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The role of metabolic syndrome and disorders in cardiovascular disease

Edited by
Albino Carrizzo, Paola Di Pietro, Jessica Gambardella and Carmine Izzo

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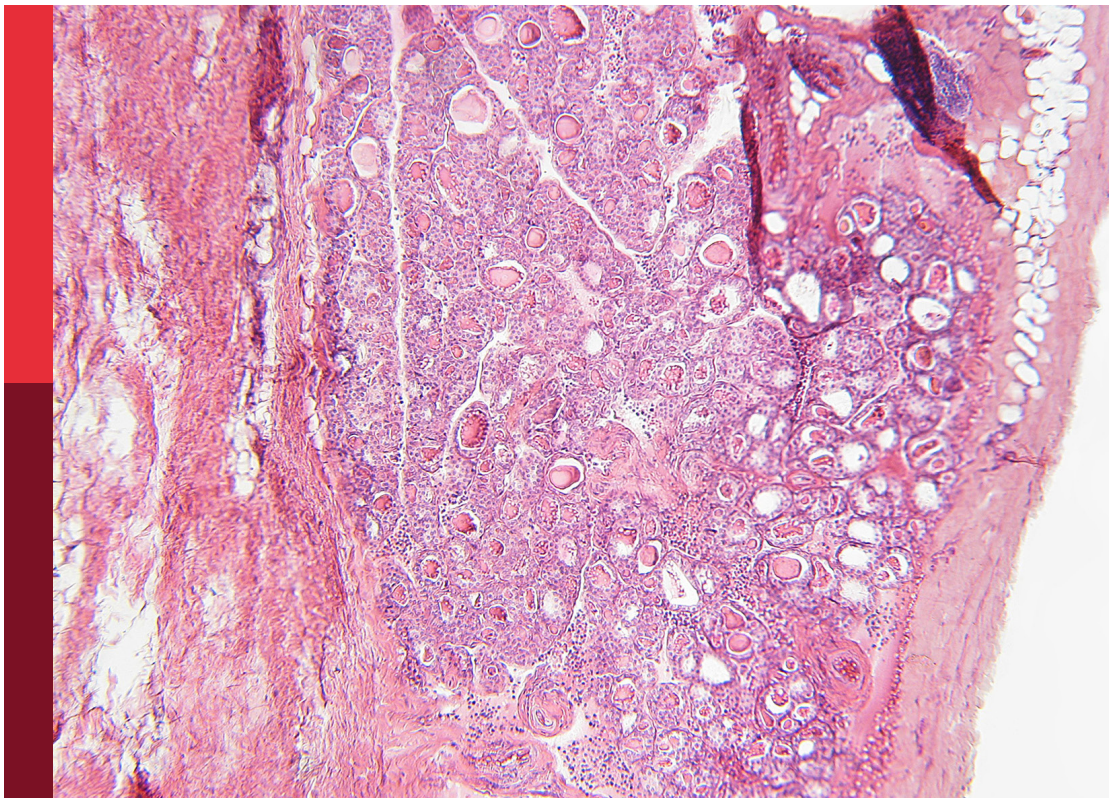

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The role of metabolic syndrome and disorders in cardiovascular disease

Topic editors

Albino Carrizzo — University of Salerno, Italy
Paola Di Pietro — University of Salerno, Italy
Jessica Gambardella — University of Salerno, Italy
Carmine Izzo — University of Salerno, Italy

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Table of contents

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EDITED AND REVIEWED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

*CORRESPONDENCE
Albino Carrizzo
albino.carrizzo@gmail.com

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Editorial: The role of metabolic syndrome and disorders in cardiovascular disease

Paola Di Pietro[1], Carmine Izzo[1] and Albino Carrizzo[1,2]*

[1]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi (SA), Italy, [2]Vascular Physiopathology Unit, IRCCS Neuromed, Pozzilli (IS), Italy

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Editorial on the Research Topic
The role of metabolic syndrome and disorders in cardiovascular disease

Metabolic syndrome (MetS) is a cluster of interrelated risk factors that includes abdominal obesity, insulin resistance, hypertriglyceridemia, and arterial hypertension and is strongly associated with an increased risk for developing atherosclerotic cardiovascular disease, diabetes mellitus, and vascular and neurological complications.

The present Research Topic, entitled "*The Role of Metabolic Syndrome and Disorders in Cardiovascular Disease*", aims at highlighting the risk factors predisposing to MetS and its related cardiovascular complications.

The prevalence of metabolic diseases has drastically risen worldwide over the last decades (1, 2). Using National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2014, Li et al. evaluate trends in MetS prevalence among US adults, showing a significant increase from 27.6% to 32.3% and, a strong gender differences, with a higher prevalence but a lower risk in women compared with men.

In accordance with other recent papers (3), the study from Cai et al. confirms the impact of obesity on the risk of hypertension in a community-based cohort study. According to the inclusion criteria, the authors analyzed a total of 2,618 subjects free from hypertension at baseline examination. After nearly 7 years of follow-up, the authors show that keeping obese status all the time increased the risk of hypertension by 30%. On the other side, losing weight after being obese was associated with a higher risk of hypertension than changing weight from normal to obesity, highlighting the importance of weight management as a preventive measure against hypertension. Interestingly, there was an inverse correlation between female subjects and increased incidence of hypertension, whereas a positive correlation was found in individuals aged more than 60 years.

In the same order of ideas, Tan et al. conduct a *post hoc* analyses of data from the TOPCAT trial (4) to explore the effect of body weight fluctuations on the prognosis in patients with heart failure and preserved ejection fraction (HFpEF). Patients were grouped in quartiles according to the variation of both BMI and waist circumference (WC), and primary endpoint, CVD death, and hospitalization for HF were evaluated as outcomes. Over a mean follow-up of 3.3 years, variability of both BMI and WC was associated with

poor prognosis of patient with HFpEF, and the risk of clinical adverse events increased with increasing variability.

In the effort to improve the management of patients with obesity and cardiovascular diseases (CVD), the meta-analysis study by Zhang et al. reports excessive BMI as an independent risk factor for preoperative oxygenation impairment in patients with acute aortic syndrome (AAS). These findings were further supported by a retrospective study including a total of 230 individuals, demonstrating a significant higher risk of preoperative oxygenation impairment in those with BMI of 25 kg/m^2 or greater. Besides, these authors observed that the risk of AAS with preoperative oxygenation impairment increased dramatically with the increased BMI, thus suggesting the potential value of BMI as an indicator for risk stratification in AAS patients.

Another important contribution to the evaluation on the influence of obesity on cardiovascular complications has been provided by two papers collected in the current Research Topic.

Although obesity has long been defined as elevated BMI, growing evidence demonstrates that subjects with similar BMIs may have different CVD risk profiles. Thus, susceptibility to cardiovascular complications is dependent upon individual differences in regional body fat distribution rather than the amount of adipose tissue (5).

In line with this notion, Du et al. evaluated the predictive value of three novel obesity indices for the detection of cardiovascular subclinical organ damage (SOD) in the general Chinese population. To clarify this issue, they examined a total of 1,773 healthy Chinese subjects and analyzed lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride-glucose (TyG), which are the product of waist circumference, BMI and blood lipid profile. The authors found a significant positive association of these indices with arterial stiffness and albuminuria, with the TyG representing the most discriminating index in identifying arterial stiffness and albuminuria, as compared with the other two indices. These data open a new avenue for the development of novel preventive approaches against cardiovascular SOD progression and adverse cardiovascular outcomes.

People with metabolic syndrome are at higher risk to develop stroke, with the highest percentage of stroke being in people over 56 years old (6). Using data from the NHANES database, the study from Chen et al. explores the association between VAI and stroke prevalence among US adults, showing that higher VAI was associated with higher stroke prevalence and report for the first time a negative correlation with age at stroke.

Since metabolic syndrome has emerged as a nonclassical complication of primary hyperparathyroidism (PHPT), with the aim at identifying unknown mechanisms underlying the link between endocrine-metabolic disorders and related-cardiac abnormalities, in their study Chen et al. examine the relationship between primary hyperparathyroidism and cardiac dysfunction. After adjustment for age, gender, BMI, duration of PHPT, hypertension, and diabetes, these authors showed that calcium and parathyroid hormone levels were positively correlated with left ventricular mass index, whereas an inverse correlation was found with diastolic dysfunction, as indicated by the decreased early diastolic mitral inflow velocity index.

Another paper by Wang et al. reports the influence of thyroid hormone levels on cardiac function. Interestingly, in euthyroid patients with valvular heart disease, thyroxine (T4) and triiodothyronine (T3) levels were significantly decreased in proportion with increasing NYHA grades. Further studies are warranted to explore the potential of hormone replacement therapy to improve clinical outcomes in patients with valvular disease.

An interesting study from Pillai et al. investigates the impact of primary hyperaldosteronism (PA) in patients with diabetes and hypertension. Using data from the National Impatient Sample, these authors demonstrated a strong association between the presence of PA in hypertensive and diabetic individuals and increased mortality and morbidity.

Yao et al. examine characteristics and risk of CVD among 1,765 Chinese individuals with diabetes mellitus, reporting that age at diagnosis, diabetes duration, hypertension and hyperlipidemia were independent risks of CVD. Further, a longer duration of diabetes (>15 years) increased the 10-year ASCVD risk prediction.

Liu et al. demonstrate the ability of estimated glucose disposal rate (eGDR) to independently predict in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Furthermore, eGDR improves the predictive ability of conventional cardiovascular risk factors to ISR, especially in patients without type 2 diabetes mellitus (T2DM).

Numerous biomarkers have been proposed to improve understanding of biological processes involved in MetS pathophysiology. In this context, Zalewska et al. demonstrate that patients with MetS had lower levels of catestatin (Cts). Further, Cts correlated positively with high density lipoprotein cholesterol and negatively with BMI, and 10-year atherosclerotic cardiovascular disease risk (ASCVD).

MetS has also been shown to be independently associated with an increased risk of new-onset atrial fibrillation (AF) (7). Given the evidence of a positive association of both dysglycaemia and hyperuricemia with the increased risk of atrial fibrillation (AF), Zhong et al. explore the relationship between serum uric acid (SUA) and AF in different fasting glucose (FBG) patterns. SUA and AF were independently correlated after adjusting for different FBG patterns. In addition, in patients with AF, SUA levels correlated with several metabolic factors in different FBG patterns. Although the retrospective nature of the study, this is the only manuscript yet to exist evaluating the association between SUA, dysglycaemia and AF, and offer new perspectives to better understanding the potential contribution of SUA in the pathogenesis of AF and its related predisposing factors.

Since SUA levels could be affected by renal function, a paper by Zhang et al. reports the usefulness of a renal function-normalized uric acid/creatinine ratio (UCR) as a valuable biomarker to predict the recurrence of AF after catheter ablation. After a mean follow-up of nearly 2 years, regression analysis revealed that UCR was an independent predictor of AF recurrence, and that increased preoperative UCR was associated with AF recurrence in patients with paroxysmal AF and in male patients, but not in patients with persistent AF as well as in female. Although the concept has been

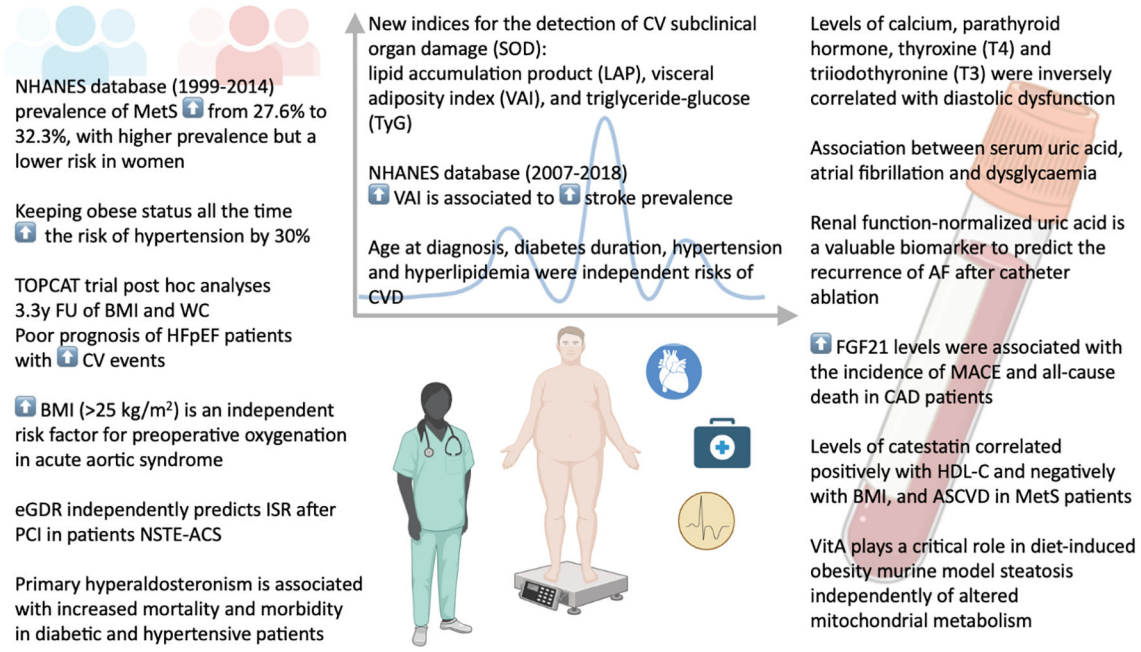

FIGURE 1
Risk factors, cardiovascular complications, and potential biomarkers in metabolic syndrome.

raised in previous reports, this study suggests a higher risk of AF recurrence in female subjects than in male. However, the sample size was relatively small and the study was performed with data from a single center, which warrants further prospective and larger studies.

Preclinical studies have reported fibroblast growth factor 21 (FGF21) as a metabolic regulator with potent beneficial effects on obesity and diabetes (8). In a meta-analysis study, Yan et al. explore the potential role of FGF21 on predicting long-term prognosis MACE among CVD patients stratified by coronary artery disease (CAD) and HF. While no association was found between blood FGF21 levels and the endpoint in HF patients, increased FGF21 levels were independently associated with the incidence of major adverse cardiovascular events and all-cause death among patients with CAD.

In the only preclinical study of this Research Topic, Shymotiuk et al. demonstrate that vitamin A (VitA), whose metabolism is impaired in patients and animal models with obesity and T2DM, plays a critical role in mediating steatosis and adverse organ remodeling in a diet-induced obesity murine model independently of altered mitochondrial metabolism.

In conclusion, the findings collected in this Research Topic (Figure 1) highlight the importance of improving the management of such a multidimensional risk factor syndrome. Apart from non-modifiable risk factors, interventions focused on lifestyle habits could be emphasized in patients with MetS. Treating each of the risk factors contributing to metabolic syndrome and exploring novel biomarkers could inform the development of additional preventive strategies for the diagnosis of MetS and its associated complications at earlier stages, ultimately leading to improved long-term survival outcomes.

Author contributions

PP: Conceptualization, Writing – original draft, Writing – review & editing. CI: Data curation, Writing – original draft. AC: Conceptualization, Writing – review & editing, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Paola Di Pietro,
University of Salerno, Italy

REVIEWED BY
Leila Warszawski,
Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione, Brazil
Yuankai Zhou,
Peking Union Medical College Hospital (CAMS), China
Mengda Cao,
Southeast University, China

*CORRESPONDENCE
Xiaoli Liu
liuxl9881@163.com
Yujie Zhou
azzyj12@163.com

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Correlation between estimated glucose disposal rate and in-stent restenosis following percutaneous coronary intervention in individuals with non-ST-segment elevation acute coronary syndrome

Chi Liu[1,2], Qi Zhao[1,2], Ziwei Zhao[1,2], Xiaoteng Ma[1,2], Yihua Xia[1,2], Yan Sun[1,2], Dai Zhang[1,2], Xiaoli Liu[1,2]* and Yujie Zhou[1,2]*

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [2]Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Clinical Center for Coronary Heart Disease, Capital Medical University, Beijing, China

Background: Insulin resistance (IR) is closely associated with in-stent restenosis (ISR) following percutaneous coronary intervention (PCI). Nevertheless, the predictive power of the newly developed simple assessment method for IR, estimated glucose disposal rate (eGDR), for ISR after PCI in individuals with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) remains unclear.

Methods: NSTE-ACS cases administered PCI in Beijing Anzhen Hospital between January and December 2015 were enrolled. The included individuals were submitted to at least one coronary angiography within 48 months after discharge. Patients were assigned to 2 groups according to ISR occurrence or absence. eGDR was derived as 21.16 - (0.09 * waist circumference [cm]) - (3.41 * hypertension) - (0.55 * glycated hemoglobin [%]). Multivariate logistic regression analysis and receiver operating characteristic (ROC) curve analysis were performed for evaluating eGDR's association with ISR.

Results: Based on eligibility criteria, 1218 patients were included. In multivariate logistic analysis, the odds ratios (ORs) of eGDR as a nominal variate and a continuous variate were 3.393 (confidence interval [CI] 2.099 - 5.488, P < 0.001) and 1.210 (CI 1.063 - 1.378, P = 0.004), respectively. The incremental effect of eGDR on ISR prediction based on traditional cardiovascular risk factors was reflected by ROC curve analysis (AUC: baseline model + eGDR 0.644 vs. baseline model 0.609, P for comparison=0.013), continuous net reclassification improvement (continuous-NRI) of -0.264 (p < 0.001) and integrated discrimination improvement (IDI) of 0.071 (p = 0.065).

Conclusion: In NSTE-ACS cases administered PCI, eGDR levels show an independent negative association with increased ISR risk.

KEYWORDS

estimated glucose disposal rate, non-ST-segment elevation acute coronary syndrome, percutaneous coronary intervention, insulin resistance, in-stent restenosis

Introduction

Although the popularization of second-generation drug-eluting stents (DESs) has largely decreased in-stent hyperproliferation, the incidence of in-stent restenosis (ISR) remains high, between 3% and 20%, which confirms coronary anatomical characteristics, patient indexes and surgical factors are highly correlated (1–3). The mechanism of ISR development is complex: besides vascular factors such as endothelial dysfunction, smooth muscle hyperplasia and inflammation (4–6), age, gender, hypertension, hyperlipidemia, diabetes and smoking are also considered risk factors for ISR (4, 7–10). Because of such complexity, accurate prediction and prevention of ISR has important clinical significance in improving prognosis in atherosclerotic cardiovascular disease (ASCVD) treated with stents.

Type 2 diabetes mellitus (T2DM) represents a major risk factor for ASCVD, which includes coronary heart disease, cerebrovascular disease and peripheral arterial disease (PAD), and also plays a key role in ISR (11). As an important pathogenetic mechanism of T2DM, insulin resistance (IR) has been shown to be correlated with the occurrence of ISR (12–14). IR measurement and assessment have attracted extensive attention recently. Hyperinsulinemic-euglycemic clamp is presently considered the gold standard for IR evaluation, but its wide clinical application is hampered by its high cost, time-consuming, complex and invasive characteristics. Using hyperinsulinemic-euglycemic clamp as a validation criterion, investigators established an estimated glucose disposal rate (eGDR) to enable the evaluation of insulin sensitivity in type 1 diabetes mellitus (T1DM) (15, 16). In the original study, waist-to-hip ratio (WHR), hypertension, and glycated hemoglobin (HbA1c) were included in the formula of eGDR. However, further studies have shown utilizing waist circumference (WC) in lieu of WHR for eGDR determination yields comparable results (15, 17). Patients with high eGDR have higher insulin sensitivity; conversely, low eGDR is associated with enhanced IR (18).

It was demonstrated that low eGDR independently predicts all-cause mortality in T2DM cases administered coronary artery bypass grafting (CABG) (19). Nevertheless, no studies have explored the relationship between eGDR and ISR. Therefore, we conducted the current work to investigate eGDR's predictive value in ISR for individuals with non-ST-elevation acute coronary syndrome (NSTE-ACS) administered percutaneous coronary intervention (PCI).

Abbreviations: DES, drug-eluting stent; ISR, in-stent restenosis; ASCVD, atherosclerotic cardiovascular disease; T2DM, type 2 diabetes mellitus; PAD, peripheral arterial disease; IR, insulin resistance; eGDR, estimated glucose disposal rate; T1DM, type 1 diabetes mellitus; WHR, waist-to-hip ratio; HbA1c, glycosylated hemoglobin; WC, waist circumference; CABG, coronary artery bypass grafting; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; CAD, coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; eGFR, estimated glomerular filtration rate; TIMI, thrombolysis in myocardial infarction; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; SYNTAX, the synergy between PCI with taxus and cardiac surgery; SD, standard deviation; OR, odds ratio; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LM, left main artery; CTO, chronic total occlusion; ROC, receiver operating characteristic; AUC, area under curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; OHA, oral hypoglycemic agents; HOMA-IR, homoeostasis model assessment of insulin resistance; CVD, cardiovascular disease; TyG, triglyceride-glucose; HDL-C, high-density lipoprotein cholesterol; VAI, visceral adiposity index; LAP, lipid accumulation product

Materials and methods

Study population

This single-center observational trial enrolled individuals diagnosed with coronary artery disease (CAD) in Beijing Anzhen Hospital between January and December 2015. Inclusion criteria were: (1) diagnosis of NSTE-ACS (including on-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina [UA]); (2) successful elective PCI; (3) coronary angiography performed at least once within 48 months after discharge. Relevant diagnostic criteria were based on the latest guidelines (20, 21). Exclusion criteria were: (1) missing baseline and/or follow-up data; (2) T1DM diagnosis; (3) history of CABG, cardiogenic shock, acute decompensated heat failure, chronic infectious disease, or cancer; (4) impaired kidney

function, with estimated glomerular filtration rate (eGFR) below 30 mL/(min × 1.73 m^2) or kidney replacement treatment; (5) serious liver dysfunction, with alanine transaminase and/or aspartate transaminase ≥ 5 times the respective upper reference limits. A total of 1218 individuals were finally included (Figure 1). The study was approved by the Hospital Clinical Research Ethics Committee and was conducted in accordance with the Helsinki Declaration.

Coronary intervention and stenting

Coronary angiography, coronary stent implantation, and perioperative management were all performed by two experienced interventional cardiologists, with the implementation path and management process based on current guidelines (21). Cases underwent antiplatelet treatment, with loading doses of 300, 300 and 180 mg for aspirin, clopidogrel and ticagrelor, respectively, prior to interventional therapy. During the procedure, 100 IU/kg unfractionated heparin was also administered for anticoagulation to maintain an activated clotting time >300 seconds. Successful stent placement was considered with residual stenosis <20% in the target lesion, as assessed by visual inspection or quantitative coronary angiography, and grade-III anterior thrombolysis in myocardial infarction (TIMI) flow.

Data collection and definitions

Demographic and clinical characteristics were recorded by hospital information center professionals. NSTE-ACS includes non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA), whose definitions refer to recognized guidelines (22). Diagnostic criteria for related diseases (T2DM, hypertension, dyslipidemia, stroke, and PAD) followed current guidelines (23–27). WC was measured by taking the distance of the midpoint line between the rib's lowest point and the iliac crest's upper border. Echocardiography-based diagnostic reports were evaluated and reviewed by two sonographers. Blood samples were collected after fasting for 8-12 hours and transported to the hospital's testing center for testing of hematological and biochemical parameters. A variety of biochemical and hematological indicators were collected. The standard enzymatic method was used to determine triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C). The homogeneous direct method was performed to determine low-density lipoprotein cholesterol (LDL-C). The enzymatic hexokinase technique was performed to detect fasting blood glucose (FBG). Other parameters and indicators were determined by the standard laboratory method in the central laboratory of the hospital. The synergy between PCI and taxus and cardiac surgery (SYNTAX) score was determined using a standard formula (http://www.syntaxscore.com).

The formula for calculating eGDR was as follows (15, 17, 28): eGDR = 21.16 - (0.09 * WC [cm]) - (3.41 * Hypertension [yes or no]) - (0.55 * HbA1c [%]).

Definition and judgment of ISR

All the 1218 patients included in this study completed a 48-month follow-up period and underwent at least one coronary angiography in our hospital within 48 months of discharge. ISR

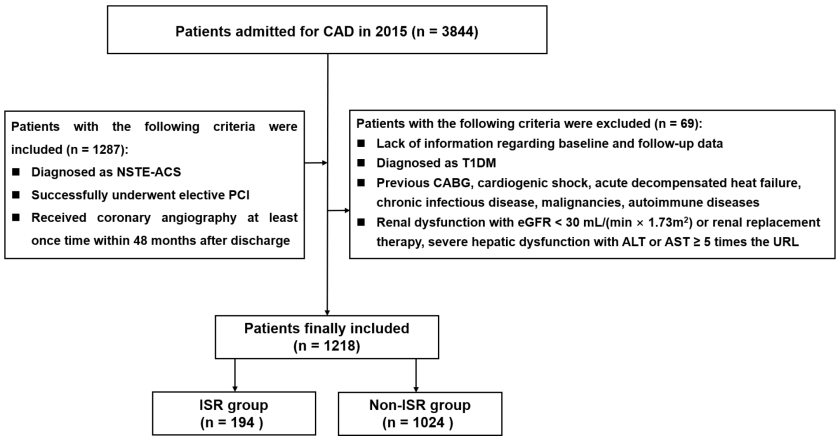

FIGURE 1
Flow diagram for the enrollment of study population. *CAD* coronary artery disease, *NSTE-ACS* non-ST-segment elevation acute coronary syndrome, *PCI* percutaneous coronary intervention, *T1DM* Type 1 Diabetes mellitus, *CABG* coronary artery bypass grafting, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *AST* aspartate transaminase, *URL* upper reference limit, *ISR* in-stent restenosis.

was considered with a stenosis ≥ 50% in diameter within the stent or involving 5 mm proximal and distal to the stent (29). Quantitative coronary angiography was used to assess coronary stenosis. Similarly, angiographic findings and the presence of ISR were examined by two independent experienced cardiologists. Participants were assigned to the ISR and non-ISR groups, based on ISR status at 48 months.

Statistical analysis

Participants' baseline data were described by the following methods. Continuous data with normal and skewed distributions were described as mean ± standard deviation (SD) and median with 25^{th} and 75^{th} percentiles, respectively, and compared by the two-sample t-test and the Mann-Whitney U test, respectively. Nominal variables were described as number and percentage, and comparison used the chi-square, continuity-adjusted chi-square, or Fisher's exact test.

Univariate logistic regression analysis was used to identify parameters associated with ISR. Baseline variables with significant associations in univariate analysis and those clinically significant for ISR development were further assessed by multivariable logistic regression analysis, excluding variates that may have collinearity. eGDR was evaluated as both nominal and continuous. Nominal variables were analyzed for the low and high eGDR groups, categorized based on median eGDR (lower eGDR [eGDR ≤ 6.92]; higher eGDR [eGDR > 6.92]). Odds ratio (OR) and 95% confidence interval (CI) were determined for each association. Four multivariable logistic regression models were built for assessing eGDR's association with ISR. In Model 1, adjustment was made for age, sex and body mass index (BMI). Model 2 was adjusted for Model 1's variables besides a history of smoking, previously diagnosed myocardial infarction (MI), a history of PCI and previously detected stroke. In Model 3, adjustment was made for Model 2's variables in addition to TG, LDL-C, high-sensitivity C-reactive protein (hs-CRP), eGFR and left ventricular ejection fraction (LVEF). Model 4 was adjusted for Model 3's variables as well as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) at discharge, left main artery (LM) lesion, bifurcation, multi-vessel lesion, chronic total occlusion (CTO) lesion, SYNTAX score, complete revascularization and DES amount.

Subgroup analysis was performed after stratification by T2DM, adjusted for model 4 variates. The area under the receiver operating characteristic (ROC) curve (AUC) was obtained to assess eGDR's predictive value in ISR. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) illustrated the incremental impact of introducing eGDR on the predictive ability of currently accepted risk models. The baseline model used for comparison included the following cardiovascular risk factors: age, sex, BMI, smoking history, family history of CAD, previously diagnosed MI, previously diagnosed PCI, previously detected stroke, hyperlipidemia, LVEF and SYNTAX score.

SPSS 26.0 and R 3.6.3 were utilized for data analysis, with two-sided $P < 0.05$ indicating statistical significance.

Results

Baseline patient features

Totally 1218 participants averaging 59.93 ± 8.90 years old were included, with a male proportion of 70.4% (n=858). Details of demographics, past medical history, laboratory tests, drug status and interventions for the non-ISR and ISR groups are presented in Table 1. In comparison with non-ISR cases, the ISR group showed elevated WC and higher rates of smoking history, drinking history, diabetes, hypertension, previous MI, and previous PCI. Regarding laboratory tests, ISR cases showed elevated FBG and HbA1c amounts, but reduced TC and LDL-C levels. For admission medication, patients with ISR had higher rates of dual antiplatelet therapy (DAPT), aspirin, P2Y12 inhibitors, β-blockers, statins, oral hypoglycemic agents (OHA) and insulin. For discharge medication, the rates of ACEI/ARB, OHA and insulin used were elevated in ISR cases. Regarding coronary angiography and PCI, ISR cases displayed elevated rates of bifurcation and SYNTAX score, but lower rates of complete revascularization. The mean length of stent was higher in the ISR group, but there was no difference in minimal stent diameter between the two groups. Baseline data grouped by median eGDR are presented in Supplementary Table S1

Predictive value of eGDR for ISR

Univariate analysis was performed for initially identifying factors associated with ISR (Supplementary Table S2). Based on univariate logistic regression analysis and clinically relevant risk factors, we screened variates and built four multivariate logistic regression models to measure eGDR's predictive value in ISR. Whether defined as a nominal variate (with higher median eGDR as reference) or a continuous variate (per 1-unit decrease), eGDR had an independent predictive value across all 4 models. After fully adjusting for potential confounders in Model 4, ORs for eGDR as a nominal variate and a continuous variate were 3.393 (2.099-5.488) and 1.210 (1.063 - 1.378), respectively (Table 2).

Subgroup analysis of the independent association between eGDR and ISR based on T2DM status was carried out (Figure 2). The results revealed eGDR's predictive potential in ISR was higher in non-T2DM cases [OR (95%CI): T2DM no 1.216 (1.025-1.442) vs. T2DM yes 0.978 (0.826–1.157), P for interaction = 0.010].

TABLE 1 Baseline characteristics of the study population based on ISR.

	Total population(n = 1218)	Non-ISR(n = 1024)	ISR(n = 194)	*P* value
Age, years	59.93 ± 8.90	59.88 ± 9.01	60.22 ± 8.32	0.627
Sex, male, n (%)	858 (70.4)	712 (69.5)	146 (75.3)	0.109
BMI, kg/m^2	26.17 ± 3.18	26.12 ± 3.19	26.45 ± 3.13	0.184
WC, cm	91.51 ± 12.33	91.21 ± 12.46	93.11 ± 11.49	0.038
Heart rate, bpm	70.14 ± 10.34	70.03 ± 10.21	70.73 ± 11.02	0.386
SBP, mmHg	130.61 ± 16.70	130.54 ± 16.44	130.97 ± 18.07	0.386
DBP, mmHg	77.02 ± 9.94	76.95 ± 9.91	77.39 ± 10.12	0.572
Smoking history, n (%)	686 (56.3)	561 (54.8)	125 (64.4)	0.013
Drinking history, n (%)	290 (23.8)	233 (22.8)	57 (29.4)	0.047
Family history of CAD, n (%)	126 (10.3)	104 (10.2)	22 (11.3)	0.620
Medical history, n (%)				
Diabetes	432 (35.5)	333 (32.5)	99 (51.0)	< 0.001
Hypertension	787 (64.6)	643 (62.8)	144 (74.2)	0.002
Hyperlipidemia	1051 (86.3)	883 (86.2)	168 (86.6)	0.891
Previous MI	235 (19.3)	185 (18.1)	50 (25.8)	0.013
Previous PCI	190 (15.6)	144 (14.1)	46 (23.7)	0.001
Previous stroke	138 (11.3)	109 (8.9)	29 (2.4)	0.083
Previous PAD	170 (14.0)	135 (13.2)	35 (18.0)	0.073
Clinical diagnosis, n (%)				0.401
UA	1017 (83.5)	859 (83.9)	158 (81.4)	
NSTEMI	201 (16.5)	165 (16.1)	36 (18.6)	
Laboratory examinations				
TG, mmol/L	1.47 (1.04, 2.06)	1.47 (1.04, 2.08)	1.43 (1.03, 1.94)	0.450
TC, mmol/L	4.14 ± 1.02	4.18 ± 1.02	3.95 ± 1.01	0.004
LDL-C, mmol/L	2.52 ± 0.86	2.55 ± 0.85	2.39 ± 0.86	0.017
HDL-C, mmol/L	0.98 ± 0.23	0.98 ± 0.24	0.96 ± 0.20	0.144
hs-CRP, mg/L	1.28 (0.57, 3.32)	1.28 (0.55, 3.20)	1.29 (0.64, 3.52)	0.092
Creatinine, μmol/L	76.13 ± 17.10	76.05 ± 17.09	76.53 ± 17.15	0.722
eGFR, mL/(min × 1.73m^2)	93.06 ± 20.39	92.87 ± 20.15	94.05 ± 21.66	0.459
Uric acid, μmol/L	346.60 ± 81.31	346.45 ± 82.22	347.40 ± 76.56	0.881
FBG, mmol/L	6.09 ± 1.74	107.96 ± 30.16	118.11 ± 36.13	< 0.001
HbA1c, mmol/mol	44.97 ± 12.72	44.35 ± 12.34	48.26 ± 14.14	< 0.001
LVEF, %	64.08 ± 6.48	64.13 ± 6.38	63.83 ± 6.95	0.557
Medication at admission, n (%)				
ACEI/ARB	285 (23.4)	234 (22.9)	51 (26.3)	0.300
DAPT	359 (29.5)	273 (26.7)	86 (44.3)	< 0.001
Aspirin	639 (52.5)	512 (50.0)	127 (65.5)	< 0.001
P2Y12 inhibitors	385 (31.6)	297 (29.0)	88 (45.4)	< 0.001
β-Blocker	268 (22.0)	209 (20.4)	59 (30.4)	0.002
Statins	361 (29.6)	292 (28.5)	69 (35.6)	0.049
OHA	220 (18.1)	169 (16.5)	51 (26.3)	0.001
Insulin	115 (9.4)	83 (8.1)	32 (16.5)	< 0.001
Medication at discharge, n (%)				
ACEI/ARB	868 (71.3)	714 (69.7)	154 (79.4)	0.006
DAPT	1217 (99.9)	1023 (99.9)	194 (100.0)	0.663
Aspirin	1218 (100.0)	1024 (100.0)	194 (100.0)	
P2Y12 inhibitors	1218 (100.0)	1024 (100.0)	194 (100.0)	
β-Blocker	1113 (91.4)	929 (90.7)	184 (94.8)	0.061

(Continued)

TABLE 1 Continued

	Total population(n = 1218)	Non-ISR(n = 1024)	ISR(n = 194)	*P* value
Statins	1192 (97.9)	1004 (98.0)	188 (96.9)	0.314
Ezetimibe	128 (10.5)	104 (10.2)	24 (12.4)	0.356
OHA	217 (17.8)	167 (16.3)	50 (25.8)	0.002
Insulin	112 (9.2)	81 (7.9)	31 (16.0)	< 0.001
Angiographic data, n (%)				
LM lesion	50 (4.1)	43 (4.2)	7 (3.6)	0.704
Bifurcation	243 (20.0)	193 (18.8)	50 (25.8)	0.027
Multi-vessel lesion	808 (66.3)	672 (65.6)	136 (70.1)	0.226
In-stent restenosis	70 (5.7)	55 (5.4)	15 (7.7)	0.195
Chronic total occlusion lesion	153 (12.6)	128 (12.5)	25 (12.9)	0.882
SYNTAX score	10.52 ± 5.29	10.38 ± 5.28	11.21 ± 5.26	0.047
Procedural information				
Minimal stent diameter, mm	2.86 ± 0.37	2.87 ± 0.36	2.83 ± 0.27	0.226
Mean length of stent, mm	22.33 ± 4.15	22.16 ± 4.02	23.19 ± 4.70	0.005
Target vessel territory, n (%)				
LM	31 (2.5)	24 (2.3)	7 (3.6)	0.305
LAD	784 (64.4)	660 (64.5)	124 (63.9)	0.886
LCX	413 (33.9)	356 (34.8)	57 (29.4)	0.146
RCA	532 (43.7)	450 (43.9)	82 (42.3)	0.666
Complete revascularization, n (%)	712 (58.5)	613 (59.9)	99 (51.0)	0.022
Number of DES	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.698

ISR in-stent restenosis, BMI body mass index, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, CAD coronary artery disease, MI myocardial infarction, PCI percutaneous coronary intervention, PAD peripheral artery disease, UA unstable angina, NSTEMI non-ST-segment elevation myocardial infarction, TG triglyceride, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, hs-CRP high-sensitivity C-reactive protein, eGFR estimated glomerular filtration rate, FBG fasting blood glucose, HbA1c glycosylated hemoglobin A1c, LVEF left ventricular ejection fraction, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, DAPT dual antiplatelet therapy, OHA oral hypoglycemic agents, LM left main artery, SYNTAX synergy between PCI with taxus and cardiac surgery, LAD left anterior descending artery, LCX left circumflex artery, RCA right coronary artery, DES drug-eluting stent.

