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ORIGINAL RESEARCH

Association of Metabolic Score for Visceral Fat (METS-VF) with Gout Risk in Patients with Hypertension and Hyperuricemia: A Multicenter Study Based on the Chinese Population

Liwei Ji[1,*], Wencai Jiang[2,*], Jinglin Huang[3,*], Yan Xu[1,*], Li Zhou[1,*], Zeng Zhao[4], Chunling Jiang[1]

[1]Department of Anesthesiology, West China Hospital, Sichuan University & The Research Units of West China (2018RU012), Chinese Academy of Medical Sciences, Chengdu, People's Republic of China; [2]Department of Cardiology, Suining Central Hospital, Suining, People's Republic of China; [3]Department of Cardiology, People's Hospital of Leshan, Leshan, People's Republic of China; [4]Department of Cardiology, Jintang County First People's Hospital, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chunling Jiang, Department of Anesthesiology, West China Hospital, Sichuan University & The Research Units of West China (2018RU012), Chinese Academy of Medical Sciences, No. 37 Wainan Guoxue Road, Chengdu, 610400, People's Republic of China, Email jiangchunling@scu.edu.cn; Zeng Zhao, Department of Cardiology, Jintang County first People's Hospital, No. 37 Wainan Guoxue Road, No. 886 Jin Guang Road, Chengdu, 610400, People's Republic of China, Email 284439901@qq.com

Background: Gout, a rheumatic disease precipitated by hyperuricemia, has become a global health concern due to its increasing prevalence, especially in China. Hyperuricemia and hypertension are significant risk factors for gout, and their coexistence amplifies this risk. Visceral adipose tissue (VAT) plays a crucial role in cardiometabolic diseases, and the metabolic score for visceral fat (METS-VF) is a non-invasive tool for estimating VAT and predicting cardiometabolic risk.

Methods: We conducted a multicenter cross-sectional study involving 8877 patients with hypertension and hyperuricemia from three Chinese medical centers between March 2021 and September 2024. We calculated the METS-VF and other obesity indices and analyzed their associations with gout risk using logistic regression models. The predictive performance of these indices was evaluated using receiver operating characteristic (ROC) curve analysis and clinical decision curve analysis (DCA).

Results: The METS-VF demonstrated a significant positive association with gout risk, independent of traditional risk factors. Each 1-standard deviation increase in the METS-VF was associated with an 82% higher odds of gout (OR=1.82, 95% CI: 1.62 to 2.03). The METS-VF outperformed other obesity indices in predicting gout risk, with a higher area under the ROC curve (AUC) value. DCA indicated that the METS-VF provided a significant net benefit across a wide range of threshold probabilities for predicting gout risk in both genders.

Conclusion: The METS-VF's robust association with gout risk in our multicenter study, independent of conventional risk factors, positions it as a potent predictor for gout. Further investigation is warranted to clarify the underlying mechanisms and the long-term predictive validity of the METS-VF across diverse populations.

Keywords: metabolic score for visceral fat, hypertension, hyperuricemia, gout, multicenter cross-sectional study

Introduction

Gout, a rheumatic disease precipitated by purine metabolism disorders and characterized by hyperuricemia, has emerged as a global health concern due to its escalating prevalence, which places a substantial burden on healthcare systems.[1] The global burden of disease (GBD) study indicates an age-standardized prevalence of 7.9 per 10,000 in men and 2.5 per 10,000 in women worldwide.[2] This trend is particularly pronounced in China, where the epidemiological situation is notably severe. Between 1990 and 2019, China witnessed a significant increase in the age-standardized prevalence rate (ASPR) of gout, with 16.2 million cases reported in 2019 and an ASPR of 12.3 per 1000 for men and 3.9 per 1000 for

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women, surpassing both global estimates and those of other Asian countries such as Japan and South Korea.[3] Contributing factors to this surge include an aging population, increased life expectancy, and a high prevalence of obesity and comorbidities.[4]

Hyperuricemia, characterized by elevated serum urate levels, is the underlying cause of gout, increasing the risk of urate crystal deposition and inflammatory attacks.[5] In China, hyperuricemia affects approximately 15% of the population, a rate that exceeds the global average and parallels the rise in hypertension, which affects 31.6% of adults.[6] The relationship between hypertension and gout is complex and bidirectional, with hypertension contributing to the pathophysiology of gout and acting as an independent risk factor for its development.[7] When hypertension and hyperuricemia coexist, the risk of gout is significantly heightened.[8–10] The complexity of this relationship is further underscored by the fact that both conditions are integral components of the metabolic syndrome, a constellation of disorders that includes obesity, insulin resistance, and dyslipidemia.[11,12] Collectively, these conditions contribute to the development of gout and other cardiovascular diseases, underscoring the metabolic syndrome's growing recognition as a significant public health concern. This interplay highlights the critical need to explore risk factors in patients with these comorbidities, with the aim of devising targeted prevention and management strategies.

Visceral adipose tissue (VAT), which encircles the abdominal organs within the peritoneal cavity, is a pivotal factor in the development of cardiometabolic diseases.[13] Its distinct metabolic activity and inflammatory profile, compared to subcutaneous adipose tissue, make it a central player in the pathogenesis of type 2 diabetes mellitus (T2DM), hypertension, and hyperuricemia, which are key components of the cardiometabolic disease spectrum.[14] Given the established link between VAT and cardiometabolic diseases, there is an urgent need for precise and accessible methods to quantify VAT and predict associated health risks.[15] While dual-energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) are the gold standards for VAT quantification, their widespread use is limited by cost and accessibility.[16] Anthropometric measures like waist circumference (WC) and body mass index (BMI) are more accessible but lack the specificity to accurately assess VAT. The metabolic score for visceral fat (METS-VF) offers a non-invasive solution by integrating clinical parameters such as age, sex, waist-to-height ratio, fasting plasma glucose (FPG), and triglyceride levels to estimate VAT and predict cardiometabolic risk.[17] Validation studies have confirmed its robust predictive performance for cardiometabolic outcomes, surpassing other VAT indices like the visceral adiposity index (VAI), metabolic score for insulin resistance (METS-IR), cardiometabolic index (CMI), and body roundness index (BRI) in forecasting T2DM incidence.[18,19] Its validation across diverse populations, including Mexican and Indian cohorts, attests to its broad applicability and reliability across different ethnic groups.[17,20]

Recent research has linked the METS-VF to the risk of hyperuricemia, suggesting its potential as a predictor for metabolic disorders beyond the traditional cardiometabolic spectrum, such as gout.[21,22] However, the relationship between METS-VF and gout prevalence, particularly in patients with comorbid hypertension and hyperuricemia, remains underexplored. This study aims to investigate the correlation between METS-VF and gout prevalence using data from a multicenter cross-sectional study, with a specific focus on patients with hypertension and hyperuricemia. It will also evaluate the predictive abilities of METS-VF against other obesity indices, including METS-IR,[23] triglyceride-glucose (TyG),[24] TyG-WC,[25] CMI,[26] Chinese visceral adiposity index (CVAI),[27] and BRI,[28] to identify the most effective index for identifying individuals at risk for gout in this high-risk population.

Materials and Methods

Study Design, Participants, and Ethics

This cross-sectional study was conducted across three medical centers: Suining Central Hospital, Jintang County First People's Hospital, and People's Hospital of Leshan. The study population included patients diagnosed with hypertension and hyperuricemia. The enrollment period at Suining Central Hospital was from March 2021 to July 2024, while at Jintang County First People's Hospital and Leshan City People's Hospital, it extended from September 2021 to September 2024. The study initially enrolled 11,051 participants.

The exclusion criteria were meticulously applied to ensure a homogeneous study population. Participants were excluded if they: (1) were under the age of 18 at the time of enrollment (n=3); (2) had used uric acid-lowering

medications, such as benzbromarone, febuxostat, or allopurinol, within the last month prior to enrollment (n=412); (3) had a history of severe malnutrition, malignant neoplasms, autoimmune diseases, or severe hepatic or renal insufficiency (n=749); (4) were pregnant, likely to be pregnant, or breastfeeding (n=21); (5) lacked complete health status indicators (n=989). After applying these exclusion criteria, the final study population comprised 8877 participants (Figure 1).

