



Optimal Cut-Off Values of Visceral Fat Area for Predicting Metabolic Syndrome Among Type 2 Diabetes Patients in Ningbo, China


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Objective: To examine the optimal cut-off values of visceral fat area (VFA) for predicting metabolic syndrome (MetS) among type 2 diabetes (T2D) patients in Ningbo China.

Methods: A total of 1017 subjects were selected from T2D patients who accepted standardized management by the National Standardized Metabolic Disease Management Center at Ningbo First Hospital from March 2018 to January 2020. Demography and medical information were collected through questionnaires. Regional adiposity was examined by a visceral fat analyzer using the dual bioelectrical impedance method.

Results: Overall, 769 (75.6%) T2D patients were defined to have MetS. Patients with MetS had higher anthropometric values and biomarkers, compared to those without MetS. VFA was significantly correlated with risk factors of MetS. Further logistic regression models showed that VFA was significantly associated with MetS in men (OR=1.02) and in women (OR=1.03) (P<0.001 for both genders) after controlling for related factors. Receiver-operating characteristic curve analysis demonstrated that the optimal cut-off values of VFA were 84.7 cm² for men and 81.1 cm² for women to predict MetS in T2D patients.

Conclusion: VFA was associated with MetS and could be an independent predictor of MetS in T2D patients.

Clinical Trial Registration: www.ClinicalTrials.gov, number: NCT03811470.

Keywords: abdominal obesity, metabolic syndrome, visceral fat area, type 2 diabetes

Introduction

Metabolic syndrome (MetS) is a cluster of conditions that contribute to the risk of cardiovascular diseases (CVD), heart disease, stroke and type 2 diabetes (T2D), which may increase all-cause mortality.^{1,2} MetS involves at least three out of five metabolic conditions, including hypertension, glucose intolerance, abdominal obesity, decreased high-density lipoprotein cholesterol (HDL-C), and increased triglyceride (TG) levels.^{3,4} The prevalence of T2D and MetS has increased rapidly in China due to rapid economic development and urbanization. The prevalence of MetS in adults was 10.5% in 2009 and 14.4% in 2014 in China^{5,6} based on the Chinese Diabetes Society (2004) criteria.⁷

Abdominal obesity, evaluated by waist circumference (WC), is known to be a critical contributor to cardio-metabolic risk factors,^{8,9} but WC is not able to distinguish visceral fat from subcutaneous adipose tissues effectively.¹⁰ Instead, abdominal visceral fat has been considered to be a more associative cardiovascular risk factor of body fat distribution than BMI and WC.¹¹⁻¹³ Previous studies showed

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that visceral fat area (VFA) was superior to BMI and WC to predict MetS and various cut-off values of VFA have been developed according to race, gender and age.^{14–17} The accurate assessment and management of visceral fat accumulation were suggested to be critical to identify the cardiovascular risks among patients with T2D. Recently, computed tomography (CT), magnetic resonance imaging and dual-energy X-ray absorptiometry were recognized as the accurate methods to evaluate the visceral adipose tissue.^{18–20} However, due to the high cost of technology and high radiation exposure, these methods have been limited in clinical practice and have not been appropriate for screening purpose for a large population yet. In contrast, the dual current pathways bioelectrical impedance analysis (BIA) method was reported to measure central abdominal fat without X-ray exposure, with an accuracy for estimated VFA which was similar to the detection results of the X-ray CT method.^{20,21} Because of its simplicity, noninvasiveness and relatively low cost, abdominal BIA can be used as a potentially good alternative measure of visceral fat accumulation.

With aging, fat mass tends to accumulate in the abdomen, and the risk of chronic diseases such as diabetes and CVD have been dramatically increased.^{22,23} Previous studies have shown that the prevalence of MetS was higher in people with T2D,^{24,25} and the cardiovascular mortality rate of subjects with metabolic syndrome was significantly increased regardless of the presence of T2D.^{24–27} Our previous research showed that the prevalence of MetS among adults in Ningbo was about 31%, which has reached a similar prevalence level of MetS in adults worldwide (20–30%).²⁸ Therefore, establishment of an abdominal obesity assessment measure to accurately identify the risk of MetS and better control the risk of CVD in T2D is needed.

