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ORIGINAL RESEARCH—CLINICAL

Metabolic Syndrome Severity Predicts Mortality in Nonalcoholic Fatty Liver Disease

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BACKGROUND AND AIMS: Previous studies have examined the effects of metabolic syndrome (MetS) presence rather than the severity on mortality risk in nonalcoholic fatty liver disease (NAFLD). We used the MetS severity score, a validated gender- and race-specific measure, to assess the relationship between MetS severity and mortality risk in NAFLD. **METHODS:** The study included 10,638 adults aged between 20 and 74 years who participated in the Third National Health and Nutrition Examination Survey. NAFLD was defined as mild, moderate, or severe hepatic steatosis on ultrasound without excessive alcohol intake and other liver diseases. Adjusted Cox proportional models were used to test the association between the MetS severity score and mortality risk related to all-cause, heart disease, diabetes, and hypertension. **RESULTS:** The median MetS severity score was significantly higher in NAFLD (0.49 [69th] vs −0.23 [41st]). An increase in the MetS severity corresponded to a linear rise in biomarkers for cardiovascular disease, insulin resistance, lipid abnormalities, and liver and kidney problems. The MetS severity score was a significant predictor for all-cause and cause-specific adjusted mortalities. A quartile increase in MetS severity score was associated with higher mortality risks from all-causes adjusted hazard ratio (aHR) 1.36 (95% confidence interval [CI]: 1.17–1.57), heart disease aHR 1.70 (95% CI: 1.17–2.47), diabetes aHR 3.64 (95% CI: 2.27–5.83), and hypertension aHR 1.87 (95% CI: 1.14–3.04). A higher MetS severity score was also associated with nonlinear increased risks of mortality in all adjusted models. **CONCLUSION:** The MetS severity score is a clinically accessible tool that can be used to identify and monitor NAFLD patients at the highest risk of mortality.

Keywords: MetS; MAFLD; NHANES III; obesity

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a significant cause of chronic liver disease in the United States (US).[1–3] NAFLD is a spectrum of histological states ranging in severity from simple intrahepatic fat accumulations, nonalcoholic fatty liver, to inflammation in the presence of ballooned hepatocytes, nonalcoholic steatohepatitis (NASH).[2–4] While the majority of NAFLD patients do not require clinical interventions, NASH increases the risk of advanced chronic liver diseases such as cirrhosis,[5] decompensated cirrhosis, and hepatocellular carcinoma.[2,6,7]

NAFLD is the hepatic manifestation of metabolic syndrome (MetS).[2,8–13] MetS is a group of metabolic abnormalities associated with increased risks of insulin resistance and cardiovascular disease (CVD).[14] The current guidelines for diagnosing MetS put forward by the American Heart Association and the National Heart Lung and Blood Institute rely on a "harmonizing definition" of this syndrome.[15] As such, MetS is dichotomously characterized by the presence of 3 of 5 metabolic abnormalities: hyperglycemia, reduced high-density lipoprotein, hypertriglyceridemia, central obesity, or hypertension.[14,16]

NAFLD increases CVD risk via multiple pathophysiological mechanisms, including systemic inflammation, hepatic insulin resistance, and altered lipid metabolism.[17–19] As a result, NAFLD is associated with coronary artery disease[20] and increased risk of coronary atherosclerotic plaques,[21] independent of the traditional risk factors. Furthermore, NAFLD increases the risks of all-cause and CVD-related mortalities compared to the general population.[22–25] The increased risk of mortality associated with NAFLD is due to higher MetS severity among NAFLD patients relative to the general population.

Previous studies have focused on assessing the relationship between metabolic abnormalities and mortality[9,26] without accounting for the effects of MetS severity on the

Abbreviations used in this paper: **aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CRP, C-Reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; HOMA-IR, Insulin Resistance; ICD-9, The International Classification of Diseases Ninth Revision; ICD-10, The International Classification of Diseases Tenth Revision; MetS, Metabolic Syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES III, the Third National Health and Nutrition Examination Survey; TG, triglyceride.**

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risk of mortality in NAFLD. The dichotomous MetS definition creates 4 main knowledge gaps in assessing the effects of MetS on the risk of mortality in NAFLD. First, the dichotomous MetS definition equally treats the effects of 3 of the 5 metabolic factors on survival in NAFLD. Second, the MetS diagnostic criteria neglect both the sole and combined impacts of all MetS features on the risk of mortality in NAFLD. Third, a dichotomous MetS categorization makes it challenging to study and monitor the clinical implications of worsening in the severity of MetS over time.[27] Fourth, a binary system for MetS definition does not account for the racial and gender disparities in MetS severity and their corresponding effects on mortality risk in NAFLD.[28] Assessing disease severity using a validated continuous measure can address the shortcomings of the current MetS definition.

The MetS severity score is a validated clinically accessible gender- and race-specific Z-score that encapsulates the combined effects of the severity of all 5 metabolic abnormalities among US adults.[29] The MetS severity score is significantly correlated with pathophysiological biomarkers of MetS, including the homeostasis model for insulin resistance, C-reactive protein, uric acid, and adiponectin.[29,30] The MetS severity score is also a significant predictor of long-term risks of CVD, type 2 diabetes mellitus, and coronary heart disease.[30–33]

Using nationally representative data, we sought to examine the relationship between MetS severity and the risks of all-cause mortality, heart disease-related mortality, diabetes-related mortality, and hypertension-related mortality among adults with NAFLD. Understanding the effects of MetS severity on the risk of mortality in NAFLD will aid clinicians in both identifying high-risk individuals and monitoring patients' progression over time.

Materials and Methods

We conducted a retrospective cohort study using the third National Health and Nutrition Examination Survey (NHANES III). The NHANES III was conducted between 1988 and 1994 by the National Center for Health Statistics. The survey aimed to assess the health and nutritional status of the noninstitutionalized US population with oversampling of non-Hispanic Blacks, Mexican Americans, and individuals aged 60 years and older. Participants in NHANES III were selected using a stratified multistage clustered probability design. The survey included cross-sectional physical examinations, interview questionnaires, and laboratory sample collections. The overall examination rate of interviewed participants was 78%.[34] The ethics review board of the Center for Disease Control and Prevention approved the NHANES III survey protocol.