The study protocol was approved by the Ethics Committee of Suining City Central Hospital (No. KYLLKS20210103), the Hospital Ethics Committee of the First People's Hospital of Jintang County (No. 20210627001), and the Ethics Committee of Leshan City People's Hospital (No. LSRYLL20210709-1). The study adhered to the ethical principles outlined in the Declaration of Helsinki, and all participants provided written informed consent.

Data Collection and Assessment Methods in the Study

In this cross-sectional study, a comprehensive dataset was assembled by extracting demographic and clinical data from the electronic medical records and health insurance databases of the participating hospitals. The data collected included detailed medical histories, lifestyle practices, medication regimens, and laboratory measurements for each participant.

The Supplementary Materials offer a detailed account of the definitions and procedural details for the measurement of various diseases under investigation. This includes the diagnosis of hypertension, hyperuricemia, diabetes mellitus, and hyperlipidemia based on specific thresholds and historical data. The detailed protocols for anthropometric measurements, such as body weight, height, waist circumference, and blood pressure, are also described.

Laboratory assessments were conducted to quantify a range of biochemical parameters, including creatinine (Cr), alanine aminotransferase (ALT), blood urea nitrogen (BUN), aspartate aminotransferase (AST), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and uric acid (UA) levels. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[29]

Calculation of Obesity-Related Metabolic Indices

In this study, we utilized a series of established formulas to calculate obesity metabolism indices. These indices included the METS-IR, METS-VF, TyG, TyG-WC, CMI, CVAI, and BRI. The formulas for these indices are as follows:

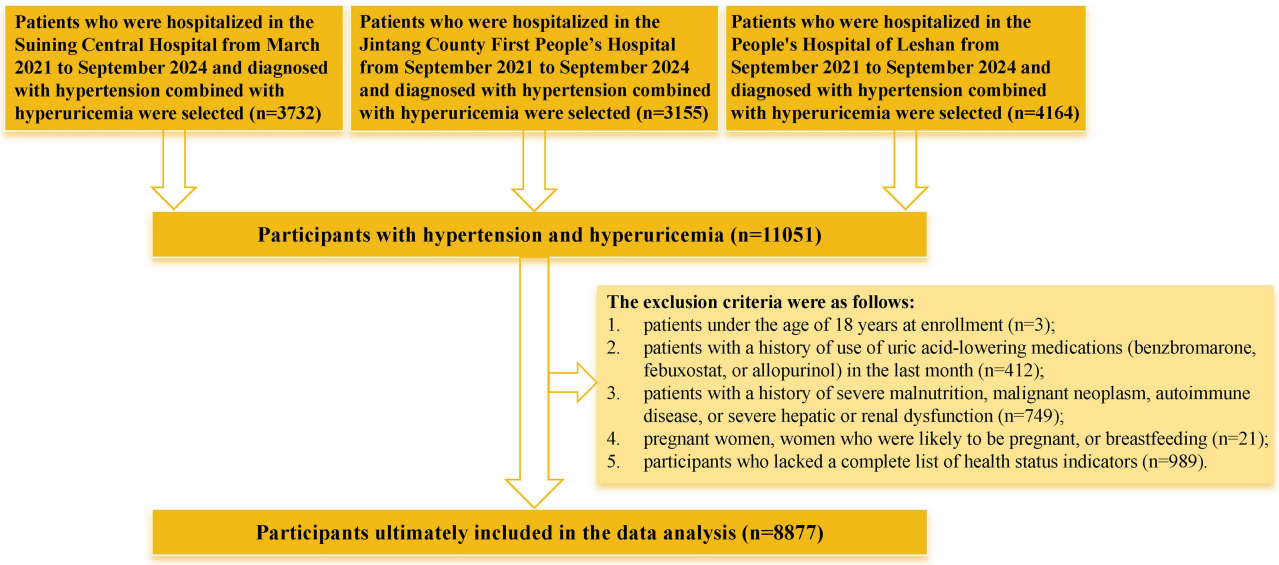

Figure 1 Flowchart of the study.

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$$METS-IR=\left(ln[2\times FPG(mg/dL)+TG(mg/dL)]\times BMI\left(kg/m^2\right)\right)/ln[HDL-C(mg/dL)]$$

$$METS-VF=4.466+0.011\times(ln\text{METS}-\text{IR})^3+3.239\times\left[ln(WC/height)^3+0.319(male\,sex)+0.594\times ln(age)\right]$$

$$TyG=\ ln[(TG\ (mg/dL)\ \times\ FPG\ (mg/dL)/2)]$$

$$TyG-WC\ =\ TyG\ \times\ WC\ (cm)$$

$$CMI\ =\ (TG\ (mmol/L)\ /\ HDL-C\ (mmol/L))\ \times\ (WC\ (cm)\ /\ height\ (cm))$$

$$CVAI(Males)=267.93+0.68\times age+0.03\times BMI\left(kg/m^2\right)+4.00\times WC(cm)+22.00\times log10TG(mmol/L)-16.32\times HDL-C(mmol/L)$$

$$CVAI(Females)=187.32+1.71\times age+4.23\times BMI\left(kg/m^2\right)+1.12\times WC(cm)+39.76\times log10TG(mmol/L)-11.66\times HDL-C(mmol/L)$$

$$BRI=364.2-365.5\times\left(1-\left[(WC(m)/(2\pi))^2/(0.5\times height(m))^2\right]\right)1/2$$

Gout Diagnosis Criteria

The diagnosis of gout in this study was based on the clinical classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[30] These criteria are widely recognized and serve to standardize the diagnostic process across the various centers participating in our multicenter investigation.

Statistical Analysis

To handle missing covariate data, we implemented multiple imputation with 20 iterations to form a complete dataset. Prior to regression analysis, we ascertained the absence of multicollinearity in our models by confirming that variance inflation factors for all predictor variables were below the threshold of 10 (Table S1). We employed both univariate and multivariate logistic regression analyses to ascertain the association between the METS-VF and the risk of gout.

A generalized additive model was utilized to explore the nonlinear dose-response relationship between the METS-VF and gout risk. Inflection points were identified using recursive partitioning, and segmented logistic regression models were developed with bootstrap resampling to estimate the precision of the turning points and reliably interpret the dose-response curve. To bolster the robustness of our findings, a series of sensitivity analyses were conducted. In stratified analyses, we systematically evaluated potential effect modifiers of the association between the METS-VF and gout risk. Likelihood ratio tests were used to statistically assess interactions between subgroups and METS-VF, thereby determining the variability of this association across different demographic and clinical subgroups defined by specified covariates.

Additionally, we assessed the diagnostic accuracy of various biomarkers for gout in both sexes using receiver operating characteristic (ROC) curve analysis. Area under the curve (AUC) values were determined to evaluate discrimination ability, and sensitivities, specificities, positive likelihood ratios (LR+), and negative likelihood ratios (LR-) were calculated to assess their predictive performance in gout diagnosis. To further substantiate the comparative performance, Delong's test was applied to ascertain the statistical significance of AUC differences. Clinical decision curve analysis (DCA) was employed to evaluate the net benefit of various biomarkers in predicting high-risk thresholds.

For detailed statistical methodologies, refer to the Supplementary Material. Analyses were executed in R (version 4.2.1) and SAS (version 9.4), with a significance level of $P < 0.05$ for two-tailed tests.