Up to date, few studies have examined the relationship between visceral fat and MetS in Chinese population. In addition, no study has explored the relationship between visceral fat and MetS in Chinese T2D patients. To fill in these research gaps, this study aimed to estimate optimal cut-off values of VFA and to investigate the risk of MetS among T2D patients in Chinese population.

Patients and Methods

Subjects

The present cross-sectional study recruited 1017 patients, diagnosed with T2D, aged from 18 to 75 years from

March 2018 to January 2020 at the outpatient department of the Endocrinology of Ningbo First Hospital, Zhejiang province, China and the National Standardized Metabolic Disease Management Center (MMC). In order to meet all the challenges of metabolic diseases, the MMC program was launched in 2016.²⁹ In MMC, patients can enjoy one-stop care, from registration, testing, evaluation, prescription to health education, and a series of comprehensive services to achieve a more convenient and accurate patient care model. T2D was diagnosed based on the definition proposed by the World Health Organization.³⁰ We defined diabetes as fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dl) or 2h oral glucose tolerance test (OGTT) glucose ≥ 11.1 mmol/L (200 mg/dl). Subjects taking anti-diabetic drugs were also considered to have diabetes. The patients were excluded if they met any of the following criteria 1) age >75 years and age <18 years; 2) diagnosis with any kind of cancer; 3) positive islet autoantibodies; 4) glomerular filtration rate (eGFR) <30 mL/min; 5) severe liver dysfunction; 6) acute infectious diseases; 7) pregnancy or lactation.

The research project was approved by the Ethics Committee of Ningbo First Hospital, China (Ethics Approval No. 2019-R057) and followed the Declaration of Helsinki. Written informed consents were obtained from all participants.

Definition of Metabolic Syndrome

MetS was defined based on the 2017 Chinese Diabetes Society's (CDS) criteria.³¹ The diagnostic criteria of MetS is the presence of three or more of the medical components: 1) abdominal obesity: WC >90 cm in men or >85 cm in women; 2) hyperglycemia: FPG ≥ 6.1 mmol/L (110 mg/dl) or 2-hour postprandial plasma glucose (2hPG) level ≥ 7.8 (140 mg/dl) mmol/L or previously diagnosed with T2D; 3) hypertension: systolic blood pressure (SBP)/diastolic blood pressure (DBP) $\geq 130/85$ mmHg or previously diagnosed with hypertension and receiving medical treatments; 4) TG ≥ 1.7 mmol/L (150 mg/dl); 5) HDL-C < 1.0 mmol/L (40 mg/dl). Since all subjects were diagnosed with T2D, MetS is defined at least two of the above medical components with the exception for 2). Based on the criteria of MetS, all subjects were divided into two groups: MetS (–) (T2D patients with no MetS) and MetS (+) (T2D patients defined as MetS).

Demographic and Clinical Characteristics

All patients were invited to complete the MMC standard questionnaires on their demography, lifestyle [smoking status (currently no smoking and currently smoking)], medical

history and medication records. Anthropometric measurements included body weight and height were measured without shoes and in light clothing by well-trained endocrinology nurses. Body weight was measured using an electronic scale to the nearest 0.1 kg and height was measured using a metal column height meter to the nearest 0.1 cm. WC was measured at the midpoint between the inferior costal margin and the iliac crest in the midaxillary line. Hip circumference was measured at the widest point over the buttocks, and the waist-hip ratio (WHR) was calculated as the ratio of waist to hip circumferences. BMI, used as a measure of general obesity, was calculated as weight (kg)/height (m²). Blood pressure was measured using an electronic sphygmomanometer on the right or left arm after a 10-minute rest and the average of blood pressure was obtained on two assessments.

Biomarker Measurements

After a 10–12h-overnight fasting, blood samples were obtained in the early morning to measure the levels of blood profiles including FPG, fasting c-peptide (FCP), fasting insulin (FINS), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), uric acid (UA) and serum creatinine (Scr). Then, the 100g flour (steamed bread meal) test was performed in all subjects to assess the 2hPG, 2-hour postprandial C-peptide (2hCP) and 2-hour postprandial insulin (2hINS) concentrations.