Participants in the NHANES III were passively followed from the interview date through December 31, 2011. A validated matching algorithm was used to link mortality outcomes with the National Death Index database.[35,36] The matching algorithm links together records from the original NHANES III survey with death certificates data to obtain all participants' underlying causes of death. The accuracy of the mortality matching algorithm to correctly determine the status of a decedent is 96.10% and 99.40% for deceased and living participants, respectively.[36] The International Classification of Diseases Ninth Revision (ICD-9) codes were reported for underlying causes of deaths occurring before 1998, while ICD-10 records were used for deaths after 1999.

Study Sample

Video images of gallbladder ultrasounds were recorded during the physical examinations for all NHANES III participants of the age range 20–74 years. Three trained ultrasound readers assessed the video images for hepatic steatosis using standardized reading protocols. A certified radiologist specializing in hepatic imaging trained all 3 ultrasound readers. Following the initial assessments, all gallbladder ultrasound readings were re-evaluated and validated by another certified radiologist. Hepatic steatosis images were then classified into normal, mild, moderate, or severe.[37]

NAFLD was identified by the presence of mild, moderate, or severe hepatic steatosis in the absence of (1) excessive drinking (ie, more than 3 alcoholic beverages per day for men and more than 2 alcoholic beverages per day for women), (2) binge drinking (ie, frequent consumption of 5 or more alcoholic beverages per day), (3) alcohol consumption restrictions due to illness, (4) positive hepatitis B virus surface antigen test, (5) positive hepatitis C virus RNA test, and (6) iron overload (ie, transferrin saturation of $\geq$50%). In addition, NAFLD patients were excluded from the study if they met any of the following criteria: (1) missing values for alcohol intake; (2) missing or an unreadable ultrasound image; (3) the participant identified race/ethnicity as "Other" since the exposure assessment is only applicable to non-Hispanic Whites, non-Hispanic Blacks, and Hispanics; (4) missing cause of death, (5) participant had a missing value for exposure, outcomes, or any of the covariates included in the adjusted analyses.

Of the total 16,573 individuals aged 20 years or older who attended the examination phase of the survey, 14,707 qualified for the gallbladder ultrasound reading, of which 13,856 participants had readable ultrasound images.[38] Accordingly, a total of 5484 participants had mild, moderate, or severe hepatic steatosis on ultrasound, of whom 3088 NAFLD patients met the study's inclusion criteria.

Exposure

The MetS severity score is a validated gender- and race/ethnicity-specific Z-score that encapsulates the relative MetS severity of all 5 metabolic abnormalities.[29] The MetS severity score was initially derived from a confirmatory factor analysis using data from the 1999–2010 NHANES.[29] Different loading coefficients were estimated for all 5 metabolic components of MetS to quantify a single latent MetS factor for all 6 gender- and race/ethnicity-specific subgroups. Accordingly, the MetS severity score is a continuous representation of the traditional MetS classification while adjusting for gender and racial/ethnic disparities in the relationship between MetS and cardiometabolic outcomes. We used individual-level data for high-density lipoprotein, systolic blood pressure, waist circumference, triglyceride (TG), and blood glucose to calculate gender- and race/ethnicity-specific MetS severity Z-scores according to the score's standardized equations.[29]

Outcomes

The primary outcomes included all-cause mortality and cause-specific mortalities related to heart disease (ie, ICD-10 codes I00-I09 [acute rheumatic fever and chronic rheumatic heart diseases], I11 [hypertensive heart disease], I13 [hypertensive heart and renal disease], I20-I25 [ischemic heart diseases], and I26-I51 [other heart diseases]), diabetes (ie, ICD-10 codes [E10-E14]), and hypertension (ie, ICD-10 codes [I10-I12]). Follow-up time was defined as the number of person-years from the interview date to either death or end of study (ie, December 31, 2011, or last follow-up date, whichever was earlier). Participants were censored if they were lost to follow-up, assumed alive at the end of the study, or if they died due to unintentional injuries (V01-X59, Y85-Y86).

Covariates

Data were gathered on multiple covariates during the interview and examination phases, including confounders and other factors used in the secondary statistical analyses. Confounder selection was based on both *a priori* knowledge from the literature and theoretical rationale. Attained age at the end of follow-up was quantified by adding the follow-up time in years to each participant's baseline age.

Statistical Analyses

The study sample was restricted to participants with values on exposure, outcomes, or any variables used in the adjusted analyses. We used complex survey methods to yield nationally representative estimates. Taylor series linearization was used to account for the effects of survey design on variance estimations. Missing values related to variance estimation were assumed not to be missing completely at random.

We examined participants' stratified characteristics by testing the difference in means for continuous variables using analysis of variance and that for categorical variables using Rao Scott Chi-Square. Age-, gender-, and race/ethnicity-adjusted mean estimates for biomarkers related to cardiovascular factors, metabolic control, lipid, liver, and kidney profiles were quantified for all MetS severity score quartiles. Linear trends of all biomarkers across the MetS severity score quartiles were tested using orthogonal polynomial contrasts. Incidence mortality rates by MetS severity score quartiles were calculated using the number of deaths divided by 1000 person-years of follow-up.

Fully adjusted Cox proportional hazard models, with attained age as the survival timescale, were used to test the association between the MetS severity score and the risk of mortality outcomes among adults with NAFLD. As such, participants' age at baseline marketed their start of follow-up, and the attained age (ie, at event or time of censoring) indicated their exit from the study. As opposed to time-on-study, the use of attained age fully accounts for the effects of the age-mortality associations at the time of event rather than solely adjusting for the impact of age at baseline.[39] All variables included in the Cox models met the proportional hazard assumption through testing the cumulative sums of martingale residuals.[40] Competing mortality risks were accounted for in all cause-specific models by censoring follow-up time at the date of death from other causes.

The dose-response relationships between MetS severity and mortality risk were evaluated using the MetS severity score percentiles as a continuous variable with a 3-knot restricted cubic spline in the adjusted Cox proportional hazard models. The 3 knots were placed at 10th, 50th, and 90th of the weighted MetS severity score percentile values for NAFLD patients.[41] Wald-Chi Square tests were used to assess the overall and nonlinear associations between the MetS severity score percentiles and the risk of mortality. A P value of less than .05 was considered statistically significant. All analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC).