Incremental efficacy of eGDR for ISR prediction

We established baseline models based on currently recognized cardiovascular risk factors as mentioned in Methods. Based on this model, addition of eGDR significantly enhanced its predictive power for ISR (AUCs of 0.644 and 0.609 for baseline model + eGDR and baseline model, respectively; P = 0.013) (Table 3, Figure 3). Estimation of continuous-NRI (-0.264, p < 0.001) also showed similar results, although IDI values (0.071, p = 0.065) were not significantly different (Table 3).

TABLE 2 Association of eGDR with ISR in multivariate logistic regression analysis.

	As nominal variate[a]		As continuous variate[b]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted	2.591 (1.866-3.598)	< 0.001	1.169 (1.087-1.256)	< 0.001
Model 1	2.983 (2.048-4.345)	< 0.001	1.218 (1.111-1.335)	< 0.001
Model 2	2.960 (2.019-4.339)	< 0.001	1.200 (1.094-1.315)	< 0.001
Model 3	3.019 (2.048-4.450)	< 0.001	1.200 (1.094-1.317)	< 0.001
Model 4	3.393 (2.099-5.488)	< 0.001	1.210 (1.063-1.378)	0.004

Model 1: adjusted for age, sex, BMI.
Model 2: adjusted for variates in Model 1 and smoking history, previous MI, previous PCI, previous stroke.
Model 3: adjusted for variates in Model 2 and TG, LDL-C, hs-CRP, eGFR, LVEF.
Model 4: adjusted for variates in Model 3 and ACEI/ARB at discharge, LM lesion, bifurcation, multi-vessel lesion, chronic total occlusion lesion, SYNTAX score, complete revascularization, number of DES.
[a]The OR was evaluated regarding the higher median of eGDR as reference.
[b]The OR was evaluated by per 1-unit decrease of eGDR.
eGDR estimated glucose disposal rate calculated, ISR in-stent restenosis, OR odds ratio, CI confidence interval.

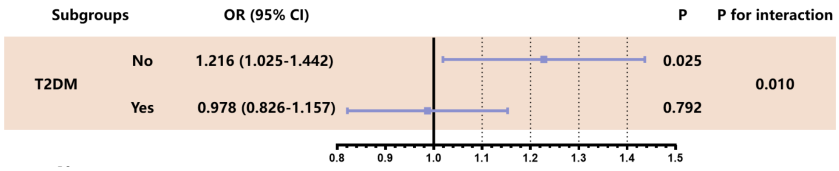

FIGURE 2
Stratified analysis of eGDR predicting ISR in T2DM subgroup. The analysis was adjusted for Model 4 except for variates applied for grouping. OR was evaluated by per 1-unit decrease of eGDR. *eGDR* estimated glucose disposal rate calculated, *ISR* in-stent restenosis, *OR* odds ratio, *T2DM* type 2 diabetes mellitus.

Prediction of ISR by eGDR based on T2DM status

In non-diabetic cases, eGDR showed an incremental effect similar to that of the general population, with AUCs of 0.671 and 0.636 for baseline model + eGDR and baseline model, respectively (P = 0.043); continuous-NRI was 0.091 (P < 0.001) and IDI was 0.081 (P = 0.103) (Table 4, Figure 4B). In contrast, in the diabetic population, addition of eGDR did not increase the predictive potential of the baseline model in ROC curve analysis (AUCs of 0.655 and 0.658 for baseline model + eGDR and baseline model, respectively; P = 0.503), and continuous-NRI (-0.021, P = 0.107) and IDI (-0.021, P = 0.394) differences were not statistically significant (Table 4, Figure 4A).

Discussion

The present work firstly assessed eGDR's association with ISR following PCI in CAD. The results revealed eGDR was independently and negatively associated with increased risk of ISR following PCI in NSTE-ACS; furthermore, eGDR improved the predictive ability of routine cardiovascular risk factors for ISR; moreover, the predictive value of eGDR for ISR was mainly reflected in patients without T2DM.

IR is the most important pathogenetic mechanism of diabetes and metabolic syndrome, with the main features including the following two aspects: decreased ability of insulin to induce glucose uptake and use; body compensation by enhanced insulin secretion for inducing hyperinsulinemia to stabilize blood sugar. Insulin resistance causes endothelial dysfunction, oxidative stress, and the activation of inflammatory responses, ultimately leading to the formation of atherosclerotic plaques (30). Currently, assessment techniques for insulin resistance mostly encompass two categories: direct assessment methods and simple surrogate assessment indicators. The hyperinsulinemic-euglycemic clamp and the insulin suppression test are both direct assessment methods for insulin resistance. By applying the hyperinsulinemic-euglycemic clamp, researchers confirmed that IR is tightly associated with coronary atherosclerotic heart disease, with a predictive role independent of other risk factors (31–33). For simple surrogate assessment indicators of IR, many clinical studies have used homoeostasis model assessment of insulin resistance (HOMA-IR) as an assessment method to explore the relationship between IR and cardiovascular disease (CVD), with consistent results. Indeed, IR is highly associated with atherosclerosis (34) and predicts CVD onset and poor prognosis in non-diabetic individuals (35–37). However, in clinical practice, fasting insulin levels are not routinely measured even in diabetics, let alone in individuals without diabetes. In addition, insulin measurement methods do not yield consistent data across laboratories, especially in case of low insulin levels. Therefore, researchers have proposed a variety of simpler alternative assessment indicators of insulin resistance, including triglyceride-glucose (TyG) index, triglyceride/high-density lipoprotein cholesterol (TG/HDL-C), visceral adiposity index (VAI) and lipid accumulation product (LAP), which are highly correlated with the incidence and prognosis of ASCVD (38–41). eGDR is also a simple surrogate measure of this type of IR.

TABLE 3 Incremental effect of eGDR on ISR prediction by existing risk model in general population.

	ROC curve analysis				Continuous-NRI			IDI		
	AUC	95% CI	P value	P for comparison	Estimation	95% CI	P value	Estimation	95% CI	P value
Baseline model[a]	0.609	0.567-0.652	< 0.001	–	–	–	–	–	–	–
+ eGDR	0.644	0.603-0.685	< 0.001	0.013	-0.264	-0.294–0.234	< 0.001	0.071	-0.004-0.147	0.065

eGDR estimated glucose disposal rate, ISR in-stent restenosis, ROC receiver-operating characteristic, NRI net reclassification improvement, IDI integrated discrimination improvement, AUC area under curve, CI confidence interval.
[a]Baseline model includes age, sex, BMI, smoking history, family history of CAD, previous MI, previous PCI, previous stroke, hyperlipidemia, LVEF, SYNTAX score.

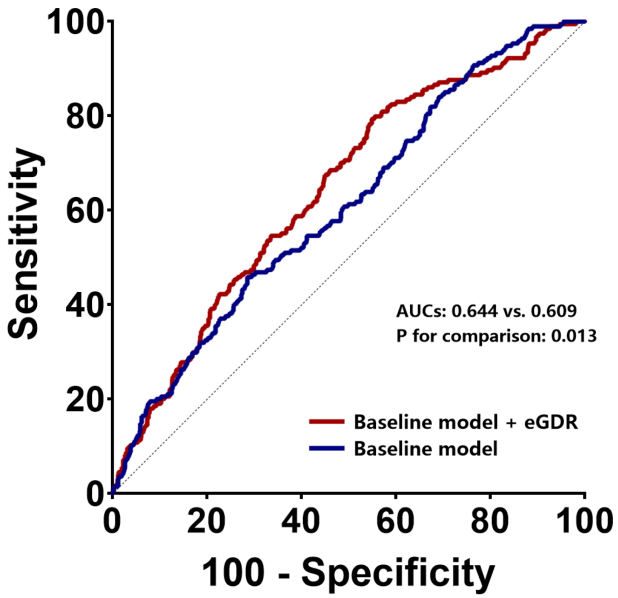

FIGURE 3
ROC curves to assess the predictive value of eGDR for ISR in general population. *ROC* receiver-operating characteristic, *eGFR* estimated glomerular filtration rate, *ISR* in-stent restenosis, *AUC* area under curve.

It has long been admitted that diabetes could predict the occurrence of ISR (42, 43), and a study suggested that diabetes is the most effective predictor of ISR (44). In addition, a meta-analysis showed ISR incidence is markedly elevated in diabetic patients in comparison with non-diabetics (45). Therefore, diabetes can almost be considered the clearest risk factor for ISR. Previously, it was shown that IR is a common feature of CVD patients undergoing stent surgery, and an important marker of restenosis after PCI, with a deterioration process related to endothelial dysfunction, nitric oxide production disorders and activity defects (13). In recent years, studies applying HOMA-IR have confirmed that insulin resistance is highly correlated with ISR occurrence after PCI, representing an independent predictor of ISR (12, 14). In addition, a study using TyG as an evaluation index of IR found that TyG is independently and positively correlated with ISR risk following DES implantation in ACS patients (46).

As for eGDR, its associations with stroke incidence and mortality in T2DM patients have been demonstrated (47). In addition, eGDR was also shown to be closely related to elevated risk of all-cause mortality after CABG in T2DM patients, independent of other cardiovascular and metabolic risk factors (19). The above findings suggest that eGDR has great potential in predicting ASCVD prognosis and ISR events after PCI. This study clarified the predictive potential of eGDR for ISR occurrence post-PCI in NSTE-ACS cases, which is consistent with previous findings. The present work not only confirmed IR could predict ISR occurrence upon PCI in NSTE-ACS cases, but

TABLE 4 Incremental effect of eGDR on ISR prediction by existing risk model in populations with and without T2DM.

	ROC curve analysis				Continuous-NRI			IDI		
	AUC	95% CI	P value	P for comparison	Estimation	95% CI	P value	Estimation	95% CI	P value
With T2DM										
Baseline model[a]	0.658	0.597-0.718	< 0.001	–	–	–	–	–	–	–
+ eGDR	0.655	0.593-0.716	< 0.001	0.503	-0.021	-0.047-0.005	0.107	-0.021	-0.068-0.026	0.394
Without T2DM										
Baseline model[a]	0.636	0.578-0.693	< 0.001	–	–	–	–	–	–	–
+ eGDR	0.671	0.615-0.728	< 0.001	0.043	0.091	0.056-0.126	<0.001	0.081	-0.016-0.178	0.103

eGDR estimated glucose disposal rate, ISR in-stent restenosis, ROC receiver-operating characteristic, NRI net reclassification improvement, IDI integrated discrimination improvement, AUC area under curve, CI confidence interval, T2DM type 2 diabetes mellitus.
[a]Baseline model includes age, sex, BMI, smoking history, family history of CAD, previous MI, previous PCI, previous stroke, hyperlipidemia, LVEF, SYNTAX score.

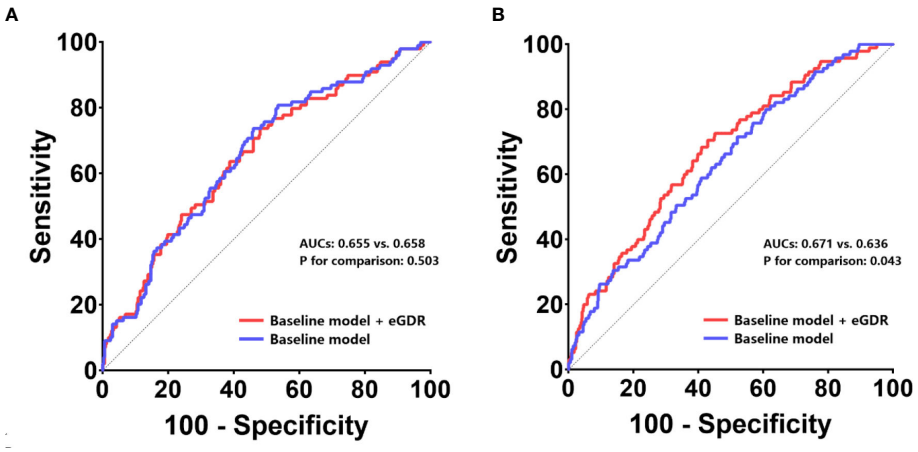

FIGURE 4
ROC curves to assess the predictive value of eGDR for ISR in populations with and without T2DM. The predictive values of the eGDR and baseline models were assessed in populations with T2DM **(A)** and without T2DM **(B)**. *ROC* receiver-operating characteristic, *eGFR* estimated glomerular filtration rate, *ISR* in-stent restenosis, *AUC* area under curve, *T2DM* type 2 diabetes mellitus.

also revealed a new and effective indicator applicable for ISR prediction. The population of this study was mainly UA patients. On the one hand, we excluded patients who underwent primary PCI due to severe and complex disease as well as confounding factors that were difficult to adjust for. On the other hand, the patient data available to our research team came from general wards with relatively few NSTEMI patients. In data analysis, we attempted to include diabetes and related variates in the multivariate analysis, but after final adjustment, eGDR lost statistical significance in ISR prediction. Therefore, a subgroup analysis was carried out based on the diabetes status. The results revealed eGDR only had a predictive value in ISR for the non-diabetic subgroup. Furthermore, incremental effect analysis in the diabetes and non-diabetes groups was also consistent with the above subgroup analysis. This could explain the lack of significance for eGDR in models incorporating diabetes and associated variates. As mentioned above, IR assessed by various methods has important predictive value for CVD development in patients without diabetes. Although such finding is novel, we believe that eGDR can predict the adverse prognosis of CVD in non-diabetic patients. However, the results of the subgroup analysis in this study need further research to verify. It is certain that eGDR has the potential as a routine evaluation index of CVD cases, which requires further investigation in large prospective trials. In the era of widespread PCI treatment, there is a lack of simple and effective evaluation methods for long-term prognosis of patients. eGDR is expected to become an effective index to evaluate the ISR risk of patients after PCI and guide follow-up treatment. Finally, whether eGDR can really be used clinically as a powerful predictor of ISR after PCI needs to be assessed *via* comparison with other IR evaluation indicators.

There were some limitations in the present study that need to be further confirmed by more rationally designed studies. First, this was a single-center observational study of Chinese individuals, with unavoidable selection bias. Therefore, multi-center trials or even randomized controlled studies with larger samples and greater racial diversity are warranted to further clarify the current results. Additionally, because of the exclusion of patients undergoing emergency PCI, UA cases in this study cohort constituted the greatest part of all cases, and the current findings might not reflect the prognostic value of eGDR for ISR in NSTEMI. Furthermore, regarding repeat coronary angiography after discharge, ISR detection was not based on intracoronary imaging, and its accuracy was insufficient. Moreover, this work did not clarify the specific time when ISR occurred within 48 months after discharge and lacked short-term and long-term ISR analyses. In addition, this study did not compare the predictive value of eGDR and other IR evaluation methods on ISR.

Conclusions

eGDR independently predicts ISR after PCI in NSTE-ACS cases and improves the predictive power of routine cardiovascular risk factors in ISR. Finally, eGDR's predictive potential in ISR was mainly demonstrated in non-T2DM patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CL made substantial contributions to data collection, data analysis and manuscript writing. YZ and XL made substantial contributions to study design and intellectual direction. QZ, ZZ, XM, YX, YS, and DZ made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1033354/full#supplementary-material

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Glossary

DES	drug-eluting stent
ISR	in-stent restenosis
ASCVD	atherosclerotic cardiovascular disease
T2DM	type 2 diabetes mellitus
PAD	peripheral arterial disease
IR	insulin resistance
eGDR	estimated glucose disposal rate
T1DM	type 1 diabetes mellitus
WHR	waist-to-hip ratio
HbA1c	glycosylated hemoglobin
WC	waist circumference
CABG	coronary artery bypass grafting
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
PCI	percutaneous coronary intervention
CAD	coronary artery disease
NSTEMI	non-ST-segment elevation myocardial infarction
UA	unstable angina
eGFR	estimated glomerular filtration rate
TIMI	thrombolysis in myocardial infarction
TG	triglyceride
TC	total cholesterol
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
FBG	fasting blood glucose
SYNTAX	the synergy between PCI with taxus and cardiac surgery
SD	standard deviation
OR	odds ratio
CI	confidence interval
BMI	body mass index
MI	myocardial infarction
hs-CRP	high-sensitivity C-reactive protein
LVEF	left ventricular ejection fraction
ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
LM	left main artery
CTO	chronic total occlusion
ROC	receiver operating characteristic
AUC	area under curve
NRI	net reclassification improvement
IDI	integrated discrimination improvement
OHA	oral hypoglycemic agents
HOMA-IR	homoeostasis model assessment of insulin resistance
CVD	cardiovascular disease
TyG	triglyceride-glucose
HDL-C	high-density lipoprotein cholesterol
VAI	visceral adiposity index
LAP	lipid accumulation product

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Monica Annunziata,
Azienda Sanitaria Locale Salerno, Italy
Davide Bonadies,
University of Salerno, Italy

*CORRESPONDENCE
Guoqiang Lin
38328513@qq.com
Qian Xu
elsiexu403@163.com

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The association between body mass index and risk of preoperative oxygenation impairment in patients with the acute aortic syndrome

Chiyuan Zhang[1], Ruizheng Shi[2], Guogang Zhang[1], Hui Bai[3], Yanfeng Zhang[3], Lei Zhang[3], Xuliang Chen[3], Zuli Fu[2], Guoqiang Lin[3]* and Qian Xu[3]*

[1]Department of Cardiovascular Medicine, the Third Xiangya Hospital, Central South University, Changsha, Hunan, China, [2]Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China, [3]Department of Cardiovascular Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China

Objective: The study aimed to determine the relationship between body mass index (BMI) and the risk of acute aortic syndrome (AAS) with preoperative oxygenation impairment.

Methods: A meta-analysis of published observational studies involving BMI and AAS with preoperative oxygenation impairment was conducted. A total of 230 patients with AAS were enrolled for retrospective analysis. All patients were divided into 2 groups (Non-oxygenation impairment group and Oxygenation impairment group). Logistic regression analysis was performed to assess the relation between BMI and the risk of preoperative oxygenation impairment after the onset of AAS. Dose-response relationship curve and subgroup analysis were conducted to test the reliability of BMI as an independent factor of it.

Results: For the meta-analysis, the quantitative synthesis indicated that excessive BMI increased the risk of preoperative oxygenation impairment (OR: 1.30, 95% CI: 1.05-1.60, $P_{heterogeneity}$ = 0.001). For the retrospective analysis, a significant association was observed after adjusting for a series of variables. BMI was significantly related to preoperative oxygenation impairment after the onset of AAS (OR: 1.34, 95% CI: 1.15-1.56, p <0.001), and compared with normal weight group (18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2), the individuals with excessive BMI were at higher risk of preoperative oxygenation impairment for the obese group (BMI ≥ 25 kg/m^2) (OR: 17.32, 95% CI: 4.03-74.48, p <0.001). A J-shape curve in dose-response relationship analysis further confirmed their positive correlation. Subgroup analysis showed that diastolic blood pressure

(DBP) ≥ 90mmHg carried an excess risk of preoperative oxygenation impairment in obese patients.

Conclusion: Excessive BMI was an independent risk factor for AAS with preoperative oxygenation impairment.

KEYWORDS

body mass index, overweight, obesity, acute aortic syndrome, preoperative oxygenation impairment

Introduction

Acute aortic syndrome (AAS) is a serious cardiovascular disease characterized by urgent onset, rapid progression, and high mortality, and often requires strict management including emergency operation (1). Studies have shown that approximately 50% of AAS patients are complicated with preoperative oxygenation impairment (2), which not only prolongs mechanical ventilation time and hospitalization, but also increases the risk of death and leads to a poorer clinical prognosis (3). Therefore, assessment of the risk factors for clinical outcomes is critical for risk stratification and management of these patients.

Preoperative oxygenation impairment is closely related to ventilation-to-perfusion mismatch and intrapulmonary shunting caused by some pulmonary pathologic changes such as alveolar epithelial and microvascular endothelial damage and immune cells recruitment to the lungs (4), but the definite pathogenesis of AAS with preoperative oxygenation impairment has not been well illustrated. It is currently considered that inflammation is involved in its occurrence and development (5, 6). The damaged aorta releases a large number of cytokines into circulation through intimal rupture, and local vascular inflammation can further develop into excessive systemic inflammation through circulation, which results in multiple organ dysfunction (6). Since the pulmonary capillary bed is an important reservoir of inflammatory cells, the lungs are often the main site of tissue damage by AAS, leading to a hypoxic state in AAS patients (6).

Overweight and obesity are increasingly becoming a medical and socio-economic problem in both developed and developing countries, and body mass index (BMI) calculated from height and weight was used as the measure of excess weight in a wide range of studies (7). In recent years, studies have revealed that excessive BMI is associated with preoperative oxygenation impairment in patients with acute aortic dissection (AD) or intramural hematoma (IMH) (2, 3), and obese AAS patients have higher levels of inflammation and oxidative stress than those with normal weight, suggesting its potential value for risk stratification in AAS patients (8). However, other studies found there is no correlation between excess weight and increased risk of preoperative oxygenation impairment such as hypoxemia in patients with AD (9, 10). Thus, the relationship between BMI and AAS with preoperative oxygenation impairment was poorly defined. In order to clarify inconsistent findings, we conducted a meta-analysis. Moreover, we performed a retrospective study to confirm these findings. We sought to evaluate the influence of excessive BMI on preoperative oxygenation impairment among AAS patients, and provide new clinical evidence for risk stratification of such patients.

Methods and material

Study selection and search strategy

The Literatures search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11) and the protocol was registered at the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42022300844. Studies published up to 1 January 2022 were searched for in PubMed, Embase and Web of Science databases and the keywords were: acute aortic syndrome (including AD, IMH, penetrating ulcer) AND oxygenation impairment (including oxygen deficiency, acute respiratory distress syndrome, acute lung injury, hypoxemia) AND preoperative AND body mass index (including obesity, overweight).

All titles and abstracts of studies were screened to select potentially eligible studies, and full texts of those eligible studies were independently reviewed by two investigators (Chiyuan Zhang and Ruizheng Shi). Studies were included if they satisfied the following criteria: (1) studies confirmed to be observational studies; (2) BMI or excess weight (such as obesity) were used as the exposure factors; (3) studies involved the occurrence of AAS with preoperative oxygenation impairment; (4) studies described the value of outcome events with odds ratio (OR) and 95% confidence interval (CI). The related references of the articles that met the requirements above were also included, and duplicated publications were excluded. Our outcome was

limited to AAS with preoperative oxygenation impairment by any of these definitions. Disagreements were discussed and solved through consensus.

Data extraction and quality assessment

We extracted the following information from each included study: first author's surname, publication year, country, ethnicity, study size, sex, number of cases, diagnostic criteria of preoperative oxygenation impairment, BMI, BMI categories, OR value with the corresponding 95% CIs and adjustment factors in the multivariable analysis. These data were independently extracted based on selection criteria. The Newcastle-Ottawa Scale (NOS) score was used to evaluate the quality of those observational studies (including case-control and cohort studies) involved (12), and studies with a score of 6 or greater were assigned as high-quality studies.

Clinical study population

We retrospectively enrolled AAS patients admitted to the Department of Cardiovascular Surgery at Xiangya Hospital from December 2018 to December 2020. The diagnosis of AAS was made by contrast-enhanced computed tomography (CT) of the aorta. Patients with the following conditions were excluded: those aged < 18 years or > 80 years, those who had a clear etiology such as iatrogenic aortic disease, secondary to cardiac surgery or a history of chronic AD or IMH, those with chronic diseases in lung, liver, kidney or malignant tumor, those with cardiac arrest, cardiac tamponade, heart failure, hypotension or shock on admission. The study was approved by the ethics committee of Xiangya Hospital (approval number 202101003, Date: January 15, 2021), and written informed consent was waived given the retrospective nature of the study.

Collection and definition of clinical variables

We collected patients' data including age, gender, BMI, current smoking, vital signs (systolic blood pressure, diastolic blood pressure, heart rate, etc.), comorbidities (hypertension, diabetes mellitus, fatty liver, etc.), laboratory tests (white blood cell count, hemoglobin, platelet, creatinine, etc.), echocardiographic and CT scan findings on admission. Preoperative oxygenation impairment was defined as an arterial oxygen tension (P_{aO2})/inspiratory oxygen fraction (F_{iO2}) ratio ≤ 200 on admission (3). All patients were divided into 2 groups based on the preoperative oxygenation impairment. Besides, in the stratified analysis, due to the differences in body size between Asians and Europeans, patients were further subdivided as: normal weight (18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2), overweight (23.0 kg/m^2 ≤ BMI < 25.0 kg/m^2) and obesity (BMI ≥ 25 kg/m^2) following the Asian criteria (13, 14). AAS is defined as classic acute AD with a patent false lumen and IMH.

Statistical analysis

For the meta-analysis, we used combined OR and 95% CI to determine the association between BMI and the risk of preoperative oxygenation impairment after the onset of AAS. The Q statistic and I^2 statistics were utilized to assess the heterogeneity among the included studies, and data were analyzed with a random effect model. To investigate the effect of potential confounders, subgroup analysis was performed based on the available characteristics of these studies and sensitivity analysis by omitting one study at each time. Publication bias was assessed with Begg's funnel plot test.

For the retrospective analysis, the continuous variables with normally distributed distributions are presented as mean ± SD, and the non-normally distributed continuous variables as median and interquartile range (IQR). The categorical variables were presented by number and percentage. We compared 2 variables using the Student t test or Mann-Whitney U test and 3 variables using the One-way ANOVA test or Mann-Whitney U test for continuous data and the chi-squared test for categorical data as appropriate. We used both univariate and multivariate logistic regression models to evaluate the relationship between BMI and AAS with preoperative oxygenation impairment. Considering the possibility of impact of other known confounding factors (age, gender, Stanford classification, current smoking, etc.), we also conducted a subgroup analysis according to these factors and a dose-response relationship analysis to test the reliability of this association.

A two-sided p value < 0.05 was considered statistically significant and all statistical analyses were performed by STATA 12.0 and R 4.0.3.

Results

Literature search and characteristics of the included studies

A flowchart of the study selection process was shown in Supplementary Figure 1. A total of 101 articles were found in PubMed (n = 22), Embase (n = 41) and Web of Science (n = 38). Then, a list of 8 article was selected after eliminating duplicate records (n = 26) and ineligible ones (n = 67) according to the title and/or abstracts screen. Ultimately, 6 articles were included in the quantitative analysis by removing 2 articles after full-text review. Supplementary Table 1 summarized the characteristics of the included studies. In detail, these studies involved 1244

patients with AAS, and the preoperative oxygenation impairment cases ranged from 21 to 235. Apart from one study conducted in Japan, others were performed in China. Diagnostic criteria of preoperative oxygenation impairment in these studies are as follows: 3 studies used P_{aO2}/F_{iO2} ratio ≤ 200, 2 studies used P_{aO2}/F_{iO2} ratio ≤ 300, 1 study used the concept of acute lung injury without clarifying the value of P_{aO2}/F_{iO2}. Besides, according to the NOS criteria, the score of these studies was 6 to 8, which was presented in Supplementary Figure 2.

Quantitative synthesis and analysis

The 6 case-control studies were included in the meta-analysis. A pooled summary showed that excessive BMI had a higher the risk of preoperative oxygenation impairment after the onset of AAS (Figure 1). The combined ORs (95% CI) were 1.30 (1.05-1.60), and the heterogeneity in these studies was relatively high (I^2 = 75.6%, P = 0.001).

To explore the source of heterogeneity of the result above, subgroup analysis and sensitivity analysis were conducted subsequently. Supplementary Table 2 summarized the results of the subgroup analysis. When stratified by Stanford classification, there was a higher risk of preoperative oxygenation impairment in Stanford type B AAS patients with excess weight. In the stratified analysis by different data forms for BMI, studies choosing BMI as continuous data had a greater risk of preoperative oxygenation impairment than those using BMI as categorical data. Moreover, the sample size was also significantly related to the risk of preoperative oxygenation impairment for AAS patients with excess weight. The sensitivity analysis revealed that none of the individual studies had a large influence on the pooled result (Supplementary Figure 3). In addition, Begg's test indicated no publication bias (P = 0.260), but the funnel plot was asymmetric, so its possibility remains to be considered (Supplementary Figure 4).

Baseline characteristics of AAS patients

A total of 285 AAS patients were enrolled from the Xiangya hospital for this retrospective study. Among them, 55 patients were excluded due to age < 18 years or > 80 years (n = 3), a history of chronic AD or IMH (n = 42), chronic lung disease (n = 6), chronic liver disease (n = 10), chronic kidney disease (n = 8), malignant tumor (n = 1), cardiac arrest (n = 1), cardiac tamponade (n = 2), hypotension or shock (n =3) (Supplementary Figure 5). Thus, 230 AAS patients were ultimately recruited for further analysis. There were 72 AAS patients with preoperative oxygenation impairment (Oxygenation impairment group) and 158 controls (Non-oxygenation impairment group), and the baseline characteristics of the patients were presented in Table 1. In detail, the patients in the oxygenation impairment group were younger and had a higher BMI (all $p < 0.05$). Obesity, fatty liver and hypertension were more common among them (all $p < 0.05$), while coronary artery disease (CAD) was more common in the Non-oxygenation impairment group ($p < 0.05$). In laboratory and imaging examination, patients with preoperative oxygenation impairment had higher levels of diastolic blood pressure (DBP), creatinine (Cr), and P_{aO2}/F_{iO2} ratio (all $p < 0.05$), and were less likely to have Stanford type A AAS and aortic regurgitation than non-oxygenation impairment patients (all

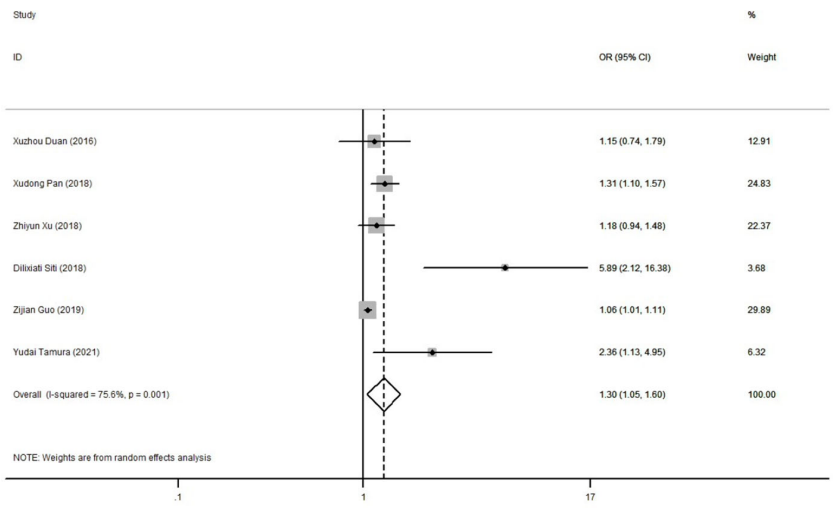

FIGURE 1
Forest plot of the risk of preoperative oxygenation impairment after the onset of AAS. Gray squares indicate the OR in each study, transparent diamond indicates the combined OR in all studies, and horizontal lines represent the 95% CI. AAS, acute aortic syndrome; OR, odds ratio; CI, confidence interval.

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TABLE 1 Baseline characteristics of study participants.

	Non-oxygenation impairment (n=158)	Oxygenation impairment (n=72)	*p* values
Age (years)	54.46 ± 13.21	50.01 ± 10.75	0.013
Sex, male (%)	117 (74.1)	60 (83.3)	0.121
BMI (kg/m^2)	23.65 (22.04-26.15)	26.63 (25.49-29.39)	<0.001
BMI, n (%)			<0.001
18.5 ≤ BMI < 23	65 (41.1)	4 (5.6)	
23 ≤ BMI < 25	37 (23.4)	8 (11.1)	
BMI ≥ 25	56 (35.4)	60 (83.3)	
Current smoking, n (%)	77 (48.7)	43 (59.7)	0.122
Medical history			
Fatty liver, n (%)	39 (34.8)	34 (57.6)	0.004
Hypertension, n (%)	107 (67.7)	60 (83.3)	0.014
CAD, n (%)	17 (10.8)	2 (2.8)	0.041
Diabetes, n (%)	6 (3.8)	1 (1.4)	0.324
Vital signs on admission			
SBP (mmHg)	142.00 (123.00-160.00)	147.50 (129.50-171.50)	0.078
DBP (mmHg)	70.00 (62.00-80.00)	76.50 (65.00-89.25)	0.018
Heart rate (/min)	75.50 (65.75-92.25)	82.5 (71.00-92.00)	0.149
Laboratory data on admission			
WBC (×10^9/L)	11.20 (8.60-13.75)	11.95 (9.53-15.00)	0.076
NE (×10^9/L)	8.80 (6.65-11.50)	10.00 (7.03-12.93)	0.144
Hb (g/L)	130.00 (120.00-139.00)	134.50 (123.00-145.00)	0.084
PLT (×10^9/L)	168.00 (130.50-213.50)	192 (137.00-226.00)	0.151
D-dimer (μg/mL)	1.55 (0.76-2.78)	1.36 (0.50-2.84)	0.465
Cr (μmol/l)	91.60 (73.95-106.85)	99.65 (84.70-127.65)	0.004
CRP (mg/l)	42.25 (8.86-92.53)	47.50 (15.30-78.90)	0.866
P_{aO2}/F_{iO2} ratio	341.00 (269.25-483.50)	171.00 (143.75-185.00)	<0.001
Ultrasound and CT findings on admission			
Stanford classification			0.036
Type A, n (%)	118 (74.7)	44 (61.1)	
Type B, n (%)	40 (25.3)	28 (38.9)	
AD, n (%)	136 (88.3)	66 (91.7)	0.446
IMH, n (%)	33 (21.4)	12 (16.7)	0.404
LVEF (%)	60.00 (56.00-67.00)	60.00 (56.00-66.00)	0.532
LVEDD (mm)	50.00 (45.00-53.50)	50.00 (47.00-54.00)	0.547
Aortic regurgitation, n (%)	127 (89.4)	48 (73.8)	0.004
Pleural effusion, n (%)	32 (22.7)	19 (28.8)	0.344
Medications on admission			
Vasodilators, n (%)	111 (70.3)	63 (87.5)	0.005

Data are presented as mean ± SD, n (%), or medians (interquartile ranges). BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; NE, neutrophile; Hb, hemoglobin; PLT, platelet; Cr, creatinine; CRP, C reactive protein; P_{aO2}/F_{iO2}, arterial oxygen tension/inspiratory oxygen fraction; AD, aortic dissection; IMH, intramural hematoma; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension.