FPG and 2hPG were assayed by the glucose oxidase method, FCP and 2hCP were determined by chemiluminescence immunoassay. Lipid profiles were analyzed by enzymatic procedures using an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan). HbA1c was determined by high-pressure liquid chromatography. UA was examined by enzymatic spectrophotometry. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as fasting serum insulin (mIU/L) × FPG (mmol/L)/22.5.³² HOMA-IR was used for further evaluation of insulin sensitivity. The eGFR was calculated following the formula: $eGFR (mL/min/1.73 m^2) = 175 \times Scr (mg/dl)^{-1.234} \times age^{-0.179} \times (1 \text{ for men; } 0.79 \text{ for women}).$ ³³

Measurement of Visceral Fat Area and Subcutaneous Fat Area

VFA and subcutaneous fat area (SFA) of all participants with a 10- to 12-h fasting were measured by well-trained nurses.

The measurements of body site for VFA and SFA were measured at the level of umbilicus with a visceral fat analyzer (DUALSCAN HDS-2000, Omron Healthcare Kyoto, Japan) using the abdominal dual BIA method.^{19,20} The resultant values were based on the impedance indicated by the difference in electrical conductivity between fat and non-fat tissue. Two paths were used to measure the impedance. The first path (A) applied low-voltage alternating current to a total of four electrodes fixed on both sides of the hands and feet. The system detected a constant micro-current value and calculated the bio-impedance value generated when passing through the limbs, thus calculating the non-fat area. The second path (B) applied a weak electric current between the electrodes placed on the abdomen and also measured the impedance. SFA of the abdomen can be calculated according to the abdominal impedance. The cross-sectional area of the abdomen at the umbilical level was calculated by the “abdominal detection unit” in advance. Afterwards, VFA was calculated following the formula: cross-sectional area - the sum areas of A and B.²⁰

Measurement of Common Carotid Intima-Media Thickness

The intimal thickness of the carotid artery was measured with high-resolution B-mode ultrasound by experienced ultrasound experts. Patients were asked to take a supine position with their heads turning to the opposite side to fully expose the carotid artery. The intima-media thickness (IMT) on the distal wall of the common carotid artery on both sides was measured at about 1 cm from the carotid bifurcation. The greater value of the IMT of carotid artery from both sides was recorded as MaxIMT for analysis. Local carotid artery IMT greater than 1.5 mm was defined as carotid plaque formation.³⁴

Statistical Analysis

Continuous variables with normal and skewed distributions were presented as mean and standard deviation (SD), and median (interquartile range). Continuous variables were analyzed by Student's *t*-test and Mann-Whitney *U*-test. Groups of categorical variables were compared by χ^2 test. Spearman correlation was conducted to examine the relationship between VFA and MetS factors. Logistic regression was used to examine the association between VFA (continuous variables; independent variable) and MetS (categorical variable; dependent variable). Associations were investigated after adjusting for related factors (age, currently smoking, HOMA-IR, UA and

currently using any kind of hypoglycemic medicines that might affect visceral fat accumulation [glucagon-like peptide-1 (GLP-1) agonists, thiazolidinediones (TZDs), glinides and sodium-dependent glucose transporters 2 (SGLT-2) inhibitors].^{35–38} Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic value of VFA for MetS in patients with T2D. The optimal cut-off values were obtained from the Youden index [maximum (sensitivity + specificity - 1)].³⁹ Results were considered statistically significant at a two-tailed level of 0.05. Statistical analyses were performed with IBM SPSS Statistics version 20.0.

Results

Clinical Characteristics of Study

Individuals

A total of 1017 T2D patients (63.7% men) with a mean age of 54 years were finally included in the current study (Table 1). Around 75.6% (n=769) patients were defined as to have MetS (MetS +). Mean values of age, BMI, BP, VFA, SFA, WHR, FPG, FINS, 2hINS, HOMA-IR, FCP, 2hCP, UA, TC, TG, LDL-C and maxIMT were significantly higher in patients with MetS compared to those without MetS. Regarding glucose-lowering medicines, only currently using any kind of hypoglycemic medicines that affect VFA was taken was significantly more in the group of patients with MetS (P=0.013).

Relationship of Visceral Fat Area with the Risk Factors of Metabolic Syndrome

Spearman correlation was performed to examine the relationship of VFA with metabolic parameters stratified by sex (Table 2). Age was only significantly associated with VFA in women ($r=0.134$, $P=0.012$). VFA was positively correlated with all other parameters of anthropometry and biomarkers except for the negative correlation with HDL-C in women, and the Spearman correlation coefficients of VFA with BMI, SFA HOMA-IR and uric acid were 0.729, 0.687, 0.343 and 0.390, respectively, while five parameters of MetS including FPG, 2hPG, HbA1c, TC and LDL-C were not associated with VFA in men.