Results

Study Sample

The study sample included 10,638 adult participants in the NHANES III who met the inclusion and exclusion criteria (Table 1). NAFLD prevalence at baseline was 26.7% (95% confidence interval [CI]: 24.3%–29.1%). Stratified by race/ethnicity, NAFLD prevalence was 26.6%, 23.2%, and 33.7% among White non-Hispanics, Black non-Hispanics, and Mexican Americans. Adults with NAFLD were more likely to be female (54.7% vs 51.0%; P value $<$ .047) and older (mean age in years, 45.3 vs 41.6; P value $<$ .001), and a higher percentage of them were Mexican Americans (7.0% vs 5.0%) and a lower proportion comprised Black non-Hispanics (9.6% vs 11.5%). The distributions of education level, marital status, and smoking status also differed by NAFLD status.

An estimated 71.4% of NAFLD patients were overweight or obese, compared with 49.7% in those without NAFLD. Similarly, adults with NAFLD had a 3.1 kg/m^2 higher average BMI than those without NAFLD. The prevalence of abdominal obesity was also significantly associated with NAFLD status (with vs without; 75.5% vs 62.3%; P value $<$ .001). In contrast, the proportion of physically active participants with an NAFLD was lower than that with no NAFLD (84.1% vs 88.8%; P value $<$ .001). The prevalence of chronic kidney disease (CKD) and a history of diabetes were higher among NAFLD patients relative to those without NAFLD (Table 1).

MetS Severity in NAFLD

An estimated 82.2% of adults with NAFLD had at least one feature of the traditionally defined MetS, while 9.3% met the criteria for all 5 metabolic abnormalities. The prevalence of MetS was higher in adults with NAFLD vs those without NAFLD (44.0% vs 20.4%; P value $<$ .001). The mean number of metabolic abnormalities was significantly higher in NAFLD adults vs those without NALFD (2.2 vs 1.4; P value $<$ .001).

The mean and median MetS severity scores and corresponding percentiles were 0.03 (51st) and −0.08 (47th). The mean MetS severity scores were significantly higher in NAFLD relative to those without NAFLD (0.49 [69th] vs −0.14 [46th]). In a receiver operating characteristic

Table 1. Sample Characteristics by Nonalcoholic Fatty Liver Disease (NAFLD) Status, the National Health and Nutrition Examination Survey (NHANES III) 1988–1994 (n = 10,638)

Characteristics	NAFLD (n = 3088)	No NAFLD (n = 7550)	*P* value[g]
Gender, % (SE)			.047
Male	45.3 (1.3)	49.0 (0.76)	
Female	54.7 (1.3)	51.0 (0.76)	
Age, (y)			<.001
Median (25th, 75th percentiles)	42.9 (32.8, 57.0)	38.6 (28.9, 51.7)	
Mean (SE)	45.3 (0.49)	41.6 (0.45)	
Age group, % (SE)			<.001
18–34	28.3 (2.0)	38.9 (1.3)	
35–49	33.1 (2.2)	32.5 (0.93)	
49–64	24.4 (1.3)	18.3 (0.73)	
65+	14.2 (0.95)	10.3 (0.70)	
Race/ethnicity, % (SE)			.001
White, non-Hispanics	83.4 (1.3)	83.5 (0.89)	
Black, non-Hispanics	9.6 (0.84)	11.5 (0.76)	
Mexican americans	7.0 (0.86)	5.0 (0.43)	
Education level, % (SE)			.001
<High school	22.3 (1.3)	20.1 (1.0)	
High school or GED	39.1 (1.5)	34.3 (0.95)	
Some college	19.4 (1.4)	22.6 (0.89)	
College degree or higher	19.2 (1.6)	23.0 (1.0)	
Marital status, % (SE)			<.001
Married[a]	73.3 (1.3)	67.6 (1.2)	
Widowed, separated, or divorced	15.5 (0.96)	15.3 (0.71)	
Single	11.2 (0.91)	17.1 (1.2)	
Have health insurance, % (SE)	89.0 (0.87)	87.4 (0.94)	.159
Alcohol intake, % (SE)			<.001
Never	14.9 (1.1)	9.0 (0.69)	
Former	34.7 (1.4)	31.0 (1.4)	
>0–1 drink/d	40.4 (1.85)	41.7 (1.4)	
>1 drink/d[f]	10.0 (1.1)	18.4 (0.97)	
Smoking status, % (SE)			<.001
Never	47.4 (1.3)	43.0 (1.2)	
Former	29.8 (1.5)	25.2 (0.78)	
Current	22.9 (1.2)	31.9 (1.0)	
Body mass index group (kg/m^2)			<.001
Median (25th, 75th percentiles)	27.9 (24.3, 32.2)	24.9 (22.3, 28.0)	
Mean (SE)	28.8 (0.31)	25.7 (0.11)	
Body mass index category[b] (kg/m^2), % (SE)			<.001
Underweight	1.9 (0.37)	2.4 (0.30)	
Healthy weight	26.8 (1.8)	47.9 (0.91)	
Overweight	33.6 (1.4)	32.9 (0.77)	
Obese	37.8 (2.0)	16.8 (0.78)	
Waist to hip ratio			<.001
Median (25th, 75th percentile)	0.93 (0.85, 0.99)	0.89 (0.83, 0.95)	
Mean (SE)	0.93 (0.004)	0.90 (0.002)	
Abdominal obesity,[c] % (SE)	75.5 (1.6)	62.3 (1.2)	<.001
Physical activity (METs/mo)			<.001
Median (25th, 75th percentile)	58.6 (14.3, 142.3)	73.6 (19.9, 164.4)	
Mean (SE)	98.0 (4.0)	116.3 (3.6)	
Physically active, % (SE)	84.1 (1.2)	88.8 (0.7)	<.001
Healthy eating index			.179
Median (25th, 75th percentile)	64.1 (53.0, 73.6)	63.1 (54.1, 72.5)	
Mean (SE)	63.8 (0.42)	63.2 (0.33)	
Healthy eating index,[d] % (SE)			.304
Poor	17.7 (1.14)	17.9 (0.82)	
Fair	70.1 (1.51)	71.4 (0.61)	
Good	12.2 (1.19)	10.7 (0.62)	

