Association of anthropometrically predicted visceral adipose tissue with mortality in patients with non-alcoholic fatty liver disease: a cohort study

Qi Shao, Bing Lu, Fenyan Tang, Zhaoxiang Wang*, Shao Zhong*

Department of Endocrinology, Affiliated Kunshan Hospital of Jiangsu University, Kunshan, Jiangsu, China

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***Corresponding authors:**
Shao Zhong,
Zhaoxiang Wang
Department of Endocrinology
Affiliated Kunshan Hospital
of Jiangsu University
Kunshan, Jiangsu
215300, China
E-mail: drzhong@163.com,
wangzhaoxiang1@ksrmyy.org

Abstract

Introduction: The objective of this study was to evaluate the association between anthropometrically predicted visceral adipose tissue (apVAT) and mortality among individuals with non-alcoholic fatty liver disease (NAFLD).
Material and methods: This study analyzed 6206 NAFLD participants from the National Health and Nutrition Examination Survey. NAFLD was identified using the United States Fatty Liver Index (USFLI) or Fatty Liver Index (FLI). Baseline apVAT, an estimate of visceral fat derived from anthropometric parameters including age, body mass index (BMI), waist circumference (WC), and thigh circumference, was calculated using validated sex-specific equations. Mortality outcomes were determined by linking data to National Death Index (NDI) records up to December 31, 2019. Cox proportional hazards models and restricted cubic splines were used to examine associations, and time-dependent receiver operating characteristic (ROC) analyses were used to compare apVAT with other obesity indices including BMI, WC, thigh circumference, waist-to-height ratio (WHtR), relative fat mass (RFM), and weight-adjusted waist index (WWI).
Results: During a median follow-up period of 187 months, 1884 deaths from all causes and 517 from cardiovascular causes were observed. Multivariable-adjusted Cox analysis showed that the highest apVAT quartile had hazard ratios of 3.83 (3.01–4.87) for all-cause mortality and 3.47 (2.13–5.65) for cardiovascular mortality, compared to the lowest quartile. A nonlinear relationship between apVAT and mortality risk was identified. apVAT showed the highest predictive value for mortality risk compared with BMI, WC, thigh circumference, WHtR, RFM, and WWI.
Conclusions: Elevated apVAT levels are correlated with increased mortality risk in NAFLD, highlighting its potential as a prognostic marker.

Key words: non-alcoholic fatty liver disease, obesity paradox, anthropometrically predicted visceral adipose tissue, mortality, National Health and Nutrition Examination Survey.

Introduction

As a prevalent metabolic-associated chronic liver disease, non-alcoholic fatty liver disease (NAFLD) is characterized by the buildup of fat within hepatocytes and affects about 25% of adults globally [1]. Its pathological spectrum ranges from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), with potential progression to liver fibrosis,

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cirrhosis, and hepatocellular carcinoma [1–3]. Beyond liver-related complications, NAFLD is increasingly recognized as a multisystem disease closely associated with obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, cardiovascular disease, and all-cause mortality [4, 5].

Obesity is a major risk factor associated with metabolic diseases, including NAFLD [6, 7]. Notably, the metabolic risk associated with obesity largely depends on the distribution of adipose tissue [8, 9]. The accumulation of visceral adipose tissue (VAT), which surrounds essential organs such as the liver, pancreas, and intestines, is recognized as a primary factor driving metabolic dysfunction and contributing to the progression of NAFLD, along with elevated cardiovascular risk and mortality [6, 10, 11]. Unlike subcutaneous fat, visceral fat exhibits metabolic activity and yields substances such as pro-inflammatory cytokines, free fatty acids, and adipokines, which worsen insulin resistance (IR) and systemic inflammation, significantly contributing to poor outcomes in NAFLD patients [12–14]. Thus, accurately quantifying visceral fat and understanding its metabolic impact are critical for risk stratification and management in individuals with NAFLD.

Direct measurement of visceral fat through imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) is often impractical in routine clinical settings due to cost and accessibility constraints [15]. Leveraging routine clinical measures, anthropometry-based prediction tools provide a cost-effective option for population-level screening and more accurately reflect adipose distribution and metabolic phenotypes [16, 17]. In this context, anthropometrically predicted VAT (apVAT) – derived from validated multivariable, sex-specific equations that include body mass index (BMI), waist circumference (WC), and thigh circumference – shows close agreement with CT-derived VAT and strong associations with biomarkers of glucose regulation, inflammation, and lipid metabolism [18–20]. Prior research highlights its superior predictive value over conventional obesity metrics [21]. Accordingly, this study focuses on apVAT and compares its performance with alternative adiposity indices – e.g., weight-adjusted waist index (WWI), relative fat mass (RFM), waist-to-height ratio (WHtR) – for predicting mortality in a nationally representative NAFLD cohort.

Material and methods

Study population

Conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention, the National Health and Nutrition Examination Survey (NHANES) uses a multistage, stratified, probability-based sampling design to generate nationally representative estimates. Survey participants complete questionnaires on health and diet, undergo physical examinations, and provide specimens for laboratory analyses [22, 23]. The protocol was reviewed and approved by the NCHS Institutional Ethics Review Board, with written informed consent secured from participants. Comprehensive methods and datasets can be accessed at https://wwwn.cdc.gov/nchs/nhanes/.

This study analyzed data from U.S. participants across 4 NHANES cycles (1999–2000 to 2005–2006), which cover complete anthropometric measurement data. Of the 41474 participants included in these cycles, missing data for calculating the United States Fatty Liver Index (USFLI), or the Fatty Liver Index (FLI) were excluded. 8943 participants with a USFLI $\geq$ 30 or FLI $\geq$ 60 were identified. Participants with excessive alcohol consumption and positive results for hepatitis B surface antigen, hepatitis C antibody, or HCV RNA were also excluded, leaving the remaining 7877 individuals classified as having NAFLD. Further exclusions included those missing data for calculating apVAT, under 20 years of age, pregnant participants, and individuals without mortality data. A total of 6206 participants were included in our analysis.