The associations of MetS with VFA were further investigated by logistic regression (Table 3). VFA was associated with 1.02 (CI 1.02–1.03) and 1.03 (CI 1.02–1.05) higher odds of developing MetS in both men and women, respectively, after controlling for potential risk factors. However, only age was associated with higher odds of

MetS only in women (OR=1.05, CI 1.02–1.08, $P<0.001$) and uric acid was associated with higher odds of MetS only in men (OR=1.00, CI 1.00–1.01, $P=0.034$).

The Optimal Cut-Off Values of Visceral Fat Area for the Metabolic Syndrome

From the ROC curve analysis, the areas under the curve of ROC values of VFA predicting MetS were 0.752 (95% CI 0.706–0.799, $P<0.001$) in men and 0.785 (95% CI 0.735–0.836, $P<0.001$) in women (Figure 1). The optimal cut-off value of VFA was 84.7 cm² (sensitivity: 74.7%, specificity: 65.8%) for men and 81.1 cm² (sensitivity: 59.2%, specificity: 88.0%) for women (Table 4).

Discussion

In this study of a large clinical MMC study, the results of the current study showed that 75.6% T2D patients in Ningbo, China, were defined to have MetS. VFA and BMI were significantly associated with higher odds of MetS in both men and women. The optimal cut-off values of VFA predicting MetS among T2D patients was 84.7cm² in men and 81.1cm² in women.

To date, no study has been conducted on VFA cut-off values among Chinese T2D patients. The prevalence of MetS in our study is relatively higher than those from previous reports.^{40–42} A recent study involving 15,492 adult patients newly diagnosed with T2D in 46 tertiary care hospitals nationwide in China from 2015 to 2017 reported that the prevalence of MetS was 68.1% using the 2017 CDS definition.^{31,40} The higher prevalence of MetS in our study can be explained that majority of our regional patients are not newly diagnosed T2D patients. Likewise, the prevalence of MetS in our study is relatively higher than the same patients in Ethiopia (66.7%)⁴¹ and in Korea (men: 46.9%; women: 65.1%) both using the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria.^{3,42}

The guidelines from the CDS (2004) adapted BMI ≥ 25 kg/m² to define abdominal obesity predicting MetS among Chinese population.⁷ Additionally, International Diabetes Federation proposed a global diagnosis definition of MetS in 2005 and suggested the differential cut-off values of WC for defining abdominal obesity that reflected different races in each country.¹⁰ However, the body fat distribution of the Chinese population is characterized by abdominal fat accumulation. Evidence showed that Asians were more inclined to have obesity-related consequences