Table 1. Continued

Characteristics	NAFLD (n = 3088)	No NAFLD (n = 7550)	*P* value[g]
Glomerular filtration rate (mL/min per 1.73 m^2)			.001
Median (25th, 75th percentile)	89.5 (76.9, 102.7)	93.1 (80.5, 106.5)	
Mean (SE)	91.5 (0.68)	94.7 (0.64)	
Chronic kidney disease,[e] % (SE)	5.0 (0.56)	3.0 (0.27)	.001
Family history of diabetes, % (SE)	48.5 (1.73)	44.7 (1.04)	.026
Family history of myocardial infarction, % (SE)	17.8 (1.03)	17.7 (0.74)	.973
History of cancer, % (SE)	7.4 (0.65)	6.6 (0.41)	.365
Follow up (y)			<.001
Median (25th, 75th percentile)	19.2 (17.5, 20.6)	19.5 (18.0, 21.1)	
Mean (SE)	18.2 (0.50)	18.7 (0.21)	

%, weighted proportion; GED, General Education Diploma; MET, metabolic equivalent; SE, standard error.
[a]Including those living with a partner.
[b]Underweight = (<18.50), healthy weight = (≥18.50–25.00), overweight = (≥25.00–30.00), and obese = (≥30).
[c]Waist to hip ratio ≥0.90 for males or ≥0.85 for females.
[d]Poor < 51%, fair < 80%, good ≥ 80%.
[e]Glomerular filtration rate <60 mL/min per 1.73 m^2.
[f]In NAFLD, up to 2 drinks per day for females and 3 drinks per day for males.
[g]Rao-Scott Chi-Square *P*-values for the difference in proportions and T-test *P*-values for the difference in means between adults with vs without nonalcoholic fatty liver disease.

analysis, the MetS severity score showed a high ability to predict the dichotomously defined MetS in NAFLD (area under the curve 0.93). A MetS severity score cutoff of 0.43 (67th) yielded an 83% sensitivity and an 87% specificity for identifying the traditionally defined MetS in the NAFLD sample.

Table 2 shows the relationship between adjusted clinical characteristics by the MetS severity score quartiles in NAFLD. A higher MetS severity corresponded to increases in biomarkers for cardiovascular factors, insulin resistance, and lipid abnormalities. The adjusted prevalence of hypertension in NAFLD adults in the first, second, third, and fourth quartiles was 29.5%, 42.9%, 56.1%, and 68.4%, respectively. Similarly, all metabolic control biomarkers had significant dose-response relationships with higher MetS severity scores. In NAFLD, the adjusted prevalence of diabetes and the traditionally defined MetS for adults in the fourth severity quartile were 38.7% and 91.2%, respectively. Increases in the MetS severity were also associated with elevated lipid, liver, and kidney profile abnormalities.

A higher MetS severity score was significantly associated with increases in alkaline phosphatase, ferritin, gamma glutamyl-transferase, aspartate aminotransferase, and alanine aminotransferase levels. The adjusted value of uric acid in adults with NAFLD was 32% higher for those in the fourth vs first MetS severity quartile. The adjusted prevalence of detectable C-reactive protein (ie, >0.3 mg/dL) was 11.5%, 33.9%, 44.4%, and 53.8% for NAFLD adults in the first, second, third, and fourth MetS severity quartiles, respectively (data not shown).

MetS Severity and Mortality in NAFLD

The mean and median follow-up timeperiods for NAFLD patients were 18.2 and 19.2 years, respectively. During the 23 years of follow-up, the cumulative all-cause mortality incidence among NAFLD adults was 29.1% (741 deaths). During the same period, the cause-specific cumulative incidence was 7.3% (174 deaths) for heart disease-related mortality, 5.7% (126 deaths) from diabetes, and 6.2% (115 deaths) related to hypertension. An estimated 46.2% of all deaths occurred among NAFLD patients in the fourth MetS severity score quartile, compared with 8.6% in the first quartile. The unadjusted cumulative all-cause mortality for NAFLD patients in the first, second, third, and fourth MetS severity quartiles were 10.2%, 24.8%, 30.6%, and 48.0%, respectively. Similarly, the cause-specific cumulative mortality associated with heart disease, diabetes, and hypertension increased with a higher MetS severity score quartile (Table 3).

In NAFLD, the all-cause mortality incidence rate was 13.5 per 1000 person-years, while the cause-specific mortality incidence rates associated with heart disease, diabetes, and hypertension were 3.2 per 1000 person-years, 2.3 per 1000 person-years, and 2.1 per 1000 person-years, respectively. The all-cause mortality rates were 4.9 per 1000 person-years and 25.3 per 1000 person-years for NAFLD patients in the first and fourth MetS severity score quartiles, respectively. The cause-specific mortality rates for heart disease, diabetes, and hypertension increased with higher MetS severity quartiles (Figure 1).

The MetS severity score was a significant predictor for adjusted all-cause and cause-specific mortalities in NAFLD. A quartile increase in MetS severity score was associated with an increase in the risk of all-cause mortality adjusted hazard ratio (aHR) 1.36 (95% CI: 1.17–1.57), heart disease-related mortality aHR 1.70 (95% CI: 1.17–2.47), diabetes-related mortality aHR 3.64 (95% CI: 2.27–5.83), and hypertension-related mortality aHR 1.87 (95% CI: 1.14–3.04) (data not shown).

Table 2. Age-, Gender-, and Race/Ethnicity-Adjusted Estimates for Clinical Characteristics Related to Cardiovascular Factors, Metabolic Control, Lipid Profile, Liver Function, and Kidney Function by Metabolic Syndrome Severity Quartiles in Adults With Nonalcoholic Fatty Liver Disease (NAFLD), the National Health and Nutrition Examination Survey (NHANES III) 1988–1994 (n = 3088)