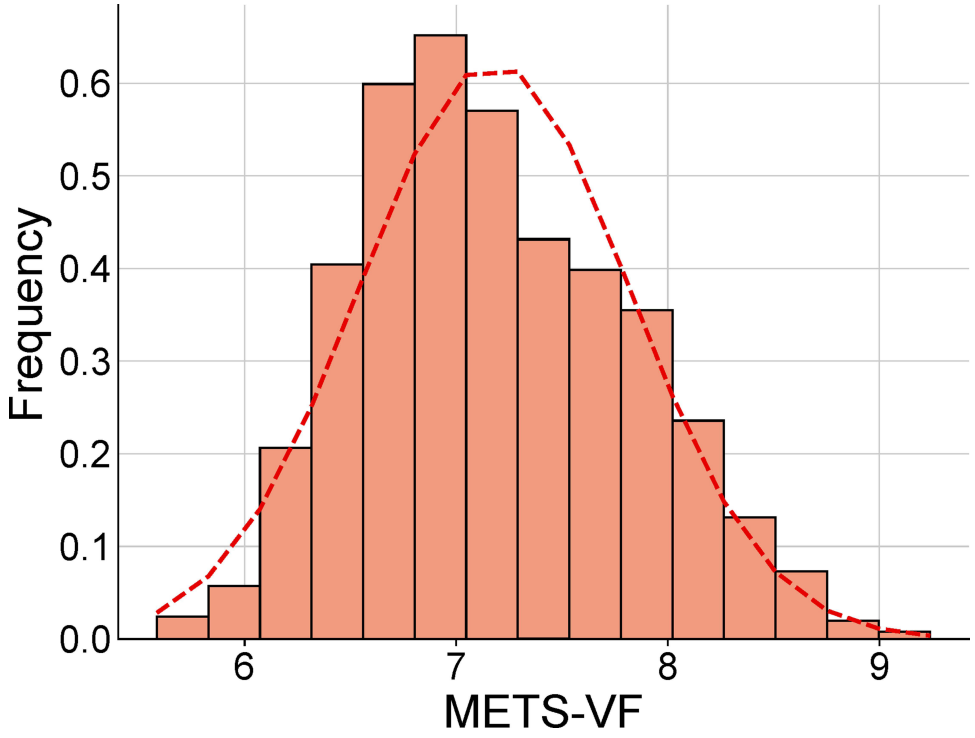

Figure 2 Frequency distribution of METS-VF.

Results

Participant Characteristics

A comparison of the characteristics of participants with and without imputation is displayed in Table S2. This table shows the distribution of key variables before and after imputation. Our analysis revealed that all variables showed no

Table 1 Characteristics by METS-VF Quartiles

Characteristics	Quartiles of METS-VF				P-value
	Quartile 1 (<6.71)	Quartile 2 (6.71–7.08)	Quartile 3 (7.09–7.67)	Quartile 4 (>7.67)	
Number	2217	2218	2220	2222	
Males, N(%)	1280 (57.74%)	1290 (58.16%)	1354 (60.99%)	1377 (61.97%)	0.007
Age, year	62.44 ± 10.13	60.62 ± 11.36	62.52 ± 11.18	60.58 ± 10.49	<0.001
Body mass index, kg/m^2	25.21 ± 2.55	27.01 ± 2.31	28.74 ± 2.27	31.26 ± 2.84	<0.001
Waist circumference, cm	87.19 ± 10.68	87.93 ± 10.72	88.47 ± 10.66	88.74 ± 10.89	<0.001
Current smokers, N (%)	671 (30.27%)	752 (33.90%)	768 (34.59%)	875 (39.38%)	<0.001
Current drinkers, N (%)	520 (23.46%)	638 (28.76%)	708 (31.89%)	787 (35.42%)	<0.001
Duration of hypertension, year	3.60 (2.10–5.60)	3.70 (2.10–5.80)	3.50 (2.10–5.60)	3.50 (2.00–5.70)	0.073
Duration of HUA, year	3.20 (1.70–5.30)	3.20 (1.70–5.50)	3.10 (1.60–5.40)	3.10 (1.70–5.20)	0.794
Systolic blood pressure, mmHg	145.53 ± 16.35	145.03 ± 17.89	146.14 ± 17.50	148.70 ± 17.14	<0.001

(*Continued*)

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Table 1 (Continued).

Characteristics	Quartiles of METS-VF				P-value
	Quartile 1 (<6.71)	Quartile 2 (6.71–7.08)	Quartile 3 (7.09–7.67)	Quartile 4 (>7.67)	
Diastolic blood pressure, mmHg	89.15 ± 13.40	90.58 ± 13.45	90.10 ± 14.24	92.85 ± 13.55	<0.001
Alanine transaminase, IU/L	23.00 (16.50–32.00)	27.00 (20.50–39.83)	31.00 (22.00–51.60)	32.00 (21.34–51.00)	<0.001
Aspartate transaminase, IU/L	19.20 (16.00–23.00)	20.41 (17.00–25.69)	21.80 (17.00–27.60)	21.97 (17.00–27.00)	<0.001
Serum creatinine, mmol/L	70.59 ± 13.35	71.66 ± 13.10	72.48 ± 12.14	72.66 ± 11.98	<0.001
Blood urea nitrogen, mmol/L	5.26 (4.38–6.11)	5.10 (4.27–6.11)	5.13 (4.31–6.10)	5.01 (4.29–6.06)	0.002
eGFR, mL/min per 1.73 m^2	95.46 ± 19.48	97.82 ± 21.85	96.25 ± 22.24	97.33 ± 20.43	<0.001
Total cholesterol, mmol/L	4.54 ± 0.86	4.57 ± 0.94	4.64 ± 0.92	4.98 ± 1.04	<0.001
Triglyceride, mmol/L	1.51 ± 0.68	1.93 ± 0.77	2.28 ± 0.91	2.78 ± 1.08	<0.001
HDL-C, mmol/L	1.13 ± 0.21	1.01 ± 0.21	0.95 ± 0.18	0.83 ± 0.15	<0.001
LDL-C, mmol/L	2.46 ± 0.86	2.53 ± 0.94	2.58 ± 0.90	2.60 ± 0.91	<0.001
Fasting plasma glucose, mmol/L	5.18 ± 1.14	5.29 ± 1.33	5.42 ± 1.20	5.63 ± 1.43	<0.001
HbA1c, %	6.35 ± 0.93	6.43 ± 1.03	7.00 ± 1.10	8.43 ± 1.65	<0.001
Serum uric acid, mmol/L	465.42 ± 50.44	463.81 ± 52.19	457.93 ± 50.11	461.74 ± 51.23	<0.001
Comorbidities, N (%)					
Diabetes	726 (32.75%)	792 (35.71%)	962 (43.33%)	995 (44.78%)	<0.001
Dyslipidemia	684 (30.85%)	720 (32.46%)	876 (39.46%)	1118 (50.32%)	<0.001
Medication use, N (%)					
Lipoprotein-lowering drugs	1036 (46.73%)	1186 (53.47%)	1168 (52.61%)	1134 (51.04%)	<0.001
Antiplatelet drugs	1260 (56.83%)	1354 (61.05%)	1276 (57.48%)	1260 (56.71%)	0.009
ACEIs/ARBs	1447 (65.27%)	1514 (68.26%)	1564 (70.45%)	1550 (69.76%)	<0.001
Beta-blockers	848 (38.25%)	932 (42.02%)	888 (40.00%)	1082 (48.69%)	<0.001
Calcium channel blocker	1640 (73.97%)	1586 (71.51%)	1612 (72.61%)	1478 (66.52%)	<0.001
Diuretics	367 (16.55%)	488 (22.00%)	563 (25.36%)	608 (27.36%)	<0.001
Hypoglycemic drugs	492 (22.19%)	604 (27.23%)	460 (20.72%)	448 (20.16%)	<0.001

Notes: Values are mean±SD, median [IQR] for skewed variables, or n (%) for categorical variables.
Abbreviations: METS-VF, metabolic score for visceral fat; HUA, hyperuricemia; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ARBs, angiotensin receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors.

significant difference before and after imputation, indicating that the imputation process did not introduce any systematic bias into the dataset.

The distribution of participants across varying METS-VF values is depicted in Figure 2. Table 1 presents a detailed stratification of the study population's clinical and demographic characteristics based on quartiles of the METS-VF, which were categorized as Quartile 1 (<6.71), Quartile 2 (6.71–7.08), Quartile 3 (7.09–7.67), and Quartile 4 (>7.67). Individuals in Quartile 4 demonstrated a relatively higher prevalence of male gender, elevated BMI, and augmented WC, along with higher frequencies of current smoking and alcohol consumption, compared to those in Quartile 1. Furthermore, a gradual increase in serum levels of ALT and AST, Cr, and TC was observed from Quartile 1 to