Table 1 Baseline Clinical Characteristics of Patients with Type 2 Diabetes

	Total N=1017	MetS (-) N=248	MetS (+) N=769	P value
Male, n (%)	648 (63.7)	151 (60.9)	497 (64.6)	0.287
Age (years)	54 (47–61)	53 (45–59)	55 (47–62)	0.022
Currently smoking, n (%)	254 (24.9)	66 (26.6)	188 (24.4)	0.493
Anthropometry and biomarkers				
SBP (mmHg)	132.95 ± 18.06	125.05 ± 15.23	135.49 ± 18.17	<0.001
DBP (mmHg)	78.56 ± 11.02	75.05 ± 10.16	79.7.0 ± 11.04	<0.001
Weight (kg)	69.23 ± 12.82	62.07 ± 10.92	71.54 ± 12.54	<0.001
BMI (kg/m ²)	25.23 ± 3.64	22.86 ± 2.84	26.00 ± 3.52	<0.001
Waist circumference (cm)	89.03 ± 9.94	81.62 ± 8.70	91.42 ± 9.11	<0.001
Hip circumference (cm)	95.06 ± 7.19	91.23 ± 6.60	96.29 ± 6.93	<0.001
WHR	0.94 ± 0.07	0.90 ± 0.10	0.94 ± 0.06	<0.001
VFA (cm ²)	93.82 ± 40.06	68.58 ± 34.65	101.98 ± 38.28	<0.001
SFA (cm ²)	179.41 ± 62.88	142.79 ± 49.11	191.23 ± 62.32	<0.001
FPG (mmol/L)	8.57 ± 2.94	8.21 ± 3.07	8.69 ± 2.89	0.027
2hPG (mmol/L)	13.63 ± 4.97	13.54 ± 5.51	13.66 ± 4.77	0.742
FINS (mIU/L)	11.30 (6.26–30.17)	7.42 (4.30–18.90)	12.30 (7.43–34.88)	<0.001
2hINS (mIU/L)	38.52 (21.44–92.32)	28.45 (15.42–66.45)	43.23 (22.97–104.5)	<0.001
HbA1c (%)	7.70 (6.50–9.20)	7.40 (6.40–9.20)	7.80 (6.60–9.20)	0.146
HOMA-IR	4.11 (2.19–11.49)	2.62 (1.44–6.97)	4.84 (2.60–13.15)	<0.001
FCP (µg/L)	1.73 (1.00–2.53)	1.32 (0.73–1.87)	1.92 (1.11–2.73)	<0.001
2hCP (µg/L)	4.08 (2.42–6.04)	3.41 (1.96–4.92)	4.26 (2.63–6.35)	<0.001
Uric acid (mmol/L)	333.86 ± 85.01	303.36 ± 80.06	343.70 ± 84.26	<0.001
Total cholesterol (mmol/L)	4.52 ± 1.24	4.17 ± 1.08	4.63 ± 1.26	<0.001
Triglycerides (mmol/L)	1.43 (1.00–2.14)	1.05 (0.79–1.37)	1.70 (1.12–2.36)	<0.001
HDL-C (mmol/L)	1.16 ± 0.29	1.16 ± 0.35	1.15 ± 0.28	0.829
LDL-C (mmol/L)	4.52 ± 1.24	2.68 ± 0.80	2.93 ± 0.89	<0.001
Max IMT (mm)	0.80 (0.60–1.00)	0.80 (0.60–0.90)	0.80 (0.60–1.00)	0.032
Carotid plaque, n (%)	365 (35.9)	70 (28.2)	295 (38.4)	0.006
Duration of diabetes (years)	6.58 (2.50–12.00)	6.50 (2.10–12.06)	6.6 (2.75–12.00)	0.363
Glucose-lowering medication treatments, n (%)				
Insulin	338 (33.2)	89 (35.9)	249 (32.4)	0.346
TZDs	25 (2.5)	5 (2.0)	20 (2.6)	0.605
Sulfonylureas	326 (32.1)	88 (35.5)	238 (30.9)	0.210
Glinides	107 (10.5)	23 (9.3)	84 (10.9)	0.537
GLP-1 agonists	135 (13.1)	33 (12.8)	102 (13.3)	0.930
Biguanides	683 (67.2)	166 (66.9)	517 (67.2)	0.993
Alpha-GIs	367 (36.1)	85 (34.3)	282 (36.7)	0.544
DPP4 inhibitors	287 (28.2)	69 (27.8)	218 (28.3)	0.937
SGLT-2 inhibitors	80 (7.9)	21 (8.5)	59 (7.7)	0.788
Currently using any kind of hypoglycemic medicines that affect VFA [‡]	681 (70.9)	54 (22.6)	280 (31.1)	0.013

Notes: Data represent mean standard deviation or median (interquartile range 25–75%). [‡]Currently using any kind of hypoglycemic medicines that affect visceral fat accumulation included GLP-1 agonists, TZDs, glinides and SGLT-2 inhibitors.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist–hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial plasma glucose; FINS, fasting plasma insulin, 2hINS, 2-hour postprandial plasma insulin; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; FCP, fasting c-peptide; 2hCP, 2-hour postprandial c-peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; max IMT, max common carotid intima-media thickness. TZD, thiazolidinedione; GLP-1 agonists, glucagon-like peptide-1 agonists; alpha-GIs, alpha-glucosidase inhibitor; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT-2 inhibitors, sodium-dependent glucose transporters 2 inhibitors.