Clinical characteristics	Q1 (n = 698)	Q2 (n = 785)	Q3 (n = 771)	Q4 (n = 834)	P_{trend}
Cardiovascular factors					
Systolic blood pressure (mm Hg), mean (SE)	120.2 (0.79)	126.2 (0.72)	130.7 (0.93)	133.5 (0.69)	<.001
Diastolic blood pressure (mm Hg), mean (SE)	71.3 (0.53)	75.7 (0.46)	78.3 (0.52)	78.9 (0.53)	<.001
Pulse rate (beats/min), mean (SE)	70.5 (0.83)	74.8 (0.67)	76.5 (0.80)	79.5 (0.74)	<.001
Hypertension, % (SE)	29.5 (3.0)	42.9 (2.1)	56.1 (3.2)	68.4 (2.3)	<.001
Metabolic control					
Plasma glucose (mg/dL), mean (SE)	96.3 (1.1)	100.3 (0.86)	102.9 (1.1)	136.6 (2.5)	<.001
Fasting plasma glucose[a] (mg/dL), mean (SE)	100.5 (1.3)	103.8 (1.1)	112.6 (2.3)	116.2 (2.6)	<.001
Serum insulin (μU/mL), mean (SE)	6.9 (0.87)	12.2 (0.61)	16.4 (0.53)	27.4 (1.5)	<.001
Fasting serum insulin[a] (μU/mL), mean (SE)	6.4 (0.76)	11.1 (0.43)	14.9 (0.56)	23.4 (1.4)	<.001
HOMA-IR,[a] mean (SE)	1.8 (0.20)	2.9 (0.13)	3.9 (0.16)	7.4 (0.43)	<.001
HbA1c, mean (SE)	5.4 (0.05)	5.5 (0.03)	5.7 (0.04)	6.6 (0.07)	<.001
Diabetes, % (SE)	8.1 (1.1)	8.9 (0.81)	10.5 (1.4)	38.7 (1.8)	<.001
Number of metabolic abnormalities,[b] mean (SE)	0.6 (0.06)	1.8 (0.04)	3.0 (0.05)	3.9 (0.04)	<.001
Metabolic syndrome,[c] % (SE)	6.2 (1.9)	22.0 (2.0)	67.4 (2.3)	91.2 (1.6)	<.001
Lipid profile					
Total cholesterol (mg/dL), mean (SE)	188.7 (2.4)	210.8 (2.2)	216.4 (1.9)	222.1 (2.4)	<.001
High-density lipoprotein cholesterol (mg/dL), mean (SE)	62.1 (1.1)	50.9 (0.57)	44.2 (0.53)	38.2 (0.57)	<.001
Hyperlipidemia, % (SE)	7.5 (2.3)	29.0 (2.3)	58.4 (2.7)	81.6 (1.8)	<.001
Low-density lipoprotein cholesterol (mg/dL), mean (SE)	112.1 (3.7)	133.2 (2.9)	134.2 (1.78)	133.8 (2.9)	<.001
Triglycerides (mg/dL), mean (SE)	76.6 (3.9)	119.9 (3.2)	176.9 (4.2)	294.7 (8.9)	<.001
Liver profile					
Alkaline phosphatase (U/L), mean (SE)	78.9 (1.6)	91.4 (1.6)	91.6 (1.7)	97.8 (1.4)	<.001
Serum albumin (g/dL), mean (SE)	4.2 (0.03)	4.1 (0.02)	4.1 (0.03)	4.1 (0.02)	.003
Bilirubin (mg/dL), mean (SE)	0.63 (0.02)	0.55 (0.01)	0.57 (0.02)	0.63 (0.02)	.781
Ferritin (ng/mL), mean (SE)	112.5 (6.5)	127.4 (5.3)	159.0 (6.7)	197.8 (8.0)	<.001
Gamma-glutamyltransferase[a] (U/L), mean (SE)	24.0 (2.2)	33.2 (2.7)	42.8 (3.9)	47.9 (3.3)	<.001
Aspartate aminotransferase (AST) (U/L), mean (SE)	22.5 (1.0)	22.2 (0.57)	24.4 (0.88)	25.3 (0.65)	.012
Alanine aminotransferase (ALT) (U/L), mean (SE)	14.2 (0.94)	19.1 (0.63)	24.5 (1.4)	25.6 (0.88)	<.001
AST/ALT ratio, mean (SE)	1.7 (0.05)	1.4 (0.04)	1.2 (0.03)	1.2 (0.03)	<.001
Kidney profile					
Urea nitrogen (mg/dL), mean (SE)	14.5 (0.30)	14.0 (0.27)	14.2 (0.22)	14.6 (0.21)	.620
Creatinine (mg/dL), mean (SE)	1.1 (0.01)	1.1 (0.01)	1.1 (0.01)	1.09 (0.01)	.188
Uric acid (mg/dL), mean (SE)	4.7 (0.08)	5.5 (0.06)	6.1 (0.06)	6.2 (0.08)	<.001

%, weighted proportion; HOMA-IR, homeostasis model for insulin resistance; SE, standard error.
[a]Among a subsample of adults who reported at least 8 h of fasting before examination.
[b](1) Hyperglycemia (ie, fasting blood glucose over 100 mg/dL, or pharmacological treatment), (2) dyslipidemia (ie, fasting HDL cholesterol level less than 40 mg/dL, in men, or 50 mg/dL, in women, or pharmacological treatment), (3) hypertriglyceridemia (ie, fasting triglyceride [TG] level over 150 mg/dL, or pharmacological treatment), (4) central obesity (ie, waist circumference over 40 inches, in men, or 35 inches, in women), or (5) hypertension (ie, systolic blood pressure [SBP] over 130 mmHg, or pharmacological treatment).
[c]At least 3 metabolic abnormalities.

In the restricted cubic spline analysis, significant nonlinear dose-response trends were observed in the relationship between increased risk of mortality and higher MetS severity scores in all adjusted models (Figure 2). The risk of mortality in NAFLD increased with higher MetS severity scores relative to the median severity value. Table 4 outlines the aHR estimates for mortality risk with the median MetS severity score value (69th) as a reference. Significant increases in the adjusted mortality risks were observed for all severity estimates above the median MetS severity value. The risks of mortality from all causes, heart disease, diabetes, and hypertension were aHR 1.94 (95% CI: 1.51–2.50), 2.88 (1.59–5.21), 12.53 (95% CI: 5.72–27.43), and 3.28 (95% CI: 1.25–8.55), respectively, times the

Table 3. Number of Deaths and Cumulative Incidence of Mortality Over 23 Years by Metabolic Syndrome Severity Quartiles in Adults With Nonalcoholic Fatty Liver Disease (NAFLD), the National Health and Nutrition Examination Survey (NHANES III) 1988–1994 (n = 3088)