Calculation of adiposity indices

In this study, apVAT (cm^2) was derived using validated, sex-specific equations incorporating age (years), BMI (kg/m^2), WC (cm), and proximal thigh circumference (cm) [20]. For men, the formula was 6 × WC – 4.41 × proximal thigh + 1.19 × age – 213.65; for women, 2.15 × WC – 3.63 × proximal thigh + 1.46 × age + 6.22 × BMI – 92.713 [20]. Other adiposity metrics were additionally derived. WWI was defined as WC divided by the square root of body weight [24, 25]. WHtR was calculated as the ratio of WC to height. RFM was computed as 64 – (20 × height/WC + (12 × sex)), where sex was coded as female = 1 and male = 0 [26].

Definition of NAFLD

The USFLI and FLI is employed to determine fatty liver [27, 28], using the formula:

$$\text{USFLI/FLI} = \frac{e^y}{1 + e^y} \times 100$$

For USFLI, y was calculated as (–0.8073 × non-Hispanic Black + 0.3458 × Mexican American) + (0.0093 × age) + (0.6151 × Ln gamma glutamyl transferase) + (0.0249 × waist circumference) + (1.1792 × Ln insulin) + (0.8242 × Ln glucose) – 14.7812. Ethnicity indicators (non-Hispanic Black and Mexican American) were assigned a value of 1 if applicable, otherwise 0. For FLI, y was calculated as 0.953 × Ln (triglyceride) + 0.139 × body mass

index + 0.718 × Ln (gamma glutamyl transferase) + 0.053 × waist circumference – 15.745.

The definition of NAFLD included a USFLI ≥ 30 or FLI ≥ 60, with exclusions for other liver diseases such as viral hepatitis (positive hepatitis B surface antigen, hepatitis C antibody, or HCV RNA) and excessive alcohol consumption (alcohol intake of ≥ 30 g/day for males and ≥ 20 g/day for females, assessed using the USDA's automated multiple-pass method through a 24-hour dietary recall) [29].

Assessment of mortality

Mortality status was tracked using the NHANES Public-Use Linked Mortality File (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm), linking participants to the National Death Index (NDI) through a probabilistic algorithm, covering deaths up to December 31, 2019. The underlying cause of death was determined using the UCOD_LEADING variable and subsequently analyzed for both all-cause mortality and cardiovascular-specific mortality. For the 1999–2006 cohort in our study, the median follow-up duration was 187 months.

Assessment of covariates

Demographic variables included age, sex, ethnicity/race, marital status, education level, family poverty-to-income ratio (PIR), and smoking status. Ethnicity was classified as Mexican American, non-Hispanic White, non-Hispanic Black, other Hispanic, and other races. Marital status was categorized as married or not married. Education levels were grouped into above high school or not above high school. Smoking history was classified as never smokers and smokers (including both former smokers and current smokers). Laboratory indicators included hemoglobin A1c (HbA1c, %), alanine aminotransferase (ALT, U/l), aspartate aminotransferase (AST, U/l), triglyceride (TG, mg/dl), total cholesterol (TC, mg/dl), high-density lipoprotein cholesterol (HDL-c, mg/dl), low-density lipoprotein cholesterol (LDL-c, mg/dl), serum creatinine (SCr, μmol/l), and serum uric acid (SUA, mg/dl). Medical history included diabetes mellitus and hypertension. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl (7 mmol/l), HbA1c ≥ 6.5%, self-reported diagnosis of diabetes, or use of hypoglycemic agents. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-reported diagnosis of hypertension, or use of antihypertensive drugs.

Statistical analysis

Our analysis complied with NHANES protocols, incorporating sample weights, clustering, and stratification to handle the complex sampling framework. Under the missing-at-random assumption, covariates with missing values were imputed iteratively using a random forest–based multiple imputation approach (missing values: education, n = 5; marital status, n = 160; PIR, n = 434; smoking history, n = 3; ALT, n = 33; AST, n = 33; HbA1c, n = 12; TG, n = 1; TC, n = 7; HDL-c, n = 8; LDL-c, n = 3435). Continuous data are expressed as weighted mean values with corresponding 95% confidence intervals (CIs); categorical data are shown as unweighted counts and weighted percentages. Group comparisons used survey-weighted linear regression (continuous) and χ^2 tests (categorical). Kaplan-Meier survival curves were plotted, and the log-rank test was applied to assess survival differences between apVAT quantiles. Using Cox proportional hazards regression models, hazard ratios (HRs) and 95% CIs were estimated to assess the relationship between apVAT and all-cause or cardiovascular mortality. We constructed four models in a stepwise manner: Model 1 (unadjusted); Model 2 (age, sex, ethnicity); Model 3 (Model 2 plus marital status, education level, PIR, and smoking); and Model 4 (Model 3 plus diabetes, hypertension, HbA1c, ALT/AST, TG, HDL-c, LDL-c, SCr, SUA). Restricted cubic splines with Cox proportional hazards regression models were applied to evaluate nonlinear relationships between apVAT and mortality risk. To identify the threshold for nonlinear associations, all values were tested, and the one with the highest likelihood was selected. Stratified analyses were performed to account for potential effect modifiers. The discriminatory power of apVAT and other anthropometric measures (WWI, RFM, WHtR, BMI, WC, and thigh circumference) for predicting all-cause and cardiovascular mortality was assessed using time-dependent receiver operating characteristic (ROC) analyses across specified durations. All statistical analyses were performed using R software (version 4.2.2), with a significance threshold of $p < 0.05$.