$p < 0.05$). After hospitalization, the oxygenation impairment group received more vasodilators ($p < 0.01$). Then, stratified analysis was performed based on BMI, which was shown in Table 2. The proportion of males and P_{aO2}/F_{iO2} ratio was positively related to BMI increase (all $p < 0.05$). In addition, the fatty liver, hypertension, preoperative oxygenation impairment, and a higher level of DBP, neutrophile (NE), and C reactive protein (CRP) were more common in excessive BMI groups (all $p < 0.05$).

The association between BMI and AAS with oxygenation impairment

To explore the relationship between BMI and the risk of AAS with preoperative oxygenation impairment, a logistic regression analysis was conducted. A significant association was observed in the study after adjusting for age, gender, fatty liver, hypertension, CAD, DBP, Cr, Stanford classification,

10.3389/fendo.2022.1018369

TABLE 2 Stratified analysis of baseline characteristics according to BMI.

	18.5 ≤ BMI < 23 (n=69)	23 ≤ BMI < 25 (n=45)	BMI ≥ 25 (n=116)	*p* values
Age (years)	55.26 ± 14.63	53.62 ± 10.34	51.54 ± 12.06	0.181
Sex, male (%)	45 (65.2)	35 (77.8)[a]	97 (83.6)[bc]	0.016
Current smoking, n (%)	30 (43.5)	23 (51.1)	67 (57.8)	0.169
Medical history				
Fatty liver, n (%)	6 (13.0)	10 (27.8)	57 (64.0)[bc]	<0.001
Hypertension, n (%)	38 (55.1)	36 (80.0)[a]	93 (80.2)[c]	<0.001
CAD, n (%)	7 (10.1)	3 (6.7)	9 (7.8)	0.774
Diabetes, n (%)	3 (4.3)	2 (4.4)	2 (1.7)	0.501
Vital signs on admission				
SBP (mmHg)	142.00 (120.00-162.00)	142.00 (118.00-157.50)	145.50 (130.00-168.75)	0.136
DBP (mmHg)	65.00 (62.00-78.00)	69.00 (62.00-80.00)	76.00 (65.00-84.75)[c]	0.010
Heart rate (/min)	75.00 (65.00-91.00)	82.00 (66.50-92.00)	82.00 (68.00-94.75)	0.331
Laboratory data on admission				
WBC ($\times10^9$/L)	11.3 (8.45-13.78)	10.6 (8.30-12.15)	11.8 (9.60-14.80)	0.090
NE ($\times10^9$/L)	8.80 (6.53-11.70)	8.40 (5.90-10.35)	9.85 (7.13-12.60)[b]	0.039
Hb (g/L)	124.00 (112.25-138.00)	129.00 (123.00-135.50)	136.00 (123.00-145.00)[c]	0.002
PLT ($\times10^9$/L)	162.00 (141.25-202.75)	182.00 (130.50-231.00)	174.50 (131.50-214.75)	0.613
D-dimer (μg/mL)	1.66 (0.83-3.06)	1.14 (0.47-2.67)	1.52 (0.78-2.81)	0.317
Cr (μmol/l)	85.30 (70.70-102.08)	91.60 (77.15-123.70)	98.35 (80.93-113.68)[c]	0.024
CRP (mg/l)	19.45 (3.96-76.80)	42.80 (9.96-117.00)	66.65 (15.38-91.93)[c]	0.022
P_{aO2}/F_{iO2} ratio	424.00 (287.50-572.50)	294.00 (209.00-440.50)[a]	200.00 (161.00-293.75)[bc]	<0.001
Ultrasound and CT findings on admission				
Stanford classification				0.901
Type A, n (%)	50 (72.5)	31 (68.9)	81 (69.8)	
Type B, n (%)	19 (27.5)	14 (31.1)	35 (30.2)	
AD, n (%)	56 (82.4)	41 (93.2)	105 (92.1)	0.078
IMH, n (%)	17 (25.0)	7 (15.9)	21 (18.4)	0.426
LVEF (%)	60.00 (56.00-66.25)	63.00 (57.00-69.00)	60.00 (56.00-65.00)	0.418
LVEDD (mm)	48.00 (44.00-52.00)	50.00 (45.00-57.00)	51.50 (47.00-54.00)[c]	0.021
Aortic regurgitation, n (%)	58 (92.1)	31 (79.5)	86 (81.9)	0.132
Pleural effusion, n (%)	18 (28.6)	8 (20.5)	25 (23.8)	0.631
Medications on admission				
Vasodilators, n (%)	50 (52.2)	29 (64.4)	95 (81.9)	0.052
Oxygenation impairment, n (%)	4 (5.8)	8 (17.8)	60 (51.7)[bc]	<0.001

Data are presented as mean ± SD, n (%), or medians (interquartile ranges).
[a]$P < 0.05$ for 18.5 ≤ BMI < 23 group vs 23 ≤ BMI < 25 group;
[b]$P < 0.05$ for 23 ≤ BMI < 25 group vs BMI ≥ 25 group;
[c]$P < 0.05$ for 18.5 ≤ BMI < 23 group vs BMI ≥ 25 group;
BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; NE, neutrophile; Hb, hemoglobin; PLT, platelet; Cr, creatinine; CRP, C reactive protein; P_{aO2}/F_{iO2}, arterial oxygen tension/inspiratory oxygen fraction; AD, aortic dissection; IMH, intramural hematoma; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension.

aortic regurgitation and vasodilators. As illustrated in Table 3, by multiple logistic regression analysis, BMI was independently related to preoperative oxygenation impairment after the onset of AAS (OR: 1.34, 95% CI: 1.15-1.56, p <0.001), and compared with the normal weight group (18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2), the individuals with excessive BMI were at higher risk of preoperative oxygenation impairment for the obese group (BMI ≥ 25 kg/m^2) (OR: 17.32, 95% CI: 4.03-74.45, p <0.001). Besides, the dose-response relationship presented a J-shaped curve, that was, the risk of AAS with preoperative oxygenation impairment increased with the increased BMI (Figure 2).

For interaction analysis, the study participants were divided into different subgroups according to gender, age, Stanford classification, current smoking, fatty liver, hypertension, CAD, diabetes, vasodilators, DBP, D-dimer, fibrinogen, etc. The results showed no interaction in most strata (p for interaction = 0.058-0.921). Only obese AAS patients with a DBP ≥ 90mmHg had an excess risk of preoperative oxygenation impairment (OR: 37.40, 95% CI: 3.84-364.57, p <0.05) (Table 4).

TABLE 3 The association between BMI and AAS with preoperative oxygenation impairment in univariate and multivariate logistic regression analysis.

	Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values
BMI	1.40 (1.25-1.56)	<0.001	1.34 (1.15-1.56)	<0.001
18.5 ≤ BMI < 23	Reference	–	Reference	–
23 ≤ BMI < 25	3.51 (0.99-12.47)	0.052	4.10 (0.82-20.48)	0.085
BMI ≥ 25	17.41 (5.95-50.93)	<0.001	17.32 (4.03-74.48)	<0.001

BMI, body mass index; AAS, acute aortic syndrome; OR, odds ratio.

Discussion

In our study, we explored the relationship between BMI and preoperative oxygenation impairment after the onset of AAS. Our meta-analysis demonstrated that excessive BMI increased the risk of AAS with preoperative oxygenation impairment. Similarly, our retrospective study further confirmed this correlation above. Multivariate logistic analysis suggested that both excessive BMI could be independent risk factors for preoperative oxygenation impairment in AAS patients. A dose-response relationship curve showed that BMI was positively correlated with the incidence of AAS with preoperative oxygenation impairment. Subgroup analysis indicated that DBP ≥ 90mmHg carried an excess risk of preoperative oxygenation impairment in obese patients with AAS. Our study provided new clinical evidence for risk stratification of AAS patients with preoperative oxygenation impairment.

Preoperative oxygenation impairment is a serious complication that occurs in patients with AAS, which is not only life-threatening but also prolongs the length of ventilator support and intensive care unit (ICU) stay (15). In recent years, with the increasing incidence of the complication, studies have focused on its relationship with BMI, but the results are controversial. For instance, Tamura Y and his colleagues found in a retrospective study of 224 Stanford type B AAS patients that obesity (defined as BMI ≥ 25 kg/m^2) was an independent risk factor of preoperative oxygenation impairment (3). Similarly, Pan X and his colleagues demonstrated that excessive BMI was significantly related to the occurrence of preoperative oxygenation impairment in patients with Stanford type A AD (2). However, two studies from China (9, 16) respectively revealed that there was no significant association between excessive BMI and the increased risk of preoperative oxygenation impairment in acute AD patients. These controversial results may be stemmed from the differences in the diagnostic criteria of oxygenation impairment, the dissimilarities in patients' inclusion criteria, and the different adjustments for identifying the risk factors of AAS with preoperative oxygenation impairment

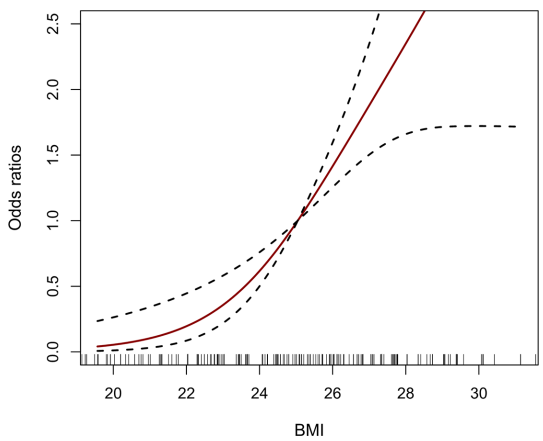

FIGURE 2
The dose-response relationship between BMI and AAS with preoperative oxygenation impairment. The vertical black bars represent individual BMI values. The solid red line and the dash black line represent the estimated OR and its 95% CI. BMI, body mass index; AAS, acute aortic syndrome; OR, odds ratio; CI, confidence interval.

In the present study, we reviewed 6 studies for meta-analysis. Based on the NOS scores, the included studies were of high quality (a score of 6-8), suggesting their reliable results. The quantitative synthesis indicated that BMI was independently related to oxygenation impairment after the onset of AAS. Similar results were observed in the subgroup analysis of the Stanford classification and different data forms for BMI. Furthermore, we retrospectively recruited 230 individuals in our center and found that preoperative oxygenation impairment occurred in approximately one-third of patients with AAS. These patients were younger, had higher BMI, DBP and Cr, more fatty liver, hypertension, used vasodilators, and had less Stanford type A AAS, CAD, and aortic regurgitation. When we further stratified all subjects according to the BMI, a significant positive correlation between BMI and P_{aO2}/F_{iO2} ratio was identified, and preoperative oxygenation impairment was more common in obese patients with AAS. We further found that overweightness is an independent risk factor of AAS with preoperative oxygenation impairment, which confirms the results of our meta-analysis. Also, the dose-response analysis and subgroup analysis proved its reliability and potential value

10.3389/fendo.2022.1018369

TABLE 4 Interaction analysis of the association with BMI and AAS with preoperative oxygenation impairment.

	No. of patients	BMI levels (kg/m^2)			*p* for interaction
		18.5-23	23-25	≥ 25	
Gender					0.136
Male	177	ref	3.58 (0.65-19.71)	25.90 (5.94-112.98)	
Female	53	ref	4.71 (0.65-34.18)	6.42 (1.15-35.90)	
Age, years					0.004
< 60	163	ref	/	/	
≥ 60	67	ref	0.69 (0.07-7.07)	2.50 (0.66-9.51)	
Stanford classification					<0.001
Type A	162	ref	3.35 (0.89-12.61)	7.91 (2.50-24.08)	
Type B	68	ref	/	/	
AD					0.704
No	24	ref	/	13.75 (1.21-156.65)	
Yes	202	ref	4.28 (1.06-17.30)	19.43 (5.71-66.13)	
IMH					0.525
No	181	ref	4.41 (1.08-17.98)	17.82 (5.18-61.29)	
Yes	45	ref	/	17.6 (1.96-157.94)	
Current smoking					0.324
No	110	ref	5.44 (0.96-30.92)	15.07 (3.26-69.63)	
Yes	120	ref	2.10 (0.32-13.75)	18.35 (4.04-83.36)	
Fatty liver					0.178
No	98	ref	3.46 (0.58-20.42)	27.77 (5.68-135.81)	
Yes	73	ref	3.33 (0.277-40.29)	5.18 (0.57-47.16)	
Hypertension					0.921
No	63	ref	/	/	
Yes	167	ref	2.05 (0.55-7.72)	9.47 (3.11-28.81)	
CAD					0.058
No	211	ref	2.90 (0.79-10.62)	17.82 (6.04-52.61)	
Yes	19	ref	/	/	
Diabetes					0.918
No	223	ref	3.54 (1.00-12.61)	16.63 (5.67-48.76)	
Yes	7	ref	/	/	
Vasodilators					0.546
No	56	ref	/	/	
Yes	174	ref	3.00 (0.77-11.70)	14.51 (4.84-43.55)	
SBP, mmHg					0.552
< 140	93	ref	1.50 (0.19-11.64)	14.79 (3.13-69.90)	
≥ 140	137	ref	6.00 (1.10-32.60)	20.09 (4.50-89.58)	
DBP, mmHg					0.044
< 90	192	ref	4.36 (1.08-17.62)	15.18 (4.43-51.99)	
≥ 90	38	ref	/	37.40 (3.84-364.57)	
D-dimer, μg/mL					0.427
< 0.5	40	ref	0.64 (0.07-5.61)	7.00 (1.10-44.61)	
≥ 0.5	188	ref	6.58 (1.24-34.80)	27.92 (6.45-120.83)	
Fibrinogen, g/L					0.078
< 4	166	ref	10.20 (1.99-52.24)	27.37 (6.26-119.68)	
≥ 4	63	ref	11.16 (2.05-49.93)	6.93 (1.34-35.99)	
ESR, mm/h					0.266
< 20	65	ref	20.00 (1.74-229.49)	22.35 (2.70-184.79)	

(Continued)

TABLE 4 Continued

	No. of patients	BMI levels (kg/m^2)			*p* for interaction
		18.5-23	23-25	≥ 25	
≥ 20	73	ref	2.04 (0.30-13.85)	8.97 (1.81-44.47)	
CRP, mg/l					0.502
< 8	18	ref	11.00 (0.35-345.06)	33.00 (1.56-697.96)	
≥ 8	74	ref	1.94 (0.36-10.43)	5.90 (1.48-23.44)	
IL-1β, pg/ml					0.454
< 5.0	43	ref	5.50 (0.61-49.54)	3.93 (0.71-21.75)	
≥ 5.0	52	ref	1.40 (0.08-25.14)	8.75 (0.99-77.19)	
TNF-α, pg/ml					0.904
< 8.1	33	ref	/	/	
≥ 8.1	49	ref	1.87 (0.24-14.65)	3.67 (0.84-16.04)	
IL-10, pg/ml					0.215
< 9.1	70	ref	1.64 (0.28-9.58)	2.75 (0.67-11.32)	
≥ 9.1	24	ref	/	/	
Aortic regurgitation					0.609
No	32	ref	1.33 (0.09-20.11)	11.2 (1.00-125.64)	
Yes	175	ref	3.53 (0.78-15.89)	15.94 (4.63-54.92)	
Pleural effusion					0.846
No	110	ref	1.83 (0.24-14.13)	14.79 (3.23-67.79)	
Yes	78	ref	2.86 (0.46-17.81)	13.75 (2.81-67.41)	

BMI, body mass index; AAS, acute aortic syndrome; AD, aortic dissection; IMH, intramural hematoma; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; IL-1β, Interleukin-1β; TNF-α, Tumor necrosis factor-α; IL-10, Interleukin-10.

for prediction. Recent studies have shown that the AAS complicated by oxygenation impairment is closely related to inflammation, and it is believed that the progression of local vascular inflammation caused by intima tear and hematoma formation in AAS plays a vital role, which can develop into systemic inflammatory reaction and result in acute lung injury (17). However, few studies have investigated its pathogenesis in obese patients. Obese patients have abundant adipose tissue, but the vascular system in the tissue is underdeveloped so adipocytes are prone to hypoxia (18). Continuous over-nutrition eventually leads to a state of chronic hypoxia within the adipose tissue in obese patients (18). Also, adipose tissue can release a variety of cytokines including inflammatory factors into circulation (19), and hypoxia has been demonstrated to be one of the most potent stimuli for the release of a series of inflammatory factors such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and activating pro-inflammatory signaling pathways (20, 21). Thus, obese patients have subclinical chronic inflammation, leading to a predisposition to a severe respiratory inflammatory response and oxygenation impairment (21). It is reported that obese patients with AAS showed an elevated IL-1β, TNF-α, and IL-6 (8), while our study also revealed that these patients had a higher level of NE and CRP (P = 0.039, 0.022), suggesting a more severe inflammatory response in such patients. These inflammatory reactants may directly destroy pulmonary vascular endothelial cells through circulation, resulting in pulmonary dysfunction and oxygenation impairment (17), and hypoxia can further stimulate adipocytes to release inflammatory cytokines, creating a vicious cycle. In addition, obesity is a significant factor for hypoxemia and ventilation in the ICU, (22). The high-fat content in the pleura or chest walls of obese patients can limit thoracic breathing and diaphragmatic activity and reduce respiratory resistance and airway resistance (22, 23).

The result of the subgroups analysis showed no interaction in most strata, which proved that obesity was a reliable independent risk factor for AAS with preoperative oxygenation impairment. We also found that obese AAS patients with DBP ≥ 90mmHg had an excess risk of oxygenation impairment. It is well known that one of the main treatments for AAS is the antihypertensive therapy, to decrease the shear stress on the aortic wall and reduce the size of the tear in the false lumen (24). Thus, the higher blood pressure in AAS, the higher the risk of aortic rupture and/or other complications such as visceral and peripheral ischemia, which can promote oxygenation impairment (25). Besides, DBP is an indicator of peripheral vascular resistance. A significantly increased DBP in patients with AAS can lead to organ malperfusion including lung and may contribute to the ventilation-blood flow mismatch and a state of hypoxia. Perhaps, it could explain the reason why DBP ≥ 90mmHg had an excess risk of oxygenation impairment in obese patients with

AAS. Furthermore, our result suggested that more severe measures should be taken in this situation.

It is the first time to estimate the association between different BMI groups and AAS with preoperative oxygenation impairment. Together with previous studies, our results supported the potential value of BMI as an indicator for risk stratification and obesity as an independent risk factor of preoperative oxygenation impairment in AAS patients, which provided potent clinical evidence for the prevention and management of such patients. The limitations of this study are listed as follows: firstly, the inclusion of case-control studies and significant heterogeneity in the meta-analysis increased bias in the results; secondly, our study included a retrospective single-center analysis and its sample size was relative small, which might not be universally representative. More large-scale prospective studies need to validate the present results in the future.

In conclusion, our findings are consistent with the general consensus that excessive BMI is an independent risk factor for AAS with preoperative oxygenation impairment. AAS patients who have a BMI of 25 or greater are at increased risk of preoperative oxygenation impairment.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Xiangya Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

QX and GL conceived the study. CZ reviewed publications, extracted the data of eligible studies for the meta-analysis, performed the statistical analysis and wrote the first draft of the paper. RS reviewed publications and extracted the data of eligible studies for the meta-analysis. GZ and HB extracted the data of eligible studies for the meta-analysis. YZ and LZ recruited the AAS patients with and without oxygenation impairment and collected their clinical data. XC and ZF performed the statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1018369/full#supplementary-material

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Yasith Mathangasinghe,
University of Colombo, Sri Lanka
Han-Yeong Jeong,
Seoul National University Hospital,
Republic of Korea

*CORRESPONDENCE
Yilong Qi
qiyilong32111@aliyun.com

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Elevated visceral adiposity index is associated with increased stroke prevalence and earlier age at first stroke onset: Based on a national cross-sectional study

Qingjie Chen, Ziwen Zhang, Ning Luo and Yilong Qi*

Department of Neurosurgery, The 902nd Hospital of The Chinese People's Liberation Army, Bengbu, China

Objective: The purpose of this study was to examine the association between the VAI (visceral adiposity index) and stroke prevalence and age at stroke in US adults.

Methods: We examined the association between VAI and stroke prevalence and age at stroke using logistic regression, subgroup analysis, and dose-response curves using participants from the National Health and Nutrition Examination Survey (NHANES) database from 2007-2018.

Results: This study ultimately included 29,337 participants aged >20 years, of whom 1022 self-reported a history of stroke, and after adjusting for all confounders, each unit increase in corrected VAI was associated with a 12% increase in the prevalence of stroke (OR= 1.12, 95% CI: 1.01, 1.24) along with an earlier age at stroke 1.64 years (β= -1.64, 95% CI: -2.84, -0.45), stratified analysis showed that the prevalence of stroke was 20% higher in the female group (OR= 1.20, 95% CI: 1.04, 1.39), black group (OR= 1.22, 95% CI: 1.01, 1.48), age ≤60 years group (OR= 1.25, 95% CI: 1.05, 1.48), hypertensive group (OR=1.15, 95% CI:1.01, 1.31), and diabetic group (OR=1.23, 95% CI:1.02, 1.48) VAI increase was positively correlated with stroke prevalence increase. The dose-response curves showed a positive linear correlation between increased VAI and stroke prevalence, while a negative linear correlation was observed between increased VAI and age at stroke.

Conclusion: Although a causal relationship cannot be proven, higher VAI was positively associated with stroke prevalence and can lead to earlier stroke onset.

KEYWORDS

stroke prevalence, stroke onset age, VAI, cross-sectional study, metabolic syndrome

1 Introduction

Globally, stroke is the third leading cause of death and the leading contributor to persistent and acquired disability in adults. Approximately 70%-80% of strokes are ischemic strokes, with hemorrhagic strokes accounting for the remainder (1, 2). From 2009 to 2012, a survey of adults aged 20 years or older showed that the overall prevalence was about 2.6% (3). Strokes occur in about 17.8% of people over 45 years old, and asymptomatic cerebral infarction occurs in 6%-28% of those over 45 years old (4). Strokes cost the country and individuals an estimated $45.5 billion each year in 2014-2015 (5), which is a serious economic burden. Public health must take stroke prevention seriously because stroke is a major public health issue.

At present, there is evidence that metabolic syndrome is a combination of risk factors for stroke development, including atherosclerotic dyslipidemia, hypertension, insulin resistance, and obesity, all of which contribute to atherosclerotic vascular disease (6). There is a high risk of stroke and recurrent stroke for people with metabolic syndrome, according to several studies (7–9). With obesity on the rise, the prevalence of metabolic syndrome is expected to rise substantially as obesity increases in the future (10). In turn, this increase in stroke prevalence may place a heavier burden on society due to the close association between metabolic syndrome and obesity. There are limited reliable indicators of obesity that can be used to predict and assess stroke risk despite obesity being strongly associated with stroke.

Adipocytes store triglycerides in adipose tissue, which controls lipid metabolism and glucose homeostasis (11). In addition to storing energy, adipose tissue performs an active endocrine function. Numerous bioactive substances are produced in the body by fat cells, lipid-resident immune cells, and endothelial cells (12). Diabetes, hypertension, cardiovascular disease, and cardiometabolic risk factors are more closely linked to visceral adipose tissue than subcutaneous adipose tissue (13–15). Body fat can be assessed with a variety of methods, including densitometry (dual-energy X-ray absorptiometry, DXA), magnetic resonance imaging (MRI), computed tomography (CT), and mechanical methods. These methods have a high degree of accuracy in assessing body fat, and the first three methods also provide fat imaging and location within the body (16). The costs and time involved in these procedures make them unsuitable for routine use in clinical practice because they are technically complex and expensive.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; PIR, ratio of family income to poverty; NCHS, National Center for Health Statistics; CI, confidence interval; OR, odds ratio; MetS, metabolic syndrome; IR, insulin resistance; TG, triglyceride; TC, Cholesterol; FPG, fasting plasma glucose, VAI, visceral adiposity index.

An adipose tissue function indicator, the visceral adiposity index (VAI) measures the distribution of abdominal fat. Based on waist circumference (WC), body mass index (BMI), triglycerides (TG), and high density lipoprotein (HDL) cholesterol, it is a novel and specific index that indirectly measures visceral adipose function (17). Compared with traditional parameters such as waist circumference and body mass index, the VAI is said to be more sensitive and specific. There has been some progress made in the use of VAI in cardiovascular disease risk assessment associated with obesity (17–19). While it has been reported that VAI is associated with stroke, a study by Zhang et al. (20) found that VAI was positively associated with angina pectoris, heart attack, stroke, hypertension, and coronary artery disease, and a study by Cui et al. (21) found an association between VAI and sudden stroke in Chinese people. However, fewer covariates were included in Zhang and Cui's study, and more covariates need to be included to assess the relationship. Furthermore, VAI and stroke onset age were included in the study, which has not yet been published. As a result, in this study, we set out to determine if VAI was useful in predicting stroke onset and stroke age in the US adult population.

2 Materials and methods

2.1 Study population

Based on National Health and Nutrition Examination Survey (NHANES) data collected between 2007 and 2018, we evaluated baseline clinical data from only participants over 20 years old who completed the stroke questionnaire, and we analyzed data on participants who explicitly responded to whether they had suffered a stroke. The questionnaire was completed by 59842 people. Exclusion criteria were as follows (Figure 1). Finally, 29337 cases, including 1022 self-reported stroke cases, were included in this study.

2.2 Data collection and definition

As an exposure variable, VAI was developed. The following sex-specific equations were used to calculate VAI, where the units for WC, BMI, and TG and HDL are cm kg/m2, and mmol/L (22). A biochemical analysis used an enzyme-based method to determine triglyceride concentrations. With the Roche Cobas 6000 chemistry analyzer and Roche Modular P chemistry analyzer, serum triglyceride concentrations were measured. Stroke presence or absence and age at stroke onset were assessed by questionnaires. The presence or absence of stroke and the age at stroke were designed as outcome variables.

Multivariate adjusted models summarized potential covariates that may confound the association between VAI

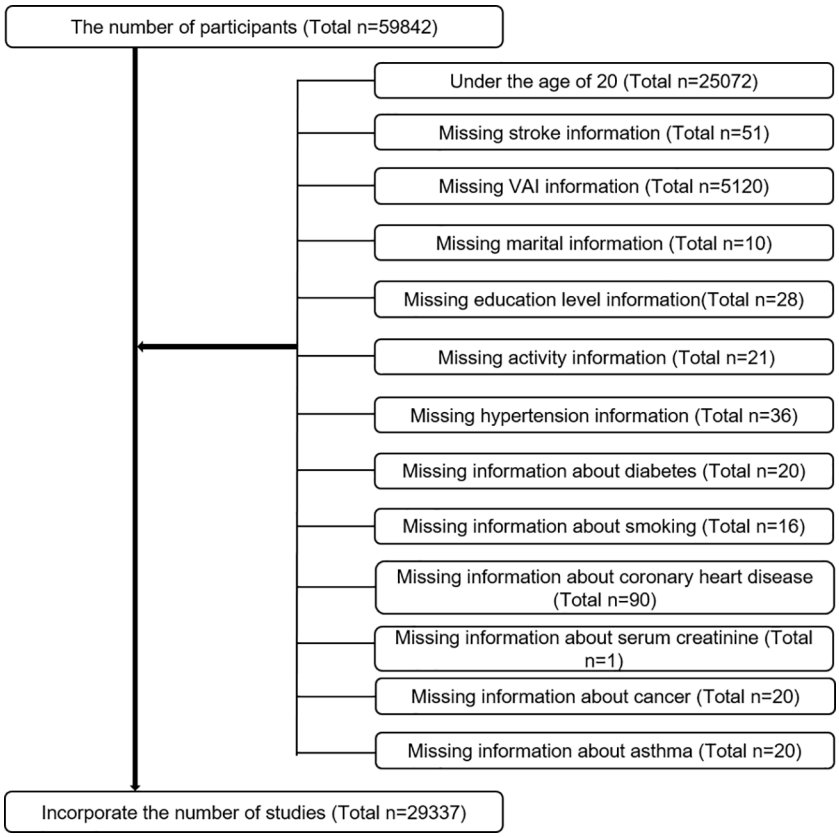

FIGURE 1
Sample selection process flow chart.

and stroke. Covariates in our study included sex (male/female), age (years), race, education level, poverty to income ratio (PIR), marital status (married or living with partner/single), alcohol consumption (drinking or not), physical activity (vigorous/moderate/below moderate), cholesterol level (mg/dl), fasting glucose (mg/dl), urine protein creatinine ratio (mg/g), smoking status (smoking or not), hypertension (smoking or not), diabetes (smoking or not), coronary heart disease (smoking or not), cancers (yes or not), and dietary intake factors, including energy intake, fat intake, sugar intake, and water intake. All participants in years 2007-2018 with two 24-hour dietary recalls will have their consumption averaged based on the two recalls. The numerical variables with more missing data were converted to categorical variables, and the lowest dichotomous was used as the benchmark. The CDC has posted all detailed measurements of the study variables online at www.cdc.gov/nchs/nhanes/. All NHANES protocols were implemented in accordance with the U.S. Department of Health and Human Services (HHS) Human Research Subject Protection Policy and were reviewed and standardized annually by the NCHS Research Ethics Review Committee. All subjects who participated in the survey signed an informed consent form. All data in this study were released free of charge by NHANES without additional authorization or ethical review.

Smoking status (SMQ020 - Smoked at least 100 cigarettes in life), diabetes (DIQ010 - Doctor told you have diabetes), coronary heart disease (MCQ160C - Ever told you had coronary heart disease), and cancer (MCQ220 - Ever told you had cancer or malignancy) were obtained from the questionnaire data. Participants were considered to have the disease when they answered "yes". For hypertension using blood pressure monitoring data from the physical examination, NHANES obtained three consecutive blood pressure readings after participants rested quietly in a seated position for 5 minutes and determined the maximum inflation level (MIL), we took the average of the three tests and converted them into categorical variables according to 140/90 mmHg, with missing values forming their own dummy variable group. The activity data was obtained from the activity questionnaire(PAQ605 - Vigorous work activity, PAQ620 - Moderate work activity, PAQ650 - Vigorous recreational activities, PAQ665 - Moderate recreational activities), when there was strenuous work or recreational activity was identified as the strenuous activity group, when there was moderate work or recreational

activity was identified as the moderate activity group, and when there was none of the above activities was considered as the inactive group.

When continuous variables have a large number of missing values, we convert them to categorical variables (23, 24), where the missing values form their own group as a dummy variable group.

2.3 Statistical methods

To demonstrate the complex, multi-stage sampling design used in selecting a representative U.S. non-institutionalized population, all statistical analyses were conducted using the sampling weights, stratification, and clustering provided in the NHANES study. A weighted survey mean and 95% confidence intervals are used to express continuous variables, and a weighted survey mean and 95% confidence intervals are used to express categorical variables. Due to the skewed distributions of VAI, LN transformations are applied to transform them into normal distributions. All covariates were screened for variance inflation factor (VIF) covariance, and if the VIF value exceeded 5, the covariate was removed. As per the guidelines, multiple logistic regression models were used to explore the VAI, different VAI triplet groups, and stroke prevalence in three different models based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (25). As far as model 1 is concerned, no adjustment for covariates was made. Several factors were adjusted in model 2, including gender, age, race, marital status, and education. Adjustments were made to all variables in model 3. To further clarify the relationship between VAI and stroke, we used a propensity score method and performed sensitivity analyses. Smoothed curve fitting (penalized spline method) and generalized additive model regression (GAM) were carried out. When a nonlinear relationship was determined to exist, likelihood ratio tests were used to determine inflection point values. Multiple regression analyses were next performed stratified by sex, age, race, hypertension, and diabetes. $p < 0.05$ was considered statistically significant. All analyses were performed using Empower software www.empowerstats.com (X&Y Solutions, Inc., Boston, Massachusetts, USA) and R version 4.0.2 (http://www.R-project.org, The R Foundation).

3 Results

The demographic characteristics of the included participants are shown in Table 1. The VAI was 0.72 (0.66,0.78) in the stroke group, higher than 0.56 (0.54,0.58) in the normal group, $p < 0.0001$. There was a significant difference between the stroke group and the normal group in the proportion of blacks, age, prevalence of hypertension, and prevalence of diabetes.

3.1 A higher VAI is associated with a higher prevalence of stroke

In the final adjusted model, all variables were included if the VIF for each indice was below 5. For stroke, a positive correlation was observed between the VAI and stroke prevalence. Based on the fully adjusted model (model 3), we found a positive association of 1.12 (95% confidence interval: 1.01, 1.21) between the LN-transformed VAI and stroke prevalence of 12%. Furthermore, in order to analyze sensitivity, the VAI was transformed into a categorical variable (dichotomous). Increased prevalence of stroke in high dichotomies compared to the lowest VAI dichotomous group, but there was no effect value (OR=1.10, 95% CI: 0.95, 1.28). (Table 2). Each unit increase in VAI value after propensity matching was associated with a 29% increase in adjusted stroke prevalence (OR=1.29,95% CI:1.14,1.47) (Supplementary Tables 1, 2).

3.2 Analysis of the dose-response and threshold effects of VAI on stroke prevalence

A generalized additive model and smoothed curve fitting were used to investigate the relationship between the VAI and stroke prevalence. According to our findings (Figure 2), stroke prevalence was linearly related to the VAI.

3.2.1 Subgroup analysis

Subgroup analyses were performed to assess the robustness of the association between VAI and stroke prevalence. The results showed that in the subgroup analysis the VAI indices in the female group (OR=1.15, 95% CI: 1.01, 1.24), black group (OR=1.22, 95% CI:1.01, 1.48), age ≤60 years group (OR=1.25, 95% CI:1.05, 1.48), hypertension group (OR=1.15, 95% CI:1.01, 1.31), and diabetes group (OR=1.23, 95% CI:1.02, 1.48) VAI increase were all positively associated with increased prevalence of stroke. (Table 3).

3.3 Elevated VAI and earlier age of stroke onset

Using the fully adjusted model 3, for every one unit increase in Ln (VAI), stroke onset age was 1.64 years earlier (OR=-1.64, 95% CI: -2.84, -0.45) (Table 4).

10.3389/fendo.2022.1086936

3.4 Analysis of the dose response and threshold effect of VAI on age at stroke onset

A generalized additive model and smoothed curve fitting were used to examine the relationship between the VAI and age at stroke onset. Based on our results, VAI increased with increasing age at stroke onset in a negative linear relationship (Figure 3).