Metabolic syndrome severity quartile	All cause		Heart disease		Diabetes		Hypertension	
	Number of deaths	% (95% CI)	Number of deaths	% (95% CI)	Number of deaths	% (95% CI)	Number of deaths	% (95% CI)
Q1	64	10.2 (8.0–13.0)	12	2.1 (1.1–4.0)	3	0.70 (0.20–2.5)	6	1.0 (0.42–2.1)
Q2	153	24.8 (20.6–29.6)[a]	32	5.2 (3.5–7.6)[a]	9	1.3 (0.67–2.4)	24	4.5 (2.8–7.2)[a]
Q3	182	30.6 (23.7–38.8)[a]	39	6.9 (4.8–10.0)[a]	18	3.2 (2.0–5.3)	26	9.3 (3.5–23.4)[a]
Q4	342	48.0 (43.5–42.7)[a]	91	14.9 (11.8–18.7)[a]	96	17.7 (13.9–22.4)[a]	59	10.8 (7.9–14.7)[a]

All-cause excluding adults who died in accidents (unintentional injuries [V01-X59, Y85-Y86]), heart disease (ie, ICD-10, codes I00-I09 [acute rheumatic fever and chronic rheumatic heart diseases], I11 [hypertensive heart disease], I13 [hypertensive heart and renal disease], I20-I25 [ischemic heart diseases], and I26-I51 [other heart diseases]), diabetes (ICD-10, codes [E10-E14]), and hypertension (ICD-10, codes [I10-I12]).
Q, quartile.
[a]Log-rank test *P* value ≤ .05 for the pairwise comparison between the severity quartile and the first quartile of the same mortality cause.

mortality risks for NAFLD patients in the 90th MetS severity percentile compared with those with median severity.

Discussion

Our study is the first to factor in the effects of MetS severity on the risk of mortality in NAFLD using nationally representative data to assess the utility of the MetS severity score. In this retrospective cohort study with a median follow-up of 19.2 years, the MetS severity was significantly higher in NAFLD patients than in participants without NAFLD. In NAFLD, increases in the MetS severity were associated with dose-response in biomarkers for CVD, insulin resistance, and lipid abnormalities. The MetS severity score was a significant predictor for all-cause and cause-specific adjusted mortalities in NAFLD. Furthermore, we found nonlinear dose-response relationships between increased adjusted mortality risk and higher MetS severity scores.

Obesity is a well-established risk for NAFLD development.[42] Obesity is marked by elevated accumulations of TG throughout the body. In the hepatocytes, increased uptake of TG results in cell-specific lipotoxicity, which raises the risk of comorbidities.[43] Individuals with high visceral

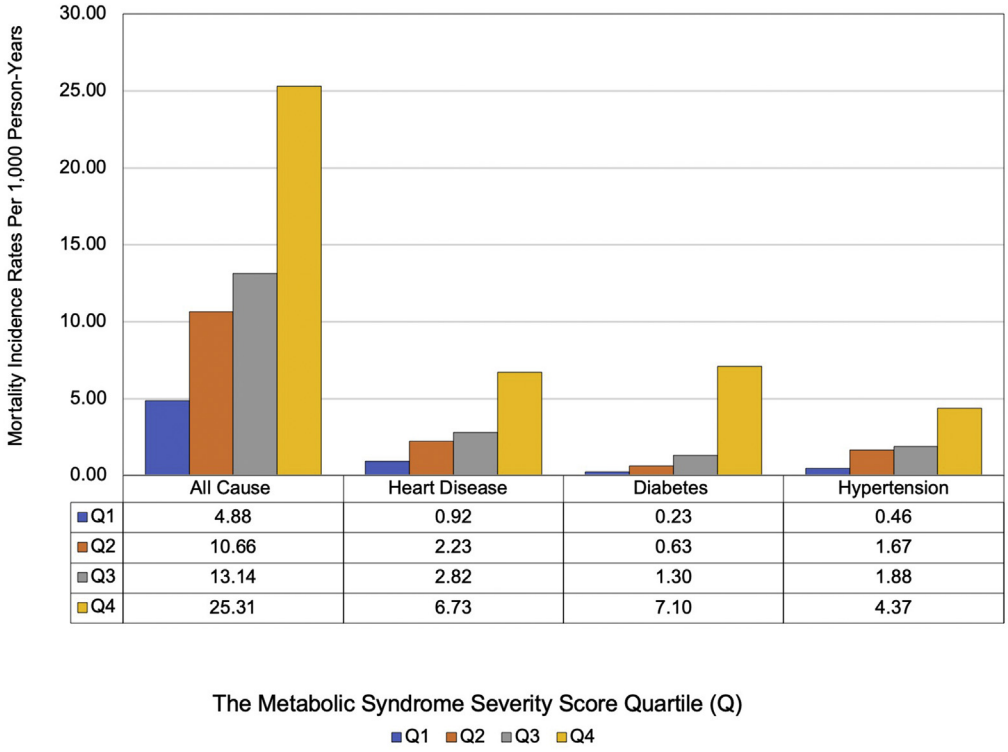

Figure 1. Incidence rates of mortality per 1000 person-years by the metabolic syndrome severity score quartile (Q) among adults with non-alcoholic fatty liver disease, the national health and nutrition examination survey (NHANES III), United States, 1988–1994 (n = 3088).