Results

Baseline characteristics

Table I presents baseline characteristics by survival status among NAFLD participants. Non-survivors exhibited advanced age, male predominance, and non-Hispanic White predominance ($p < 0.001$). They demonstrated less favorable socioeconomic profiles: higher unmarried rates, lower education, reduced PIR, and elevated smoking ($p < 0.001$). Anthropometric assessment revealed lower BMI and thigh circumference, but elevated WC ($p < 0.05$). apVAT levels were substantially higher than in survivors ($p < 0.001$). Metabolic profiling indicated elevated HbA1c ($p < 0.001$), reduced ALT/AST

Table I. Baseline characteristics of NAFLD participants based on survival status

Characteristic	Overall (n = 6206)	Survivors (n = 4322)	Non-survivors (n = 1884)	P-value
Age [years], *n* (%)				< 0.001
< 60	3607 (72.18)	3246 (83.86)	361 (29.43)	
≥ 60	2599 (27.82)	1076 (16.14)	1523 (70.57)	
Sex, *n* (%)				0.510
Female	2863 (45.44)	2059 (45.73)	804 (44.38)	
Male	3343 (54.56)	2263 (54.27)	1080 (55.62)	
Race, *n* (%)				< 0.001
Mexican American	1612 (8.51)	1239 (9.72)	373 (4.1)	
Other Hispanic	253 (4.76)	204 (5.23)	49 (3.03)	
Non-Hispanic White	3005 (72.24)	1911 (70.04)	1094 (80.32)	
Non-Hispanic Black	1161 (10.24)	828 (10.38)	333 (9.7)	
Other race	175 (4.25)	140 (4.63)	35 (2.85)	
PIR	2.98 (2.89, 3.07)	3.09 (2.99, 3.18)	2.58 (2.45, 2.71)	< 0.001
Above high school, *n* (%)	2535 (51.37)	1944 (54.79)	591 (38.84)	< 0.001
Married, *n* (%)	3791 (63.59)	2704 (64.71)	1087 (59.48)	0.007
Smoking history, *n* (%)	3069 (49.59)	1964 (46.43)	1105 (61.17)	< 0.001
Diabetes, *n* (%)	1473 (18.63)	726 (13.71)	747 (36.64)	< 0.001
Hypertension, *n* (%)	3124 (46.32)	1796 (40.49)	1328 (67.66)	< 0.001
BMI [kg/m^2]	33.31 (33.04, 33.57)	33.60 (33.27, 33.92)	32.24 (31.90, 32.58)	< 0.001
WC [cm]	110.22 (109.66, 110.78)	110.02 (109.37, 110.68)	110.94 (110.24, 111.64)	0.046
Thigh	57.66 (57.29, 58.03)	58.56 (58.14, 58.98)	54.37 (53.85, 54.88)	< 0.001
ApVAT	242.22 (239.43, 245.00)	232.68 (229.79, 235.57)	277.13 (273.81, 280.45)	< 0.001
ALT/AST	1.13 (1.12, 1.15)	1.17 (1.15, 1.18)	1.01 (0.97, 1.04)	< 0.001
HbA1c (%)	5.76 (5.72, 5.80)	5.65 (5.61, 5.69)	6.18 (6.09, 6.27)	< 0.001
TG [mg/dl]	199.66 (194.37, 204.94)	199.96 (193.49, 206.43)	198.55 (190.36, 206.74)	0.798
TC [mg/dl]	208.89 (207.49, 210.28)	209.28 (207.84, 210.71)	207.46 (204.48, 210.44)	0.246
HDL-c [mg/dl]	45.94 (45.47, 46.40)	45.63 (45.06, 46.21)	47.06 (46.31, 47.81)	0.006
LDL-c [mg/dl]	124.94 (123.91, 125.97)	126.02 (124.86, 127.18)	120.99 (119.14, 122.84)	< 0.001
SCr [µmol/l]	81.54 (80.43, 82.64)	78.31 (77.42, 79.20)	93.35 (90.14, 96.57)	< 0.001
SUA [mg/dl]	5.90 (5.85, 5.95)	5.84 (5.79, 5.88)	6.15 (6.05, 6.24)	< 0.001

Caption: Weighted means (95% CI) for continuous variables and unweighted counts with weighted percentages for categorical variables. Group comparisons used survey-weighted linear regression (continuous) and χ^2 tests (categorical). PIR – poverty-to-income ratio, BMI – body mass index, WC – waist circumference, apVAT – anthropometrically predicted visceral adipose tissue, ALT/AST – alanine aminotransferase/aspartate aminotransferase ratio, HbA1c – hemoglobin A1c, TG – triglycerides, TC – total cholesterol, HDL-c – high-density lipoprotein cholesterol, LDL-c – low-density lipoprotein cholesterol, SCr – serum creatinine, SUA – serum uric acid, NAFLD – non-alcoholic fatty liver disease.

ratio (p < 0.001), adverse lipid metabolism (lower LDL-c, higher HDL-c; both p < 0.001) and compromised renal function (elevated SCr and SUA; both p < 0.001). Diabetes and hypertension were more prevalent (p < 0.001). Table II demonstrates characteristics across apVAT quartiles (Quartiles 1–4) (Q1–Q4). Higher quartiles were associated with advanced age, male predominance, and non-Hispanic White ethnicity (p < 0.001). Marriage rates increased across quartiles (p < 0.001), as did smoking history (p < 0.001). Education level did not vary significantly (p = 0.239). PIR varied significantly among quartiles (p = 0.008). Anthropometric measures showed graded increases in BMI, WC, along with variable thigh circumference (p < 0.001). Biochemical parameters revealed progressive metabolic dysfunction: elevated HbA1c (p < 0.001), decreased ALT/AST ratio (p = 0.002), lipid changes (TG, TC, HDL-c, and LDL-c; all p < 0.001), and renal impairment (rising SCr and SUA; both p < 0.05). Diabetes and hypertension prevalence increased substantially (p < 0.001). Both all-cause and cardiovascular mortality rates progressively increased across apVAT quartiles (p < 0.001).