4 Discussion

As a result of industrialization and urbanization, there has been an increase in the consumption of food and lifestyle, suggesting that these changes are risk factors for stroke development (26, 27) . Thus, epidemiological studies of stroke onset associated with metabolic syndrome are reasonable. As well, VAI is more sensitive and specific than traditional waist

TABLE 1 Baseline characteristics of participants, weighted.

Characteristic	Non-stroke formers (*n* = 28315)	Stroke formers (*n* = 1022)	P-value
Age(years)	46.78 (46.34,47.23)	63.53 (62.32,64.74)	<0.0001
Serum Cholesterol (mg/dl)	194.20 (193.19,195.22)	184.53 (180.65,188.41)	<0.0001
Ln(VAI)	0.56 (0.54,0.58)	0.72 (0.66,0.78)	<0.0001
Serum Creatinine(mg/dl)	0.87 (0.87,0.88)	1.05 (1.01,1.10)	<0.0001
Serum Glucose(mg/dl)	99.12 (98.56,99.67)	112.35 (109.10,115.61)	<0.0001
Gender(%)			0.0133
Male	48.66 (48.06,49.26)	43.21 (38.98,47.55)	
Female	51.34 (50.74,51.94)	56.79 (52.45,61.02)	
Race(%)			<0.0001
Mexican American	14.82 (12.92,16.94)	7.83 (6.21,9.83)	
White	66.66 (63.79,69.41)	69.36 (64.97,73.42)	
Black	10.49 (9.19,11.94)	15.48 (12.88,18.49)	
Other Race	8.03 (7.19,8.96)	7.33 (5.31,10.05)	
Education Level(%)			<0.0001
Less than high school	20.02 (18.65,21.46)	34.03 (30.25,38.02)	
High school	28.89 (27.76,30.05)	30.46 (26.63,34.58)	
More than high school	51.09 (49.22,52.96)	35.52 (31.08,40.22)	
Marital Status(%)			0.0199
Cohabitation	64.14 (62.88,65.39)	58.83 (54.15,63.35)	
Solitude	35.86 (34.61,37.12)	41.17 (36.65,45.85)	
Alcohol(%)			0.0009
Yes	61.23 (59.76,62.68)	53.91 (49.87,57.89)	
No	18.47 (17.39,19.60)	23.41 (19.97,27.24)	
Unclear	20.30 (19.21,21.43)	22.69 (19.39,26.36)	
Diabetes(%)			<0.0001
Yes	8.87 (8.41,9.35)	29.42 (26.14,32.93)	
No	91.13 (90.65,91.59)	70.58 (67.07,73.86)	
Smoked(%)			<0.0001

(Continued)

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TABLE 1 Continued

Characteristic	Non-stroke formers (*n* = 28315)	Stroke formers (*n* = 1022)	P-value
Yes	43.77 (42.56,44.99)	59.92 (56.02,63.69)	
No	56.23 (55.01,57.44)	40.08 (36.31,43.98)	
Physical Activity(%)			<0.0001
Never	25.77 (24.83,26.75)	48.58 (44.45,52.73)	
Moderate	31.90 (30.99,32.82)	32.45 (28.65,36.50)	
Vigorous	42.33 (41.24,43.42)	18.96 (15.84,22.54)	
Asthma(%)			<0.0001
No	85.52 (84.85,86.17)	75.82 (72.52,78.85)	
Yes	14.48 (13.83,15.15)	24.18 (21.15,27.48)	
Coronary Artery Disease			<0.0001
Yes	2.98 (2.64,3.35)	19.20 (15.86,23.05)	
No	97.02 (96.65,97.36)	80.80 (76.95,84.14)	
Cancers			<0.0001
Yes	9.63 (9.17,10.10)	23.08 (19.11,27.59)	
No	90.37 (89.90,90.83)	76.92 (72.41,80.89)	
Ratio of Family Income to Poverty			<0.0001
<1.3	19.66 (18.48,20.90)	31.17 (27.34,35.27)	
≥1.3<3.5	32.60 (31.35,33.87)	39.59 (35.19,44.17)	
≥3.5	40.45 (38.59,42.33)	22.31 (18.49,26.65)	
Unclear	7.29 (6.67,7.96)	6.93 (5.27,9.07)	
Total Kcal(%)			<0.0001
Lower	38.86 (38.07,39.65)	52.72 (48.30,57.10)	
Higher	46.40 (45.47,47.33)	33.97 (30.25,37.89)	
Unclear	14.75 (13.94,15.59)	13.31 (10.59,16.61)	
Total Sugar(%)			0.0444
Lower	36.40 (35.58,37.22)	40.86 (37.04,44.79)	
Higher	37.22 (36.31,38.13)	36.63 (32.36,41.12)	
Unclear	26.38 (25.61,27.17)	22.51 (19.25,26.15)	
Total Fat(%)			<0.0001
Lower	38.42 (37.49,39.35)	50.85 (47.00,54.70)	
Higher	46.83 (45.89,47.78)	35.83 (32.50,39.31)	
Unclear	14.75 (13.94,15.59)	13.31 (10.59,16.61)	
High Blood Pressure(%)			<0.0001
No	78.26 (77.24,79.24)	62.32 (57.94,66.51)	
Yes	12.70 (12.09,13.33)	24.13 (21.04,27.52)	
Unclear	9.04 (8.23,9.94)	13.55 (10.34,17.55)	

(Continued)

TABLE 1 Continued

Characteristic	Non-stroke formers (*n* = 28315)	Stroke formers (*n* = 1022)	P-value
Urine Albumin Creatinine Ratio(%)			<0.0001
Lower	54.86 (53.90,55.82)	32.04 (27.12,37.40)	
Higher	44.59 (43.64,45.54)	65.28 (60.10,70.12)	
Unclear	0.55 (0.46,0.67)	2.68 (1.87,3.83)	
Total Water(%)			<0.0001
Lower	38.42 (37.49,39.35)	50.85 (47.00,54.70)	
Higher	46.83 (45.89,47.78)	35.83 (32.50,39.31)	
Unclear	14.75 (13.94,15.59)	13.31 (10.59,16.61)	

Data of continuous variables are shown as survey-weighted mean(95%CI), P value was calculated by survey-weighted linear regression.Data of categorical variables are shown as survey-weighted percentage (95%CI), P value was calculated by survey-weighted Chi-square test.

circumference and BMI for obesity (18, 19, 28) . Therefore, in this study, we investigated the relationship between VAI levels and stroke in a large U.S. population and found that after adjusting for all confounders, increased VAI levels were positively correlated with stroke prevalence, and age at stroke was negatively correlated with increased VAI levels. The age of first stroke onset was 1.64 years earlier with each unit increase in VAI after correction, and the prevalence of stroke increased 12% after correction.

Stroke affects both physical and mental health severely, placing an immense burden on our society in terms of morbidity, quality of life, and healthcare costs. These pressures continue to rise throughout the world, making stroke prevention particularly crucial. The VAI can also be used to find specific populations adapted to the index and prevent strokes from occurring more often. Consequently, we performed subgroup analyses on females, blacks, those aged >60, hypertensives, and diabetics and found elevated VAI levels were positively associated with increased stroke prevalence. According to several previous related studies, we suspect this finding to be accurate. As previously reported, VAI differences have been found in correlation studies of atherosclerosis, cardiovascular disease, and asymptomatic cerebral infarction (17, 21, 29–31) . A study by Li et al (32) showed that women with VAI were associated with intracranial atherosclerosis, but not men. The findings of Nakagomi (33) also indicate that VAI increases atherosclerosis in women and the association is stronger. As well as predicting cardiometabolic disease in older women, VAI has been found useful in cardiovascular disease studies - a score of 2.71 can be used to identify high-risk women (34). Based on the same study by Mohammadreza (35), women were independently at an increased risk of cardiovascular disease after VAI. According to a Korean study published in 2020, high VAI levels were associated with an increased risk of asymptomatic cerebral infarction in healthy females, particularly (36). Nakagomi (33) speculates that the possible explanation for the above findings is either differences in hormone levels between men and women or differences in the composition of visceral adipose tissue and subcutaneous adipose tissue. However, the etiologic mechanism behind these findings remains unclear. As a result of our study, VAI has a greater effect on stroke risk among younger people than those older than 60 years of age. So far, it seems that young and middle-aged individuals have different risk factors for stroke compared to elderly individuals. Atherosclerosis (including atrial fibrillation), hypertension and diabetes mellitus are the three most common

TABLE 2 Analysis between VAI with stroke prevalence.

Characteristic	Model 1 OR(95%CI)	Model 2 OR(95%CI)	Model 3 OR(95%CI)
Ln(VAI)	1.20 (1.11, 1.29)	1.22 (1.12, 1.33)	1.12 (1.01, 1.24)
Categories			
Lower	1	1	1
Higher	1.30 (1.14, 1.47)	1.25 (1.10, 1.43)	1.10 (0.95, 1.28)

Model 1=no covariates were adjusted.
Model 2=Model 1+age, gender, race education, marital status were adjusted.
Model 3=Model 2+, diabetes, blood pressure, asthma, PIR, total water, total kcal, total sugar, smoked, physical activity, alcohol use, serum cholesterol, coronary artery disease, serum creatinine urine albumin creatinine ratio, cancers and serum glucose were adjusted.

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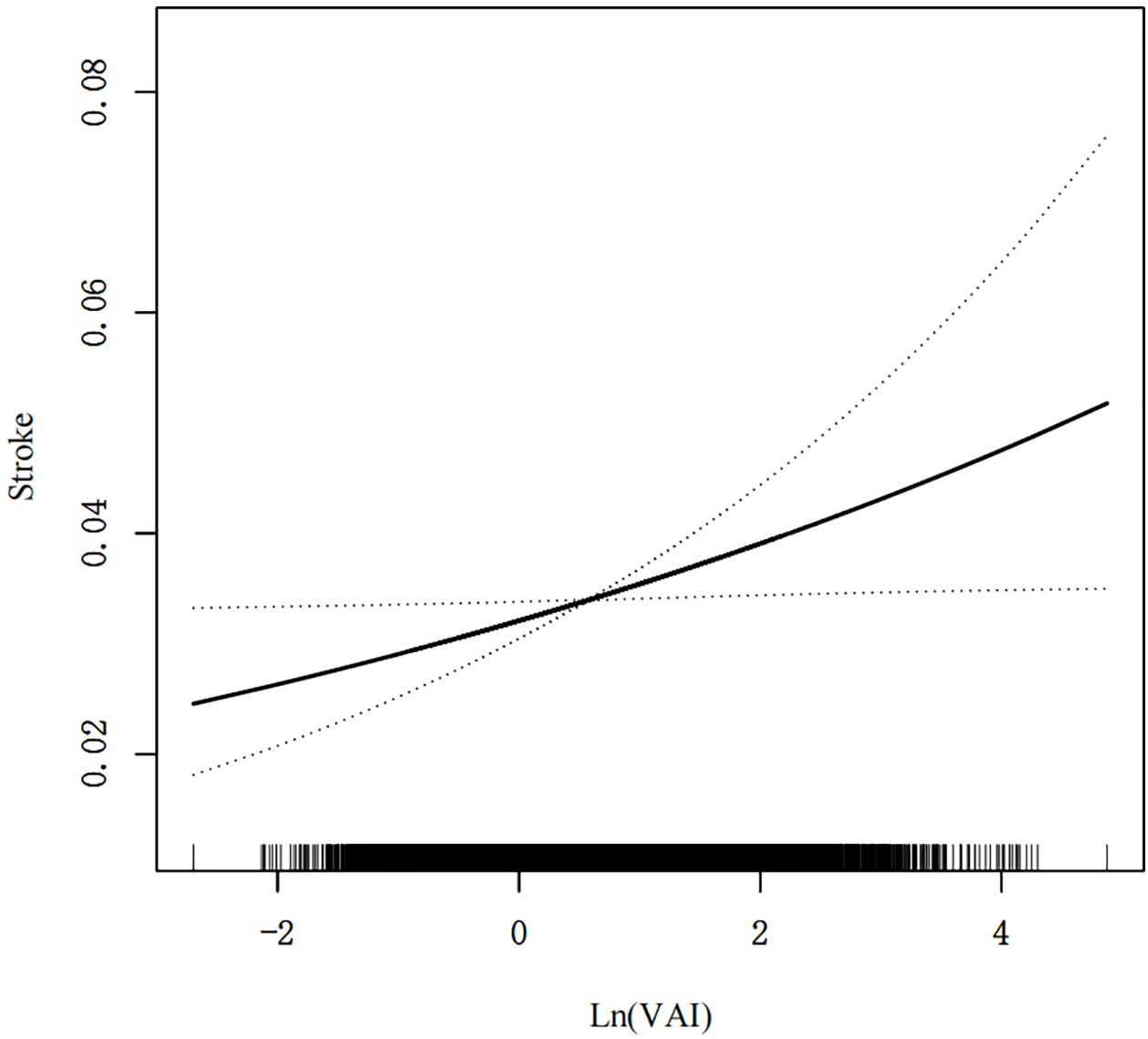

FIGURE 2
Density dose-response relationship between VAI with stroke prevalence. The area between the upper and lower dashed lines is represented as 95% CI. Each point shows the magnitude of the VAI and is connected to form a continuous line. Adjusted for all covariates except effect modifier.

risk factors in the elderly (37). Among young and middle-aged stroke patients, dyslipidemia, smoking and hypertension are the most prevalent vascular risk factors (38–40), while VAI levels are also affected by dyslipidemia, which makes it possible to predict stroke prevalence in young and middle-aged individuals. It is well known that stroke risk differs by race and ethnicity, and in younger populations these differences are even more pronounced. It is important to note that variations in prevalence are largely determined by the racial composition of the study population. There was an increased prevalence of strokes among young Hispanics and blacks in the Northern Manhattan study (41). The hospitalization rate for stroke was significantly higher among young blacks and Hispanics in another Florida study (42). A second study from American Point found that young and middle-aged blacks had up to five times the stroke risk, compared to young and middle-aged whites. Blacks had an increased prevalence of stroke due to the elevated VAI found in our study, which may explain the increased prevalence of stroke among blacks. The increased prevalence of stroke in populations with hypertension and diabetes is not surprising given that both of these factors are known to be risk factors for stroke (43).

In terms of mortality, stroke is one of the top three causes of death worldwide, as well as one of the leading causes of

TABLE 3 Subgroup analysis between VAI with stroke prevalence.

Characteristic	Model 1 OR(95%CI)	Model 2 OR(95%CI)	Model 3 OR(95%CI)
Stratified by gender			
Male	1.01 (0.91, 1.13)	1.13 (1.00, 1.27)	1.06 (0.92, 1.22)
Female	1.43 (1.29, 1.60)	1.35 (1.20, 1.53)	1.20 (1.04, 1.39)
Stratified by race			
Mexican American	1.10 (0.90, 1.34)	1.01 (0.82, 1.26)	0.98 (0.75, 1.28)
White	1.36 (1.22, 1.52)	1.30 (1.15, 1.46)	1.14 (0.99, 1.32)
Black	1.37 (1.18, 1.59)	1.29 (1.10, 1.52)	1.22 (1.01, 1.48)
Other Race	1.04 (0.79, 1.38)	0.92 (0.68, 1.25)	0.67 (0.44, 1.01)
Stratified by age			
<60	1.39 (1.22, 1.58)	1.52 (1.33, 1.74)	1.25 (1.05, 1.48)
≥60	1.04 (0.94, 1.15)	1.10 (0.99, 1.22)	1.01 (0.89, 1.14)
Stratified by hypertension			
YES	1.28 (1.16, 1.41)	1.25 (1.12, 1.39)	1.15 (1.01, 1.31)
NO	0.95 (0.82, 1.09)	1.11 (0.95, 1.30)	1.02 (0.84, 1.22)
Stratified by diabetes			
YES	1.07 (0.93, 1.23)	1.19 (1.02, 1.39)	1.23 (1.02, 1.48)
NO	1.08 (0.98, 1.18)	1.10 (1.00, 1.22)	1.08 (0.95, 1.21)

Model 1=no covariates were adjusted.
Model 2=Model 1+age, gender, race education, marital status were adjusted.
Model 3=adjusted for all covariates except effect modifier.

disability. If stroke continues for a longer period of time, the risk of a second stroke increases, as does the poorer prognosis. The long-term socioeconomic consequences of stroke in young patients are also significant. According to a recent study, young stroke patients spend an average of $34,886 in hospitalization for ischemic stroke, $150,307 for subarachnoid hemorrhage, and $94,482 for cerebral hemorrhage (44). The correlation between VAI and age at first stroke was another important finding in this study. As a consequence of our results, every unit increase in VAI will result in a 1.64 year increase in the age of stroke onset. VAI was linearly correlated negatively with age at first stroke even when smoothing curves were fitted. This finding is heartening and has not yet been reported. It is hypothesized that treating and managing VAI levels at younger ages can reduce the risk of stroke. However, the veracity of the present results may be limited by the sample size and needs to be further confirmed by a multicenter prospective study with a large sample.

Several advantages are associated with our study. An extensive quality assurance and quality control process is followed by the NHANES 2007-2018 sample, which represents a representative sample of the U.S. population. Secondly, we adjusted for confounding covariates to ensure our results were reliable and applicable to a wide range of individuals. Our study does, however, have some limitations. We were unable to establish a causal relationship between VAI and stroke due to the fact that we used the NHANES database, a cross-sectional study. In addition, the data on medication history and stroke type classification were not disclosed in the database, which may have contributed to recall bias. Third, the

TABLE 4 Analysis between VAI with stroke age onset.

Characteristic	Model 1 β(95%CI)	Model 2 β(95%CI)	Model 3 β(95%CI)
Ln(VAI)	-0.79 (-1.92, 0.35)	-1.34 (-2.51, -0.18)	-1.64 (-2.84, -0.45)

Model 1=no covariates were adjusted.
Model 2=Model 1+gender, race education, marital status were adjusted.
Model 3=Model 2+, diabetes, blood pressure, asthma, PIR, total water, total kcal, total sugar, smoked, physical activity, alcohol use, serum cholesterol, coronary artery disease, serum creatinine urine albumin creatinine ratio, cancers and serum glucose were adjusted.

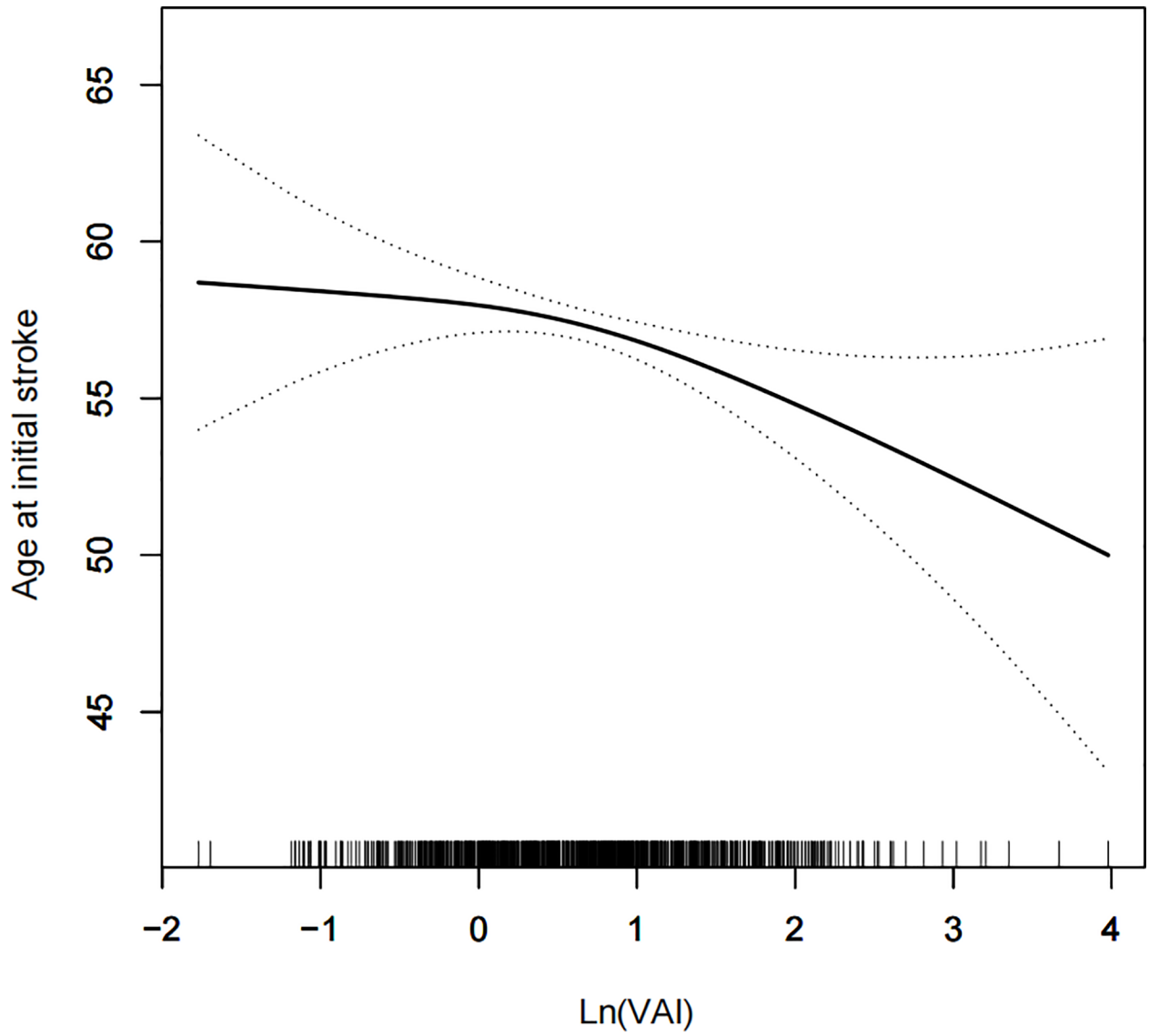

FIGURE 3
Density dose-response relationship between VAI with onset age of stroke. The area between the upper and lower dashed lines is represented as 95% CI. Each point shows the magnitude of the VAI and is connected to form a continuous line. Adjusted for all covariates except effect modifier.

diagnosis of stroke was made by means of a questionnaire, which can be subject to recall bias. It is noteworthy that the present study showed that VAI is associated with stroke onset and, for the first time, evaluated its role in age at first stroke onset.

5 Summary

The VAI is associated with higher stroke prevalence and a younger age at first stroke. Although the causal relationship between VAI management and stroke occurrence cannot be clearly established, we hypothesize that managing VAI levels at a younger age may reduce the occurrence of strokes and delay stroke onset.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by NCHS Research Ethics Review Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QC: Conceptualization, Methodology, Software. ZZ: Data curation, Writing original draft. NL: Visualization, Investigation. YQ: Writing - review & editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1086936/full#supplementary-material

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Nagisa Morikawa,
Kurume University, Japan
Rongjing Ding,
Peking University, China

*CORRESPONDENCE
Huan Ma
mahuandoctor@163.com
Qingshan Geng
gengqsh@163.net

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Incidence and long-term specific mortality trends of metabolic syndrome in the United States

Weiya Li, Xinfan Qiu, Huan Ma* and Qingshan Geng*

Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Purpose: Metabolic syndrome (MetS) is extremely prevalent and related to severe diseases and death. This study aims to investigate the incidence and mortality trends among MetS over the past few decades. The gender and age differences of MetS are also explored.

Patients and methods: Adults with MetS were screened in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2014. The mortality data were also acquired. Then we assessed the incidence and mortality trends of MetS in the United States.

Results: Our study included 14171 participants with a mean age of 46.8 ± 19.3 years, of whom 7354 (51.9%) were women. Among them, 4789 participants were subsequently diagnosed with MetS. From 1999 to 2014, the overall trend of MetS incidence increased (from 27.6 to 32.3%; adjusted odds ratios [aOR], 1.71; 95% confidence interval [CI], 1.42-2.05; *P*-value <0.001, P for trend <0.001). In more detail, the incidence of MetS rose first but subsequently plateaued and declined. Obvious downward trends were observed from 29.6 to 2.7% for all-cause mortality (aOR, 0.12; 95%CI, 0.07-0.21; *P*-value <0.001, P for trend <0.001) and 4.8 to 0.8% for cardio-cerebrovascular mortality (aOR, 0.17; 95%CI, 0.05-0.61; *P*-value =0.007, P for trend <0.001). All-cause mortality decreased yearly, whereas cardio-cerebrovascular death increased briefly before declining and stabilizing. Similarly, the temporal mortality trends in MetS patients of different ages and genders had the same results. Specifically, the incidence of MetS was higher in women than in men (adjusted P =0.003; OR, 1.14; 95%CI, 1.05-1.24), but the mortality was significantly lower after an average of 7.7 years of follow-up (all-cause mortality, adjusted P <0.001; hazard ratio [HR], 0.68; 95%CI, 0.57-0.81; cardio-cerebrovascular mortality, adjusted P =0.004; HR, 0.55; 95%CI, 0.37-0.83).

Conclusion: From 1999 to 2014, the incidence of MetS in U.S. adults significantly increased overall, while the mortality rate of MetS had a considerable downward trend. Both trends showed marked gender differences, being more prevalent and at lower risk in women compared with men. It is important to identify the factors that will curb the incidence of MetS and decrease mortality, especially in male patients.

KEYWORDS

metabolic syndrome, trend, NHANES, mortality, incidence

1 Introduction

Metabolic syndrome (MetS) is a group of disorders that include abdominal obesity, insulin resistance, hypertriglyceridemia, low high-density lipoproteins (HDL), and arterial hypertension (1). Numerous studies have demonstrated that MetS is a cluster of interrelated risk factors associated with cancer, stroke, diabetes, and other comorbidities (2–4). Even in the general population, MetS is believed to be an indicator marker for the development of cardiovascular (CV) events (4, 5).

Along with modern risk factors for heart metabolism such as population aging, unhealthy lifestyles characterized by physical inactivity, and poor diet (6, 7). It has been estimated that the incidence of MetS affects 20-30% of the adult population globally (8), causing considerable health, social, and economic burdens. According to the findings of the 2010 Global Burden of Disease (GBD), high blood pressure, high total cholesterol, a high body mass index, and high fasting plasma glucose, respectively, account for 53%, 29%, 23%, and 16% of global disability-adjusted life years (9).

MetS is also associated with an increase in premature deaths (10–12). Previous studies have indicated that individuals with MetS were three times more likely to suffer a stroke or heart attack and two times more likely to die from these conditions compared with individuals without MetS (13). However, the annual trends of mortality in patients with MetS have not been reported. In addition, the duration of incidence in MetS trends in recent decades remains unclear (8, 14–16). Hence, we performed an updated investigation utilizing the NHANES data to explore long-term trends in MetS incidence and mortality among U.S. adults between 1999 and 2014.

Previous research has demonstrated significant gender and age differences in the prevalence and prognosis of MetS, while the gender and age differences in long-term trends have rarely been described. The Committee of the European Parliament recently recommended including gender differences in the policy planning, delivery, and monitoring of health services, citing gender and age as unique and important clinical demographic characteristics (17). Age and gender are also the two most important factors contributing to the increasing prevalence of MetS from a pathogenetic point of view (18). Moreover, as a result of the acceleration of population aging, the amount of elderly population is gradually rising. MetS incidence and mortality are several times higher in the elderly population than in the younger population (17, 19). Attention to gender medicine is a key requirement for the improvement of health strategies. Refining the assessment of age-stratified risk in patients with MetS will also facilitate the treatment of high-risk groups with greater precision. Therefore, gender and age differences in incidence and mortality in MetS patients have also been explored as a secondary objective. Our study may provide essential information for policymakers, clinicians, and concerned stakeholders in the U.S. so as to better manage MetS and improve prognosis.

2 Material and methods

2.1 Study design and participants

Our study aimed to investigate the incidence and mortality trends of MetS in the U.S. general adult population from 1999 to 2014. The National Health and Nutrition Examination Survey (NHANES) is a series of cross-sectional research studies conducted every two years to monitor the health of the U.S. population. The study protocols were approved by the National Center for Health Statistics (NCHS) institutional review board, and all the participants signed a written informed consent (20, 21). Well-trained medical personnel, modern testing equipment, medical reports, and the economic compensation participants received all enhance the credibility of NHANES data. Anyone can obtain details on enrollment, procedures, and population characteristics for NHANES by visiting https://www.cdc.gov/nchs/nhanes/index.htm. After excluding participants due to the lack of relevant and necessary medical data, a total of 14171 individuals, among them 4789 patients with MetS, entered the final analysis (Figure 1).

2.2 MetS covariates and assessment

We divided educational levels into three categories (high school or less; some college; college graduate or above). “Non-Hispanic White”, “Mexican American”, “Non-Hispanic Black”, and “Other” were the categories used to describe race. A medical history of cardiovascular disease was defined as suffering from coronary heart disease, heart failure, or angina pectoris. The family poverty income ratio (PIR), calculated by dividing family income by the poverty guidelines issued by the Department of Health and Human Services (DHHS), was used to assess poverty levels. The Federal Register used each year’s DHHS poverty guidelines to determine financial eligibility for certain federal programs. We used a simple criterion and considered a family income index of less than 100% to be below the poverty line, while a ratio of 100% or higher was defined as being above the poverty line. In our study, PIR was divided into five levels (<100%; 100% -199%; 200% -299%; 300% -399%; ≥400%) (22). The criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) were commonly used worldwide, and we used this criterion to assess whether the participants had MetS (23).

MetS is diagnosed in adults when three or more of the following criteria are met: a waist circumference of ≥102 cm in men and ≥88 cm in women, high circulating triglycerides ≥150 mg/dL, low HDL <40 mg/dL for men and <50 mg/dL for women, high fasting blood glucose ≥100 mg/dL, and a diagnosis of arterial hypertension (1).

2.3 Follow-up and outcomes

The average follow-up time for MetS participants in this study was about 7.7 years. All-cause, cardiovascular, and cerebrovascular mortality were included as endpoints. We defined cardio-cerebrovascular mortality (I00-I09, I11, I13, I20-I51 for cardiovascular mortality; I60-I69 for cerebrovascular mortality) according to the International Classification of Diseases, 10th Clinical Modification (ICD-10) system codes. Based on a probabilistic match, the mortality data was linked from NHANES to death certificate data in the National Death Index by NCHS. Survival status has been ascertained from other sources, including links to administrative data from the Social Security Administration and the Centers for Medicare & Medicaid Services. Those with a follow-up time

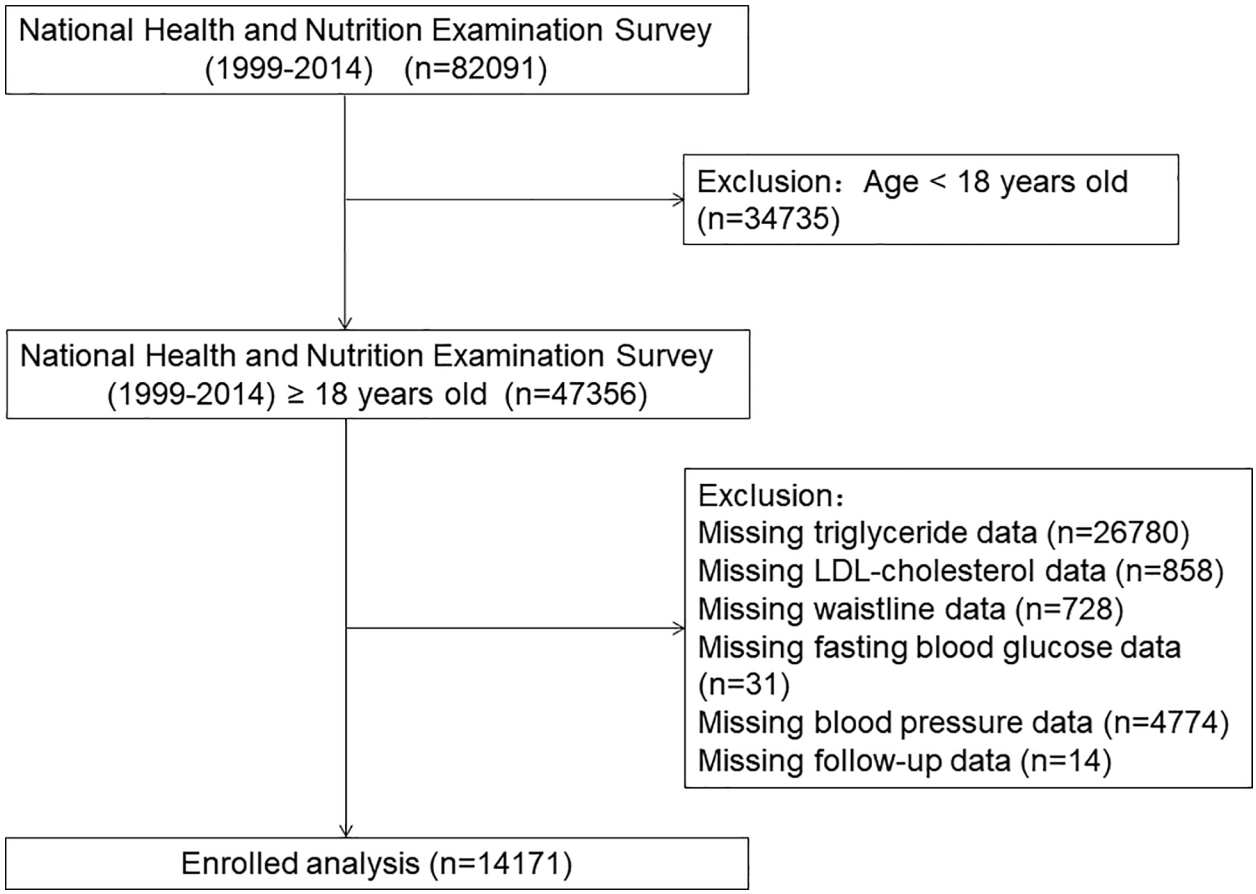

FIGURE 1
The research flow chart.

of 100 years or more were considered lost data and ineligible for mortality analyses. On average, 94.8% of survey participants were eligible for the mortality follow-up. The following website can be visited to learn more details about mortality variables: (https://www.cdc.gov/nchs/data-linkage/mortalitypublic.htm).

2.4 Statistical analysis

According to the years included, all participants were divided into eight groups (1999 through 2000, 2001 through 2002, 2003 through 2004, 2005 through 2006, 2007 through 2008, 2009 through 2010, 2011 through 2012, and 2013 through 2014). All baseline characteristics were summarized as mean ± SD, number, and percentage, or median when appropriate. Comparisons among the eight groups were made by one-way analysis of variance (ANOVA), and Pearson chi-squared tests were used for categorical variables.

Every two years from 1999 to 2014, we analyzed the incidence of MetS. The odds ratio (OR) and 95% confidence interval (CI) for MetS were calculated using single-factor and multi-factor logistic regression analyses. The all-cause and cardio-cerebrovascular mortality rates were used during an average of 7.7 years of follow-up to assess the prognostic trends in MetS patients. We used Cox regression models to investigate the temporal trend of mortality from 1999 to 2014. Models 1, 4, and 7 were not adjusted for any covariates; after adjusting for age and gender, we obtained Models 2, 5, and 8; Models 3, 6, and 9 were adjusted for multivariate variables like demographics (age, gender, ethnicity), medical and social history (education level, poverty grade, cardiovascular or cerebrovascular disease history, smoking), and laboratory examinations (CCR, hemoglobin A1c). The graphs show unadjusted and adjusted ORs (aOR), hazard ratios (HR), and 95% CI for the incidence and mortality of MetS over this time period.