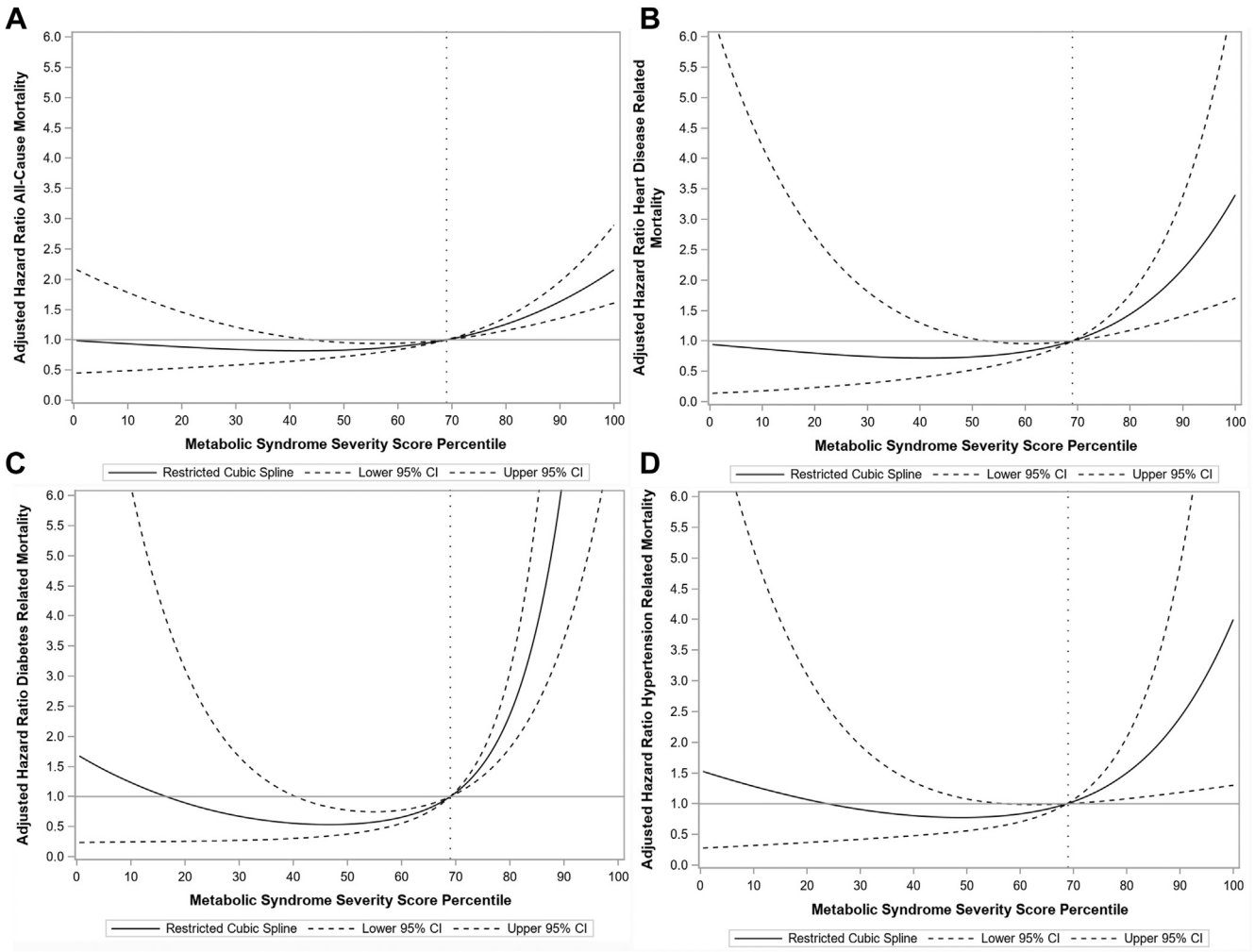

Figure 2. Adjusted hazard ratios of mortality related to (A) all-cause (B) heart disease (C) diabetes (D) hypertension for different metabolic syndrome severity score percentiles relative to the median severity percentile (69th) as the reference level, the national health and nutrition examination survey (NAHNES III), United States, 1988–1994 (n = 3088).

adiposity may suffer from increased plasma-free fatty acids due to impaired insulin function related to peripheral insulin resistance.[44] Studies have reported the prevalence of steatosis and NASH to be 65% and 20%, respectively, in individuals with BMI 30.0–39.9 kg/m^2 and 85% in morbidly obese patients (BMI $\geq$ 40 kg/m^2).[45] Similarly, the prevalence of NASH and NAFLD among obese patients undergoing bariatric surgery is 37% and 91%, respectively.[46] Our study findings highlight similar results for the increased obesity burden in NAFLD patients.

Our study shows that both the prevalence and severity of MetS were significantly higher in NAFLD patients. A recent US-based study revealed significant associations between individual components of MetS and NAFLD. In individuals with increased waist circumference, the prevalence of NAFLD (31%, 8.7% with advanced fibrosis) greatly exceeded controls.[37] NAFLD patients with increased waist circumference were predominantly female, older, and less educated in the present study. NAFLD prevalence in subjects with diabetes (41%, 18% with advanced fibrosis) also greatly exceeded control prevalence. NAFLD prevalence in subjects with high TG levels was 35% (8% with advanced fibrosis).

An increase in the severity of MetS was associated with clinical characteristics related to cardiovascular factors, metabolic control, lipid profile, liver function, and kidney function. A meta-analysis of 27 cross-sectional studies reported an association between NAFLD and markers of atherosclerosis, including increased carotid intima-media thickness, coronary calcification, endothelial dysfunction, and arterial stiffness, independent of traditional cardiometabolic risk factors and MetS.[47] In turn, the pooled odds ratio of CVD in NAFLD relative to NAFLD-free adults is 2.02 (95% CI: 1.81–2.31).[48] According to a meta-analysis of 19 observational studies, the risk of diabetes is HR 2.22 (95% CI: 1.84–2.60) in NAFLD patients compared with that in those with no NAFLD.[49] The risk of MetS in NAFLD compared with no NAFLD ranges between risk ratio 1.80 and 3.22.[50] NAFLD patients have 2.12- and 1.79-folds increase in odds and risks of CKD, respectively.[51] Our finding

Table 4. Adjusted Hazard Ratios of Mortality Related to (A) All-Cause, (B) Heart Disease, (C) Diabetes, and (D) Hypertension for Different Metabolic Syndrome Severity Score Percentiles Relative to the Median Severity Percentile as the Reference Level, the National Health and Nutrition Examination Survey (NAHNES III), United States, 1988–1994 (n = 3088)

	All cause	Heart disease	Diabetes	Hypertension
Metabolic syndrome severity percentile	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
50th	Reference	Reference	Reference	Reference
60th	1.16 (1.10–1.23)	1.27 (1.11–1.45)	1.74 (1.46–2.05)	1.29 (1.05–1.59)
70th	1.36 (1.21–1.53)	1.64 (1.24–2.16)	3.21 (2.24–4.60)	1.72 (1.11–2.67)
80th	1.61 (1.34–1.93)	2.14 (1.40–3.27)	6.10 (3.49–10.66)	2.33 (1.18–4.61)
90th	1.94 (1.51–2.50)	2.88 (1.59–5.21)	12.53 (5.72–27.43)	3.28 (1.25–8.55)
99th	2.16 (1.61–2.90)	3.41 (1.70–6.81)	18.92 (7.59–47.13)	3.98 (1.30–12.18)