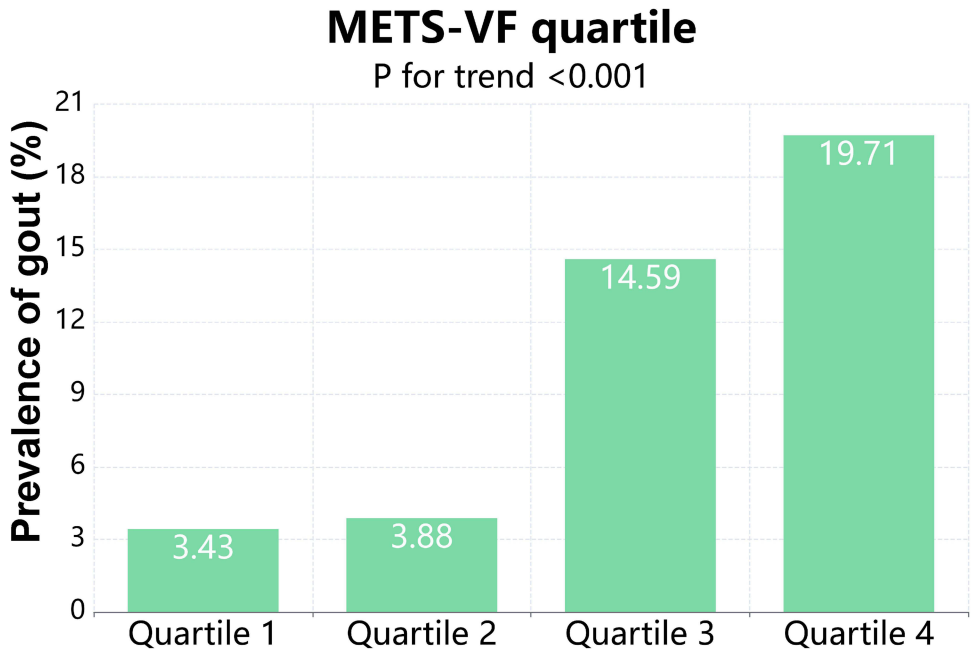

Figure 3 Association of METS-VF quartiles with gout prevalence.

Quartile 4. In contrast, HDL-C levels were observed to decrease across the quartiles. The prevalence of comorbidities, including diabetes and dyslipidemia, rose significantly with ascending METS-VF quartiles ($P < 0.01$). Concordantly, the prevalence of gout was substantially lower among participants with lower METS-VF values compared to those with higher METS-VF values, as illustrated in Figure 3.

Relationship Between METS-VF and Gout Risk

In our multivariable regression analysis, as detailed in Table 2, we observed a significant positive association between the METS-VF and the risk of gout. This association remained robust after adjusting for multiple potential confounding

Table 2 The Association Between METS-VF and Risk of Gout in Different Models

Exposure	Model 1	Model 2	Model 3	Model 4
	OR (95% CI), P value	OR (95% CI), P value	OR (95% CI), P value	OR (95% CI), P value
METS-VF (per 1-SD increment)	2.11 (1.97, 2.26) <0.001	2.03 (1.89, 2.18) <0.001	1.86 (1.67, 2.07) <0.001	1.82 (1.62, 2.03) <0.001
METS-VF quartile				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.14 (0.83, 1.56) 0.425	1.12 (0.82, 1.54) 0.475	0.91 (0.65, 1.26) 0.560	0.88 (0.62, 1.24) 0.454
Quartile 3	4.81 (3.72, 6.23) <0.001	4.70 (3.62, 6.09) <0.001	3.54 (2.64, 4.73) <0.001	3.59 (2.66, 4.83) <0.001
Quartile 4	6.92 (5.38, 8.89) <0.001	6.59 (5.11, 8.51) <0.001	4.80 (3.41, 6.75) <0.001	4.60 (3.23, 6.55) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, drinking and smoking status were adjusted. Model 3: Model 2 plus adjustment for duration of hypertension, duration of HUA, diabetes, dyslipidemia, alanine transaminase, aspartate transaminase, serum creatinine, blood urea nitrogen, eGFR, total cholesterol, triglyceride, HDL-C, LDL-C, fasting plasma glucose, HbA1c, and serum uric acid. Model 4: Model 3 plus adjustment for use of lipoprotein-lowering drugs, antiplatelet drugs, ACEIs/ARBs, beta-blockers, calcium channel blockers, diuretics, and hypoglycemic drugs.

Abbreviations: OR, odds ratio; CI, confidence interval; METS-VF, metabolic score for visceral fat; HUA, hyperuricemia; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ARBs, angiotensin receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors.

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variables in the fully adjusted Model 4, where, each 1-standard deviation increase in the METS-VF was associated with an 82% higher odds of developing gout (odds ratio [OR] = 1.82, 95% confidence interval [CI]: 1.62 to 2.03).

In an effort to dissect this relationship with greater precision, we categorized the METS-VF into quartiles. Within the framework of Model 4, which incorporated comprehensive adjustments for confounding factors, Quartile 2, when compared to the reference Quartile 1, did not demonstrate a statistically significant elevation in gout risk (OR = 0.88, 95% CI: 0.62, 1.24). In contrast, a pronounced and significant escalation in gout risk was observed for Quartiles 3 and 4 relative to Quartile 1, with odds ratios of 3.59 (95% CI: 2.66, 4.83) and 4.60 (95% CI: 3.23, 6.55), respectively. These findings underscore the gradient relationship between higher METS-VF quartiles and an elevated risk of gout.

Dose-Response and Threshold Effect Analysis

In our analysis to delineate the nonlinear relationship and threshold effects between the METS-VF and the risk of gout, we employed a smooth curve fitting technique, as illustrated in Figure 4. This methodological approach uncovered a significant dose-response association between METS-VF and gout risk.

The two-piecewise logistic regression model, presented in Table 3, identified an inflection point in the METS-VF at 7.42 in the fully adjusted Model 4. For METS-VF values exceeding this threshold, the OR for gout was not statistically significant, with an OR of 1.10 (95% CI: 0.93 to 1.30). Conversely, for METS-VF values below the threshold of 7.42, there was a pronounced and statistically significant increase in the odds of gout, with an OR of 3.91 (95% CI: 3.09 to 4.94) per 1-standard deviation increment.

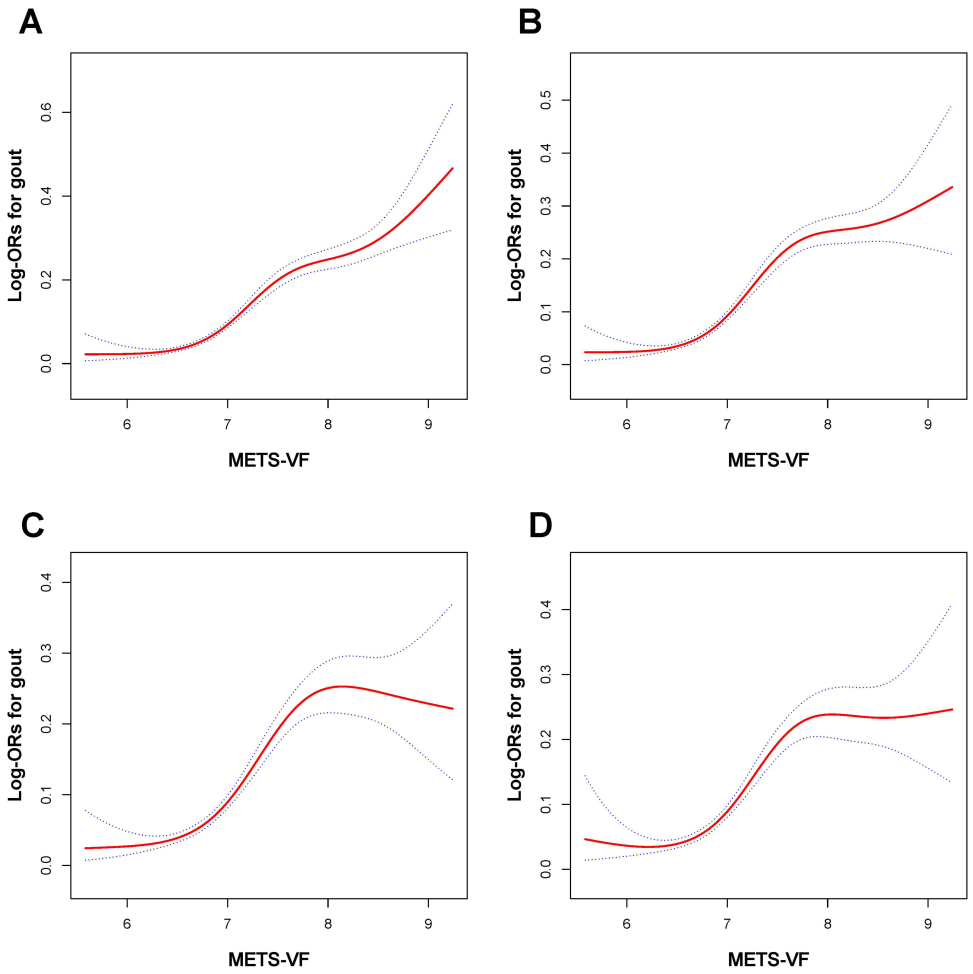

Figure 4 Dose-response relationship between METS-VF and the risk of gout. (**A**) Presents the crude results from the unadjusted model. (**B**–**D**) Illustrate the findings from the multivariable-adjusted models, which account for potential confounders.