Survival patterns among apVAT quartiles

With a median follow-up of 187 months, 1884 mortality events occurred, including 517 cardio-

Table II. Baseline characteristics grouped by apVAT quartiles (Q1–Q4)

Characteristic	Q1	Q2	Q3	Q4	*P*-value
Age [years], *n* (%)					< 0.001
<60	1409 (94.43)	998 (77.12)	694 (62.49)	506 (50.93)	
≥ 60	143 (5.57)	553 (22.88)	857 (37.51)	1046 (49.07)	
Sex, *n* (%)					< 0.001
Female	918 (60.36)	933 (55.98)	710 (42.11)	302 (20.02)	
Male	634 (39.64)	618 (44.02)	841 (57.89)	1250 (79.98)	
Race, *n* (%)					< 0.001
Mexican American	498 (13.48)	453 (8.9)	373 (6.77)	288 (4.11)	
Other Hispanic	83 (6.77)	81 (5.89)	62 (4.23)	27 (1.72)	
Non-Hispanic White	576 (61.68)	680 (70.98)	798 (75.41)	951 (82.64)	
Non-Hispanic Black	333 (12.56)	294 (10.29)	278 (9.44)	256 (8.3)	
Other race	62 (5.51)	43 (3.95)	40 (4.15)	30 (3.22)	
PIR	2.82 (2.70, 2.94)	3.04 (2.92, 3.16)	3.06 (2.92, 3.19)	3.02 (2.89, 3.14)	0.008
Above high school, *n* (%)	691 (53.67)	641 (52.65)	603 (49.87)	600 (48.85)	0.239
Married, *n* (%)	864 (58.15)	941 (62.24)	970 (66.86)	1016 (68.00)	< 0.001
Smoking history, *n* (%)	654 (44.53)	706 (46.57)	782 (50.18)	927 (58.19)	< 0.001
Diabetes, *n* (%)	155 (7.41)	321 (14.79)	437 (20.88)	560 (33.54)	< 0.001
Hypertension, *n* (%)	406 (25.79)	744 (42.75)	922 (53.66)	1052 (66.49)	< 0.001
BMI [kg/m^2]	30.74 (30.47, 31.00)	32.34 (32.02, 32.66)	33.50 (33.19, 33.81)	37.15 (36.62, 37.69)	< 0.001
WC [cm]	99.98 (99.42, 100.54)	106.61 (106.15, 107.06)	112.07 (111.55, 112.59)	124.18 (123.37, 124.99)	< 0.001
Thigh	57.35 (56.91, 57.80)	57.29 (56.86, 57.72)	57.00 (56.49, 57.50)	59.10 (58.45, 59.75)	< 0.001
ApVAT	171.42 (170.25, 172.60)	219.25 (218.49, 220.01)	258.93 (258.07, 259.79)	332.42 (329.53, 335.31)	< 0.001
ALT/AST	1.17 (1.15, 1.19)	1.13 (1.11, 1.15)	1.12 (1.10, 1.14)	1.11 (1.09, 1.13)	0.002
HbA1c (%)	5.47 (5.42, 5.53)	5.69 (5.63, 5.75)	5.88 (5.81, 5.95)	6.05 (5.98, 6.12)	< 0.001
TG [mg/dl]	209.72 (197.64, 221.81)	205.63 (194.72, 216.54)	191.08 (181.68, 200.48)	190.30 (182.92, 197.68)	0.014
TC [mg/dl]	212.15 (208.86, 215.44)	215.05 (212.05, 218.06)	209.56 (206.81, 212.30)	197.65 (195.26, 200.04)	< 0.001
HDL-c [mg/dl]	46.01 (45.15, 46.86)	46.95 (46.03, 47.88)	46.05 (45.11, 46.98)	44.63 (44.01, 45.26)	< 0.001
LDL-c [mg/dl]	126.77 (124.61, 128.94)	129.55 (127.25, 131.85)	126.58 (124.51, 128.66)	116.05 (114.23, 117.87)	< 0.001
SCr [µmol/l]	74.21 (72.90, 75.52)	79.80 (77.78, 81.83)	82.74 (81.19, 84.30)	90.71 (87.96, 93.47)	< 0.001
SUA [mg/dl]	5.47 (5.40, 5.54)	5.77 (5.68, 5.87)	6.09 (6.01, 6.18)	6.35 (6.26, 6.43)	< 0.001
All-cause mortality, *n* (%)	157 (8.04)	331 (14.64)	585 (25.93)	811 (39.88)	< 0.001
Cardiovascular mortality, *n* (%)	33 (1.20)	87 (3.98)	166 (7.37)	231 (11.24)	< 0.001

Caption: Weighted means (95% CI) for continuous variables and unweighted counts with weighted percentages for categorical variables. Group comparisons used survey-weighted linear regression (continuous) and χ^2 tests (categorical). PIR – poverty-to-income ratio, BMI – body mass index, WC – waist circumference, apVAT – anthropometrically predicted visceral adipose tissue, ALT/AST – alanine aminotransferase/aspartate aminotransferase ratio, HbA1c – hemoglobin A1c, TG – triglycerides, TC – total cholesterol, HDL-c – high-density lipoprotein cholesterol, LDL-c – low-density lipoprotein cholesterol, SCr – serum creatinine, SUA – serum uric acid, NAFLD – non-alcoholic fatty liver disease.

vascular-related deaths. Among NAFLD patients, Kaplan-Meier survival estimates indicated markedly inferior survival outcomes in the highest apVAT quartile relative to the lowest quartile (Figure 1). This association was evident for both all-cause and cardiovascular mortality, with statistical significance confirmed by log-rank testing (p < 0.001).