All-cause excluding adults who died in accidents (unintentional injuries [V01-X59, Y85-Y86]), heart disease (ICD-10, codes I00-I09 [acute rheumatic fever and chronic rheumatic heart diseases], I11 [hypertensive heart disease], I13 [hypertensive heart and renal disease], I20-I25 [ischemic heart diseases], and I26-I51 [other heart diseases]), diabetes (ICD-10, codes [E10-E14]), and hypertension (ICD-10, codes [I10-I12]). Adjusted for attained age, gender, race/ethnicity, education level, marital status, access to health insurance, alcohol intake, smoking status, body mass index, abdominal obesity, physical activity, healthy eating index percentile, chronic kidney disease, family history of diabetes, family history of myocardial infarction, and history of cancer.

of higher MetS severity could help to explain the increased risks of diabetes, MetS, CVD, and CKD in NAFLD.[17,49,50,52,53]

NAFLD has been shown in several studies to increase the risk of mortality from all-cause, liver-related, and CVD-related factors. In NAFLD, the most common causes of death are CVD, malignancies, and liver disease.[2] The incidence rate of all-cause mortality was higher in NAFLD vs no NAFLD (13.52 deaths per 1000 person-years vs 11.75 deaths per 1000 person-years). Those estimates are similar to the findings of a global meta-analysis where the incidence rate of all-cause mortality was 11.77 deaths per 1000 person-years.[12] In a meta-analysis of forty cohort studies, NAFLD patients had higher all-cause mortality than the general population, with a pooled odds ratio of 1.57 (95% CI: 1.18–2.10).[48] Similarly, compared with the adults without NAFLD, NAFLD patients have an HR of 9.32 (95% CI: 9.11–9.33) for liver-related[54] and a pooled odds ratio of 1.59 (95% CI: 1.42–1.78) for CVD-related mortality.[48]

The association between MetS and the risk of mortality in NAFLD has been assessed in multiple studies.[55–57] In a population-based study using NHAES III data, the risk of overall mortality and CVD-related mortality was HR 2.22 (95% CI: 1.26–3.91) and HR 4.58 (95% CI: 1.53–13.76), respectively, for NAFLD patients with vs without MetS. Metabolic dysfunction-associated fatty liver disease was a significant predictor of all-cause mortality compared with NAFLD.[58,59] Our study adds to those findings by accounting for the effects of the aggregate MetS severity on survival in NAFLD. In our study, significant nonlinear dose-response trends were observed in the relationship between increased risk of mortality and a higher MetS severity score in all adjusted models. Specifically, the risk of mortality in NAFLD increased with higher MetS severity scores than with the median severity value.

Currently, there are no approved pharmacologic or other modalities of treatment for NAFLD.[60] Lifestyle modifications suggested as treatments for NAFLD follow those recommended for MetS and include increasing physical activity and weight loss.[61] Such lifestyle changes, including diet and exercise, have been shown to reduce the risk of developing NAFLD and improve existing NAFLD. In a meta-analysis of 6 cohort studies (32,657 participants), the highest level of physical activity was associated with a 21% reduction in the risk of NAFLD development relative to the lowest physical activity levels.[62] A meta-analysis of randomized trials showed that weight loss, meeting or exceeding 7%, can improve histological markers of disease; however, fewer than 50% of subjects across several trials achieved this level of weight loss.[52] The percentage of physically active adults in our study was significantly lower than that of the non-NAFLD population. This finding is comparable to results from a population study where NAFLD patients spent less time than controls participating in any level of physical activity.[63]

One of the strengths of our study is that the NAFLD cohort in this database mirrors the real-world patient population in the US. Data used in this cohort for NAFLD assessment are also commonly collected in the primary care setting. Results from our study can aid both clinicians and public health practitioners to plan and execute secondary and tertiary prevention efforts related to long-term mortality risk in NAFLD. Secondary prevention efforts could utlize the MetS severity score as a screening tool to identify NAFLD patients at the highest risk of mortality. The MetS severity score could also be used as a tertiary prevention tool, whereby the progression of severity is monitored over time to guide interventions to mitigate the chances of more MetS severity in NAFLD. The latter is particularly valuable for clinicians to dynamically assess and manage their patients with NAFLD based on the estimated risk of adverse outcomes.

Our study has several limitations. NAFLD assessment was done using ultrasonography, which could result in

misclassifications; however, the ultrasonography images were assessed by 3 trained ultrasound readers using standardized reading protocols. Furthermore, we could not evaluate the role of NASH and NASH-cirrhosis in survival due to the lack of liver biopsy data; however, NASH and NASH-cirrhosis are associated with higher MetS severity, which is expected to reaffirm our findings of the MetS severity's ability to predict mortality in NAFLD. Ascertainments of exposure and baseline characteristics were conducted cross-sectionally. The cross-sectional assessment is expected to be nondifferential in the exposed and unexposed groups. Alcohol intake was assessed based on self-reporting, which might result in underestimation.

In conclusion, NAFLD in US adults is marked by significantly higher MetS severity than that in non-NAFLD US adults. In NAFLD, an increase in the MetS severity corresponds to a linear rise in biomarkers for CVD, insulin resistance, and lipid abnormalities. A quartile increase in the MetS severity score was associated with a nonlinear dose-response increase in the risks of all-cause, heart disease-related, diabetes-related, and hypertension-related mortality. Significant increases in adjusted mortality risks among adults with NAFLD were observed for all severity estimates above the median MetS severity values. These findings demonstrate the utility of MetS severity as a driving force of increased risk of mortality in NAFLD. While current treatment options for patients with NAFLD are limited and indirect, the MetS severity score could be potentially used as a clinical tool to identify and monitor at-risk patients over time.

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Mohamed I. Elsaid developed the main concept and designed and conducted the statistical analysis. Vinod K. Rustgi, John F.P. Bridges, and Na Li advised on the main concepts and study design. The first draft of the manuscript was written by Mohamed I. Elsaid. All authors contributed to the manuscript revisions. All authors approved the final draft of the manuscript.

Conflicts of Interest:
The authors disclose no conflicts. Vinod K. Rustgi is a member of the Board of Editors. Their paper was handled in accordance with our conflict of interest policy. See https://www.ghadvances.org/content/authorinfo#conflict_of_interest_policy for full details.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data used in this study are publicly available by the center for disease control and prevention (CDC) https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx. Study materials are available upon request.