We conducted additional subgroup analyses to observe the incidence and mortality trends of MetS in different age (≥65 and <65 years old) and gender (men and women) groups. In the exploratory analysis, we employed binary logistic regression to investigate the gender difference in MetS among all participants over these 16 years, using a COX proportional risk model to analyze the gender and age differences in mortality among all MetS patients. All analyses were performed with SPSS version 25, and a P value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

Between 1999 and 2014, a total of 14171 participants from the NHANES were included in this study. Among them, 4789 individuals were subsequently diagnosed with MetS. The average follow-up time was

92.9 ± 51.2 months. Overall, the mean age was 46.8 ± 19.3 years old, and 7354 (51.9%) of the participants were women. In patients with MetS, the ratios regarding unqualified waist, high circulating triglycerides, low HDL, high fasting blood glucose, and diagnosis of arterial hypertension were 87.7%, 54.3%, 78.3%, 24.7%, and 80.7%, respectively. All data about baseline characteristics are described in Table 1.

In addition, the incidence of MetS had a reverse association with the level of education (r =- 0.076, p <0.001). MetS was positively correlated with a history of cardiovascular disease (r =0.062, p <0.001) and smoking ≥100 cigarettes (r =0.101, p <0.001).

3.2 Trends in the incidence of MetS

From 1999-2000 to 2013-2014, a total of 4789 (33.8%) participants in the general population developed MetS. Compared with 1999-2000, MetS incidence in 2013-2014 increased significantly, from 27.6 to 32.3% (adjusted odds ratios [aOR], 1.71; 95% CI, 1.42–2.05; *P*-value <0.001, P for trend <0.001) (Figure 2A; Table 2). The incidence of MetS displayed a significant upward trend over the course of 16 years. In all MetS patients, unqualified waist, low HDL, and high fasting blood glucose contributed the most to MetS, with a total percentage of 87.7%, 78.3%, and 80.7% respectively. As for each component of the MetS separately, the unqualified waist had a slight and small upward trend from 87.5 to 91.1% overall. Both low HDL and high fasting blood glucose had a significant upward trend from 70.4 to 77.7% and 70.4 to 85.6%, respectively, while high circulating triglycerides decreased from 66 to 44.1%, and arterial hypertension went from 30.1 to 24.2%.

3.3 Trends of all-cause and cardio-cerebrovascular mortality in MetS patients

During the average of 7.7 years of follow-up, there were a total of 693 (14.5%) and 141 (2.9%) patients with MetS who experienced all-cause and cardio-cerebrovascular death, respectively. Compared with 1999-2000, the all-cause mortality rate in 2013-2014 significantly decreased from 29.6 to 2.7% (Figure 2B; Table 2; adjusted odds ratios [aOR], 0.12; 95%CI, 0.07-0.21; *P*-value <0.001, P for trend <0.001), and the cardio-cerebrovascular mortality rate in 2013-2014 significantly decreased from 4.8 to 0.8% (Figure 2C; Table 2; adjusted odds ratios [aOR], 0.17; 95% CI, 0.05-0.61; *P*-value =0.007, P for trend <0.001).

3.4 Subgroup analysis

In our study, 2260 (47.2%) men and 2529 (52.8%) women were diagnosed with MetS. The incidence of MetS displayed an upward trend in both groups (Figure 3A; men: 26.2 to 31.9%, P for trend <0.001; women: 28.7 to 32.6%, P for trend <0.001, P for interaction = 0.012).

There were 371 (16.4%) all-cause deaths in men and 322 (12.7%) in women during the period of follow-up among patients with MetS. In general, a downward trend in all-cause mortality appeared in two gender groups (Figure 3B; men: 25.7 to 2.4%, P for trend <0.001; women: 15.5 to 1.7%, P for trend <0.001; P for interaction = 0.598). 80 men (3.5%) and 61 women (2.4%) experienced cardio-cerebrovascular death in patients with MetS. The cardio-cerebrovascular mortality of the two groups both displayed a significant downward trend over 16 years (Figure 3C; men: 3.8 to 0.6%, P for trend <0.001; women: 2.4 to 0.4%, P for trend <0.001; P for interaction = 0. 811).

From 1999-2000 to 2013-2014, 1570 (50.3%) participants older than 65 developed MetS, which was significantly higher than 3219 (29.1%) of patients <65. The risk of suffering from MetS in the two groups showed an upward trend (Figure 3D; ≥ 65-year-old group, 42.7 to 48.3%, P for trend = 0.025; <65-year-old group, 23.4 to 27.9%, P for trend < 0.001; P for interaction = 0.846).

All-cause death occurred in 493 (31.4%) MetS patients in the ≥65-year-old group and 200 (6.2%) in the <65- year-old-group, respectively. Both groups showed a downward trend in all-cause mortality (Figure 3E; ≥65 group: 61.6 to 5.6%, P for trend <0.001; <65 group: 8.8 to 1.1%, P for trend <0.001; P for interaction <0.001). Cardio-cerebrovascular death occurred in 107 (6.8%) patients over the age of 65, while it occurred in 34 (1.1%) patients <65. Due to insufficient death samples, we used per 1000 person-2 years to describe mortality. There were downward trends in both groups, (Figure 3F; ≥65 group, 92.9 to 19.4 per 1000 person-2 years, P for trend < 0.001; <65 group, 13.5 to 0.7 per 1000 person-2 years, P for trend <0.001; P for interaction =0.002). Interestingly, the downward trends in mortality in these two age groups had statistically significant differences (both P for interaction < 0.05).

3.5 Exploratory analysis

We conducted further analysis to explore the differences in incidence and mortality between different genders and ages over 16 years. Overall, there were 2529 (52.8%) women and 2260 (47.2%) men who developed MetS. There were 3219 (29.1%) participants aged <65 years and 1570 (50.3%) participants aged≥65 years who were diagnosed with MetS. In the binary logistic regression, women had a higher incidence than men after adjustment of multivariate variables (age, education level, ethnicity, cardiovascular or cerebrovascular disease history, CCR, poverty grade, HbA1c, smoking ≥100 cigarettes) (adjusted P= 0.003; OR, 1.14; 95% CI, 1.05-1.24). Older participants (≥65 years) had a higher incidence of MetS than that in the younger group (≥65 years) after adjustment of multivariate variables (gender, education level, ethnicity, cardiovascular or cerebrovascular disease history, CCR, poverty grade, HbA1c, smoking ≥100 cigarettes) (adjusted P <0.001; OR, 2.58; 95%CI, 2.30-2.89).

Unexpectedly, women had a lower risk than men, no matter if it was all-cause (16.4% vs. 12.7%) or cardio-cerebrovascular mortality (3.5% vs. 2.4%) after a long-term follow-up. In the COX proportional risk model, the mortality of men was lower than that of women and achieved statistical significance (for all-cause mortality, P <0.001; HR, 0.71; 95%CI, 0.61-0.82; For cardio-cerebrovascular mortality, P =0.006; HR, 0.76; 95%CI, 0.45-0.88). The same conclusion still existed after adjusting for multivariate variables (age, gender, education level, ethnicity, cardiovascular or cerebrovascular disease history, CCR, poverty grade, HbA1c, smoking ≥100 cigarettes)

10.3389/fendo.2022.1029736

TABLE 1 Characteristics of included general adults in NHANES from 1999–2002 to 2011–2014.

Characteristic	Overall	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	*P*-value
	N=14171	N=1506	N=1659	N=1670	N=1663	N=1872	N=2077	N=1806	N=1918	
Demographic										
Age, years	46.8 ± 19.3	45.5 ± 20.0	45.5 ± 19.8	46.3 ± 20.7	45.2 ± 20.1	48.9 ± 18.6	47.7 ± 18.7	46.9 ± 18.3	47.9 ± 18.3	<0.001
Gender, n(%)										0.158
Women	7354(51.9)	686(45.6)	798(48.1)	813(48.7)	808(48.6)	932(49.8)	978(47.1)	901(49.9)	901(47.0)	
Men	6817(48.1)	820(54.4)	861(51.9)	857(51.3)	855(51.4)	940(50.2)	1099(52.9)	905(50.1)	1017(53.0)	
Race, n(%)										<0.001
Non-Hispanic White	6469(45.6)	635(42.2)	856(51.6)	824(49.3)	815(49.0)	862(46.0)	959(46.2)	676(37.4)	842(43.9)	
Mexican American	2743(19.4)	467(31.0)	385(23.2)	365(21.9)	320(19.2)	335(17.9)	428(20.6)	185(10.2)	258(13.5)	
Non-Hispanic Black	2860(20.2)	268(17.8)	303(18.3)	363(21.7)	401(24.1)	380(20.3)	341(16.4)	429(23.8)	375(19.6)	
Other	2099(14.8)	136(9.0)	115(6.9)	118(7.1)	127(7.6)	295(15.8)	349(16.8)	516(28.6)	443(23.1)	
BMI, kg/m2	28.3 ± 6.5	27.8 ± 6.2	27.7 ± 6.1	28.0 ± 6.2	28.5 ± 6.7	28.2 ± 6.2	28.7 ± 6.7	28.5 ± 6.6	28.8 ± 7.2	<0.001
Social history										
Educational level, n(%)										<0.001
High school or less	6624(46.7)	790(59.4)	762(51.1)	798(53.9)	759(51.1)	951(53.6)	1006(51.1)	763(44.4)	795(43.9)	
Some college	3589(25.3)	313(23.6)	436(29.3)	399(27.0)	421(28.4)	450(25.4)	546(27.7)	482(28.0)	542(30.0)	
College graduate or above	2841(20.0)	226(17.0)	292(19.6)	283(19.1)	304(20.5)	373(21.0)	417(21.2)	474(27.6)	472(26.1)	
Smoking≥100 cigarettes in life, n(%)										<0.001
No	7082(50.0)	700(52.7)	756(50.7)	753(50.8)	749(50.5)	928(52.3)	1085(55.0)	991(57.7)	1120(58.4)	
Yes	6085(42.9)	629(47.3)	734(49.3)	728(49.2)	734(49.5)	848(47.7)	888(45.0)	727(42.3)	797(41.6)	
Poverty income ratio, n(%)										<0.001
<100%	2773(19.6)	254(19.4)	277(17.9)	334(21.1)	290(18.3)	355(20.6)	432(22.8)	408(24.6)	423(23.7)	
100%-199%	3403(24.0)	330(25.3)	385(24.8)	425(26.9)	399(25.1)	441(25.6)	545(28.8)	441(26.6)	437(24.5)	
200%-299%	1971(13.9)	199(15.2)	246(15.9)	253(16.0)	247(15.6)	299(17.4)	264(14.0)	215(13.0)	248(13.9)	
300%-399%	1567(11.1)	171(13.1)	190(12.3)	175(11.1)	231(14.5)	201(11.7)	201(10.6)	190(11.5)	208(11.7)	
≥400%	3368(23.8)	352(27.0)	453(29.2)	395(25.0)	421(26.5)	425(24.7)	449(23.7)	405(24.4)	468(26.2)	
Medical history										
Cardiovascular disease	1018(7.2)	81(6.1)	111(7.5)	132(9.0)	113(7.7)	161(9.2)	153(7.8)	126(7.4)	141(7.8)	0.072
Stroke, n (%)	447(3.2)	29(2.2)	42(2.8)	55(3.7)	60(4.0)	67(3.8)	65(3.3)	68(4.0)	61(3.4)	0.093
cardio-cerebrovascular disease, n (%)	1291(9.1)	99(7.5)	133(9.0)	167(11.4)	147(10.0)	204(11.6)	193(9.9)	168(9.8)	180(10.0)	0.008
Laboratory examination										
CCR, mg/min	118.8 ± 51.0	147.7 ± 68.0	115.2 ± 50.0	114.2 ± 47.3	115.5 ± 48.0	114.5 ± 45.4	116.8 ± 47.2	116.9 ± 46.5	114.6 ± 48.3	<0.001
HbA1c,%	5.6 ± 1.0	5.4 ± 0.9	5.5 ± 0.9	5.5 ± 0.9	5.5 ± 1.0	5.7 ± 1.1	5.7 ± 0.9	5.7 ± 1.1	5.7 ± 1.0	<0.001

BMI, Body Mass Index; CCR, Creatinine Clearance Rate; HbA1c, hemoglobin A1c.

(Figure 4A for all-cause mortality, adjusted P <0.001; HR, 0.68; 95% CI, 0.57-0.81; Figure 4B for cardio-cerebrovascular mortality, adjusted P =0.004; HR, 0.55; 95%CI, 0.37-0.83). In terms of the mortality of patients with MetS, the older age group still had a higher mortality risk than the lower age group after multivariate variables were adjusted (Figure 4C for all-cause mortality, adjusted P <0.001; HR, 2.6; 95%CI, 2.09-3.23; Figure 4D for cardio-cerebrovascular mortality, adjusted P <0.001; HR, 2.48; 95%CI, 1.48-4.14).

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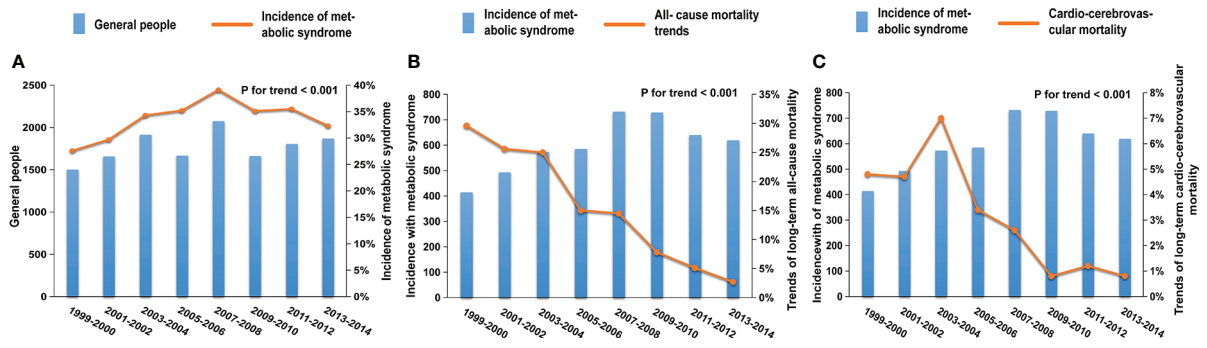

FIGURE 2
Trends in the incidence and mortality of MetS patients in the NHANES from 1999 to 2014; **(A)** The prevalence of MetS increased significantly from 27.6 to 32.3% (adjusted odds ratios [aOR], 1.71; 95%CI, 1.42-2.05; P-value <0.001, P for trend <0.001); trends in all-cause **(B)** and cardio-cerebrovascular **(C)** mortality of MetS patients in the NHANES from 1999 to 2014. After an average of 7.7 years of follow-up, the all-cause mortality (from 29.6 to 2.7%; [aOR], 0.12; 95%CI, 0.07-0.21; P-value <0.001, P for trend <0.001) and cardio-cerebrovascular mortality (from 4.8 to 0.8%; [aOR], 0.17; 95%CI, 0.05- 0.61; P-value =0.007, P for trend <0.001) of MetS patients showed obvious downward trends.

TABLE 2 Odds ratios for prevalence and hazard ratios for all-cause, cardiovascular, and cerebrovascular mortality from 1999-2002 to 2011-2014.

Odds ratios for the prevalence of MetS				MetS all-cause mortality hazard ratios				MetS cardiovascular and cerebrovascular mortality hazard ratios			
Years	Odds ratios	*P*-value	P for trend	Years	Hazard ratios	*P*-value	P for trend	Years	Hazard ratios	*P*-value	P for trend
Model 1				Model 4				Model 7			
1999-2000	1(reference)	–	<0.001	1999-2000	1(reference)	–	<0.001	1999-2000	1(reference)	–	<0.001
2001-2002	1.11(0.95-1.30)	0.18		2001-2002	1.00(0.78-1.28)	0.969		2001-2002	1.07(0.59-1.95)	0.823	
2003-2004	1.37(1.18-1.60)	<0.001		2003-2004	1.03(0.81-1.32)	0.811		2003-2004	1.67(0.97-2.87)	0.066	
2005-2006	1.43(1.23-1.66)	<0.001		2005-2006	0.85(0.64-1.12)	0.238		2005-2006	1.13(0.60-2.12)	0.703	
2007-2008	1.69(1.46-1.95)	<0.001		2007-2008	0.08(0.06-0.11)	<0.001		2007-2008	0.09(0.04-0.17)	<0.001	
2009-2010	1.43(1.23-1.65)	<0.001		2009-2010	0.06(0.04-0.08)	<0.001		2009-2010	0.04(0.01-0.09)	<0.001	
2011-2012	1.45(1.25-1.68)	<0.001		2011-2012	0.08(0.05-0.11)	<0.001		2011-2012	0.10(0.04-0.23)	<0.001	
2013-2014	1.25(1.08-1.45)	0.003		2013-2014	0.11(0.07-0.18)	<0.001		2013-2014	0.20(0.07-0.53)	0.001	
Model 2	1(reference)			Model 5				Model 8			
1999-2000		–	<0.001	1999-2000	1(reference)	–	<0.001	1999-2000	1(reference)	–	<0.001
2001-2002	1.13(0.95-1.30)	0.145		2001-2002	1.15(0.89-1.47)	0.282		2001-2002	1.31(0.72-2.40)	0.382	
2003-2004	1.38(1.18-1.62)	<0.001		2003-2004	0.97(0.76-1.24)	0.821		2003-2004	1.60(0.93-2.74)	0.09	
2005-2006	1.51(1.28-1.76)	<0.001		2005-2006	0.79(0.60-1.04)	0.098		2005-2006	1.07(0.57-2.00)	0.834	
2007-2008	1.60(1.37-1.90)	<0.001		2007-2008	0.14(0.11-0.18)	<0.001		2007-2008	0.18(0.09-0.34)	<0.001	

(Continued)

TABLE 2 Continued

Odds ratios for the prevalence of MetS				MetS all-cause mortality hazard ratios				MetS cardiovascular and cerebrovascular mortality hazard ratios			
Years	Odds ratios	*P*-value	P for trend	Years	Hazard ratios	*P*-value	P for trend	Years	Hazard ratios	*P*-value	P for trend
2009-2010	1.38(1.19-1.60)	<0.001		2009-2010	0.10(0.07-0.14)	<0.001		2009-2010	0.07(0.03-0.18)	<0.001	
2011-2012	1.45(1.24-1.69)	<0.001		2011-2012	0.12(0.08-0.24)	<0.001		2011-2012	0.19(0.08-0.45)	<0.001	
2013-2014	1.20(1.02-1.40)	0.023		2013-2014	0.14(0.09-0.24)	<0.001		2013-2014	0.29(0.11-0.80)	0.016	
Model 3				Model 6				Model 9			
1999-2000	1(reference)	–	<0.001	1999-2000	1(reference)	–	<0.001	1999-2000	1(reference)	–	<0.001
2001-2002	1.71(1.41-2.07)	<0.001		2001-2002	1.14(0.85-1.52)	0.66		2001-2002	1.37(0.70-2.70)	0.359	
2003-2004	2.20(1.82-2.65)	<0.001		2003-2004	0.81(0.61-1.06)	0.103		2003-2004	1.32(0.71-2.46)	0.386	
2005-2006	2.47(2.04-2.98)	<0.001		2005-2006	0.67(0.49-0.91)	0.008		2005-2006	0.80(0.39-1.65)	0.548	
2007-2008	2.33(1.94-2.79)	<0.001		2007-2008	0.13(0.10-0.18)	<0.001		2007-2008	0.15(0.07-0.32)	<0.001	
2009-2010	1.88(1.57-2.25)	<0.001		2009-2010	0.10(0.07-0.14)	<0.001		2009-2010	0.06(0.02-0.18)	<0.001	
2011-2012	2.15(1.78-2.59)	<0.001		2011-2012	0.09(0.06-0.14)	<0.001		2011-2012	0.13(0.04-0.36)	<0.001	
2013-2014	1.71(1.42-2.05)	<0.001		2013-2014	0.12(0.07-0.21)	<0.001		2013-2014	0.17(0.05-0.61)	0.007	

Model 1, Model 4, and Model 7: unadjusted.
Model 2, Model 5, and Model 8: adjusted for age and gender.
Model 3, Model 6, and Model 9: adjusted for multivariate variables (age, gender, education level, ethnicity, cardiovascular and cerebrovascular disease history, CCR, poverty grade, HbA1c, smoking≥100 cigarettes).

To further explore the impact of each component of the MetS on mortality, all five factors were put into a Cox proportional regression model. And we found that high fasting blood glucose had the highest HR (2.28 for all-cause mortality and 2.79 for cardio-cerebrovascular mortality) and was the only significant factor to increase mortality (P <0.001 for all-cause mortality and P =0.001 for cardio-cerebrovascular mortality).

4 Discussion

To the best of our knowledge, this is the first study to explore the trends in long-term mortality over the MetS span of 16 years in the United States. Our research suggests that nearly 34% of all adults and 50% of those aged ≥65 years were estimated to have MetS and showed an upward trend from 1999 to 2014 overall. The all-cause and cardio-cerebrovascular mortality of patients with MetS were 14.5% and 2.9%, respectively. Fortunately, mortality rates showed a significant downward trend from 1999 to 2014 overall.

According to our graphics and data analysis results, with the boundary of 2008, the incidence trend of adult MetS rose before 2008 and then decreased. The same trend existed in women, regardless of the age subgroup (Figures 3A, D), while in the men's subgroup an obvious decline was observed until 2012, which had a statistically significant difference in overall trends compared with women (P for interaction =0.012; Figure 3A). Similar to previous studies of older adults (19, 24), half of the elderly over 65 years old suffer from MetS. This is a worrying finding since the U.S. will soon experience a massive increase in its older population (25), which may cause the prevalence of MetS to increase even more than it already has. We cannot reduce MetS vigilance due to the disease's stable incidence in recent years, especially among the elderly.

The all-cause mortality of MetS patients showed a continuous decline, whether in general or across all subgroups (Figures 2B, 3B, E). Compared with the younger MetS subgroup (<65), the older group (≥65) had a more remarkable drop that reached statistical significance (P for interaction <0.001; Figure 3B). The trend of cardio-cerebrovascular mortality in MetS patients continued decreasing, in addition to a brief increase in 2001-2004 (Figures 2C, Figures 3C, F). There was no statistical difference in the mortality trends between men and women. In the younger subgroup, the decreasing trend of mortality was relatively stable, while an obviously declining trend was observed in the older subgroup (P for interaction = 0.002; Figure 3F). More attention should be paid to the prognosis of older patients with

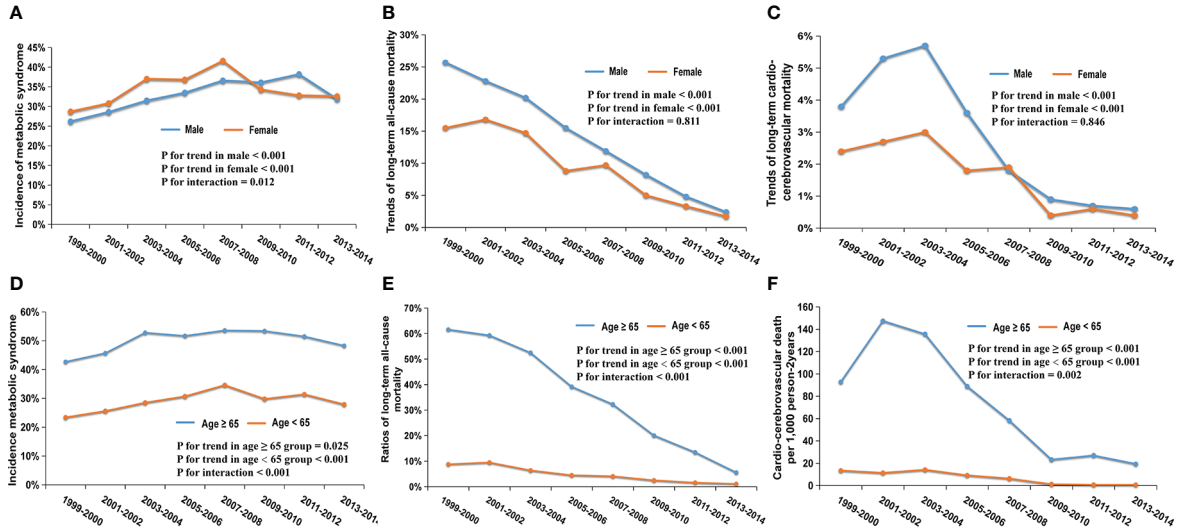

FIGURE 3
Trends in the incidence and mortality of different gender and age subgroups from 1999 to 2014; **(A)** Trends in the incidence of MetS among men (P for trend <0.001) and women (P for trend <0.001); **(B)** Trends of 7.7-year all-cause mortality among men (P for trend<0.001) and women (P for trend <0.001); **(C)** Trends of 7.7-year cardio-cerebrovascular mortality among men (P for trend<0.001) and women (P for trend <0.001); **(D)** Trends in the incidence of MetS among ≥65 years (P for trend=0.025) and <65 years (P for trend <0.001); **(E)** Trends of 7.7-year all-cause mortality among ≥65 years (P for trend<0.001) and <65 years (P for trend <0.001); **(F)** Trends of 7.7-year cardio-cerebrovascular mortality among ≥65 years (P for trend<0.001) and <65 years (P for trend <0.001).

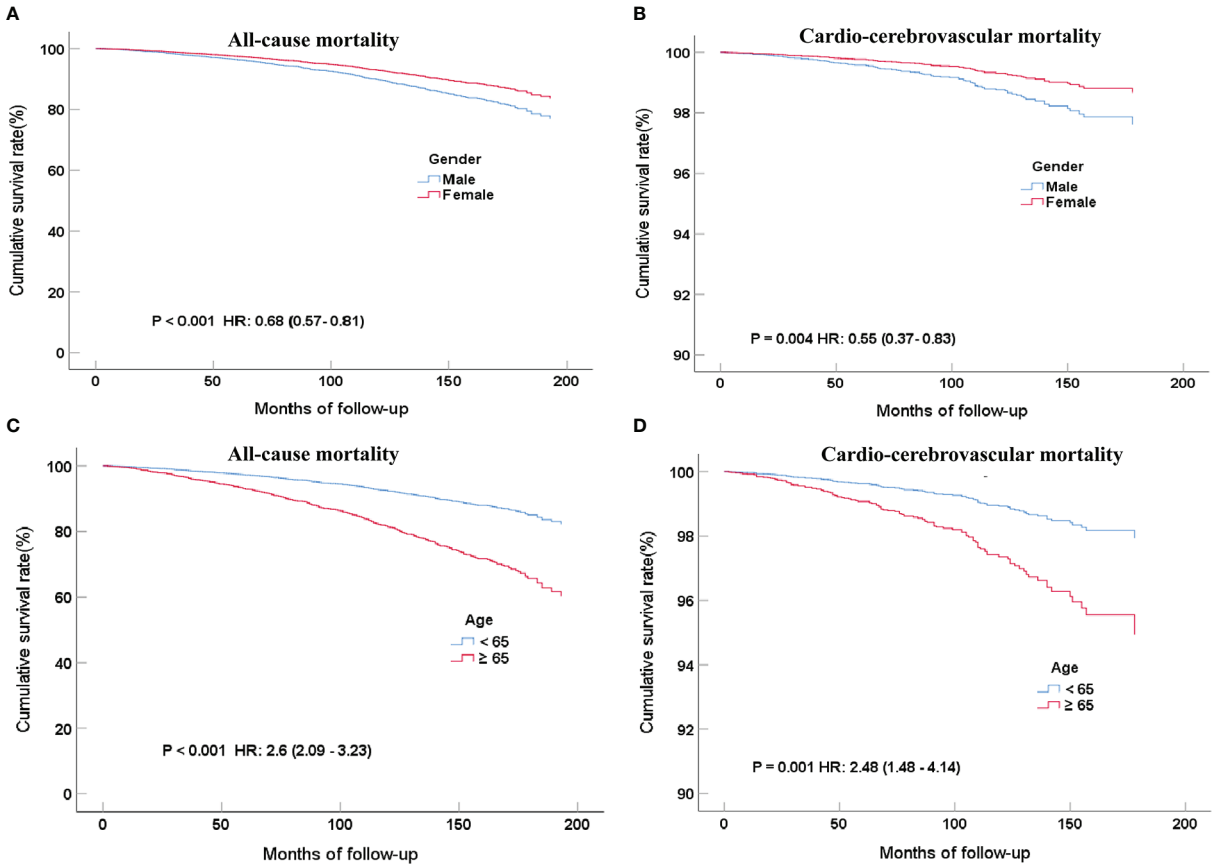

FIGURE 4
COX regression curves for all-cause **(A)** and cardio-cerebrovascular **(B)** mortality rates of MetS patients grouped by gender after multi-factor adjustment and 7.7 years of follow-up; COX regression curves for all-cause **(C)** and cardio-cerebrovascular **(D)** mortality rates of MetS in different age groups after multi-factor adjustment and 7.7 years of follow-up.

MetS. Abdominal obesity, as an important component of MetS, still has a rising trend in the U.S (25). More emphasis on abdominal obesity may reduce mortality even further.

Interestingly, for all participants, women have a higher incidence of MetS than men, but men have a higher death ratio than women, which reached statistical significance. Future research needs to explore specific reasons for the high mortality rate of men with MetS, so as to improve their prognosis by correcting hazardous factors.

Although the incidence and mortality of MetS in different age groups showed a downward trend, the incidence and mortality of MetS in older people were significantly higher. With the aging population in the U.S., more attention should be given to medical care issues to reduce the national medical burden.

MetS is thought to be a chronic, low-grade inflammatory state caused by the complex interaction of environmental and genetic factors (13). MetS was accounted for by heritability estimates ranging between approximately 10 and 30% (26). Environmental factors such as physical inactivity, an unhealthy diet, stress, and tobacco use are also closely related to the incidence of MetS. People with low education levels appeared to be more likely to suffer from MetS, which is consistent with previous research. People with a high level of education may be more mindful of inactivity, unhealthy eating patterns, and risky behaviors. In addition, they are more likely to take care of themselves by exercising, ordering regular health check-ups, and avoiding risky behaviors such as smoking and drinking too much (27, 28). All of these reasons might explain this (29). Previous studies have shown that smoking, even at low levels (mean <30 cigarettes weekly), is associated with MetS (30–32). This conclusion is consistent with our findings. A long history of cardiovascular disease (like coronary heart disease, heart failure, and angina pectoris) was positively linked to MetS. The reason might be that cardiovascular disease is closely associated with glycolipid metabolism, hypertension, and obesity, which together make for an easier MetS diagnosis (33–37). Knowledge of the factors influencing the increasing incidence of MetS in different populations is needed to assist in the prevention of cardiovascular disease and type 2 diabetes.

Our results suggest that MetS generally exists in the general population, especially in women and the elderly. It is critical to improving prevention treatments for MetS patients with high mortality risk, particularly among the elderly and male populations. In addition to this, the incidence of MetS in women is high, but the mortality is relatively low. A higher prevalence of MetS may be attributable to physical and psychological factors. The average age of women in our study was 54.6 years old, which may mean increased abdominal obesity and a reduction in HDL-cholesterol after menopause and make it easier to meet the MetS diagnostic criteria (17). Women are also more likely than men to develop MetS because of work stress and low socioeconomic status (17). It is a long-standing belief and undeniable evidence that women are more protected from CV events than men (17). Previous research demonstrated that men with MetS had a higher risk of severe CVs and mortality than women (38, 39). Some studies supported the opposite conclusion or described men and women as having equal risk (17). The association between MetS and poor prognosis may be affected by the study design (e.g., MetS definition, duration of follow-up, level of follow-up loss, and adjustment for covariates), study subjects (e.g., race, gender, and pre-morbid conditions) (40). HDL cholesterol levels and smoking were thought to play a significant role in explaining the gender difference in coronary heart disease incidence and mortality (41). In our study, men had a higher smoking rate and a higher percentage of unqualified HDL cholesterol. Men had a significantly higher prevalence of cardiovascular and cerebrovascular disease histories (16.7% vs. 12.1%, Chi-squared Test, P<0.001), indicating a worse pre-morbid condition than women. However, the exact underlying reasons merit verification through a further, rigorous prospective study.

Several limitations in our study should still be acknowledged. First, we used more stringent diagnostic criteria for MetS, which may have allowed us to underestimate its incidence while applying only objective data will reduce our MetS classification error. Second, the sample of the U.S. general population may limit its applicability to other regions and populations. Thirdly, we have not included the factors that may affect the incidence and mortality trends in MetS patients, such as exercise and nutrition. Despite all of the above, our study is important because we detailed the latest trends in MetS mortality in the United States by using a nationally representative sample. Finally, the NDI only includes deaths that occurred in the U.S. or a U.S. territory, so it may not include the deaths of all survey participants, resulting in an underestimation of mortality.

5 Conclusion

From 1999 to 2014, the incidence of MetS in U.S. adults considerably increased overall, while the mortality rate had a significant downward trend. Both trends showed marked gender differences, with women exhibiting greater prevalence and lower risk than men. It is important to identify the factors that will reduce MetS incidence and mortality, particularly in male patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found on: https://www.cdc.gov/nchs/data-linkage/mortalitypublic.htm.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the People's Hospital of Guangdong Province. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WL, and XQ: conceptualization and methodology. WL and HM: formal analysis. HM and QG: supervision and validation. WL, XQ, and HM: writing and revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Albino Carrizzo,
University of Salerno, Italy

REVIEWED BY
Stanislovas S. Jankauskas,
Albert Einstein College of Medicine, United States
Yujiao Zhang,
Shandong First Medical University, China

*CORRESPONDENCE
Huachen Jiao
liyixuan0531@163.com

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Association between serum uric acid levels and atrial fibrillation in different fasting glucose patterns: A case-control study

Xia Zhong[1], Huachen Jiao[2*], Dongsheng Zhao[1], Mengqi Yang[1] and Jing Teng[1]

[1]Department of First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China, [2]Department of Cardiology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China

Background: Previous studies have shown both dysglycaemia and hyperuricemia are associated with an increased risk of atrial fibrillation (AF), while the relationship between serum uric acid (SUA) levels and AF in different fasting glucose patterns (FBG) is unclear. Therefore, this study aimed to determine the association between SUA and AF in different FBG patterns.

Methods: A total of 1840 patients in this case-control study were enrolled, including 920 AF patients and 920 controls. Patients were divided into three groups according to the different FBG patterns: normoglycemic, impaired fasting glucose (IFG), and diabetes mellitus (DM). Multivariate logistic regression models were performed to evaluate the relationship between SUA and AF in different FBG patterns. Pearson correlation analysis was used to explore the correlation between SUA and metabolic factors. Receiver operating characteristic (ROC) curve models indicated the diagnostic efficiency of SUA for diagnosing AF.

Results: SUA was independently associated with AF after adjusting for all confounding factors in different FBG patterns(normoglycemic: OR=1.313, 95% CI:1.120-1.539; IFG: OR=1.386, 95% CI:1.011-1.898; DM: OR=1.505, 95% CI:1.150-1.970). Pearson's correlation analysis suggested that SUA in AF patients was correlated with several different metabolic factors in different FBG patterns ($p<0.05$). ROC curve analysis showed that SUA in the normoglycemic group combined with CHD and APOB [AUC: 0.906 (95% CI: 0.888-0.923)], in the IFG group combined with CHD and Scr [AUC: 0.863 (95% CI: 0.820-0.907)], in the DM group combined with CHD and SBP [AUC: 0.858 (95% CI: 0.818-0.898)] had the highest AUC for predicting AF.