Table 2 Spearman Correlation Between VFA and Metabolic Parameters

	VFA (cm ²)			
	Men (n=648)		Women (n=369)	
	r	P value	r	P value
Age (years)	0.042	0.291	0.134	0.012
SBP (mmHg)	0.309	<0.001	0.246	<0.001
DBP (mmHg)	0.215	<0.001	0.157	0.003
BMI (kg/m ²)	0.659	<0.001	0.729	<0.001
SFA (cm ²)	0.665	<0.001	0.687	<0.001
FPG (mmol/L)	0.049	0.224	0.177	<0.001
2hPG (mmol/L)	0.021	0.607	0.116	<0.001
FINS (mIU/L)	0.337	<0.001	0.328	<0.001
2hINS (mIU/L)	0.267	<0.001	0.216	<0.001
HbA1c (%)	-0.016	0.692	0.211	<0.001
HOMA-IR	0.325	<0.001	0.343	<0.001
FCP (μg/L)	0.310	<0.001	0.286	<0.001
2hCP (μg/L)	0.206	<0.001	0.148	0.006
Uric acid (mmol/L)	0.235	<0.001	0.390	<0.001
Total cholesterol (mmol/L)	0.032	0.420	0.045	<0.001
Triglycerides (mmol/L)	0.337	<0.001	0.384	<0.001
HDL-C (mmol/L)	-0.215	<0.001	-0.241	<0.001
LDL-C (mmol/L)	0.012	0.765	0.116	0.029

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial plasma glucose; FINS, fasting plasma insulin, 2hINS, 2-hour postprandial insulin; HbA1c, glycated hemoglobin A1c; FCP, fasting c-peptide; 2hCP, 2-hour postprandial c-peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

at a lower BMI or a lower WC because of higher body fat mass deposition, compared to Caucasians.^{43,44} Around 14% abdominal fat mass deposition was reported in Chinese, although their BMI was lower than cut-off value of 25 kg/m².⁴⁵ VFA is suggested to be a more accurate measurement than both WC and BMI for defining abdominal obesity.¹⁴⁻¹⁷ Comparable results have been reported in China on healthy Chinese population, VFA ≥80 cm² was proposed as an optimal cut-off value for predicting MetS and WC of 90 cm for men and 85 cm for women proposed as the cut-off values for the diagnosis of abdominal obesity in China.¹⁶ A 7.8-year follow-up

Table 3 Logistic Regression Analysis of Associated with MetS[§] in Patients with Type 2 Diabetes

	Men (n=648)		Women (n=369)	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (year)	1.01 (0.99–1.03)	0.400	1.05 (1.02–1.08)	<0.001
VFA (cm ²)	1.02 (1.02–1.03)	<0.001	1.03 (1.02–1.05)	<0.001
Uric acid (mmol/L)	1.00 (1.00–1.01)	0.034	1.00 (0.99–1.01)	0.094
HOMA-IR	1.00 (0.99–1.01)	0.618	1.02 (0.99–1.04)	0.138
Currently smoking [§]	1.33 (0.85–2.09)	0.210	0.52 (0.24–1.12)	0.092
Currently using any kind of hypoglycemic medicines that affect VFA [§]	0.88 (0.55–1.40)	0.577	1.56 (0.84–2.87)	0.156

Notes: [§]MetS (-), currently no smoking and currently no hypoglycemic medicines treatment [human glucagon-like peptide-1 (GLP-1) agonists, thiazolidinediones (TZDs), glinides and sodium-dependent glucose transporters 2 (SGLT-2) inhibitors] are references in the models.

Abbreviations: CI, confidence interval; VFA, visceral fat area; HOMA-IR, homeostasis model assessment for insulin resistance.

study, conducted on healthy adults, indicated that abdominal obesity in an independent risk factor causing T2D and VFA ≥90 cm² was proposed as the cut-off values to define