Hazard ratios of apVAT and mortality risk

Table III summarizes the association between apVAT and both all-cause and cardiovascular mor-

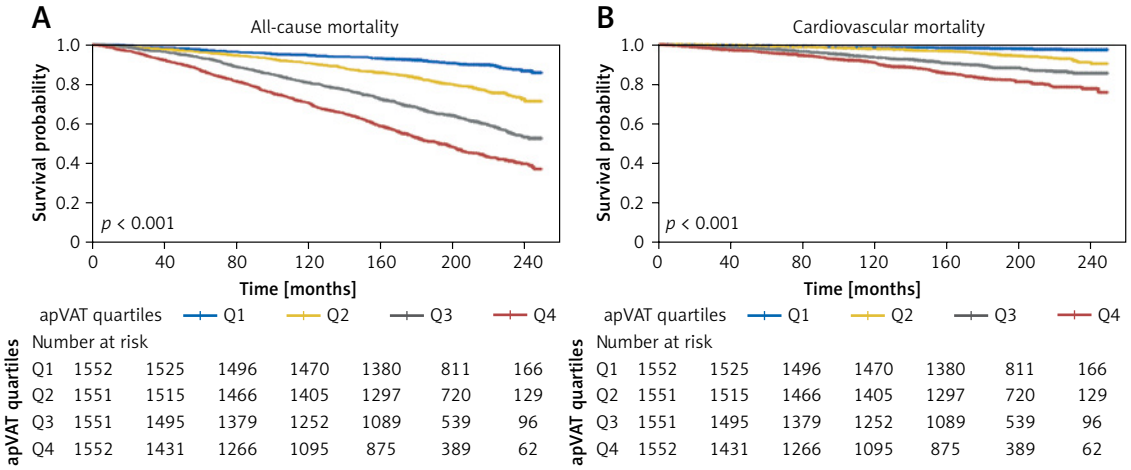

Figure 1. Kaplan-Meier survival curves illustrating all-cause and cardiovascular mortality across apVAT quartiles

Table III. Relationship between apVAT and all-cause and cardiovascular mortality in individuals with NAFLD

apVAT	Number of deaths	Model 1	Model 2	Model 3	Model 4
		HR (95% CI) *P*-value			
All-cause mortality					
Per SD increase	1884/6206	1.75 (1.68, 1.82) < 0.001	1.35 (1.28, 1.43) < 0.001	1.31 (1.24, 1.39) < 0.001	1.91 (1.77, 2.07) < 0.001
Quantiles					
Q1	157/1552	Ref.	Ref.	Ref.	Ref.
Q2	331/1551	2.25 (1.86, 2.72) < 0.001	1.15 (0.94, 1.40) 0.163	1.18 (0.97, 1.43) 0.106	1.26 (1.03, 1.55) 0.024
Q3	585/1551	4.48 (3.75, 5.34) < 0.001	1.68 (1.39, 2.03) < 0.001	1.65 (1.36, 2.00) < 0.001	2.20 (1.78, 2.70) < 0.001
Q4	811/1552	7.24 (6.10, 8.59) < 0.001	2.31 (1.90, 2.81) < 0.001	2.17 (1.79, 2.64) < 0.001	3.83 (3.01, 4.87) < 0.001
P for trend		< 0.001	< 0.001	< 0.001	< 0.001
Cardiovascular mortality					
Per SD increase	517/6206	1.82 (1.69, 1.96) < 0.001	1.38 (1.25, 1.53) < 0.001	1.33 (1.20, 1.48) < 0.001	1.78 (1.52, 2.08) < 0.001
Quantiles					
Q1	33/1552	Ref.	Ref.	Ref.	Ref.
Q2	87/1551	2.80 (1.88, 4.18) < 0.001	1.35 (0.89, 2.04) 0.154	1.38 (0.91, 2.10) 0.125	1.37 (0.89, 2.09) 0.150
Q3	166/1551	6.00 (4.13, 8.73) < 0.001	2.05 (1.37, 3.05) < 0.001	2.00 (1.34, 2.99) < 0.001	2.26 (1.47, 3.48) < 0.001
Q4	231/1552	9.71 (6.74, 13.99) < 0.001	2.73 (1.82, 4.11) < 0.001	2.54 (1.69, 3.82) < 0.001	3.47 (2.13, 5.65) < 0.001
P for trend		< 0.001	< 0.001	< 0.001	< 0.001

HR – hazard ratio, 95%CI – 95% confidence interval, SD – standard deviation, apVAT – anthropometrically predicted visceral adipose tissue, NAFLD – non-alcoholic fatty liver disease. Model 1: Non-adjusted. Model 2: Adjusted for age, sex, and ethnicity. Model 3: Adjusted for age, sex, ethnicity, marital status, education level, PIR, and smoking history. Model 4: Adjusted for age, sex, ethnicity, marital status, education level, PIR, smoking history, diabetes, hypertension, HbA1c, ALT/AST, TG, HDL-c, LDL-c, SCr, and SUA.

tality risk across four Cox proportional hazards regression models of increasing adjustment. When apVAT was analyzed as a continuous variable, each standard deviation (SD) increase in apVAT was significantly associated with a progressively higher risk of mortality across all models. For all-cause mortality, the HRs (95% CIs) per SD increase in apVAT were 1.75 (1.68–1.82) in Model 1, 1.35 (1.28–1.43) in Model 2, 1.31 (1.24–1.39) in Model 3, and 1.91 (1.77–2.07) in Model 4 (all $p < 0.001$). Similarly, for cardiovascular mortality, the HRs (95% CIs) per SD increase were 1.82 (1.69–1.96), 1.38 (1.25–1.53), 1.33 (1.20–1.48), and 1.78 (1.52–2.08), respectively, across Models 1 to 4 (all $p <$

0.001). In addition, when apVAT was categorized into quartiles, a clear dose-response relationship was observed. In the unadjusted model (Model 1), the HRs (95% CIs) for all-cause mortality across quartiles were 1.00 (reference), 2.25 (1.86–2.72), 4.48 (3.75–5.34), and 7.24 (6.10–8.59); after full adjustment for confounding factors in Model 4, the HRs (95% CIs) were 1.00 (reference), 1.26 (1.03–1.55), 2.20 (1.78–2.70), and 3.83 (3.01–4.87) (p for trend < 0.001). For cardiovascular mortality, the HRs (95% CIs) across quartiles increased from 1.00 (reference), 2.80 (1.88–4.18), 6.00 (4.13–8.73), to 9.71 (6.74–13.99) in Model 1, and from 1.00 (reference), 1.37 (0.89–2.09), 2.26 (1.47–3.48), to 3.47 (2.13–5.65) in Model 4 (p for trend < 0.001).