Conclusion: Findings implied a significant association between SUA and AF in different FBG patterns and provide specific models combined with other factors (CHD, APOB, SCr, SBP), which might contribute to the diagnosis of AF.

KEYWORDS

atrial fibrillation, serum uric acid, glucose metabolism, inflammation, diabetes mellitus

Introduction

With the life expectancy increasing, the dramatic rise in prevalence and incidence of atrial fibrillation(AF) is emerging as an urgent public health concern worldwide (1, 2). Currently, AF is affecting about 33.5 million individuals involving 2.5-3.5% of the population in several countries (3). It is estimated that the global prevalence of AF will increase by more than 60% by 2050, and the prevalence of AF in China will be ~2.3-fold higher than the equivalent predicted in the United States (1, 4). Although the pathophysiology of AF is not well understood, it is increasingly recognized that inflammation and oxidative stress have been recognized as potential essential mechanisms for the onset and maintenance of AF. When associating inflammation and oxidative stress with the development of AF, it is significant to mention the culprit of cardiovascular and non-cardiovascular outcomes, including myocardial infarction, heart failure, stroke, cognitive decline, as well as a higher risk of all-cause mortality in this phenomenon (5). Despite multifaceted efforts, the management of the AF population remains a concern. Recently, serum biomarkers are emerging as popular indices increasingly showing potential value in AF risk stratification and adjunctive treatment decisions.

Hyperuricemia is a metabolic disease caused by a disturbance of purine metabolism or uric acid excretion, which increases the risk of cardiovascular disease through various pathways. As reported previously, increased serum uric acid (SUA) levels may contribute to the development of AF through the activation of xanthine oxidoreductase (XOR) and the activation of the NLRP3 inflammasome induced by monosodium urate (MSU) crystals (6), meanwhile, it is also associated with vasoconstriction, endothelial dysfunction, and insulin resistance (7). In recent years, numerous studies have established the correlation between elevated SUA and AF, and hyperuricemia has also been recognized as an independent competing risk factor for AF (8). Several meta-analyses indicated that elevated SUA is associated with an increased risk of AF (9–11). Several other studies have reported contradictory sex associations between elevated SUA and AF (12–16).

Moreover, studies have shown that elevated SUA contributes to cardiovascular disease, and might be associated with abnormal lipid and glucose metabolism (17). In detail, hyperuricemia can trigger abnormalities in glucose metabolism, such as hyperinsulinemia or diabetes (DM) status; and impaired renal function due to abnormal glucose metabolism ultimately induces hyperuricemia (18). Nevertheless, very little information is currently available regarding the relationship between SUA and AF in patients with T2DM; in particular, there is no evidence to determine whether the association between SUA and AF is consistent in different FBG metabolism patterns. Therefore, we conducted this case-control study based on Chinese adults to evaluate the relationship between SUA and AF under different FBG metabolism conditions.

Materials and methods

Study design and data source

All data involved in this case-control study are based on the electronic medical record database of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine. This database contains anonymously obtained clinical, demographic, and medication information, and several studies focusing on assessing the relationship between serum biomarkers and AF have already been conducted based on this database (19–22). We reviewed clinical information from 920 patients with AF who were diagnosed by specialized cardiologists and required hospitalization between January 2019 and September 2021, who were diagnosed on admission and were admitted for systemic care for an episode of AF. Meanwhile, we matched patients with sinus rhythm and non-atrial fibrillation collected during the same time period in a 1:1 ratio, and a total of 1840 patients were enrolled, including 920 patients with AF and 920 age- and sex-matched (1:1) non-AF patients with sinus rhythm. Patients with AF were identified as having a prolonged duration of arrhythmia, with a 12-lead ECG recorded or lasting at least 30 seconds (23). Inclusion criteria were as follows: 1) aged 28-85 years; 2) complete medical information. Exclusion criteria were as follows: 1) congenital heart disease, valvular disease, heart failure, or cardiac surgery; 2) severe infection, malignant tumor, or autoimmune disease; 3) severely impaired liver function, or hyperthyroidism; 4) impaired renal function; patients with estimated glomerular filtration rate(eGFR)<60 mL/(min·1.73m^2) and clinical symptoms were diagnosed with impaired renal function when assessed by their professional physicians; 5) currently undergoing treatment anticoagulants, diuretics and lipid-lowering drugs other than statins that may affect blood lipid levels; 6) patients who received uric acid lowering drugs and antidiabetic drugs because of drug intolerance or refusal; 7) pregnant or lactating women. The study This study was approved by the ethical committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (NO.20200512FA62) and the informed consent was waived due to data being anonymized.

Study variables

We reviewed all patient medical data including demographic variables and clinical variables based on an electronic medical record database. Age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP); comorbidities, medication, and laboratory parameters were collected and included. Specifically, comorbidities included hypertension and coronary heart disease (CHD); medication information included β-blockers, CCBs, ACEI/ARB, and statins;

laboratory indicators included serum uric acid (SUA), fasting blood glucose (FBG), triglycerides (TG), cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), lipoprotein (a) [Lp (a)], aspartate aminotransferase (AST); alanine aminotransferase (ALT); serum creatinine (SCr), and albumin (ALB). Hyperuricemia was diagnosed if SUA > 7.0 mg/dL in men or > 6.0 mg/dL in women (24). In addition, patients were divided into three groups according to the different FBG patterns (25): normoglycemic group (FBG < 6.1 mmol/L), impaired fasting glucose (IFG) group (6.1–7.0 mmol/L), and diabetes mellitus (DM) group (FBG ≥ 7.0 mmol/L or receiving hypoglycemic therapy).

Statistical analysis

Statistical analysis was performed by SPSS version 26.0, GraphPad Prism version 9.0.0, and python version 3.6.8. Quantitative data were expressed as means ± standard deviations(SD) or medians (interquartile ranges), and differences between groups were compared using the T-test or the Mann-Whitney U test. Categorical variables were described as frequencies (percentages) and chi-square tests were applied to analyze differences between groups. Pearson correlation analysis was used to assess the correlation between SUA and several metabolic factors in different FBG patterns. Taking AF as the dependent variable, multivariate logistic regression models were used to adjust for confounding factors and showed the relationship between SUA and AF in different FBG groups. The receiver operating characteristic (ROC) curve model revealed the diagnostic efficiency of SUA combined with related indicators for diagnosing AF in different FBG states. A $p < 0.05$ was considered to be significant, and two-tailed.

Results

Baseline characteristics of the individuals

Table 1 shows the baseline characteristics of the AF and control populations in different fasting glucose patterns, including 1203 normoglycemic patients, 283 patients with impaired fasting glucose, and 354 patients with diabetes. Compared with the controls, AF patients were more likely to experience CHD and hypertension and use β-blockers, CCBs, ACEI/ARB, and statins (all $p<0.005$) in different FBG metabolism patterns; meanwhile, there were significant differences under different FBG patterns in SBP, DBP, TC, LDL-C, HDL-C, APOA1, APOB, SCr, ALB, and SUA (all $p < 0.05$).

Figure 1 shows the gender differences in SUA levels between AF patients and controls under different FBG metabolic patterns. In the normoglycemic group, SUA levels in males (6.07 ± 1.87 vs. 5.69 ± 1.21 mg/dL, p=0.003, Figure 1A) and females (5.72 ± 1.55 vs. 4.54 ± 1.21 mg/dL, p<0.001, Figure 1A) with AF were significantly higher than controls. In the IFG group, SUA levels in males (6.27 ± 2.13 vs. 5.71± 1.17 mg/dL, p=0.049, Figure 1B) and females (5.41 ± 1.13 vs. 4.78 ± 1.42 mg/dL, p=0.005, Figure 1B) with AF were significantly higher than controls. In the DM group, SUA levels in males (5.87 ± 1.84 vs. 5.14 ± 1.43 mg/dL, p=0.004, Figure 1C) and females (5.86 ± 1.88 vs. 4.90 ± 1.49 mg/dL, p<0.001, Figure 1C) with AF were also significantly higher than controls.

Figure 2 shows the comparison of the rate of hyperuricemia between the AF group and the control group under different FBG patterns. In the normoglycemic group, the rate of hyperuricemia in the AF group was significantly higher than those in the control group (73.88 vs. 26.12 %, $p < 0.001$, Figure 2A). In the IFG group, the rate of hyperuricemia in the AF group was significantly higher than those in the control group (66.67 vs. 33.33 %, $p < 0.001$, Figure 2B). In the DM group, the rate of hyperuricemia in the AF group was also significantly higher than those in the control group (70.24 vs. 29.76 %, $p < 0.001$, Figure 2C).

Multivariate logistic regression to reveal the association between SUA and AF in different FBG patterns

Table 2 shows the relationship between SUA and AF in different FBG groups after adjusting for confounding factors. First, we found that SUA was significantly associated with AF under three FBG metabolism patterns (normoglycemic pattern: OR=1.353, 95% CI:1.195-1.531, p<0.001; IFG pattern: OR=1.378, 95% CI:1.107-1.715, p=0.004; DM pattern: OR=1.348, 95% CI:1.112-1.633, p=0.002, Table 2) after adjusting for age, gender, hypertension, CHD, CCBs, β-blockers, ACEI/ARB, and statins. Then, we further adjusted for TC, LDL-C, HDL-C, APOA1, APOB, SCr, and ALB, the consequence indicated that SUA still independently associated with AF in different FBG metabolism patterns (normoglycemic pattern: OR=1.451, 95% CI:1.303-1.617, p<0.001; IFG pattern: OR=1.402, 95% CI:1.101-1.786, p=0.006; DM pattern: OR=1.460, 95% CI:1.221-1.746, p<0.001, Table 2). Finally, we adjusted for all these factors and found that SUA remains a significantly relevant factor for AF in different FBG patterns(normoglycemic pattern: OR=1.313, 95% CI:1.120-1.539, p=0.001; IFG pattern: OR=1.386, 95% CI:1.011-1.898, p=0.042; DM pattern: OR=1.505, 95% CI:1.150-1.970, p=0.003, Table 2).

Correlation analysis of the SUA in AF patients with metabolic factors

Figure 3 shows the correlation between the SUA in AF patients and several metabolic factors under the normoglycemic pattern. Pearson correlation analysis suggested that HDL-C ($r = -0.249$, $p < 0.001$) and APOA1 ($r = -0.203$, $p < 0.001$) were negatively correlated with SUA,whereas FBG ($r = 0.102$, p=0.014) and SCr ($r = 0.225$, $p < 0.001$) were positively correlated with SUA. Figure 4 shows the correlation between the SUA in AF patients and several metabolic factors under the IFG pattern. Pearson correlation analysis suggested that HDL-C ($r = -0.179$, p=0.036) was negatively correlated with SUA, whereas LDL-C ($r = 0.190$, p=0.025) and SCr ($r = 0.218$, p=0.010) were positively correlated with SUA. Interestingly, we didn't find a correlation between SUA and metabolic factors under the DM pattern in the AF population.

SUA combined with related indicators for diagnosing AF in different FBG patterns

Figure 5 shows the receiver operating characteristic (ROC) curve model of SUA for diagnosing AF in the normoglycemic pattern. In the normoglycemic pattern, the ROC curve analysis suggested that the AUCs for taking SUA, CHD, and APOB to predict AF were 0.63, 0.83, and 0.74, respectively (Figure 5A); SUA combined with CHD and APOB had the highest AUC for predicting AF [AUC: 0.906 (95% CI: 0.888-0.923)] (Figure 5D), followed by SUA combined with CHD [AUC: 0.872(95% CI: 0.851–0.893); Figure 5B] and APOB [AUC: 0.776(95% CI: 0.750–0.802); Figure 5C]. In the IFG pattern, the ROC curve analysis showed that the AUCs for using SUA, CHD, and SCr to

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TABLE 1 Baseline characteristics of paroxysmal AF group and controls.

Variables	Normoglycemic group (N=1203)			IFG group (N=283)			DM group (N=354)		
	AF group (N=590)	Control group (N=613)	P value	AF group (N=138)	Control group (N=145)	P value	AF group (N=192)	Control group (N=162)	P value
Age, years	67.75 ± 11.12	66.56 ± 12.17	0.077	69.28 ± 9.19	68.94 ± 9.43	0.759	70.83 ± 8.17	73.09 ± 8.52	0.011*
Gender			0.840			0.208			0.709
Men	293 (49.66)	308 (50.24)		76 (55.07)	69 (47.59)		91 (47.40)	80 (49.38)	
Women	297 (50.34)	305 (49.76)		62 (44.93)	76 (52.41)		101 (52.60)	82 (50.62)	
CHD, n (%)	513 (86.95)	130 (21.21)	<0.001*	122 (88.41)	42 (28.97)	<0.001*	177 (92.19)	55 (33.95)	<0.001*
Hypertension, n (%)	377 (63.90)	160 (26.10)	<0.001*	100 (72.46)	60 (41.38)	<0.001*	141 (73.44)	88 (54.32)	<0.001*
SBP, mmHg	129.74 ± 18.78	132.95 ± 18.89	0.003*	131.96 ± 19.44	139.83 ± 19.72	0.001*	133.77 ± 20.81	143.00 ± 20.50	<0.001*
DBP, mmHg	77.77 ± 13.48	80.85 ± 11.69	<0.001*	79.67 ± 14.18	84.57 ± 12.91	0.003*	78.84 ± 13.63	82.38 ± 12.59	0.012*
FBG, mmol/L	5.16 ± 0.53	5.30 ± 0.44	<0.001*	6.50 ± 0.24	6.48 ± 0.24	0.484	9.27 ± 2.81	9.45 ± 2.65	0.538
TG, mmol/L	1.00[0.74-1.41]	1.06[0.79-1.45]	0.079	1.12[0.78-1.52]	1.22[0.95-1.68]	0.011*	1.19[0.91-1.68]	1.23[0.92-1.77]	0.802
TC, mmol/L	4.20 ± 1.09	5.03± 1.06	<0.001*	4.15 ± 1.13	5.19 ± 1.05	<0.001*	4.18 ± 1.07	4.88 ± 1.25	<0.001*
LDL-C, mmol/L	2.50 ± 0.91	2.97 ± 0.84	<0.001*	2.53 ± 0.84	3.13± 0.84	<0.001*	2.47 ± 0.87	2.84 ± 0.92	<0.001*
HDL-C, mmol/L	1.10 ± 0.29	1.22 ± 0.31	<0.001*	1.04 ± 0.29	1.19 ± 0.27	<0.001*	1.02 ± 0.34	1.13 ± 0.31	0.002*
APOA1, g/L	1.14 ± 0.26	1.23± 0.25	<0.001*	1.14 ± 0.26	1.24 ± 0.21	<0.001*	1.11 ± 0.29	1.19 ± 0.27	0.008*
APOB, g/L	0.77 ± 0.24	0.98± 0.23	<0.001*	0.86 ± 0.79	1.04± 0.24	0.011*	0.82 ± 0.25	0.99 ± 0.28	<0.001*
Lp (a), mg/L	14.00[6.80-30.08]	14.70[7.20-28.45]	0.814	15.15[7.23-30.93]	12.70[6.15-27.00]	0.497	14.05[6.70-30.10]	16.40[6.28-32.13]	0.550
AST, U/L	20.00[16.00-25.00]	19.00[16.00-23.00]	0.001*	20.00[16.75-27.00]	19.00[16.00-24.00]	0.088	19.00[16.00-25.00]	17.00[14.00-23.25]	0.061
ALT, U/L	15.00[12.00-22.00]	16.00[12.00-22.00]	0.412	18.50[11.00-28.00]	18.00[13.00-25.50]	0.813	17.00[12.00-24.00]	18.00[13.00-25.00]	0.381
SCr, μmoI/L	72.00[60.00-83.25]	63.00[54.00-74.00]	<0.001*	72.00[58.00-88.25]	62.00[53.00-74.00]	<0.001*	70.00[57.00-87.00]	58.00[52.00-68.00]	<0.001*
SUA, mg/dL	5.89 ± 1.72	5.12 ± 1.34	<0.001*	5.88 ± 1.80	5.22 ± 1.38	0.001*	5.87 ± 1.86	5.02 ± 1.46	<0.001*
ALB, g/L	38.11± 4.29	40.04 ± 4.05	<0.001*	38.49 ± 4.67	40.91 ± 3.62	<0.001*	37.42± 5.54	39.60 ± 4.75	<0.001*
β-blockers, n (%)	462 (78.31)	79 (12.89)	<0.001*	107 (77.54)	32 (22.07)	<0.001*	152 (79.17)	42 (25.93)	<0.001*
CCBs, n (%)	200 (33.90)	85 (13.87)	<0.001*	56 (40.58)	31 (21.38)	<0.001*	75 (39.06)	45 (27.78)	<0.001*
ACEI/ARB, n (%)	327 (55.42)	73 (11.91)	<0.001*	77 (55.80)	22 (15.17)	<0.001*	109 (56.77)	40 (24.69)	<0.001*
statins, n (%)	377 (63.90)	122 (19.90)	<0.001*	94 (68.12)	40 (27.59)	<0.001*	134 (69.79)	49 (30.25)	<0.001*

Data were presented as mean±SD, median [interquartile range], or n (%).
*Statistically significant value (P<0.05).
AF, atrial fibrillation; IFG, impaired fasting glucose; DM, diabetes mellitus; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; APOA1, apolipoprotein A1; APOB, apolipoprotein B; Lp (a), lipoprotein (a); AST, aspartate aminotransferase; ALT, alanine aminotransferase; SCr, serum creatinine; SUA, serum uric acid; ALB, albumin.

diagnose AF were 0.60, 0.80, and 0.65, respectively (Figure 6A); SUA combined with CHD and SCr had the highest AUC for diagnosing AF [AUC: 0.863 (95% CI: 0.820-0.907)] (Figure 6D), followed by SUA combined with CHD [AUC: 0.844(95% CI: 0.796–0.891); Figure 6B] and APOB [AUC: 0.650(95% CI: 0.587–0.714); Figure 6C]. In the DM pattern, the ROC curve analysis indicated that the AUCs for taking SUA, CHD, and APOB to predict AF were 0.64, 0.79, and 0.64, respectively (Figure 7A); SUA combined with CHD and SBP had the highest AUC for diagnosing AF [AUC: 0.858 (95% CI: 0.818-0.898)] (Figure 7D), followed by SUA combined with CHD [AUC: 0.849(95% CI: 0.807–0.890); Figure 7B] and SBP [AUC: 0.678(95% CI: 0.623–0.734); Figure 7C].

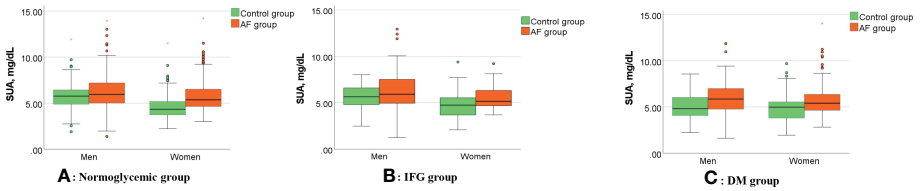

FIGURE 1
Gender differences in SUA levels between AF patients and controls under different FBG metabolic patterns. **(A–C)** Compared with controls, SUA levels of the AF patients were significantly higher in the men (all p<0.05) and women (all p<0.05) in different FBG patterns. AF, atrial fibrillation; SUA, serum uric acid; IFG, impaired fasting glucose; DM, diabetes mellitus.

Discussion

In this Chinese case-control study, we investigated the association between SUA and AF and the correlation between SUA and metabolic factors in different FBG metabolism states. We found that males and females with AF had higher SUA levels and rates of hyperuricemia than those with controls in different FBG patterns. Meanwhile, there was a significant relationship between SUA and AF, which persisted even after adjusting for all confounding factors. SUA can be an independent risk factor for AF in different FBG metabolism patterns. Furthermore, SUA in AF patients was correlated with several different metabolic factors in different FBG patterns. Moreover, SUA and CHD are the two most significant factors for predicting AF, while factors including APOB, SCr, and SBP might help to further improve the diagnostic efficiency.

Detection of AF in patients with abnormal glucose metabolism poses a diagnostic challenge. SUA is the end product of adenine and guanine metabolism in the human body (26), and its increased level may be related to cardiometabolic and cardiovascular disease development by affecting lipid and glucose metabolism (17). Hyperuricemia, defined as SUA levels higher than 7 mg/dL in men or 6 mg/dL in women (27), has been identified as a significant risk factor for AF (6, 8), but the detailed relationships and mechanisms between SUA levels and AF remain unknown. In recent years, increased SUA levels have been reported to be associated with the induction of atrial remodeling by the inflammation and oxidative damage in the pathological process of AF, thus predicting the onset of AF (28–30); this has also been supported by a mendelian randomization analysis (31) and several meta-analyses (9, 32–34). Some studies have also explored the relationship between SUA level and AF from different perspectives. An updated meta-analysis (11) reported the relationship between SUA levels and different types of AF, SUA levels were significantly different among patients with new-onset, paroxysmal, and persistent AF; in detail, patients with persistent AF had the highest level of SUA, followed by paroxysmal AF, and the lowest level was new-onset AF. Several earlier studies investigated the gender-specific association between SUA level and AF. Suzuki et al. indicated there was an independent association between SUA levels and AF in women; both Chen et al. (35) and Lin et al. (16) have also reported similar findings. However, several other studies have reported an association between SUA levels and AF risk in both sexes (29, 36, 37). A recent Chinese study (38) showed that SUA>396.5μmol/L in AF patients indicates a severe degree of atrial fibrosis, and early intervention should be considered. Evidence suggests that elevated SUA may be involved in the occurrence and development of atrial fibrosis by inducing oxidative stress and inflammation. SUA is a marker of oxidative stress, and its increased level indicates the increase of oxidative damage. Xanthine oxidoreductase promotes oxidative stress through the formation of electron radical superoxide anion, and the upregulation of xanthine oxidase activity by elevated SUA increases oxidative damage (39). In an oxidative stress state, on the one hand, the accumulation of reactive oxygen species (ROS) and the activation of inflammatory response lead to cell necrosis and endothelial dysfunction, promote atrial muscle fiber, and lead to atrial structural remodeling; on the other hand, oxidative damage changes the level of ion channels and affects the energy of atrial contraction myofibrils, leading to atrial electrical remodeling (40, 41).

The growing recognition of the strong links between diabetes, hyperuricemia, and AF has spurred our interest in unraveling their

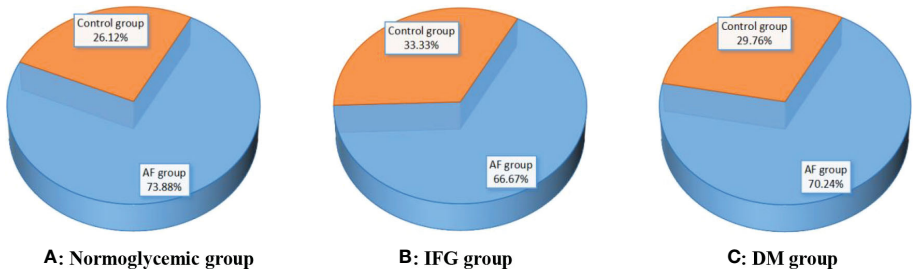

FIGURE 2
Comparison of the rate of hyperuricemia between the AF group and the control group under different FBG patterns. **(A–C)** Compared with controls, the rate of hyperuricemia in the AF group was significantly higher than those in the control group (all p < 0.001). AF, atrial fibrillation; IFG, impaired fasting glucose; DM, diabetes mellitus.

TABLE 2 Association between SUA and AF in different FBG patterns.

Models	Normoglycemic group (n=1203)		IFG group (N=283)		DM group (N=354)	
	OR 95% CI	P value	OR 95% CI	P value	OR 95% CI	P value
Model 1	1.407 (1.296-1.528)	<0.001*	1.308 (1.116-1.533)	0.001*	1.375 (1.193-1.584)	<0.001*
Model 2	1.353 (1.195-1.531)	<0.001*	1.378 (1.107-1.715)	0.004*	1.348 (1.112-1.633)	0.002*
Model 3	1.451 (1.303-1.617)	<0.001*	1.402 (1.101-1.786)	0.006*	1.460 (1.221-1.746)	<0.001*
Model 4	1.313 (1.120-1.539)	0.001*	1.386 (1.011-1.898)	0.042*	1.505 (1.150-1.970)	0.003*

Model 1: crude, no adjustment.
Model 2: adjusting for age, gender, hypertension, CHD, CCBs, β-blockers, ACEI/ARB, and statins.
Model 3: adjusting for TC, LDL-C, HDL-C, APOA1, APOB, SCr, and ALB.
Model 4: adjusting for all these factors.
*Statistically significant value (P<0.05).

mechanistic links. To date, there is no information on the relationship between SUA levels and AF in different patterns of glucose metabolism, although an association between elevated SUA and AF in individuals with T2DM has been demonstrated. A 10-year follow-up study by Valbusa et al. (42) revealed that elevated SUA is closely related to an increased incidence of AF in patients with type 2 diabetes after adjustment for risk factors for AF. Another two small retrospective studies by Mantovani et al. (43, 44) indicated that hyperuricemia is independently correlated with an increased risk of both AF and paroxysmal AF in patients with T2DM.

To the best of our knowledge, this is the first study describing the relationship between SUA levels and AF in different FBG metabolism patterns. In this study, we observed that AF had higher SUA levels and rates of hyperuricemia in both sexes than those with controls, and SUA can be an independent risk factor for AF in different FBG patterns after adjusting for multiple confounding factors. More importantly, we explored the ROC curve model of SUA for diagnosing AF and evaluated the diagnostic performance in different FBG metabolism patterns. Herein, We know that SUA and CHD are significant predictors of AF, while APOB, SCr, SBP, and

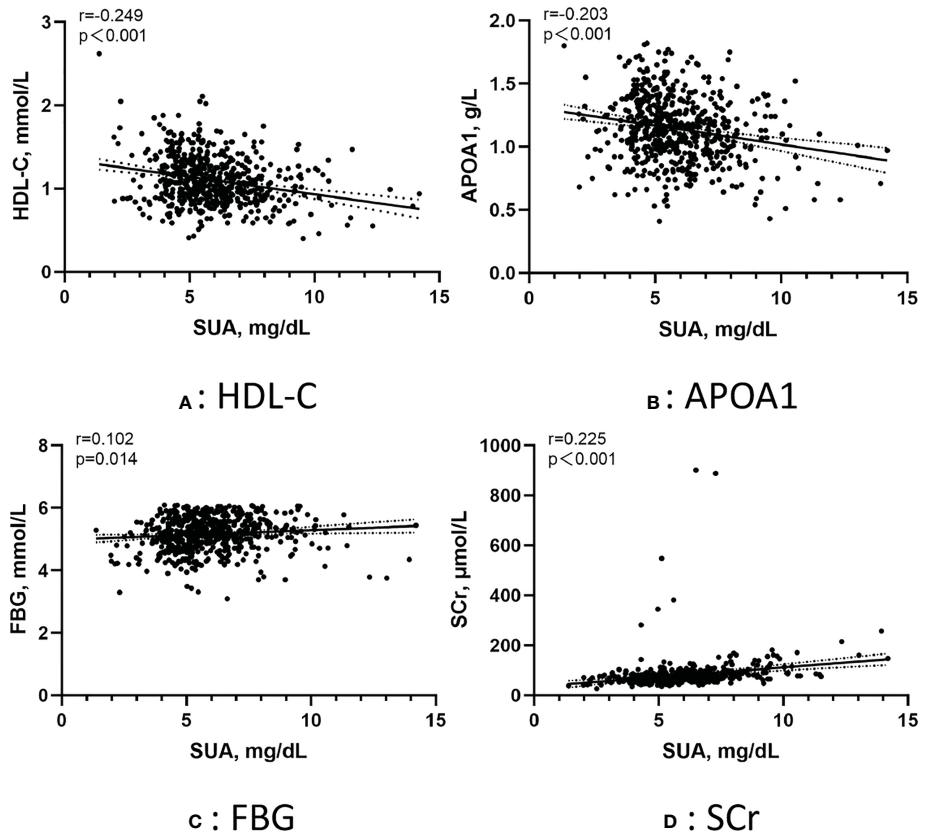

FIGURE 3
Pearson correlation of the SUA in AF patients with metabolic factors under the normoglycemic pattern. **(A)** Correlation between SUA and HDL-C; **(B)** Correlation between SUA and APOA1; **(C)** Correlation between SUA and FBG; **(D)** Correlation between SUA and SCr. SUA, serum uric acid; HDL-C, high-density lipoprotein cholesterol; APOA1, apolipoprotein A1; FBG, fasting blood glucose; SCr, serum creatinine.

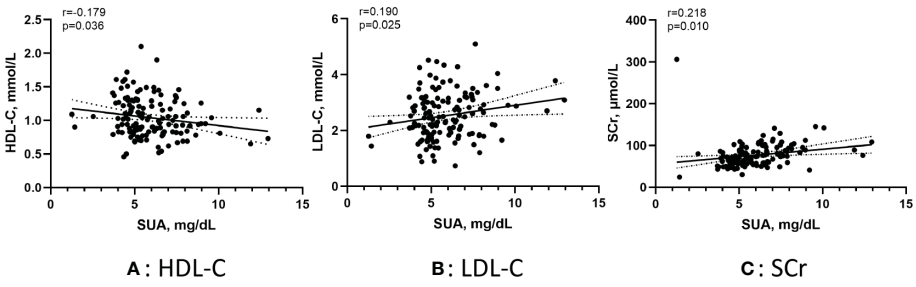

FIGURE 4
Pearson correlation of the SUA in AF patients with metabolic factors under the IFG pattern. **(A)** Correlation between SUA and HDL-C; **(B)** Correlation between SUA and LDL-C; **(C)** Correlation between SUA and SCr. SUA, serum uric acid; IFG, impaired fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine.

other factors may also contribute to improving the diagnostic efficiency of AF. From a clinical point of view, the role of diabetes in promoting AF has been beyond doubt. In addition to already diagnosed diabetes mellitus, increased impaired fasting glucose in prediabetes is also associated with an increased risk of future AF (45). A study has shown that a 10 mg/dL elevate in FBG was associated with an increased risk of AF (46); additional evidence has also shown that a 1 mmol/L increase in FBG was associated with a 33% increased

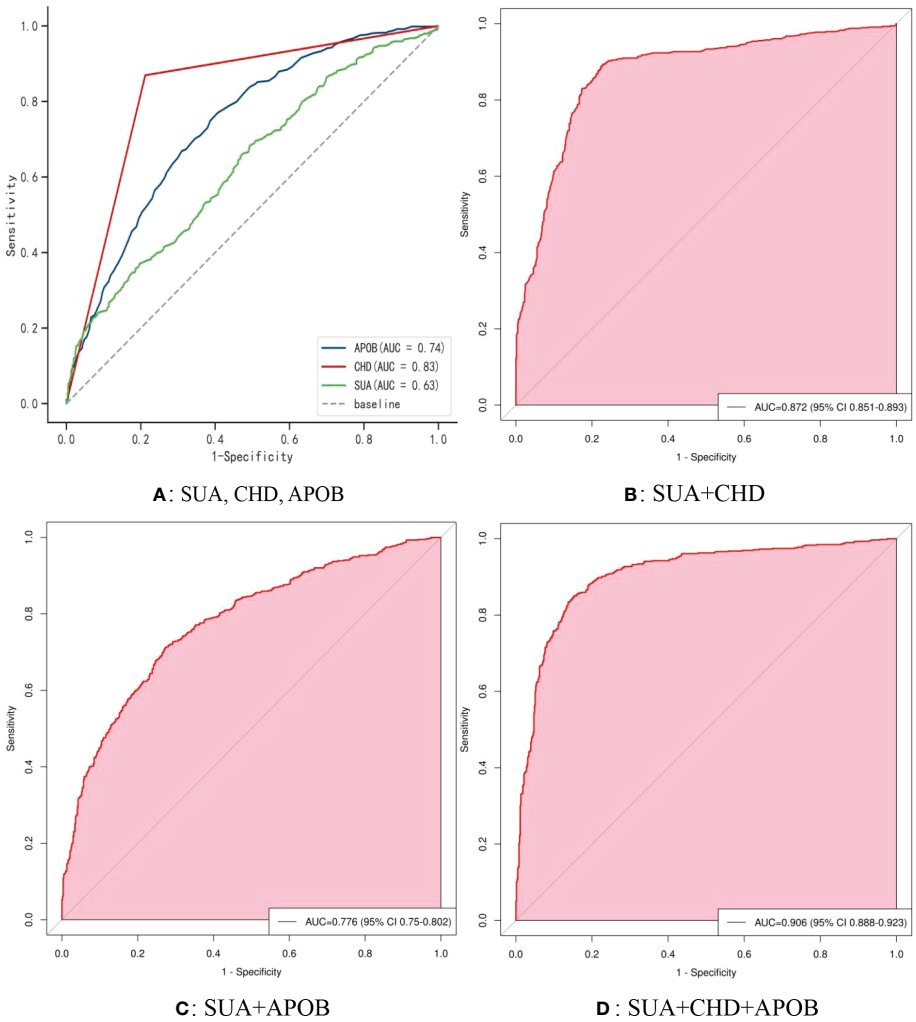

FIGURE 5
The receiver operating characteristic (ROC) curve model of SUA for diagnosing AF in the normoglycemic pattern. **(A)** Performance of SUA, CHD, and APOB for predicting AF. **(B)** Performance of SUA combined with CHD for predicting AF. **(C)** Performance of SUA combined with APOB for predicting AF. **(D)** Performance of SUA combined with CHD and APOB for predicting AF. SUA, serum uric acid; CHD, coronary heart disease; APOB, apolipoprotein B.