Table 3 Results of Two-Piecewise Logistic Regression Model

Exposure: METS-VF (per 1-SD Increment)	Model 1	Model 2	Model 3	Model 4
	OR (95% CI), P value	OR (95% CI), P value	OR (95% CI), P value	OR (95% CI), P value
Inflection point of METS-VF				
≤ 7.42 (slope A)	4.30 (3.53, 5.24) <0.001	4.43 (3.62, 5.41) <0.001	4.02 (3.21, 5.04) <0.001	3.91 (3.09, 4.94) <0.001
> 7.42 (slope B)	1.30 (1.13, 1.49) <0.001	1.18 (1.03, 1.36) 0.019	1.12 (0.95, 1.32) 0.180	1.10 (0.93, 1.30) 0.283
Slope B to slope A	0.30 (0.23, 0.41) <0.001	0.27 (0.20, 0.36) <0.001	0.28 (0.20, 0.38) <0.001	0.28 (0.20, 0.39) <0.001
P for log likelihood ratio test	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, drinking and smoking status were adjusted. Model 3: Model 2 plus adjustment for duration of hypertension, duration of HUA, diabetes, dyslipidemia, alanine transaminase, aspartate transaminase, serum creatinine, blood urea nitrogen, eGFR, total cholesterol, triglyceride, HDL-C, LDL-C, fasting plasma glucose, HbA1c, and serum uric acid. Model 4: Model 3 plus adjustment for use of lipoprotein-lowering drugs, antiplatelet drugs, ACEIs/ARBs, beta-blockers, calcium channel blockers, diuretics, and hypoglycemic drugs.
Abbreviations: OR, odds ratio; CI, confidence interval; METS-VF, metabolic score for visceral fat; HUA, hyperuricemia; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ARBs, angiotensin receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors.

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the association between the METS-VF and gout risk, accounting for potential biases and confounding factors. In the first sensitivity analysis, we excluded participants with missing covariate data, as presented in Table S3. The adjusted ORs for gout risk associated with per 1-SD increment in METS-VF remained significant across all models, ranging from 1.87 to 2.09, indicating that our findings are not attributable to missing data.

To address the influence of outliers, we conducted a second sensitivity analysis after excluding participants whose METS-VF values were more than three standard deviations from the mean, as detailed in Table S4. The significant association between METS-VF and gout risk was maintained, with ORs varying from 1.84 to 2.08, suggesting that extreme values do not significantly impact our results.

In a third sensitivity analysis, we excluded individuals with a BMI greater than 30 kg/m² to isolate the effect of METS-VF independent of severe obesity, as shown in Table S5. The ORs for gout risk associated with METS-VF remained significant, confirming the robustness of our findings against the confounding effect of excessive adiposity.

Considering the potential impact of diabetes medication on gout risk, we performed a sensitivity analysis excluding participants on such medications, as depicted in Table S6. The significant association between METS-VF and gout risk was unchanged, with ORs ranging from 1.80 to 2.11, highlighting the independence of our findings from diabetes treatment effects. Similarly, to control for the confounding effect of diuretic therapy on uric acid metabolism, we conducted an analysis excluding participants on diuretics, as presented in Table S7. The significant relationship between METS-VF and gout risk persisted, with ORs varying from 1.90 to 2.15.

Finally, to evaluate the robustness of our primary outcome to unmeasured confounders, we calculated E-values for the association between METS-VF and gout risk, as shown in Table S8. The E-values, which represent the strength of association that would be required for an unmeasured confounder to fully explain away the observed association, were substantial, further validating the robustness of our findings.

Overall, these sensitivity analyses substantiate the reliability and generalizability of our results, demonstrating that the significant association between the METS-VF and gout risk is not significantly influenced by missing data, outliers, severe obesity, diabetes medication, or diuretic use.

Subgroup Analysis

We further examined the robustness of the association between METS-VF and the risk of gout across various demographic and clinical settings, employing Model 4, which incorporated all relevant covariates as adjusted in our previous models, with the exception of those used to establish the subgroups. The stability of the relationship between METS-VF

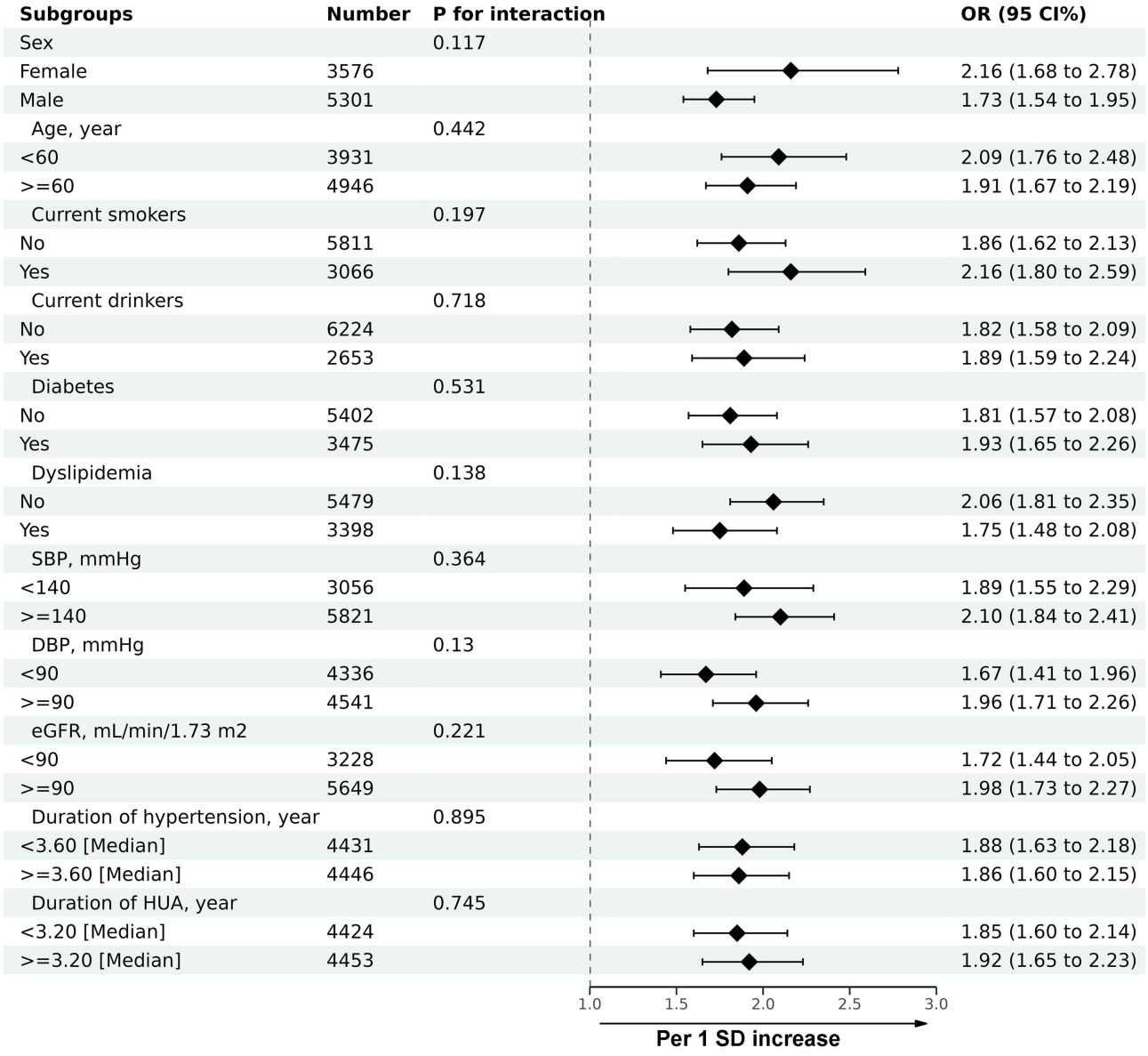

Figure 5 Stratification analysis of METS-VF levels (per SD) and the risk of gout.

and gout risk was assessed in the defined strata. As shown in Figure 5, the association was found to be consistent across all subgroups, with no significant interactions observed, and all P-values for interaction were greater than 0.05. This indicates that the effect of METS-VF on gout risk is not significantly modified by the considered demographic and clinical factors, suggesting that the relationship between METS-VF and gout risk is robust and generalizes across different population subgroups.