Non-linear relationships between apVAT and mortality risk

Using Cox proportional hazards regression models with restricted cubic splines, after adjusting for age, sex, ethnicity, marital status, education level, PIR, smoking history, diabetes, hypertension, HbA1c, ALT/AST, TG, HDL-c, LDL-c, SCr, and SUA, a significant nonlinear relationship was found between apVAT and mortality (Figure 2). The turning point for all-cause mortality was identified at 347.40 units (p < 0.001 for overall association, p = 0.027 for nonlinearity), while cardiovascular mortality exhibited a turning point at 305.78 units (p < 0.001 for overall association, p = 0.045 for nonlinearity). Both outcomes demonstrated J-shaped curves with substantially increased risk beyond their respective turning points.

Predictive value of apVAT for mortality risk assessment

Figure 3 demonstrates that apVAT exhibits superior predictive performance for mortality risk assessment compared to conventional obesity indicators, with time-dependent ROC analysis revealing

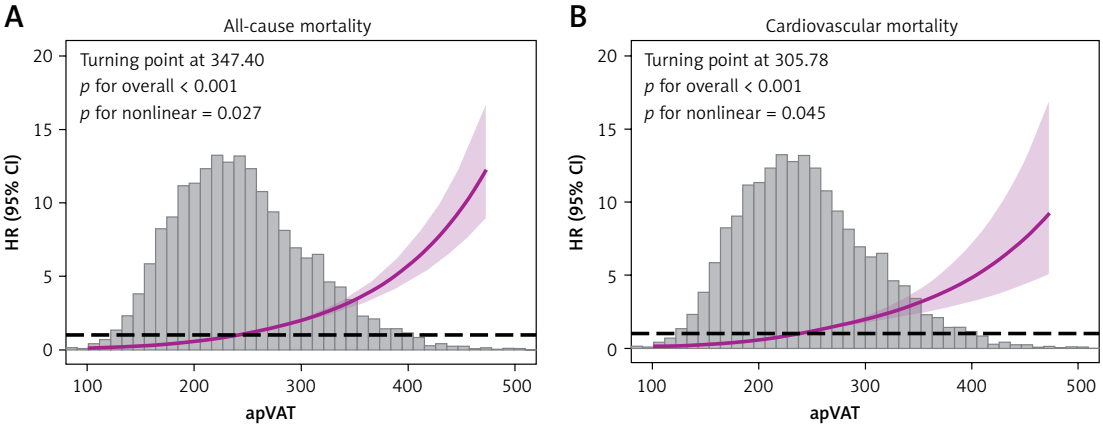

Figure 2. Restricted cubic splines illustrating nonlinear associations between apVAT and mortality outcomes. Histograms represent the distribution of apVAT values among study participants. The solid curves show the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause (**A**) and cardiovascular (**B**) mortality, estimated using restricted cubic spline models

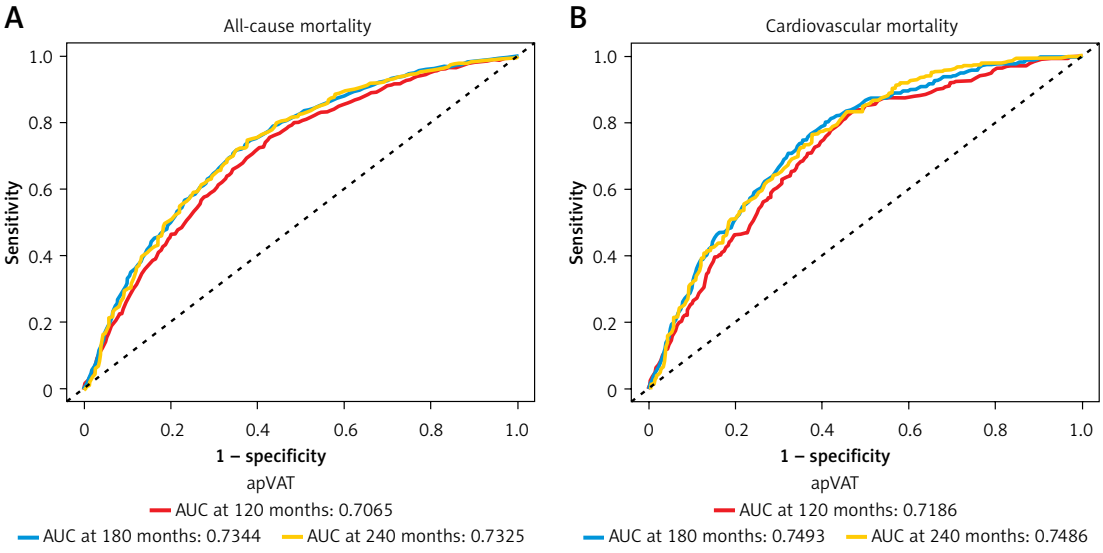

Figure 3. Time-dependent ROC curves for apVAT predicting all-cause (**A**) and cardiovascular (**B**) mortality

significantly larger area under the curve (AUC) values (Supplementary Figures S1, S2). For all-cause mortality, apVAT achieved excellent AUC values of 0.7065, 0.7344, and 0.7325 at 120, 180, and 240 months respectively, substantially outperforming BMI (AUC: 0.5763–0.5968), WC (AUC: 0.5211–0.5556), thigh circumference (AUC: 0.6649–0.6897), WHtR (AUC: 0.5409–0.5575), WWI (AUC: 0.6917–0.6985), and RFM (AUC: 0.4941–0.5056). For cardiovascular mortality, apVAT demonstrated even stronger predictive power with outstanding AUC values of 0.7186, 0.7493, and 0.7486, markedly surpassing all other adiposity measures including BMI (AUC: 0.5641–0.5786), WC (AUC: 0.5325–0.5655), thigh circumference (AUC: 0.6425–0.6763), WHtR (AUC: 0.5636–0.5675), WWI (AUC: 0.6983–0.7018), and RFM (AUC: 0.5052–0.5100).

