baseline metabolic markers may fail to capture the long-term cumulative exposure required to drive mortality endpoints during the available follow-up period. And the length of follow-up period may influence the outcomes of the study. A cohort study of adults in the US identified a J-shaped, nonlinear association between AIP and ACM, with a significant increase in risk observed only beyond a certain threshold (AIP >0.0905).[40] In contrast, another study reported that elevated AIP was significantly associated with diabetes-related mortality but not with ACM or CVM.[41] These differences may stem from variations in population characteristics, follow-up duration, and the extent of covariate adjustment. The average follow-up duration in

these two studies was approximately 8 to 10 years, whereas the median follow-up duration in our study was 4.5 years. As follow-up duration lengthens, the cumulative exposure risk of metabolic indicators may increase, leading to statistically significant differences in elevated all-cause mortality and even cardiovascular mortality rates.

The strengths of our study include the use of a large, nationally representative sample (NHANES) with rigorous weighting procedures, ensuring high generalizability. We employed advanced statistical methodologies, including Competing Risk Models and Restricted Cubic Splines, to capture non-linear relationships and account for non-CVD deaths, providing a more accurate estimation of CVD risk than traditional models.

Several limitations of this study should be acknowledged. First, a considerable number of participants were excluded due to missing FLI values or other key covariates, which may have introduced selection bias, diminished the representativeness of the analytic cohort, and thereby constrained the generalizability of our findings. Additionally, the reliance on FLI, a biochemical marker-based definition of MASLD, introduces the possibility of misclassification and does not account for potential confounders such as genetic factors. Second, cardiovascular mortality ascertainment based on self-reported information may be susceptible to misclassification because of the absence of systematic clinical adjudication. Third, FIB-4, AIP, and TyG were calculated from a single baseline assessment; thus, we could not account for longitudinal variability in lipid and metabolic parameters, nor fully address potential confounding from lipid-lowering therapies and metabolic fluctuations during follow-up. Fourth, the evaluation of hepatic steatosis and fibrosis relied on serum biomarkers and VCTE rather than liver

biopsy; although these non-invasive approaches are the standard of care and widely used in large-scale epidemiological studies, some degree of measurement error cannot be excluded. In addition, the observational design inherently limits causal inference, and residual confounding may persist despite multivariable adjustment. Finally, the relatively small number of CVD events in certain low-risk subgroups may have reduced statistical power for more granular stratified analyses.

To rigorously validate our primary findings, we evaluated the prognostic performance of the studied indices across multiple alternative modeling strategies. Specifically, the FIB-4 index was analyzed as a linear continuous variable (per 1-SD increment), a non-linear continuous parameter (utilizing restricted cubic splines to capture dose-response gradients), and a categorical variable (applying established age-stratified clinical cutoffs: 1.3/2.67 for individuals aged <65 years and 2.0/2.67 for those ≥65 years). Across all these distinct analytical approaches, the significant and superior predictive value of elevated FIB-4 for both all-cause and cardiovascular mortality remained remarkably robust and directionally consistent. In contrast, the metabolic indices (AIP and TyG) consistently failed to demonstrate significant independent prognostic utility regardless of whether they were modeled continuously or categorically (as tertiles). Collectively, these multi-model sensitivity analyses confirm that our comparative conclusions are highly stable and not artifacts of a specific variable categorization strategy.

Conclusion

Collectively, our study definitively establishes that in patients with MASLD, the extent

of liver fibrosis (assessed by FIB-4) is a superior and robust predictor of both all-cause and cardiovascular mortality compared to the lipid-metabolic indices AIP and TyG, may represent a more proximate determinant of survival in MASLD than metabolic indices alone, supporting broader clinical adoption of fibrosis-oriented risk stratification in population health and preventive cardiometabolic care.While metabolic markers reflect the underlying risk factors, fibrosis reflects the severity of end-organ damage. Clinicians should prioritize fibrosis assessment over metabolic ratios when risk-stratifying MASLD patients for long-term survival. The significant, non-linear association between FIB-4 and cardiovascular death reinforces the critical need for aggressive cardiovascular risk management in patients with identified liver fibrosis.

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Author contributions
The study design was conceived by YYL and ZZ. YYL and NK organized the data, conducted the analyses, and wrote and edited the manuscript. ZZ and ZCZ contributed to the interpretation of the results, revision, and finalization of the manuscript. All authors have reviewed and approved the final version of the manuscript.

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Data availability
The datasets that were used and evaluated in this study can be obtained from the corresponding author upon making a reasonable request.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent. The authors have disclosed no conflicts of interest.

Competing interests
The authors declare no competing interests.

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