Predictive Performance and Clinical Utility of the METS-VF for Gout

The predictive performance of the METS-VF and several other obesity-related metabolic indices for gout risk was assessed using the AUC, along with their corresponding 95% CIs. These values are presented in Table 4 and Figure 6 for the total population and stratified by gender.

In the total population, the METS-VF, along with the METS-IR, TyG-WC, TyG, CMI, CVAI, WC, BMI, and BRI, demonstrated significant predictive accuracy for identifying individuals at risk for gout. The METS-VF notably exhibited

Table 4 Comparative Diagnostic Performance of Multiple Biomarkers in Gout Identification

Test	AUC	95% CI Low	95% CI Upp	Specificity	Sensitivity	Positive-LR	Negative-LR	Delong's Test
Overall								
METS-VF	0.720	0.703	0.736	0.633	0.771	2.099	0.363	Reference
METS-IR	0.668	0.649	0.688	0.545	0.734	1.611	0.489	<0.001
TyG-WC	0.652	0.634	0.670	0.607	0.643	1.637	0.588	<0.001
CVAI	0.640	0.622	0.658	0.626	0.613	1.637	0.619	<0.001
TyG	0.623	0.603	0.643	0.709	0.509	1.747	0.693	<0.001
BRI	0.595	0.576	0.614	0.628	0.530	1.426	0.748	<0.001
CMI	0.574	0.555	0.594	0.635	0.509	1.393	0.774	<0.001
WC	0.536	0.517	0.556	0.665	0.448	1.337	0.830	<0.001
BMI	0.531	0.511	0.551	0.626	0.476	1.272	0.837	<0.001
Male								
METS-VF	0.774	0.753	0.795	0.609	0.905	2.317	0.155	Reference
METS-IR	0.741	0.715	0.766	0.569	0.899	2.086	0.177	<0.001
CVAI	0.714	0.689	0.739	0.698	0.686	2.275	0.449	<0.001
TyG-WC	0.686	0.657	0.715	0.442	0.840	1.505	0.362	<0.001
TyG	0.655	0.624	0.686	0.785	0.497	2.313	0.641	<0.001
BRI	0.646	0.616	0.675	0.515	0.757	1.562	0.471	<0.001
CMI	0.635	0.606	0.664	0.673	0.598	1.825	0.598	<0.001
WC	0.616	0.583	0.649	0.717	0.491	1.734	0.710	<0.001
BMI	0.595	0.565	0.626	0.554	0.645	1.446	0.641	<0.001
Female								
METS-VF	0.690	0.668	0.713	0.606	0.758	1.924	0.400	Reference
TyG-WC	0.634	0.612	0.657	0.600	0.649	1.620	0.586	<0.001
METS-IR	0.631	0.605	0.658	0.747	0.505	1.994	0.663	<0.001
TyG	0.610	0.584	0.636	0.831	0.375	2.218	0.752	<0.001
CVAI	0.597	0.573	0.621	0.584	0.597	1.437	0.689	<0.001
WC	0.581	0.559	0.604	0.491	0.707	1.387	0.598	<0.001
BRI	0.567	0.542	0.591	0.704	0.427	1.443	0.814	<0.001
CMI	0.540	0.514	0.565	0.803	0.294	1.489	0.880	<0.001
BMI	0.496	0.470	0.522	0.707	0.370	1.265	0.890	<0.001

Abbreviations: AUC, area under the curve; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; TyG, triglyceride glucose; BMI, body mass index; WC, waist circumference; CMI, cardiometabolic index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; CI, confidence interval; LR, likelihood ratio.

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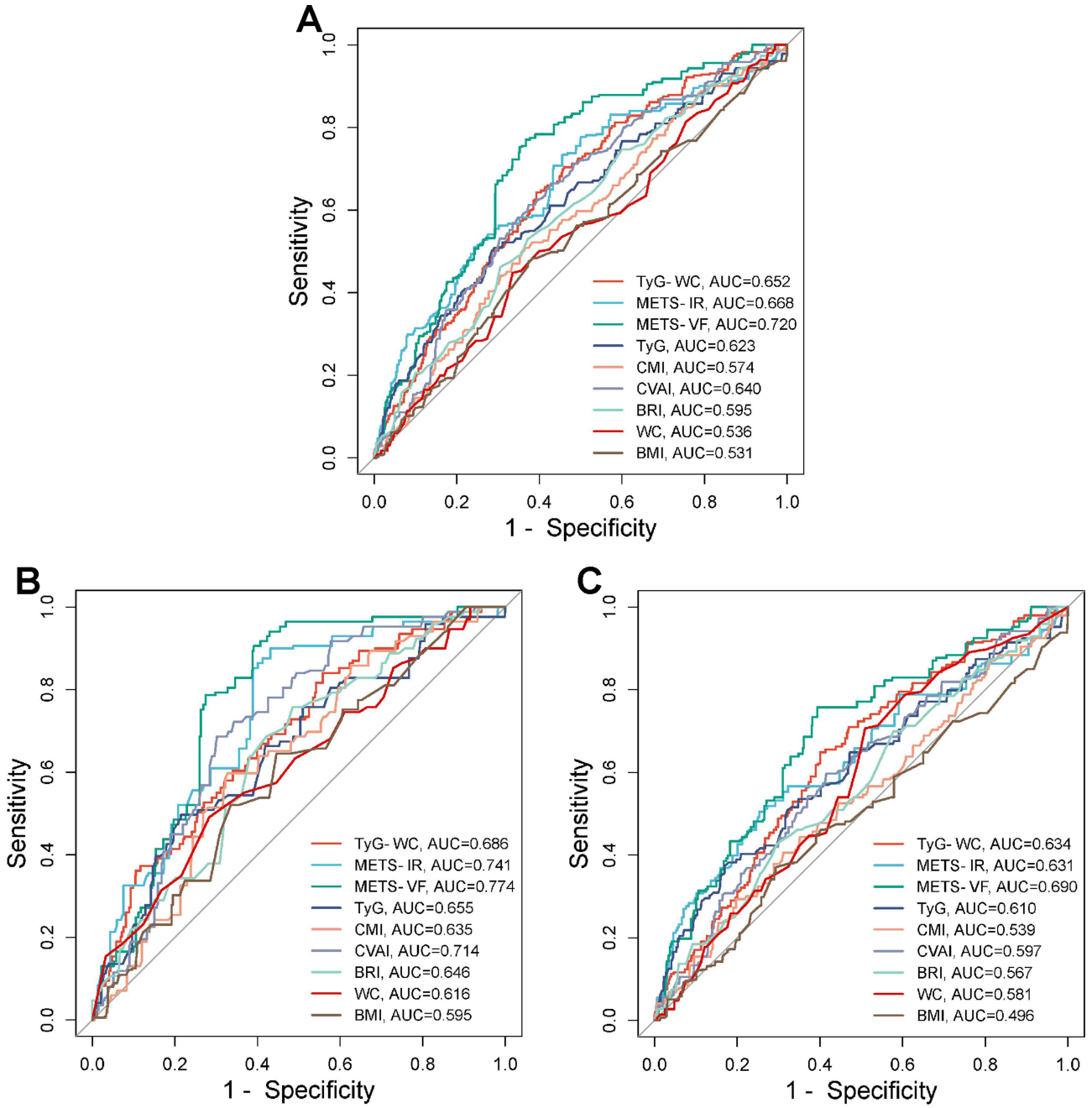

Figure 6 Receiver operating characteristic (ROC) curves for gout diagnosis using multiple biomarkers in the total population and stratified by gender. (**A**) ROC curves for the total population. (**B**) ROC curves for the male subset. (**C**) ROC curves for the female subset.

a higher AUC value compared to TyG, CMI, CVAI, WC, BMI, and BRI, with AUC values that were similar to those of METS-IR and TyG-WC (Figure 6A).