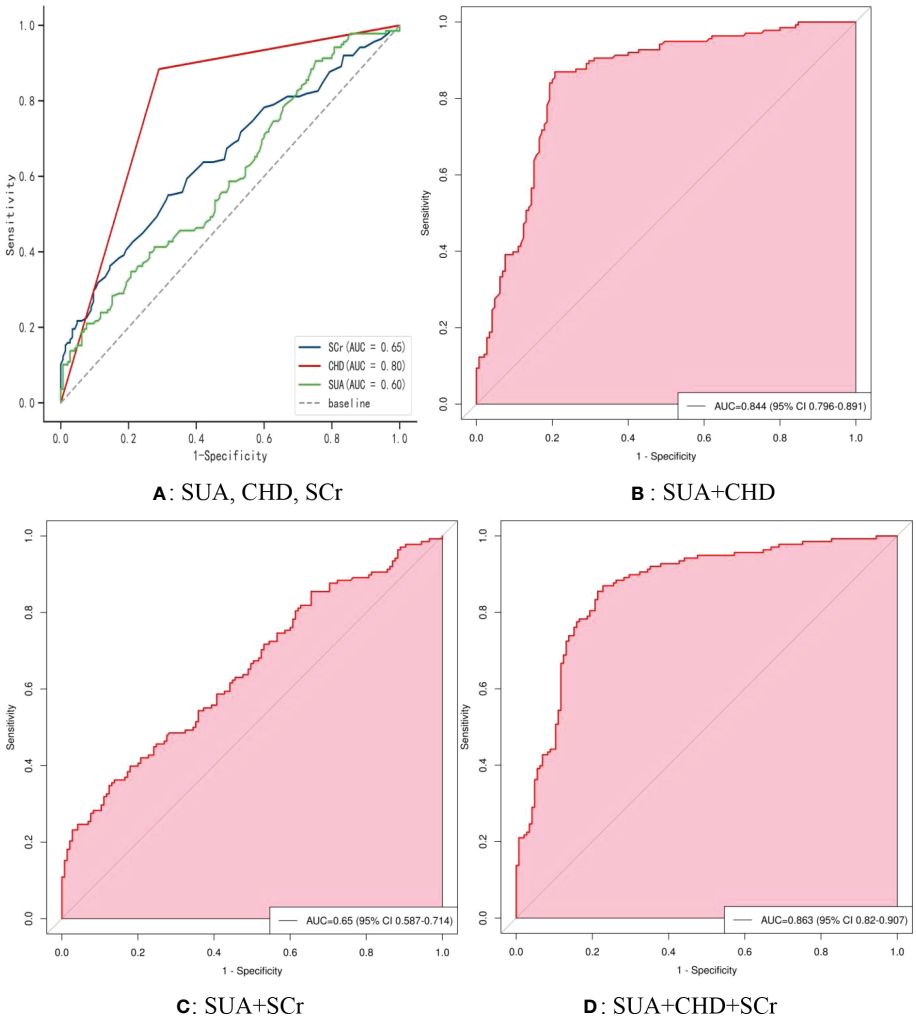

FIGURE 6
The receiver operating characteristic (ROC) curve model of SUA for diagnosing AF in the IFG pattern. **(A)** Performance of SUA, CHD, and FBG for predicting AF. **(B)** Performance of SUA combined with CHD for predicting AF. **(C)** Performance of SUA combined with FBG for predicting AF. **(D)** Performance of SUA combined with CHD and FBG for predicting AF. IFG, impaired fasting glucose; SUA, serum uric acid; CHD, coronary heart disease; FBG, fasting blood glucose.

risk of atrial fibrillation in people who did not progress to diabetes. Therefore, it is recommended to start with prediabetes and to screen regularly for AF as IFG/T2DM progresses.

Although the pathophysiological mechanism of SUA level and AF with dysglycaemia remains controversial, the influence of concomitant risk factors such as coronary heart disease, hypertension, and metabolic dysfunction on the risk of AF should be considered. The association between diabetes and AF has been suggested to be caused by a number of diabetes-related factors, such as hypertension and obesity (47). Prehypertension and IFG, the prior stages of hypertension and diabetes, are considered potential independent risk factors of AF, especially when systolic and diastolic blood pressure elevation combined with IFG significantly increases the risk of new AF (48). Particularly, elevated SUA, a regulator of glucose and lipid metabolism, suggests a mechanism of impaired metabolic homeostasis (49). Therefore, the increase of SUA is likely to drive the association between abnormal blood glucose and AF. From this standpoint, it can be speculated that with the increase in SUA levels and dysglycemia, may play an important role in the progression of inflammation and oxidative stress in AF (50). Moreover, the possibility of preventing the development of AF by modifying risk factors associated with dysglycaemia, metabolic syndrome, and sedentary lifestyle has recently been highlighted (45). On this basis, we further investigated the correlation between SUA and metabolic factors under different FBG patterns. We found that SUA was positively correlated with FBG and SCr, whereas was negatively correlated with HDL-C and APOA1 in normoglycemic patients; SUA was positively correlated with LDL-C and SCr, whereas was negatively correlated with HDL-C in the IFG pattern. Increased SUA levels may be related to decreased renal excretion (51), and promote the progression of renal injury by activating the renin-angiotensin system and destroying vascular endothelial function (52) while inducing the activation of oxidative stress and inflammatory pathways. Elevated SCr is usually indicative of renal injury, which might explain our findings.

Atherosclerosis and CHD are the key factors that trigger AF and inflammatory mechanisms. The prominent role of inflammation in the pathogenesis of atherosclerosis and its complications including AF cannot be ignored, and its inducing factors are still unclear, but

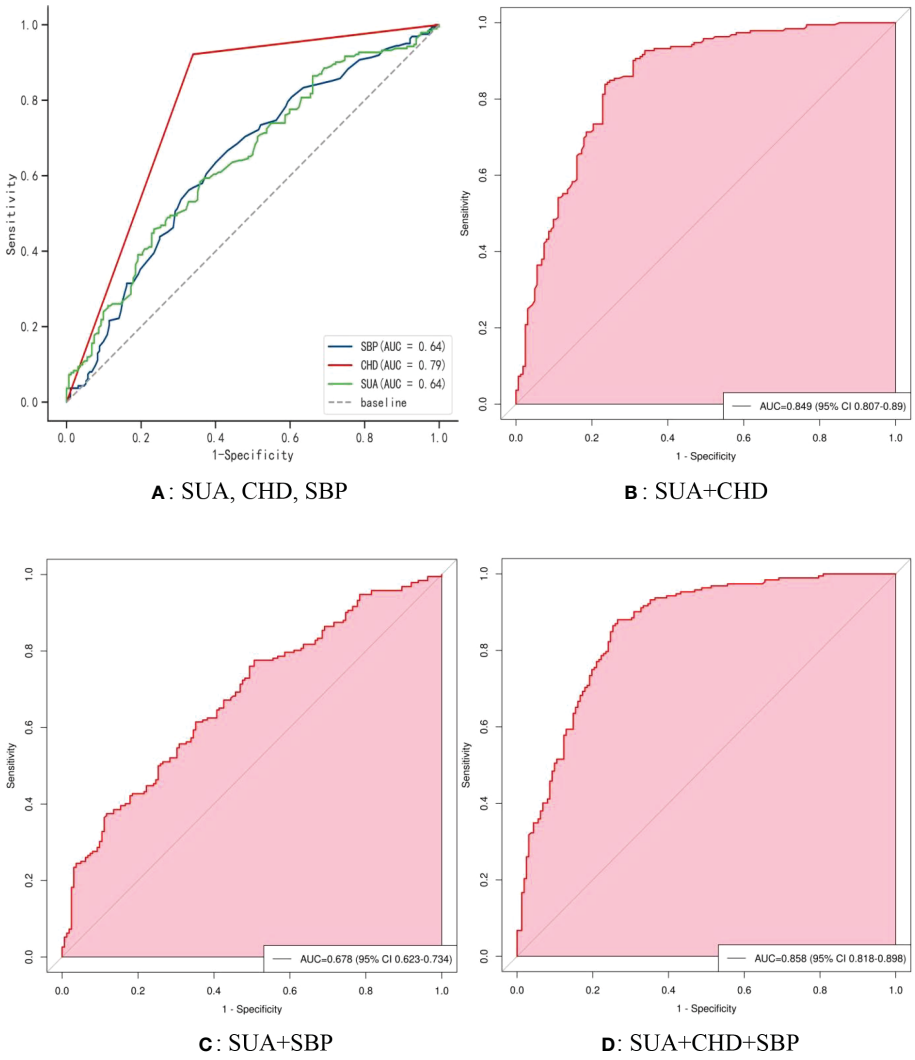

FIGURE 7
The receiver operating characteristic (ROC) curve model of SUA for diagnosing AF in the DM pattern. **(A)** Performance of SUA, CHD, and SBP for predicting AF. **(B)** Performance of SUA combined with CHD for predicting AF. **(C)** Performance of SUA combined with SBP for predicting AF. **(D)** Performance of SUA combined with CHD and SBP for predicting AF. DM, diabetes mellitus; SUA, serum uric acid; CHD, coronary heart disease; APOB, apolipoprotein B; SBP, systolic blood pressure.

lipid disorders cannot be excluded (53). Elevated SUA has also been proposed to be associated with unstable coronary plaques (54). In addition, ample evidence implicates that insulin resistance and the insulin resistance (metabolic) syndrome contribute to the increase of cardiovascular risk in patients with T2DM (55). Insulin resistance, a precursor to metabolic syndrome and DM, appears at almost any stage of atherosclerotic disease, from endothelial dysfunction to accelerated atherosclerotic progression, plaque vulnerability, and finally coronary events (56). Finally, from the consequence of the ROC curve, we recommend the use of SUA, CHD, and APOB to predict AF in normoglycemic patients; SUA, CHD, and SCr to predict AF in IFG patients; SUA, CHD, and SBP to predict AF in DM patients. Collectively, these findings are supported by previous evidence and contribute to a better understanding of the relationship between SUA, dysglycemia, and AF pathology.

Several limitations of the current study should be acknowledged. First, a major limitation of this study is its retrospective design, which, while preventing any knowledge of causality, can form a hypothesis for future studies to confirm. Second, the size of the population and the number of research centers is indeed limited; in this context, it is inevitable to increase the heterogeneity and inaccuracy. Third, in this study, SUA and FBG at a single point are not representative of the overall status, which may have affected the output of the results. Glycosylated hemoglobin (HbA1c) has not been routinely analyzed and was limited to a small population, so it is not currently included in the analysis. Fourth, we failed to focus on subgroup analyses of AF type, sex, and age, which may have missed some important information; additionally, information on the type of diabetes is also not available. Fifth, markers of inflammation and oxidative stress were not evaluated, which could have confounded the current results. Finally, we cannot exclude residual confounding factors, including body mass index (BMI), physical activity, smoking, and drinking. Meanwhile, we only focused on the population diagnosed with AF on admission, some patients had AF before admission and were ignored due to delay in treatment and unclear diagnosis, especially asymptomatic AF. Notwithstanding these limitations, our

study is the first to explore the association between SUA levels and AF in different patterns of FBG metabolism and has significant strengths, including a relatively complete dataset and the ability to adjust for multiple confounding factors, while also exploring the performance of SUA levels in diagnosing AF. Importantly, it provides a new perspective to further understand the pathologic process of AF and the possibility of tightly managing SUA levels to reduce the risk of AF in dysglycemic modes.

Conclusions

In conclusion, increased SUA and AF were independently correlated in different FBG metabolic patterns. Moreover, this relationship may be driven by several risk factors for AF, including CHD, APOB, SCr, and SBP. Elevated SUA, as a key regulator of glucose and lipid metabolism, may contribute to complex inflammation and oxidative stress in AF. The current findings offer the possibility of preventing AF in different stages of FBG metabolism to a certain extent: in the normoglycemic pattern, SUA, CHD, and APOB levels should be monitored with emphasis; in the FIG pattern, SUA, CHD, and SCr level should be monitored; in the DM pattern, attention should be paid to the levels of SUA, CHD, and SBP. The exact mechanisms of SUA participation in glycemic metabolism or the pathogenesis of AF and evaluation of SUA-lowering therapies, as well as their impact on clinical outcomes, remain to be investigated longitudinally.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HJ was the main coordinator of the project and was responsible for the study design. XZ and HJ drafted the manuscript of the present paper. MY and JT were involved in the supervising of data collection and stratification. XZ and DZ contributed to data assembly and analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Paola Di Pietro,
University of Salerno, Italy

REVIEWED BY
Davide Bonadies,
University of Salerno, Italy
Anna Eremkina,
Endocrinology Research Center, Russia
Monica Annunziata,
Azienda Sanitaria Locale Salerno, Italy
Sudhaker D. Rao,
Henry Ford Hospital, United States
Catherine McManus, Columbia University Irving Medical Center, United States

*CORRESPONDENCE
Xue Lin
linxuepumch@qq.com
Xiaoping Xing
xingxp2006@126.com

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The preliminary study on cardiac structure and function in Chinese patients with primary hyperparathyroidism

Rong Chen[1], An Song[1], Ou Wang[1], Yan Jiang[1], Mei Li[1], Weibo Xia[1], Xue Lin[2*] and Xiaoping Xing[1*]

[1]Department of Endocrinology, Key Laboratory of Endocrinology, National Health Commission, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China, [2]Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China

Purpose: Recent evidences show that primary hyperparathyroidism (PHPT) patients have a high prevalence of cardiovascular diseases. However, the reported changes in cardiac status are inconsistent in previous studies. The present work evaluated the cardiac structure and function in PHPT patients by echocardiography.

Methods: PHPT patients and age- and sex-matched healthy controls were enrolled in this case-control study. Biochemical parameters were retrospectively collected from PHPT patients. Cardiac function and structure were assessed in all subjects using echocardiography.

Results: A total of 153 PHPT patients and 51 age- and sex-matched healthy controls were enrolled in this study. The mean serum calcium and parathyroid hormone (PTH) levels in PHPT patients were 2.84 ± 0.28mmol/L and 206.9 (130.0, 447.5) pg/ml, respectively. Left ventricular ejection fraction (LVEF) and early to late mitral annular velocity (E/A) were significantly lower in PHPT patients than in healthy controls (68.2 ± 6.0 vs. 70.7 ± 16.7%, 1.0 ± 0.5 vs. 1.4 ± 0.5, respectively, p both < 0.05). The left ventricular mass index (LVMI) and the relative wall thickness (RWT) were not significantly different between the two groups. However, the difference in LVEF between PHPT patients without hypertension and diabetes and the control groups disappeared. The majority of PHPT patients had normal cardiac geometry; however, a proportion of them exhibited concentric remodeling (normal LVMI, RWT≥0.42). Serum calcium, corrected calcium, ionized calcium and PTH were inversely related to E/A, whereas serum phosphorus and 24-hour urine calcium were positively related to E/A. Furthermore, biochemical parameters were not correlated with LVEF.

Conclusions: These findings demonstrate that PHPT patients exhibit diastolic cardiac dysfunction reflected by decreased E/A, as well as possible cardiac structural abnormalities. The serum calcium, phosphorus, and parathyroid hormone levels may influence cardiac structure and function.

KEYWORDS

primary hyperparathyroidism, echocardiography, cardiac structure, cardiac function, China

Introduction

Primary hyperparathyroidism (PHPT) is the third most prevalent endocrine disorder in Western countries after diabetes mellitus and thyroid diseases, characterized by increased calcium levels combined with elevated or inappropriately normal parathyroid hormone (PTH) levels (1, 2). Asymptomatic PHPT has become increasingly widespread in China as general health checkups and routine biochemical screening have become more popular. Previous investigations indicate an increase proportion of asymptomatic PHPT patients in Shanghai, China, from 5.9% to 35.0% from 2005–2007 to 2017–2019 (3, 4). Increased serum calcium and PTH concentrations affect multiple organs, manifesting as bone resorption or osteoporosis, kidney stone, renal function impairment, peptic ulcer, and so on (5, 6). Recent evidences show that non-classical manifestations of PHPT, including the involvement of cardiovascular system, have attracted increased attentions. However, according to the latest PHPT recommendations from the 4th international workshop (7), it is stated that the existence and reversibility of PHPT cardiovascular symptoms remain unresolved concerns.

Studies have revealed that PHPT patients having cardiac structural and functional abnormalities are characterized by a higher left ventricular mass index (LVMI) and a lower ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity (E/A) than controls (8–10). LVMI has been extensively investigated as a risk factor for cardiovascular mortality in the general population, with a few studies reporting increased LVMI in PHPT (9, 11). The E/A is a common parameter used to assess diastolic ventricular function. Furthermore, a few researchers have discovered that parathyroidectomy potentially improve cardiac structure and function (12, 13). However, there are conflicting findings on the abnormality of cardiac structure and function in PHPT patients. A prospective case-control study has found that PHPT patients without cardiovascular risk factors show no difference in cardiac morphology and function, compared to the age-matched healthy controls (14). Elsewhere, an investigation looking into the cardiovascular effects of PTH has revealed that LVMI and E/A ratios are not significantly different between healthy and PHPT subjects (15). In addition, several studies have found no significant difference in the echocardiographic parameters before and after parathyroidectomy (9, 15, 16).

Most of the existing studies have small sample sizes (n=20-100), and the echocardiogram changes in PHPT are still controversy. Furthermore, the clinical profiles of PHPT patients have been demonstrated to vary by region. Liu et al. and Meng et al. have found that Chinese PHPT patients have more severe PHPT clinical phenotypes than Americans (3, 17). Research on cardiovascular manifestations in Chinese PHPT patients is largely scarce. The present investigation primarily aimed to evaluate cardiac structure and function using echocardiography in PHPT patients and analyze the factors influencing cardiac structure and function.

Materials and methods

Subjects

A total of 272 PHPT patients admitted to the endocrine ward in Peking Union Medical College Hospital (PUMCH) between January 2015 and December 2021 were enrolled in the study. PHPT was diagnosed by hypercalcemia combined with increased or inappropriately normal intact PTH level. Asymptomatic PHPT was defined as PHPT lacking apparent signs or symptoms of hypercalcemia or high levels of parathyroid hormone (18), such as gastrointestinal disorders, osteoporosis, fragility fractures, nephrolithiasis and nephrocalcinosis. Inclusion criteria were as follows: patients aged 18 and over; patients having received preoperative cardiac ultrasound examination; patients with complete clinical data. Familial or syndromic hyperparathyroidism, such as multiple endocrine neoplasia, familial hypocalciuric hypercalcemia and hyperparathyroidism-jaw tumor syndrome, were excluded based on medical history in combination with laboratory and imaging examination. Patients with coronary artery disease, cardiomyopathy and chronic systemic diseases, such as severe hepatorenal disease, were also excluded. Finally, 153 PHPT patients were included in this investigation, whereas 51 age- and sex-matched healthy subjects with echocardiograms were recruited from the PUMCH health examination center as the control group. All the healthy controls had no history of systemic diseases, including metabolic bone diseases. Serum biochemical indicators such as liver and kidney function, glucose, calcium, and PTH levels were all within normal ranges. This study was approved by the Ethics Committee of PUMCH and conducted in accordance with the principles in the Declaration of Helsinki.

Clinical parameters

Data on demographics and medical history were obtained from PUMCH medical records, including gender, age, duration of PHPT, and target organ involvement of PHPT such as nephrolithiasis, nephrocalcinosis, subperiosteal resorption, osteoporosis and fragility fractures, etc. Lateral cephalogram and anteroposterior hand X-rays were used to assess the existence of subperiosteal bone resorption in PHPT patients. Bone mineral density (BMD) was measured by Dual-energy X-ray absorptiometry (American GE-Lunar). The osteoporosis diagnosis was based on BMD. A T score of -2.5 or less indicated osteoporosis in postmenopausal women or men 50 years and older. Z scores ≤ - 2.0 were classified as "below the expected range for age" for premenopausal women or men less than 50 years old. Fractures were assessed by the clinical history and lateral spine X-ray. Urolithiasis or renal calcification was evaluated using ultrasound. Anthropometric indexes were measured by the trained physicians, including height, weight, and heart rate. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters. Body surface area (BSA) was calculated using Du Bois' formula (19).

Laboratory parameters

PHPT patients had their fasting venous blood samples collected in the morning. Total serum calcium, serum phosphorus, albumin, serum alkaline phosphatase (ALP), serum creatinine, and total 25-hydroxyvitamin (25OHD) were measured using an automated biochemical analyzer (Beckman Coulter AU5800, USA). Albumin-adjusted total calcium was calculated using the albumin correction

formula (20): [40-albumin(g/l)]*0.02+total serum calcium (mmol/L). Plasma-ionized calcium was quantified using a radiometer ABL800 FLEX blood-gas analyzer (ABL800 FLEX, Denmark). Serum β-C-terminal peptide of type I collagen (β-CTX) and intact PTH were quantified using chemiluminescence immunoassay (Siemens ADVIA Centaur, Germany). The 24-hour urine calcium was tested using the NM-BAPTA assay (Roche Cobas c702, Switzerland). The intra-assay and inter-assay coefficients of variations (CVs) in 25OHD were 5.9% and 6.5%, respectively. PTH had intra-assay and inter-assay CVs of 2.6% and 5.8%, respectively. The intra-assay and inter-assay CVs for the other laboratory parameters were < 3.5%.

Transthoracic echocardiography

All subjects underwent echocardiographic examinations; they were evaluated by a group of senior cardiologists using a transthoracic echocardiogram (VIVID E9, GE Ultrasound, USA) with an m5s-D probe. Echocardiographic measurements were taken in Doppler mode and M-mode (21). Parameters, including interventricular septum end-diastolic thickness (IVSd), left ventricular posterior wall end-diastolic thickness (LVPWd), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular fractional shortening (FS) and left ventricular ejection fraction (LVEF), were all measured. Left ventricular mass (LVM, grams) was calculated using the method described by the American Society of Echocardiography (22). LVM index (LVMI, g/m^2) was calculated by dividing LVM by BSA. Abnormal LVMI is defined as a value greater than 95 g/m^2 in women and 115 g/m^2 in men. The relative wall thickness (RWT) was calculated as follows: (2 × LVPWd)/LVEDD. The combination of RWT and LVMI classified cardiac morphology into four types: normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy (21). RWT permitted categorization of normal LVMI as normal geometry (RWT ≤ 0.42) or concentric remodeling (RWT>0.42), and an increase in LVMI to be classified as concentric (RWT>0.42) or eccentric (RWT ≤ 0.42) hypertrophy. The E/A was calculated using the Doppler mode.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median and inter-quartile ranges if not normally distributed. Continuous variables between the PHPT and control groups were compared using the student's independent t-test or Mann-Whitney test. Categorical variables were expressed as numbers or percentages. The correlations between laboratory parameters and echocardiographic variables in PHPT group were examined using Hierarchical linear regression analysis, being adjusted for age, gender, duration of PHPT, BMI, hypertension, and diabetes mellitus. All data were analyzed using SPSS software version 19.0 (Chicago, IL, USA). $p < 0.05$ denoted statistical significance.

Results

General clinical characteristics of healthy controls and PHPT patients

A total of 153 PHPT subjects were included in the study (Table 1). The PHPT and control groups had similar gender distributions (women 52.9%, men 47.1%). The mean ages of the PHPT and control groups were 56.4 ± 10.5 years and 57.0 ± 11.0 years, respectively. The PHPT group had 55 (35.9%) patients with hypertension and 31(20.3%) with diabetes mellitus. Nephrolithiasis and nephrocalcinosis presented in 56 and 10 PHPT patients, respectively. Radiological evidence of subperiosteal resorption was revealed in 21 PHPT patients. Osteoporosis and fractures were reported in 70 and 24 PHPT patients, respectively. Moreover, nearly 26% of PHPT patients were asymptomatic. The median duration of PHPT was 2.0 (0.5, 6.0) years. The serum calcium and plasma ionized calcium were 2.84 ± 0.28 and 1.43 ± 0.14mmol/L, respectively, and serum PTH was 206.9 (130.0, 447.5) pg/ml in PHPT group. PHPT patients had significantly higher weight, BMI, and heart rate than controls.

Echocardiographic parameters and cardiac geometry in PHPT patients and controls

As illustrated in Table 1, the PHPT group reported significantly lower FS than the control group (38.4 ± 4.5% vs. 40.4 ± 5.6%, p=0.020). The LVEF was significantly lower in the PHPT group than in the control group (68.2 ± 6.0% vs. 70.7 ± 6.7%, p=0.012). The PHPT group had a significantly lower E/A compared with the controls (1.0 ± 0.5 vs. 1.4 ± 0.5), with a p-value less than 0.001. LVMI and RWT were not significantly different between the PHPT patients and controls. The PHPT group included 83 patients without hypertension and diabetes mellitus, who had significantly lower LVMI, LVPWd, and E/A than the healthy controls (LVMI 69.4 ± 15.2 vs. 74.57 ± 12.8g/m^2, p=0.040; LVPWd 8.0 ± 1.1 vs. 8.3 ± 1.3mm, p=0.012; E/A 1.0 ± 0.3 vs. 1.3 ± 0.4, p<0.001). The LVEF showed no disparity between this subset of PHPT patients and controls. Furthermore, symptomatic and asymptomatic PHPT patients showed no statistical difference in terms of LVMI, RWT, LVEF, and E/A.

Of the 122 PHPT patients without diabetes, 39 had hypertension. Hypertensive PHPT patients showed significantly higher LVMI and RWT (LVMI 81.5 ± 18.9 vs. 69.4 ± 15.2g/m^2, p<0.001; RWT 0.37 ± 0.05 vs. 0.35 ± 0.05, p=0.002), as well as significantly lower E/A (E/A 0.81 ± 0.24 vs. 1.02 ± 0.33, p<0.001) compared with the patients without hypertension. There was no difference in LVEF between hypertensive and normotensive PHPT patients (LEVF 68.2 ± 6.6 vs. 68.4 ± 5.2%, p=0.816).

Figure 1 depicts the main characteristics of the cardiac geometry of female and male PHPT patients. A majority of PHPT patients had RWT less than 0.42 and normal LVMI. Among the 81 females, 75 had normal LVMI (less than 95 g/m^2), and 66 had RWT less than 0.42. Six female patients had LVMI greater than 95 g/m^2, two of whom had

TABLE 1 Demographical, physical examination, and echocardiographic parameters in PHPT and healthy control subjects.

	PHPT (n=153)	Control (n=51)	*p*
Gender (F/M)	81/72	27/24	1.000
Age (y)	56.4 ± 10.5	57.0 ± 11.0	0.712
Duration of PHPT (y)	2.0(0.5, 6.0)	–	–
Height (cm)	164.1 ± 8.8	164.5 ± 7.1	0.770
Weight (kg)	66.3 ± 12.5*	62.4 ± 8.8	0.039
BMI (kg/m^2)	24.5 ± 3.2*	23.0 ± 2.1	0.000
Heart rate (per min)	79.1 ± 11.4*	68.4 ± 10.2	0.000
Hypertension (n/%)	55/35.9%	0	–
Diabetes mellitus (n/%)	31/20.3%	0	–
Serum calcium (mmol/L)	2.84 ± 0.28	–	–
Corrected calcium (mmol/L)	2.76 ± 0.31	–	–
Plasma ionized calcium (mmol/L)	1.44 ± 0.14	–	–
Serum albumin (g/L)	44.0 ± 5.0	–	–
Serum phosphorus (mmol/L)	0.80 ± 0.18	–	–
Serum PTH (pg/ml)	206.9(130.0, 447.5)	–	–
Serum ALP (U/L)	174.2 ± 230.1		
Serum β-CTX (ng/ml)	1.18 ± 0.90		
Serum 25OHD (ng/ml)	14.7 ± 6.7	–	–
Serum creatinine (umol/L)	76.5 ± 28.1	–	
24hUCa(mmol)	8.2 ± 4.0	–	–
LVEDD(mm)	46.4 ± 4.0	46.8 ± 4.1	0.565
FS(%)	38.4 ± 4.5*	40.4 ± 5.6	0.020
LVEF(%)	68.2 ± 6.0*	70.7 ± 6.7	0.012
LVMI(g/m^2)	73.5 ± 17.7	74.5 ± 12.8	0.726
RWT(mm)	0.35± 0.05	0.36 ± 0.07	0.595
LVSd(mm)	8.3 ± 1.4	8.0 ± 1.1	0.104
LVPWd(mm)	8.2 ± 1.1	8.3 ± 1.3	0.456
E/A	1.0 ± 0.5*	1.4 ± 0.5	0.000

The date represents the means ± SD or median(interquartile).
*p < 0.05 was considered a statistically significant group difference between PHPT and control. The normal range of E/A was >0.8 in both females and males.
PHPT Primary hyperparathyroidism, BMI body mass index, PTH parathyroid hormone, 25OHD serum 25-hydroxyvitamin, ALP alkaline phosphatase, β-CTX β-C-terminal peptide of type I collagen, 24hUCa 24-hour urine calcium, LVEDD left ventricular end-diastolic diameter, FS left ventricular fractional shortening, LVEF left ventricular ejection fraction, LVMI left ventricular mass index, RWT relative wall thickness, IVSd interventricular septum end-diastolic thickness, LVPWd left ventricular posterior wall end-diastolic thickness, E/A ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity.

RWT greater than 0.42. Among the 72 male patients, 69 had normal LVMI (less than 115 g/m^2), and 58 had RWT less than 0.42. Three male patients had LVMI greater than 115 g/m^2 and RWT greater than 0.42.

Determinants of the echocardiographic parameters in the PHPT group

Table 2 shows the correlations between biochemical and echocardiographic parameters in the PHPT cohort. Notably, after adjusting for age, gender, BMI, duration of PHPT, hypertension, and diabetes, the corrected calcium and PTH levels were positively correlated with LVMI (r =0.164, p=0.036, r=0.298, p<0.001, respectively), whereas serum phosphorus was negatively correlated with LVMI (r=-0.167, p =0.044). Serum phosphorus was also negatively related to RWT (r=-0.230, p=0.008). There was no correlation established between biochemical parameters with LVEF. In addition, serum calcium, corrected calcium, plasma ionized calcium, and PTH were negatively correlated with E/A (r =-0.215, r =-0.243, r = -0.242, r = -0.234, all p were<0.05). Serum phosphorus and 24-hour urine calcium were positively correlated with E/A (r =0.188, r =0.169, p<0.05).

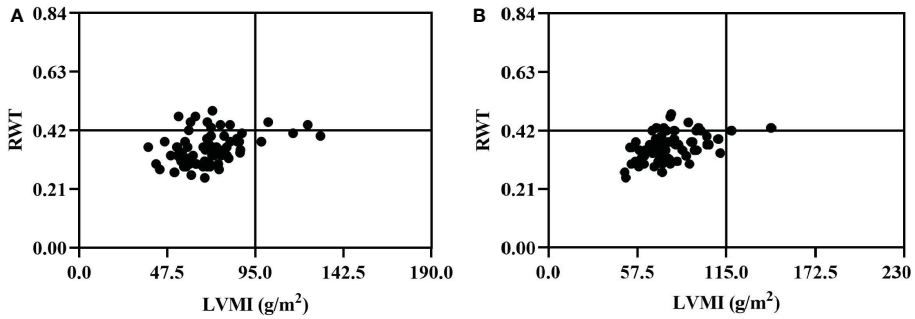

FIGURE 1
Cardiac geometry of female **(A)** and male **(B)** patients in 153 PHPT. The normal range of RWT was less than 0.42 in both females and males, and the normal range of LVMI was less than 95.0 g/m^2 in women and less than 115.0 g/m^2 in men. PHPT, Primary hyperparathyroidism; LVMI, left ventricular mass index; RWT, relative wall thickness.

Discussion

PHPT in China is not as frequent as in Western countries, and their clinical spectrums differ significantly (3, 23). This is the first and relatively large sample-size investigation in mainland China to examine changes in cardiac structure and function in PHPT patients, which could provide evidence for future research and treatment decisions. This study suggested that PHPT patients had lower E/A than controls, and their serum calcium and PTH levels were inversely correlated with E/A. Moreover, PHPT patients showed a tendency towards concentric remodeling.

In this case-control research, we found no difference in LVMI between PHPT and healthy control groups, which corroborated with previous studies. In comparative research (14), Farahnak et al. also did not find a significant increase in LVMI in mild PHPT patients without cardiovascular risk factors/diseases compared to age-matched healthy controls. Jessica and colleagues (24) discovered no significant differences in LVMI between normo-calcemic PHPT, PHPT, and control groups in subjects without high cardiovascular

TABLE 2 The hierarchical linear regression analysis between biochemical and echocardiographic parameters in 153 PHPT patients after adjustments of confounding factors.

Echocardiographic parameters	Biochemical parameter	R^2	ΔR^2	ΔF	Standardization coefficient	*p*
Model	–	0.125	0.125	3.463	–	0.003
LVMI	Ca	0.142	0.017	2.904	0.134	0.090
	cCa	0.151	0.026	4.467	0.164	0.036
	iCa	0.132	0.008	1.278	0.091	0.260
	Pi	0.149	0.024	4.126	-0.167	0.044
	PTH	0.207	0.082	15.023	0.298	0.000
	ALP	0.154	0.029	5.040	0.179	0.056
	β-CTX	0.136	0.011	1.891	0.109	0.171
	25OHD	0.126	0.001	0.176	-0.035	0.676
	24hUCa	0.128	0.003	0.549	0.060	0.460
Model	–	0.042	0.042	1.062	–	0.388
RWT	Ca	0.049	0.007	1.042	0.084	0.309
	cCa	0.057	0.016	2.405	0.127	0.123
	iCa	0.043	0.001	0.136	0.031	0.713
	Pi	0.088	0.046	7.308	-0.230	0.008
	PTH	0.049	0.007	1.117	0.089	0.292
	ALP	0.043	0.001	0.184	0.036	0.668
	β-CTX	0.042	0.001	0.077	-0.023	0.782

(Continued)

TABLE 2 Continued

Echocardiographic parameters	Biochemical parameter	R^2	ΔR^2	ΔF	Standardization coefficient	*p*
	25OHD	0.058	0.016	2.514	-0.137	0.115
	24hUCa	0.042	0.000	0.001	-0.002	0.977
Model	–	0.049	0.049	1.255	–	0.282
LVEF	Ca	0.049	0.000	0.012	-0.009	0.913
	cCa	0.049	0.000	0.007	-0.007	0.933
	iCa	0.050	0.000	0.071	-0.023	0.790
	Pi	0.052	0.003	0.525	0.063	0.470
	PTH	0.050	0.001	0.125	0.030	0.724
	ALP	0.055	0.006	0.948	0.082	0.332
	β-CTX	0.054	0.005	0.796	0.074	0.374
	25OHD	0.054	0.005	0.762	0.076	0.384
	24hUCa	0.049	0.000	0.018	-0.012	0.892
Model	–	0.228	0.228	7.182	–	0.000
E/A	Ca	0.272	0.044	8.824	-0.215	0.003
	cCa	0.285	0.057	11.584	-0.243	0.001
	iCa	0.282	0.054	10.895	-0.242	0.001
	Pi	0.258	0.031	5.979	0.188	0.016
	PTH	0.278	0.051	10.171	-0.234	0.002
	ALP	0.234	0.006	1.127	-0.081	0.290
	β-CTX	0.241	0.013	2.518	-0.118	0.115
	25OHD	0.247	0.019	3.584	0.146	0.060
	24hUCa	0.254	0.026	5.045	0.169	0.026

ΔR^2 R Square Change, ΔF F Change, Standardization coefficient represents the change of the dependent variable every time the independent variable changes a unit.
Model, adjusted for age, gender, duration of PHPT, body mass index, hypertension, and diabetes mellitus.
PHPT Primary hyperparathyroidism, LVMI left ventricular mass index, RWT relative wall thickness, LVEF left ventricular ejection fraction, E/A ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity, Ca serum calcium, cCa corrected calcium, iCa serum ionized calcium, Pi serum phosphorus, PTH parathyroid hormone, ALP alkaline phosphatase, β-CTX β-C-terminal peptide of type I collagen, 25OHD serum 25-hydroxyvitamin, 24hUCa 24-hour urine calcium.

risk. On the other hand, previous research findings into the change of LVMI in PHPT remained inconsistent. Kepez (9) found that LVMI was higher in PHPT patients (n=22) than controls in a small-scale investigation examining left ventricular performance in patients with PHPT. A recent study by Purra (8) found that symptomatic PHPT patients (n=100) had significantly higher LVMI compared with healthy controls when the two groups were matched for cardiovascular system risk factors. The differences can be explained by differences in subject recruiting conditions. The variations in LVMI in PHPT patients, as well as the effects of PTH on the cardiovascular system, warrant further investigation. In the present work, LVMI was found to be higher in PHPT patients with hypertension than in PHPT patients without hypertension. Active treatment for hypertension may help PHPT patients with these diseases improve their cardiac structure.