Stratified analysis and sensitivity analysis

Subgroup analyses for all-cause and cardiovascular mortality are presented in Figure 4. Significant

All-cause mortality	HR 95% CI	*P* for Interaction
Age [years]		
< 60	2.10 (1.84, 2.41)	0.034
≥ 60	1.81 (1.66, 1.98)	
Sex		
Female	2.27 (1.98, 2.61)	0.002
Male	1.87 (1.72, 2.03)	
Race		
Mexican American	1.96 (1.71, 2.25)	0.070
Other Hispanic	2.79 (1.95, 4.01)	
Non-Hispanic White	1.87 (1.71, 2.04)	
Non-Hispanic Black	1.97 (1.72, 2.26)	
Other race	2.58 (1.89, 3.52)	
Married		
No	2.01 (1.82, 2.23)	0.104
Yes	1.86 (1.70, 2.03)	
Above high school		
No	1.98 (1.80, 2.18)	0.301
Yes	1.87 (1.69, 2.07)	
PIR		
< 1.3	1.95 (1.75, 2.18)	0.609
1.3–3.5	1.88 (1.71, 2.05)	
≥ 3.5	1.98 (1.75, 2.25)	
Smoking history		
No	2.02 (1.82, 2.25)	0.106
Yes	1.87 (1.71, 2.04)	
BMI [kg/m^2]		
< 25	1.26 (0.96, 1.64)	0.380
25–30	1.52 (1.35, 1.70)	
≥ 30	1.45 (1.35, 1.55)	
Diabetes		
No	1.94 (1.78, 2.12)	0.389
Yes	1.85 (1.65, 2.07)	
Hypertension		
No	2.02 (1.79, 2.29)	0.207
Yes	1.87 (1.71, 2.04)	

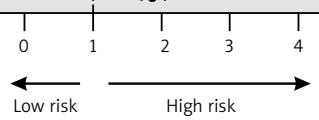

Figure 4. Subgroup analysis of apVAT and mortality risk. Adjustments were made for age, sex, ethnicity, marital status, education level, PIR, smoking history, diabetes, hypertension, HbA1c, ALT/AST, TG, HDL-c, LDL-c, SCr, and SUA, excluding subgroup factors

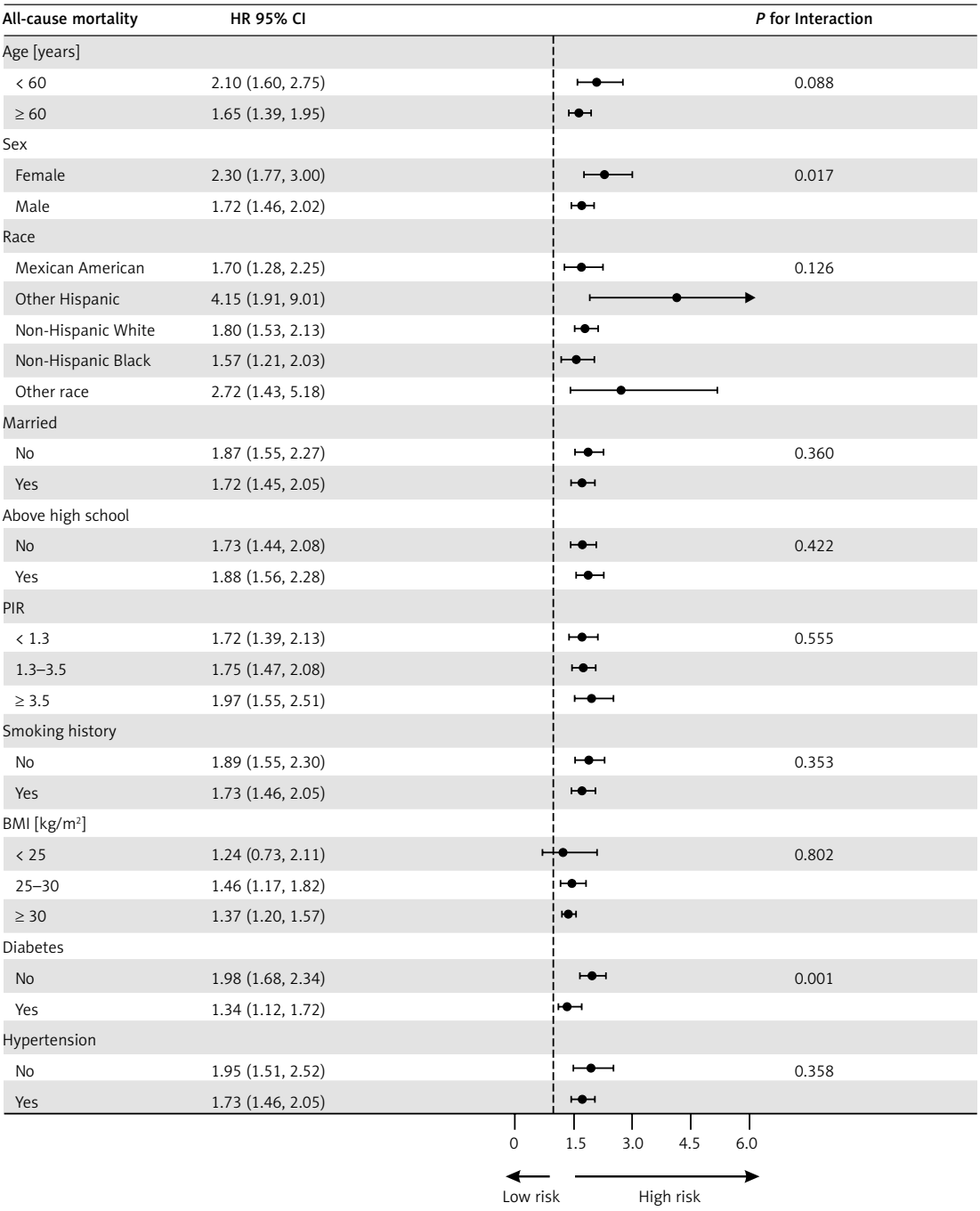

Figure 4. Cont.