Gender-specific analysis revealed that the METS-VF, METS-IR, TyG-WC, and CMI were effective in predicting gout risk among males, with the METS-VF showing a higher AUC than METS-IR, TyG-WC, and CMI (Figure 6B). Among females, the METS-VF had a higher AUC value than TyG, CMI, CVAI, WC, BMI, and BRI, and comparable AUC values to METS-IR and TyG-WC (Figure 6C).

The predictive performance of these indices was further evaluated by calculating their sensitivities, specificities, LR+, and LR-. The METS-VF's higher AUC value, coupled with its relatively high sensitivity and specificity, positions it as a robust biomarker for gout risk prediction across different genders. To further substantiate the comparative performance,

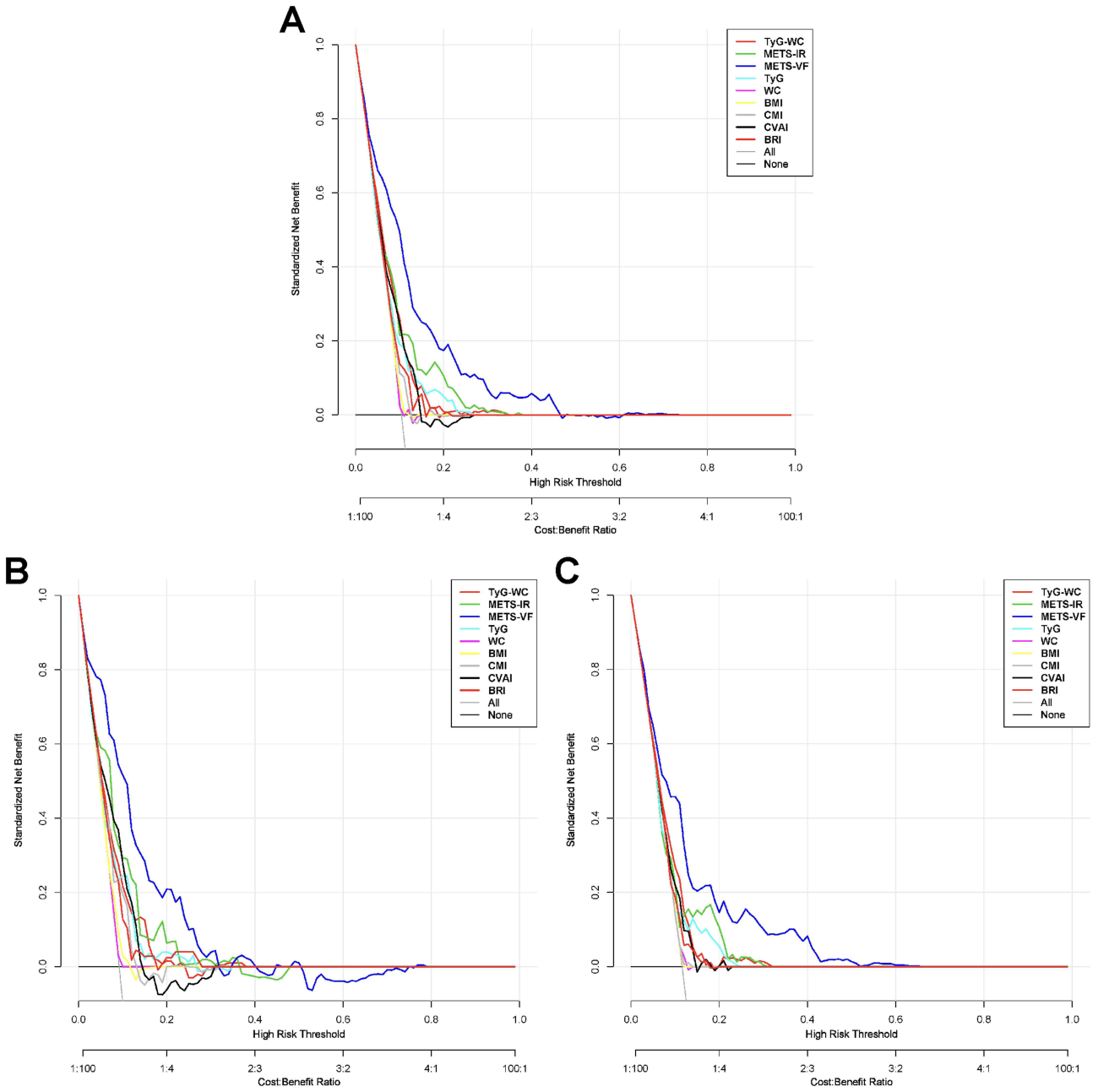

Figure 7 Decision curve analysis (DCA) for gout diagnosis using multiple biomarkers in total population and by gender. (**A**) ROC curves for the total population. (**B**) ROC curves for the male subset. (**C**) ROC curves for the female subset.

Delong's test was applied to ascertain the statistical significance of AUC differences. The test results, as presented in Table 4, indicate that the differences in AUC between METS-VF and other indices, including METS-IR, TyG-WC, TyG, CVAI, CMI, WC, BMI, and BRI, are statistically significant ($P < 0.05$). This suggests that METS-VF has a superior discriminative ability for predicting gout risk compared to these other indices.

These results suggest that the METS-VF performs robustly in predicting gout risk across different genders, outperforming some indices. The consistent performance of the METS-VF in both men and women underscores its potential utility as a reliable predictor of gout risk.

Additionally, this study employed DCA to evaluate the clinical usefulness of various obesity-related metabolic indices by quantifying the probability of net benefit across thresholds ranging from 0.0 to 1.0. Figure 7 presents the DCA outcomes, which are crucial for determining the practical utility of these indices. Panel A illustrates that the METS-VF

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provides a greater net benefit than other indices for the total population, indicating its effectiveness in gout risk prediction. Panel B confirms the METS-VF's superior net benefit in males, while Panel C demonstrates a similar advantage in females. These findings suggest that the METS-VF provides a significant net benefit across a wide range of threshold probabilities for predicting gout risk in both genders, highlighting its potential clinical utility in gout diagnosis and risk stratification.

In summary, the findings above indicate that the combined predictive value of the METS-VF for gout risk is superior to other indices, underscoring its potential as a valuable tool in the clinical assessment of gout risk.

Discussion

In this multicenter cross-sectional analysis, we assessed the relationship between the METS-VF and the risk of gout in patients with hypertension and hyperuricemia. The study, which included 8877 participants, demonstrated a positive correlation between increasing quartiles of METS-VF and the prevalence of gout. After adjusting for potential confounders, METS-VF remained significantly associated with gout risk, indicating its role as an independent predictor. The dose-response relationship between METS-VF and gout risk highlights the potential influence of visceral adiposity in the development of gout. The data suggest that higher METS-VF quartiles are associated with an increased odds ratio for gout, which may reflect the contribution of visceral fat metabolism to hyperuricemia. The nonlinear relationship, as identified through generalized additive modeling, indicates that the association between METS-VF and gout risk may be more complex than a linear progression. Subgroup analyses showed that the association between METS-VF and gout risk was consistent across various demographic and clinical subgroups, suggesting that the predictive value of METS-VF is not significantly modified by factors such as age, sex, or comorbidities. This finding is noteworthy given the known metabolic diversity associated with visceral adiposity. Furthermore, our study compared the predictive performance of METS-VF with other obesity indices, including METS-IR, TyG, and CMI. The METS-VF demonstrated a higher AUC and comparable sensitivity and specificity, suggesting its utility in gout risk stratification.

The complex interaction between VAT and the metabolic abnormalities associated with hyperuricemia and gout has attracted considerable research interest. VAT, characterized by its high metabolic activity, is now recognized for its multifaceted role beyond mere energy storage.[31] It functions as an endocrine organ, secreting a multitude of adipokines and cytokines.[32] These bioactive substances are capable of modulating systemic inflammation and insulin resistance, which are pivotal in the pathophysiology of hyperuricemia and gout.[33] The increased release of free fatty acids from VAT can result in ectopic fat deposition within the kidneys, thereby impairing the excretion of urate and contributing to hyperuricemia.[34] Additionally, VAT-derived inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), can influence urate metabolism directly, exacerbating hyperuricemia and elevating the risk of gout.[35] Consequently, the clinical assessment of VAT assumes significant relevance in the context of hyperuricemia and gout.