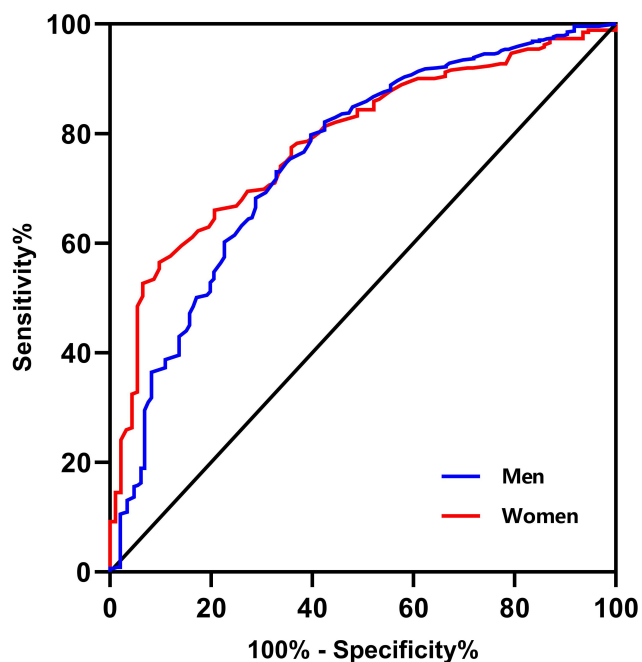


Figure 1 ROC curves for cut-off value of VFA to predict MetS. In men: area under the curve=0.752, 95% CI 0.706–0.799, P<0.001. Sensitivity and specificity at a VFA of 84.7 cm² were 74.7% and 65.8%, respectively. In women: area under the curve=0.785, 95% CI 0.735–0.836, P<0.001. Sensitivity and specificity at a VFA of 81.1 cm² were 59.2% and 88.0%, respectively.

Table 4 Cut-Off Values of VFA to Identify MetS in Patients with Type 2 Diabetes

Sex	Cut-Off Values	Sensitivity (%)	Specificity (%)
Men	84.7	74.7	65.8
Women	81.1	59.2	88.0

abdominal obesity.⁴⁶ In addition, VFA cut-off value of 100 cm² was proposed for Japanese adults to define abdominal obesity indicating the risk of obesity-related diseases with NCEP-ATP III definition.^{3,15} Kim et al reported that the optimal VFA using NCEP-ATP III definition associated with an increased risk of obesity-related diseases was 103.8 cm² in Korean adults in both genders.^{3,17} Our VFA cut-off values were much lower than the results from Japanese and Korean studies. It might be caused by the various definitions of MetS.

Considering the gender-specific cut-off values for VFA in our study, VFA was significantly correlated with risk factors of T2D, especially in women. Logistic regression model, as expected, illustrated VFA indicated a significantly increased risk of MetS in patients with T2D. Previous studies suggested that the VFA cutoff value was associated with MetS.^{16,17} The mechanisms between VFA, and MetS and various components are complex and unclear yet. The possible mechanisms might be that visceral fat can secrete various hormones and inflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, which can affect the insulin sensitivity of peripheral tissues.^{47,48} With a higher rate of lipolysis of visceral fat than subcutaneous fat, decomposed products of VFA, such as free fatty acids and glycerin, directly enter the liver through the portal vein circulation, stimulating liver lipoprotein synthesis and gluconeogenesis, reducing liver insulin removal, and increasing blood glucose and insulin resistance.^{49,50} Thus, excessive visceral fat accumulation is more likely to induce diabetes, MetS and CVD. Our results also confirmed that insulin resistance and abdominal obesity were important features of MetS in diabetes. Moreover, age was found to be associated with high odds of MetS in women in our study. Recent studies indicated that age is a key factor playing a role in developing MetS.^{51,52} No cut-off value of VFA has been standardized among Chinese T2D patients yet. Lee et al⁵² and his colleagues reported that cut-off values increased with age, particularly among women, which in line with our finding. Due to post-menopause, women tend to be

sensitive to accumulate fat mass in waist area.⁵³ With no stratification of age, it might explain the lower sensitivity in our study.

The present study has some limitations. First, causality between VFA and MetS cannot be inferred according to the nature of cross-sectional study design. Second, VFA results might be affected by gender, age, medication, and the shape of the human body or the distribution of water in the patients' body. Then, due to different lifestyles and regional patients from Ningbo, China, thus, the findings cannot be generalized to the general Chinese population. The last but not least, considering the small sample size, subgroup of age could not be analyzed.

Conclusions

The present study is the first study reporting the gender-specific optimal cut-off values of VFA for T2D patients in Ningbo, China, and predicted the optimal cut-off values of VFA be 84.7 cm² in men and 81.1 cm² in women. Our results demonstrated that MetS was common in T2D patients. VFA was a strong risk factor for the development of the MetS among T2D patients. Therefore, T2D patients with a VFA over the optimal cut-off values should be closely monitored for the development of MetS, and further prospective studies are needed to validate the relationship between the suggested VFA cut points and MetS in people with T2D.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

The study was ethically approved by the Ethics Committee of Ningbo First Hospital, China (Ethics Approval No. 2019-R057) and followed the Declaration of Helsinki.

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Disclosure

The authors declared no conflicts of interest for this work.

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