interactions were observed for sex in both outcomes (p = 0.002 and 0.017, respectively), indicating a stronger association between higher apVAT and mortality in females. For all-cause mortality, age showed a significant interaction (p = 0.034), with a stronger relationship between apVAT and mortality among participants younger than 60 years. For cardiovascular mortality, a significant interaction was identified for diabetes status (p = 0.001), suggesting higher apVAT-related mortality risk among individuals without diabetes. No significant interactions were observed for other subgroups.

To confirm the reliability of the results, we carried out sensitivity analyses by focusing solely on NAFLD participants with a USFLI ≥ 30 or an FLI ≥ 60. These above findings were also consistent with our main results (Supplementary Tables SI, SII).

Discussion

To our knowledge, this is the first study to investigate apVAT–mortality associations in a large NAFLD cohort. In multivariable Cox regression anal-

yses, higher apVAT levels were robustly associated with elevated risks of all-cause and cardiovascular mortality among individuals with NAFLD. Additionally, apVAT provided enhanced predictive capability for mortality risk relative to both traditional and emerging anthropometric indices. Restricted cubic spline analyses further identified a nonlinear association between apVAT and mortality.

The "obesity paradox" continues to present challenges in epidemiological studies, as the intricate dynamics of anthropometric indices make it difficult to accurately determine biologically driven risks of disease [9, 30, 31]. In line with the World Health Organization's characterization of obesity as an abnormal or excessive accumulation of adiposity that compromises health, it is essential to distinguish lean mass from patterns of fat distribution [32]. Traditional obesity indicators, such as BMI and WC, often fail to effectively distinguish body fat distribution [33, 34]. In contrast, apVAT offers a non-invasive, cost-effective, and easily accessible tool for assessing visceral fat and its associated metabolic risks. Results from ROC analysis in our study also indicated that apVAT offers improved discrimination and clinical value over traditional anthropometric indices. It could be attributed to its comprehensive incorporation of multiple body measurements (WC, thigh circumference, BMI, age, and sex) that collectively capture both central obesity and peripheral fat distribution. Unlike WWI and RFM, which focus primarily on central adiposity, apVAT accounts for the protective effects of lower body fat. We also observed a J-shaped relationship between apVAT and mortality. Several previous studies have also emphasized that higher body fat content is nonlinearly associated with an increased risk of mortality [35–37]. At lower apVAT levels, the risk of all-cause and cardiovascular mortality appears to be low or relatively stable. This might be because, within this range, metabolic function remains largely intact, and fat distribution and metabolic markers are within a relatively healthy range [38]. However, when apVAT exceeds a certain threshold, the risk of all-cause and cardiovascular mortality begins to rise significantly. This threshold effect likely reflects the onset of metabolic decompensation, where the accumulation of visceral fat leads to inflammation, IR, and increased cardiovascular burden, triggering rapid disease progression and heightened mortality risk [38]. Subgroup analyses revealed significant heterogeneity in the apVAT–mortality association across sex, age, and diabetes status. The stronger association observed in female patients may reflect more pronounced metabolic dysregulation resulting from the loss of estrogen-mediated protective effects on adipose tissue distribution [39]. Elevated risk in younger individuals (< 60 years) suggests that early visceral fat accumulation represents a more aggressive phenotype, while the attenuated association in older populations might also reflect competing risks from age-related comorbidities. Additionally, in non-diabetic populations, the accumulation of visceral fat may serve as an early driving factor for cardiovascular mortality. In contrast, diabetic populations often exhibit multiple metabolic abnormalities (e.g., hyperglycemia, dyslipidemia, chronic inflammation), which may overshadow the independent effect of apVAT [40, 41].

This study has several limitations that should be acknowledged. Firstly, dietary quality and physical activity are key lifestyle factors that strongly influence metabolic health and mortality risk. Indicators such as the Healthy Eating Index and Bouts of Weekly Walking could have provided more comprehensive adjustment for these dimensions [42–44]. Secondly, although our research leveraged a large-scale cohort, anthropometric data collection was confined to the baseline assessment. The potential value of apVAT trajectory changes in informing the clinical management of NAFLD requires further investigation. Additionally, an international consensus has recommended replacing NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD), which is defined by the presence of at least one cardiometabolic risk factor rather than by exclusion of alcohol use or other liver diseases [45]. Although conceptually different, studies indicate that nearly all NAFLD cases meet MASLD criteria, showing high clinical and diagnostic overlap [46]. Given that our study applied exclusion-based diagnostic criteria, we retained the term NAFLD, while recognizing MASLD as the updated nomenclature for future research. Finally, the association between apVAT and mortality risk in NAFLD needs to be further validated across different regions and ethnic groups.

In conclusion, elevated apVAT levels are strongly linked to increased risks of all-cause and cardiovascular mortality in individuals with NAFLD. This suggests that apVAT could be a valuable marker for predicting mortality risk in this population.

Data availability

The datasets generated and/or analyzed during the current study are available in the NHANES database (https://wwwn.cdc.gov/nchs/nhanes/).

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Ethical approval

This study involving human participants was reviewed and approved by the Ethics Review Board of the National Center for Health Statistics (NCHS) (https://www.cdc.gov/nchs/nhanes/about/erb.html). The patients/participants provided their written informed consent to participate in this study.

Conflict of interest

The authors declare no conflict of interest.

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