The bidirectional relationship between chronic kidney disease (CKD) and gout is well-documented.[36] CKD can contribute to the development of gout by impairing renal urate excretion, leading to increased serum urate levels. Conversely, gout can exacerbate CKD through chronic inflammation and the deposition of monosodium urate crystals in the kidneys. Recent studies have shown that the presence of gout is associated with a faster decline in kidney function and a higher risk of end-stage renal disease.[37] Furthermore, the interplay between CKD and metabolic syndrome is also significant. Metabolic syndrome is a known risk factor for the development of CKD, and the presence of CKD can further exacerbate the metabolic abnormalities associated with metabolic syndrome, creating a vicious cycle.[38]

The traditional metrics for obesity, including BMI and WC, are valuable for population-level assessments but exhibit limitations in discerning the distribution of adipose tissue.[39] BMI, for instance, does not distinguish between fat mass and lean body mass, nor does it account for the differential distribution of fat within visceral and subcutaneous compartments.[40] Similarly, WC, despite its capacity to approximate abdominal obesity, lacks the specificity to differentiate between VAT and subcutaneous adipose tissue (SAT).[41] This distinction is particularly significant in the context of metabolic diseases, where VAT is increasingly recognized for its atherogenic and diabetogenic properties.[42–44] In this regard, the METS-VF represents a substantial advancement over these traditional measures.[45] The METS-VF is a composite metric that integrates anthropometric measures with clinical parameters, as well as the METS-IR score, alongside demographic factors including age and sex.[46–48] This comprehensive approach enables a more refined

estimation of VAT, which is more closely correlated with adverse metabolic outcomes than total body fat or abdominal girth alone.[20] The METS-VF's superiority is further highlighted by its capacity to capture the metabolic dysfunction associated with VAT. Unlike WC and BMI, which provide only indirect and partial estimates of VAT, the METS-VF has been validated against more objective modalities such as DXA and MRI, demonstrating a stronger correlation with actual VAT content. This rigorous validation process has established the METS-VF as a reliable and precise instrument for assessing VAT across diverse populations, including those with varying ethnic backgrounds. Furthermore, the METS-VF's predictive capabilities extend to a spectrum of metabolic diseases. It has been shown to be a more robust predictor of T2DM, carotid atherosclerosis, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and chronic kidney disease compared to traditional indices.[19,49–52] This enhanced predictive power is attributed to the METS-VF's comprehensive reflection of the metabolic burden imposed by VAT, which encompasses both the quantity and quality of adipose tissue.

While the precise mechanisms by which VAT contributes to gout remain to be fully delineated, several plausible biological pathways have been posited. Firstly, VAT functions as an active endocrine organ, secreting a spectrum of adipokines and pro-inflammatory cytokines, including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1).[53,54] These inflammatory mediators can precipitate a state of chronic, low-grade inflammation, potentially facilitating the deposition of monosodium urate crystals in the joints, a defining feature of gout.[55] Secondly, VAT is intricately linked to the pathogenesis of insulin resistance, a condition marked by a diminished capacity of insulin to stimulate glucose uptake in peripheral tissues.[56,57] This resistance can augment renal urate reabsorption, thereby curtailing urate excretion and precipitating hyperuricemia, a precursor to gout.[58] Thirdly, VAT is known to modulate lipid metabolism, often leading to elevated levels of circulating free fatty acids (FFAs).[59,60] Elevated FFA levels can impair renal blood flow and function, thereby reducing urate excretion. Additionally, FFAs can directly stimulate hepatic de novo purine synthesis, augmenting urate production and exacerbating hyperuricemia.[34,61] Fourthly, the chronic inflammatory milieu induced by VAT can foster the formation of urate crystals in joints and surrounding tissues.[54,62,63] VAT-derived cytokines can activate immune cells, such as macrophages, which play a central role in initiating the inflammatory cascade characteristic of gout.[64,65] Fifthly, VAT has been implicated in the development of endothelial dysfunction, which can lead to diminished nitric oxide bioavailability and increased vascular resistance.[13,66] This can result in reduced renal perfusion and impaired urate excretion, contributing to hyperuricemia.[67,68] Furthermore, endothelial dysfunction can promote a pro-inflammatory and pro-thrombotic state, potentially exacerbating gout by impeding the resolution of inflammatory responses in the joints.[33,69]

The current study, designed to investigate the correlation between the METS-VF and the risk of gout in patients with comorbid hypertension and hyperuricemia, boasts several methodological strengths. Firstly, the large cohort of 8877 participants recruited from multiple medical centers enhances the external validity of our findings and allows for a robust analysis of the relationship under scrutiny. The multicenter design ensures a broader representation of the patient population, which is critical for capturing the diversity inherent in a multiethnic and geographically dispersed demographic. A further strength lies in the rigorous application of exclusion criteria, which has resulted in a homogeneous study population. This approach minimizes the confounding effects that could arise from the presence of diverse comorbidities and ensures that the observed associations are less likely to be attributable to factors other than those under investigation. The comprehensive data collection, encompassing demographic details, medical histories, lifestyle practices, and laboratory measurements, provides a rich dataset that allows for a thorough adjustment for potential confounders. The utilization of advanced statistical methodologies, including multiple imputation for handling missing data and generalized additive models to explore nonlinear relationships, adds a layer of sophistication to our analysis. These methods are particularly adept at capturing complex relationships that may not be evident using more traditional linear models. The employment of ROC curve analysis and DCA further solidifies our findings by providing a quantitative assessment of the predictive performance and clinical utility of the METS-VF in comparison to other obesity indices.

In this study, we acknowledge several limitations that are crucial for a balanced interpretation of our findings. The cross-sectional design of our research is a primary limitation, as it precludes the establishment of causal relationships. We are limited to reporting associations at a single point in time, which does not allow us to determine the temporal sequence

of events. Therefore, we cannot definitively establish whether changes in METS-VF precede the development of gout or occur as a consequence of the disease. The generalizability of our results is limited by the homogeneity of our study population, which is exclusively composed of adults of Chinese descent. This demographic constraint may restrict the applicability of our findings to other ethnic groups with different genetic backgrounds and risk factor profiles for gout. Additionally, our reliance on self-reported data for certain variables, such as lifestyle factors, introduces the potential for information bias. This bias may stem from social desirability or recall inaccuracies, which could affect the precision of our estimates. Despite our efforts to control for a range of potential confounders, we acknowledge the possibility of residual confounding due to unmeasured variables. Genetic predispositions, alcohol intake, levels of physical activity, and dietary habits are known to influence both METS-VF and gout risk, and their absence in our analysis could introduce bias. Furthermore, our study did not include direct measures of visceral fat, such as those obtained through imaging techniques like CT or MRI. The METS-VF, while a convenient proxy, may not fully capture the subtle variations in fat distribution that could be critical for understanding gout pathogenesis. The indirect assessment of visceral fat in our study could introduce variability and reduce the precision of our estimates. A significant limitation is the potential for selection bias in our cohort. Participants were recruited from specific medical centers, which may not be representative of the broader population of patients with hypertension and hyperuricemia. This selection bias could affect the generalizability of our findings to all individuals with these conditions, particularly those who do not seek or have access to medical care within these centers. The exclusion criteria, while necessary to ensure a homogeneous study population, may have resulted in the exclusion of patients with significant comorbidities that could influence both METS-VF and gout risk. This exclusion may have led to an underestimation of the true burden of gout risk associated with METS-VF in a more diverse and clinically complex patient population.

Future research endeavors should aim to address these limitations by employing longitudinal study designs, incorporating diverse and representative cohorts, utilizing direct measures of visceral fat, and accounting for a comprehensive range of potential confounders, including genetic factors, physical activity levels, and lifestyle behaviors.

Conclusion

This multicenter cross-sectional study demonstrates a robust association between the METS-VF and gout risk in patients with hypertension and hyperuricemia. The METS-VF, an easily calculable index integrating clinical parameters, emerged as a significant predictor of gout, independent of traditional risk factors. Its superior predictive performance over other obesity indices highlights its potential utility in clinical practice for gout risk stratification. These findings underscore the importance of assessing visceral adiposity in the management of patients with metabolic disorders. Further research is warranted to explore the mechanistic links and long-term predictive validity of METS-VF in diverse populations.

Informed Consent Statement

Written informed consent was obtained from all participants before commencement of the study.

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Disclosure

The authors declare no conflicts of interest associated with the study.

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