Relatively few studies have investigated RWT alterations in PHPT patients. The present study found no significant difference in RWT between the PHPT and healthy control groups, consistent with previous investigations (9, 14). Furthermore, serum phosphorus was shown to be negatively linked to RWT. The examination of RWT paired with LVMI revealed that, while the RWTs of the majority of PHPT patients were less than 0.42, a few patients might have borderline concentric remodeling (RWT greater than 0.42 with normal LVMI). It had been demonstrated that left ventricular concentric remodeling was more common in hypertensive patients. One-third of the patients in a population-based sample of subjects with moderate hypertension had left ventricular concentric remodeling; for patients with uncomplicated mild hypertension, it was an independent predictor of cardiovascular disease (25). In our investigation, we discovered higher RWT in the PHPT with hypertension group comparing to the PHPT without hypertension group. As a result of the high prevalence of hypertension in PHPT, we hypothesized that concentric remodeling in our research was connected to hypertension. Thus we recommended that clinicians paid attention to blood pressure and ventricular concentric remodeling in PHPT patients.

While we discovered lower LVEF in the PHPT groups than in the control groups, there was no significant difference in LVEF between the PHPT subgroup without hypertension and diabetes and the control groups. Furthermore, there was no correlation between

laboratory parameters and LVEF. These findings are consistent with previous research. Yilmaz et al. (26) discovered that LVEF did not differ significantly between asymptomatic PHPT and control groups with matched cardiac risk factors. Agarwal (13), in a prospective case-control study, found no significant difference in LVEF between normotensive symptomatic PHPT patients and healthy controls. Satu et al. (27) discovered that PHPT patients had lower LVEF than healthy controls, although the cardiovascular disease of the former was not ruled out. The findings suggested that in PHPT patients, the deterioration of systolic cardiac function caused by other factors outweighed the positive inotropic effect of serum calcium. Another possible explanation might be the age variations across studies. The mean age of PHPT patients in Satu's study was older than that in other studies, and aging reduced the capacity of the heart to pump blood. The third possible explanation for this discrepancy was that most studies had relatively small sample sizes. Therefore, clinical studies with large sample sizes are needed.

In addition, we found significantly lower E/A in PHPT patients compared with controls, indicating diastolic dysfunction. Diastolic dysfunction was also linked to higher serum calcium, PTH, 24-hour urine calcium, and lower serum phosphorus levels. These findings were consistent with previous studies. Purra et al. (8) discovered that patients with symptomatic PHPT had significantly lower early to late mitral annular velocity compared with matched controls for age, gender, and cardiovascular risk factors. Yılmaz et al. (26) found that E/A was significantly lower in asymptomatic PHPT than in controls after controlling for cardiovascular risk factors. Furthermore, a recent study (8) demonstrated that PHPT patients had lower E velocity and E/A than controls, and serum calcium was significantly negatively correlated with E/A. The major causes of diastolic cardiac function impairment are decreased left ventricular active diastolic performance and increased left ventricular stiffness. In PHPT patients, abnormal serum calcium and phosphorus metabolism are crucial in the pathogenesis of diastolic cardiac dysfunction. Calcium overload of cardiomyocytes impairs mitochondria and other structures of cardiomyocytes, causing necrosis, apoptosis, and subsequent fibrosis (28). PTH causes cardiac dysfunction *via* different mechanisms. PTH may boost aldosterone synthesis *via* direct or indirect mechanisms, which may have a deleterious influence on diastolic dysfunction (29). A previous study showed that the PTH receptor was expressed in the adrenal gland (30). PTH could directly activate renin-angiotensin-aldosterone by binding to PTH/PTH-related peptide receptors (31). On the other hand, PTH indirectly stimulates aldosterone secretion by increasing serum calcium levels. In other aspects, higher PTH levels exacerbate arterial stiffness, endothelial dysfunction, and arterial hypertension (32), all of which could contribute to diastolic cardiac dysfunction.

One of the strengths of this study is that we provide echocardiography data from the largest cohort of PHPT patients to date. This is the first time in mainland China that the echocardiographic characteristics of PHPT patients have been studied. However, there are some limitations to our investigation. Firstly, the study is limited by its retrospective design. The examination of changes in cardiac structure and function during long-term follow-up and the inferences of causality could not be validated. In addition, E/A cannot be solely used to determine the severity of diastolic dysfunction in patients. However, the decrease in E/A is a clinically significant indication that patients have diastolic dysfunction, particularly grade I diastolic dysfunction. An in-depth evaluation of diastolic function should be realized by comprehensive echocardiography in future studies. Furthermore, despite controlling for hypertension and other cardiovascular risk factors, not all cardiovascular diseases were excluded from PHPT. Third, we lacked particular laboratory data on calcium phosphate metabolism in controls. Additionally, because this study included only hospitalized PHPT patients with comprehensive clinical data, its generalizability might be compromised. Last but not least, there is a lack of post-parathyroidectomy echocardiographic examinations of the effect of parathyroidectomy on cardiac structure and function.

Conclusion

Diastolic cardiac dysfunction and possible cardiac structural abnormalities, which tend to be centripetal remodeling, are discovered in this group of Chinese PHPT patients. Serum calcium, phosphorus, and PTH levels are shown to be strongly related to various cardiac structure and function parameters, lending credence to the influence of PHPT on the cardiovascular system. Our findings suggest that cardiovascular disease should be a concern among PHPT patients, and the clinical significance of cardiac dysfunction needs to be investigated further. In addition, PHPT patients should manage their blood pressure and blood glucose levels to reduce cardiac structure and function damage.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of Peking Union Medical College Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RC designed, analyzed, and wrote the manuscript, AS conducted data collection, OW reviewed, YJ, ML and WX conducted data interpretation, and XL and XX designed and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Albino Carrizzo,
University of Salerno, Italy

REVIEWED BY
Paula Miotto,
The University of Melbourne, Australia
Carmine Izzo,
University of Salerno, Italy

*CORRESPONDENCE
Christian Riehle
riehle.christian@mh-hannover.de

†These authors have contributed equally to this work and share first authorship

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Vitamin A regulates tissue-specific organ remodeling in diet-induced obesity independent of mitochondrial function

Ivanna Shymotiuk[1†], Natali Froese[1†], Christopher Werlein[2], Lea Naasner[1], Malgorzata Szaroszyk[1], Mark P. Kühnel[2,3], Danny D. Jonigk[2,3], William S. Blaner[4], Adam R. Wende[5], E. Dale Abel[6], Johann Bauersachs[1] and Christian Riehle[1*]

[1]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany, [2]Institute of Pathology, Hannover Medical School, Hannover, Germany, [3]Biomedical Research in End-stage and Obstructive Lung Disease Hannover (BREATH), German Lung Research Centre (DZL), Hannover, Germany, [4]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, United States, [5]Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, United States, [6]Department of Medicine, David Geffen School of Medicine and University of California, Los Angeles (UCLA), Health, Los Angeles, CA, United States

Background: Perturbed mitochondrial energetics and vitamin A (VitA) metabolism are associated with the pathogenesis of diet-induced obesity (DIO) and type 2 diabetes (T2D).

Methods: To test the hypothesis that VitA regulates tissue-specific mitochondrial energetics and adverse organ remodeling in DIO, we utilized a murine model of impaired VitA availability and high fat diet (HFD) feeding. Mitochondrial respiratory capacity and organ remodeling were assessed in liver, skeletal muscle, and kidney tissue, which are organs affected by T2D-associated complications and are critical for the pathogenesis of T2D.

Results: In liver, VitA had no impact on maximal ADP-stimulated mitochondrial respiratory capacity (V_{ADP}) following HFD feeding with palmitoyl-carnitine and pyruvate each combined with malate as substrates. Interestingly, histopathological and gene expression analyses revealed that VitA mediates steatosis and adverse remodeling in DIO. In skeletal muscle, VitA did not affect V_{ADP} following HFD feeding. No morphological differences were detected between groups. In kidney, V_{ADP} was not different between groups with both combinations of substrates and VitA transduced the pro-fibrotic transcriptional response following HFD feeding.

Conclusion: The present study identifies an unexpected and tissue-specific role for VitA in DIO that regulates the pro-fibrotic transcriptional response and that results in organ damage independent of changes in mitochondrial energetics.

KEYWORDS

mitochondria, vitamin A, diet-induced obesity, type 2 diabetes, liver, kidney, skeletal muscle

Introduction

The number of patients suffering from diabetes mellitus is dramatically increasing with a current estimate that 1 in 10 people have diabetes worldwide reaching a total number of 537 million adults (www.idf.org). Most of these patients suffer from type 2 diabetes (T2D). Peripheral insulin resistance is a cardinal feature of T2D. Mitochondrial dysfunction is associated with insulin resistance and T2D (1, 2). Landmark studies reported impaired mitochondrial capacity in skeletal muscle from insulin resistant individuals (3) and T2D patients (4). Similarly, mitochondrial dysfunction has been reported in various tissues from rodent models with diet-induced obesity (DIO) and T2D (5, 6). A close interplay between insulin resistance and mitochondrial dysfunction exists, which provides a challenge to separate cause and effects (1).

Vitamin A (VitA) metabolism is perturbed in obese and T2D patients and animal models (7–9). Dietary VitA attenuates oxidative stress and preserves mitochondrial function (10–12), and mitochondrial dysfunction is associated with the development of T2D (13). Our previous studies using the same experimental model identified a transcriptional program, by which VitA preserves cardiac energetic gene expression in DIO that might attenuate subsequent onset of mitochondrial dysfunction and diabetic cardiomyopathy (14). Liver, skeletal muscle, and kidney tissue each have a very high mitochondrial content (15) and are major contributors of T2D-associated complications, including adverse remodeling and mitochondrial dysfunction, which is similar to cardiac tissue (6).

However, the impact of VitA on mitochondrial energetics and the development of obesity- and T2D-associated organ damage in liver, skeletal muscle, and kidney is incompletely understood, which we aimed to investigate in the present study. To address this important question, we used our murine model of impaired liver retinoid levels and DIO, in which mice with germline deletion of *Lecithin retinol acyltransferase* (*Lrat*$^{-/-}$) (16) are subjected to VitA-deficient (VAD) normocaloric and VAD high fat diet (HFD) feeding (14). *Lrat*, a key enzyme of VitA metabolism, is responsible for the storage of VitA metabolites as retinyl esters. Global *Lrat* gene deletion decreases hepatic retinoid levels and *Lrat*$^{-/-}$ mice have impaired tissue retinoid levels in the absence of dietary VitA compared to WT controls (16–19). In the present study, the use of VAD diets minimizes VitA availability in *Lrat*$^{-/-}$ mice, both under normocaloric conditions and following HFD feeding (14). Using this model, we assessed the impact of VitA on mitochondrial energetics and organ damage in liver, skeletal muscle, and kidney that are critical for the development of T2D and that are major targets of T2D-associated complications.

Materials and methods

Animals

Previously, *Lrat*$^{-/-}$ mice (16) and wildtype littermate controls (*Lrat*$^{+/+}$) were examined for cardiac phenotypes and study (14). Specifically, mice were obtained by breeding mice with heterozygous *Lrat* germline deletion (*Lrat*$^{+/-}$) and were on a mixed C57BL/6J/129Sv genetic background. Dietary treatments started at 8 weeks of age for the duration of 20 weeks total (Figure 1A). Wildtype mice were fed with normal chow diet (13% kcal from fat; group indicated as "NCD") or HFD (60% kcal from fat; group indicated as "HFD"). *Lrat*$^{-/-}$ mice were fed with normocaloric VAD diet (13% kcal from fat; group indicated as "VAD") or VAD HFD (60% kcal from fat; group indicated as "VAD HFD") (14). The composition of mouse diets is provided in Supplemental Table 1. All diets were purchased from Altromin (Lage, Germany). Animals were housed with free access to food and water and 12 h light/dark cycles. All studies were performed in male mice under random fed conditions. Experiments were performed in accordance with protocols approved by local state authorities (Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit, protocol number: #17/2702). The current manuscript in contrast focused on non-cardiac organs, i.e., liver, kidney, and skeletal muscle, in these same animals to determine tissue-specific differences. HFD feeding increased body weight independent of VitA (Figure 1B). Body weight data presented in Figure 1B represent a subgroup of a previously published animal cohort that was used in our prior report (14).

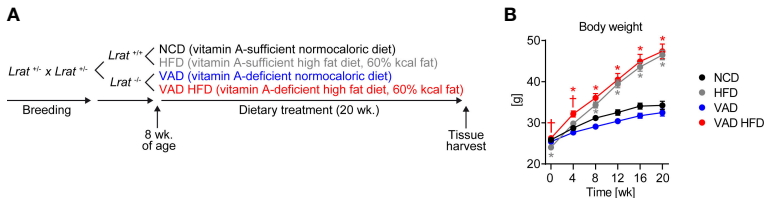

FIGURE 1
Experimental paradigm and increase in body weight independent of VitA following HFD feeding. **(A)** Mice with homozygous *Lrat* germline deletion (*Lrat*$^{-/-}$) and wildtype controls (*Lrat*$^{+/+}$) were obtained by breeding mice with heterozygous *Lrat* germline deletion (*Lrat*$^{+/-}$). Dietary treatment started at 8 weeks of age for a duration of 20 weeks total. **(B)** Body weight data are reported as mean values ± SE and represent a subgroup of a previously published animal cohort (14). Two-way ANOVA was performed to analyze differences by HFD feeding and VitA. Results of *post-hoc* analyses for each comparison are summarized by symbols as defined: # p<0.05 for HFD feeding, $ p<0.05 for VitA, and & p<0.05 for the interaction between HFD feeding and VitA. Body weight following 0 ($, &), 4 (#, &), 8 (#, &), 12 (#), 16 (#), and 20 (#) weeks of dietary feeding (n=17-18/group). *p < 0.05 vs. normocaloric diet same VitA availability, † p<0.05 vs. VitA sufficiency same caloric diet.

Measurement of mitochondrial oxygen consumption in isolated mitochondria

Immediately after harvest liver, quadriceps muscle, and kidneys were placed in ice-cold STE1 buffer (250 mmol/L sucrose, 5 mmol/L Tris/HCl, 2 mmol/L EGTA, pH 7.4). Tissues were minced and either incubated in 2.5 mL STE2 buffer (STE1 containing [wt/vol] 0.5% BSA, 5 mmol/L $MgCl_2$, 1 mmol/L ATP, and 2.5 U/mL protease Subtilisin A) for 4 min (quadriceps muscle) or immediately proceeded to homogenization (liver and kidney tissue). All tissues were homogenized using a Teflon pistil in a Potter-Elvejhem homogenizer. Quadriceps muscle homogenates were further diluted with 2.5 mL STE1 buffer containing Complete Mini protease inhibitor cocktail (Roche, Mannheim, Germany), centrifuged at 8,000 g for 10 min, and the resulting pellet was resuspended in 4 mL STE1 buffer. Next, all tissues homogenates were centrifuged at 800 g for 10 min and supernatants were centrifuged at 8,000 g for 10 min. Pellets obtained from mitochondrial isolation were resuspended in 200 µL STE1 buffer each. State III oxygen consumption rates (V_{ADP}) were determined in 300 µg of mitochondria by using a Clark-type oxygen electrode (Strathkelvin, North Lanarkshire, Scotland) with 20 µmol/L palmitoyl-carnitine (PC)/2 mmol/L malate or 10 mmol/L pyruvate/5 mmol/L malate as substrates as previously described (14).

Hydroxyacyl-coenzyme A dehydrogenase (HADH) and citrate synthase (CS) enzyme activity assays

HADH and CS activity in liver, skeletal muscle, and kidney tissue were determined as previously described (20).

Immunoblotting

Protein extraction and immunoblotting were performed as previously described (14). Proteins were resolved by SDS-PAGE, electrotransferred to PVDF membranes, and primary antibodies were incubated at 4°C overnight. Primary and secondary antibodies used are listed in Supplemental Table 2. Proteins were detected with horseradish peroxidase (HRP)-conjugated secondary antibodies (GE HealthCare, Chicago, IL, USA) and densitometric quantification was performed using the software Image J.

Stereological and histopathological analysis of tissue sections

Tissues were fixed in 4% buffered formaldehyde, stored > 24 h prior to further processing, embedded in paraffin, and cut into 2 µm thick sections. Hematoxylin and eosin (H&E), Picrosirius red (PSR) and wheat germ agglutinin (WGA)/DAPI fluorescence staining were performed as previously described (14). Microscopy of H&E and PSR stains was performed using a BX43 light microscope (Olympus, Tokyo, Japan) and an Observer.Z1 fluorescence microscope (Zeiss, Wetzler, Germany) for WGA/DAPI stains. Liver fat content was assessed as area percentage of hepatocytes with macro- or microvesicular cytoplasmatic fat inclusions. Hepatic fibrosis was evaluated according to the ISHAK score (21), and liver sections were scored for steatosis, lobular inflammation, and hepatocyte ballooning according to the NAFLD activity score (NAS) (22). For immunohistological quantification of skeletal muscle fiber area, sections were deparaffinized, stained with WGA, and sections with WGA staining of the cellular membrane were selected for stereological quantification, which was performed using the AxioVision software (Zeiss, Wetzler, Germany). Kidney sections showing cortex and medulla were evaluated for histopathologic abnormalities with focus on the presence of tubular ischemia and necrosis, glomerular ischemia, microthrombi, arteriosclerosis and glomerulosclerosis. Sections were analyzed by an experienced pathologist blinded for the group of mice investigated.

Quantitative RT-PCR analysis (qPCR)

RNA isolation from tissues, cDNA synthesis and quantitative real-time PCR were performed as previously described (14). Primers are listed in Supplemental Table 3.

Statistical analysis

Data are presented as means ± standard error (SE). Data sets were analyzed by 2-way ANOVA for multi-group comparisons with Holm-Šídák's *post hoc* analysis to determine significance levels by HFD feeding and VitA. Statistical analysis was performed using GraphPad Prism 8 software (GraphPad Software, Inc., La Jolla, CA). For all analyses, a p-value of <0.05 was considered significantly different.

Results

VitA regulates liver fibrotic gene expression and steatosis in DIO independent of altered mitochondrial metabolism

PC/malate-supported V_{ADP} was not different between the HFD and VAD HFD groups and interestingly increased following HFD feeding under VAD conditions (Figure 2A). No difference in V_{ADP} with pyruvate/malate as substrates was detected between groups (Figure 2B). CS activity declined following HFD feeding independent of VitA (Figure 2C). Activity of HADH, a key enzyme of mitochondrial fatty acid oxidation (FAO), was not different between groups (Figure 2D). Protein abundance of selected respiratory chain subunits, MnSOD, UCP3, and 4 hydroxynonena (4-HNE) adducts was relatively unchanged between groups (Figures 2E, F). Consistent with the changes in

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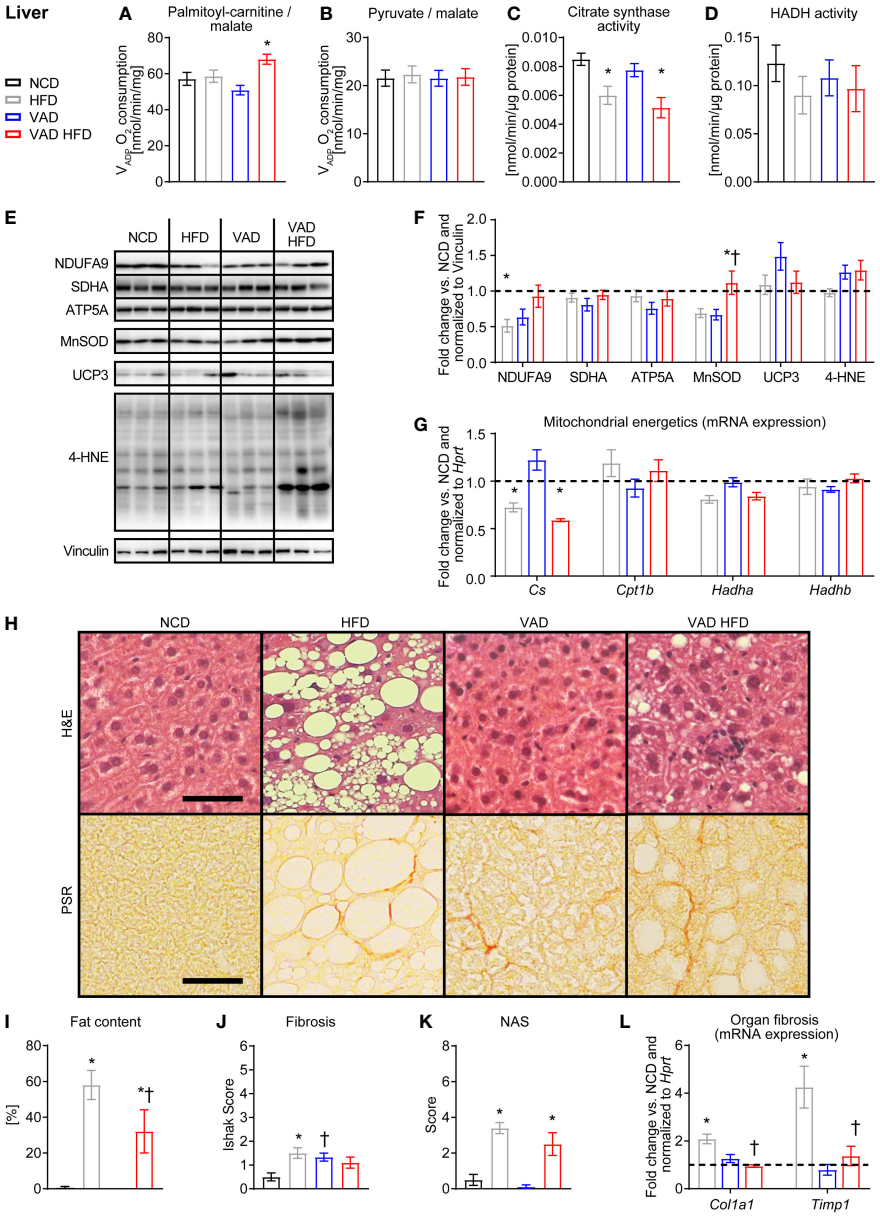

FIGURE 2
VitA modulates steatosis and fibrosis in liver tissue in DIO independent of mitochondrial function. Data are reported as mean values ± SE. Two-way ANOVA was performed to analyze differences by HFD feeding and VitA. Results of *post-hoc* analyses for each comparison are summarized by symbols as defined: # $p<0.05$ for HFD feeding, $ $p<0.05$ for VitA, and & $p<0.05$ for the interaction between HFD feeding and VitA. V_{ADP} of isolated liver mitochondria with **(A)** palmitoyl-carnitine (#, &) and **(B)** pyruvate each combined with malate as substrates (n=7-8). **(C)** Citrate synthase (#) and **(D)** HADH activity in liver tissue (n=6-8). **(E)** Representative immunoblots and **(F)** densitometric analysis of NDUFA9 (&), SDHA, ATP5A, MnSOD (&), UCP3, and 4-HNE ($) normalized to Vinculin. Data are presented as fold change relative to NCD (assigned as 1.0; dashed line), n=6. **(G)** mRNA expression of transcripts involved in mitochondrial energetics (*Cs:* #, &; *Hadha:* #). Data are presented as fold change relative to NCD and normalized to *Hprt* (assigned as 1.0; dashed line), n=7-8. **(H)** Representative H&E and PSR stains of liver sections (scale bars: 50 µm each). Quantification of **(I)** fat content (#), **(J)** fibrosis (&), and **(K)** NAFLD activity scores (NAS, #), n=9-10. **(L)** mRNA expression of transcripts involved in organ fibrosis (*Col1a1:* #, $, &; *Timp1:* #, $, &). Data are presented as fold change relative to NCD and normalized to *Hprt* (assigned as 1.0; dashed line), n=7-8. *p < 0.05 vs. normocaloric diet same VitA availability, † $p<0.05$ vs. VitA sufficiency same caloric diet.

activity, qPCR analysis showed decreased *Citrate synthase (Cs)* mRNA expression following HFD feeding independent of VitA status. Expression of selected FAO genes was not different between groups (Figure 2G). Histopathological analysis revealed reduced DIO-mediated hepatic steatosis in the VAD HFD group relative to the HFD group. Similarly, HFD feeding increased fibrosis relative to NCD, which was attenuated in the VAD HFD group (Figures 2H–K and Supplemental Table 4). HFD feeding increased mRNA expression of the pro-fibrotic transcripts *Tissue inhibitor of metalloproteinase 1 (Timp1)* and *Alpha-1 type I collagen (Col1a1)* (Figure 2L), which was attenuated in the VAD groups. Together, these data indicate that VitA mediates the pro-fibrotic transcriptional response, adverse remodeling, and steatosis in DIO independent of mitochondrial oxidative capacity.

VitA status does not influence mitochondrial function and morphological structure following HFD feeding in skeletal muscle

Like liver tissue, mitochondrial dysfunction in skeletal muscle alters whole body metabolism in T2D (23). V_{ADP} in skeletal muscle mitochondria was not different between the HFD and VAD HFD group with PC/malate as substrates but was increased in the VAD HFD relative to the VAD group (Figure 3A). Pyruvate/malate-supported V_{ADP} and CS activity were similar between groups (Figures 3B, C). HADH activity trended to increase following HFD feeding independent of VitA (HFD vs. NCD: + 58.0%, p=0.11; VAD HFD vs. VAD: + 84.8%, p=0.06; Figure 3D). Immunoblotting analysis revealed that VitA preserves protein abundance of NDUFA9 and ATP5A both under normocaloric and HFD feeding conditions (Figures 3E, F). Expression of selected transcripts involved in FAO and mitochondrial energetics was not changed between groups (Figure 3G). Histological and stereological analysis showed no gross morphological differences between groups. Mean cross-sectional area of skeletal muscle fibers presented as percentage of total fibers was evenly distributed between groups (Figures 3H, I). *Col1a1* and *Col3a1* mRNA expression was not different between groups (Figure 3J).

VitA mediates the HFD-induced pro-fibrotic transcriptional response in kidney tissue independent of mitochondrial energetics

No difference in kidney mitochondria V_{ADP} with PC and pyruvate each combined with malate as substrates was detected between groups (Figures 4A, B). Similarly, HADH and CS enzymatic activity, protein abundance of selected respiratory chain subunits, UCP3, MnSOD, and 4-HNE adducts and mRNA expression of mitochondrial energetics genes were relatively unchanged between groups (Figures 4C–G). Histological analysis of kidney sections with focus on tubular ischemia and necrosis, glomerular ischemia, microthrombi, arteriosclerosis, and glomerulosclerosis showed a regular morphologic phenotype with no difference between groups (Figure 4H). Interestingly, the HFD-induced increase in the collagen subtype expression *Col1a1* and *Col3a1* was attenuated in the VAD HFD group (Figure 4I). These data indicate that VitA mediates the pro-fibrotic transcriptional response in DIO independent of mitochondrial capacity.

Discussion

Mitochondrial dysfunction is associated with T2D (1, 2), and perturbations in VitA metabolism are observed in T2D patients and animal models (7–9, 24). The relationship between VitA metabolism and the development of mitochondrial dysfunction and end-organ damage in T2D is incompletely understood. The present study reveals that VitA regulates the pro-fibrotic transcriptional response and adverse organ remodeling in DIO in a tissue-specific manner that is independent of mitochondrial energetics and oxidative stress.

Our data show that pathological remodeling of liver tissue following HFD feeding is exacerbated by VitA signaling independent of mitochondrial capacity (Figure 2). Previous rodent studies investigated the impact of HFD feeding and T2D on liver mitochondrial energetics; however, the results have not been consistent. The parameters that contribute to the opposing results include the species, the duration of the dietary treatment, the genetic background, and the genetic modification of the models investigated. Hepatic retinol levels are inversely correlated with the severity of steatosis (8) and non-alcoholic fatty liver disease (NAFLD) in patients (25). One proposed mechanism for increased steatosis following excess caloric intake is hyperinsulinemia-mediated lipogenesis, which may contribute to hypertriglyceridemia (23, 26). Our previous report utilizing the same experimental protocol indicates impaired insulin sensitivity and glucose tolerance following HFD feeding as determined by insulin tolerance tests (ITT) and glucose tolerance tests (GTT), whereas VAD following normocaloric feeding had no effect (14). VAD attenuated HFD-induced development of T2D as indicated by attenuated glucose intolerance in GTT and a trend towards attenuated insulin resistance in ITT for the comparison VAD HFD relative to HFD (14). Importantly, basal serum insulin levels were not increased in the HFD group relative to the VAD HFD group (14). Together, these data indicate that VitA mediates HFD feeding-induced steatosis by mechanisms that are independent of circulating insulin levels, although effects on modulation of insulin action in hepatocytes remain to be explored.

Despite the well-characterized association between insulin resistance, T2D, and skeletal muscle mitochondrial dysfunction the cause and consequence remain a subject of discussion (27). Previous studies reported impaired skeletal muscle mitochondrial capacity in insulin resistant (3) and T2D patients (4), while others reported no impairment (27, 28). In the present study, HFD feeding did not affect skeletal muscle mitochondrial respiratory capacity under VitA-sufficient conditions (Figures 3A, B), which is like our results obtained from liver mitochondria (Figures 2A, B). Histological analysis and gene expression analysis for markers of organ fibrosis showed no difference between groups (Figures 3H–J), which reveals that VitA regulates tissue-specific organ remodeling and damage in DIO. Previous studies reported muscle atrophy following 38-weeks of HFD feeding in mice (29), which contrasts to the present study reporting no difference in mean cross-sectional area of skeletal muscle fibers between groups (Figures 3H, I). The different phenotypes reported following HFD feeding might emanate from the genetic background of the mice used and the duration of dietary treatment.

Mitochondrial dysfunction contributes to diabetic nephropathy (30). In the present study, no difference in mitochondrial capacity was detected between groups (Figures 4A–D). Mitochondria were isolated from total kidneys and activity of mitochondrial enzymes was determined in total kidney homogenates. Kidneys consist of different cell types and regions, i.e., medulla and cortex, that

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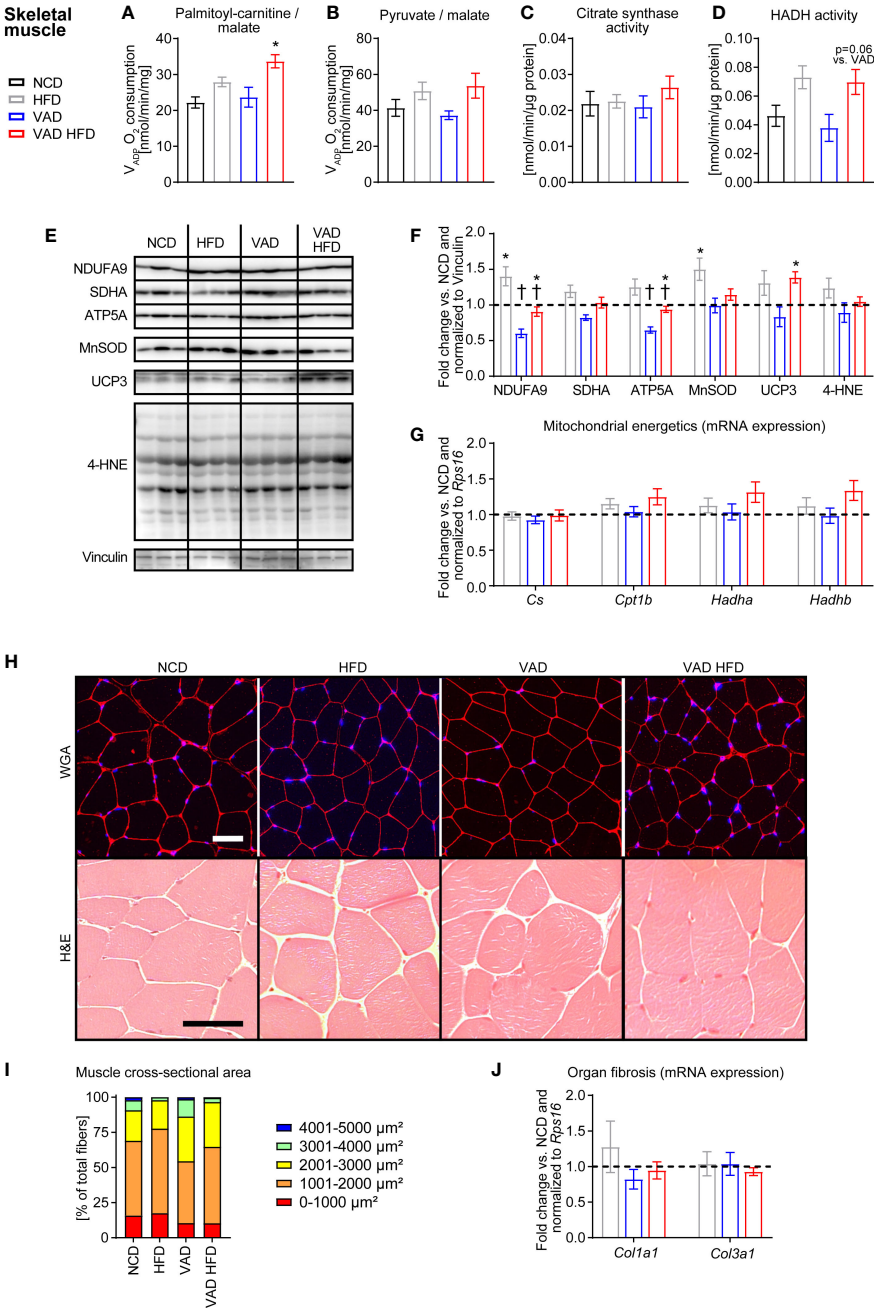

FIGURE 3
VitA does not impair skeletal muscle mitochondrial function and morphological structure in DIO. Data are reported as mean values ± SE. Two-way ANOVA was performed to analyze differences by HFD feeding and VitA. Results of *post-hoc* analyses for each comparison are summarized by symbols as defined: # p<0.05 for HFD feeding and $ p<0.05 for VitA. No significant effect for the interaction between HFD feeding and VitA was determined. V_{ADP} of isolated skeletal muscle mitochondria with **(A)** palmitoyl-carnitine (#) and **(B)** pyruvate (#) each combined with malate as substrates (n=6-8). **(C)** Citrate synthase and **(D)** HADH (#) activity in skeletal muscle (n=7-8). **(E)** Representative immunoblots and **(F)** densitometric analysis of NDUFA9 (#, $), SDHA (#, $), ATP5A (#, $), MnSOD (#),UCP3 (#), and 4-HNE normalized to Vinculin. Data are presented as fold change relative to NCD (assigned as 1.0; dashed line), n=6. **(G)** mRNA expression of transcripts involved in mitochondrial energetics presented as fold change relative to NCD and normalized to *Rps16* (assigned as 1.0; dashed line), n=8. **(H)** Representative WGA and H&E stains of skeletal muscle sections (scale bars: 50 µm each). **(I)** Mean cross-sectional area of skeletal muscle fibers presented as percentage of total fibers (# for 4001-5000 µm^2, n=5-6). **(J)** mRNA expression of transcripts involved in organ fibrosis presented as fold change relative to NCD and normalized to *Rps16* (assigned as 1.0; dashed line), n=8. *p < 0.05 vs. normocaloric diet same VitA availability, † p<0.05 vs. VitA sufficiency same caloric diet.

differentially adapt to the diabetic milieu (30). The protocol used for mitochondria isolation does not discriminate compartment and cell type-specific mitochondrial capacity, which might exist. Changes in mitochondrial bioenergetics precede histological changes in kidneys from type 1 diabetic rats (31). These data are in concert with the present study reporting preserved mitochondrial capacity following HFD and VAD in the absence of gross morphological changes (Figure 4H). The attenuated transcriptional response of collagen

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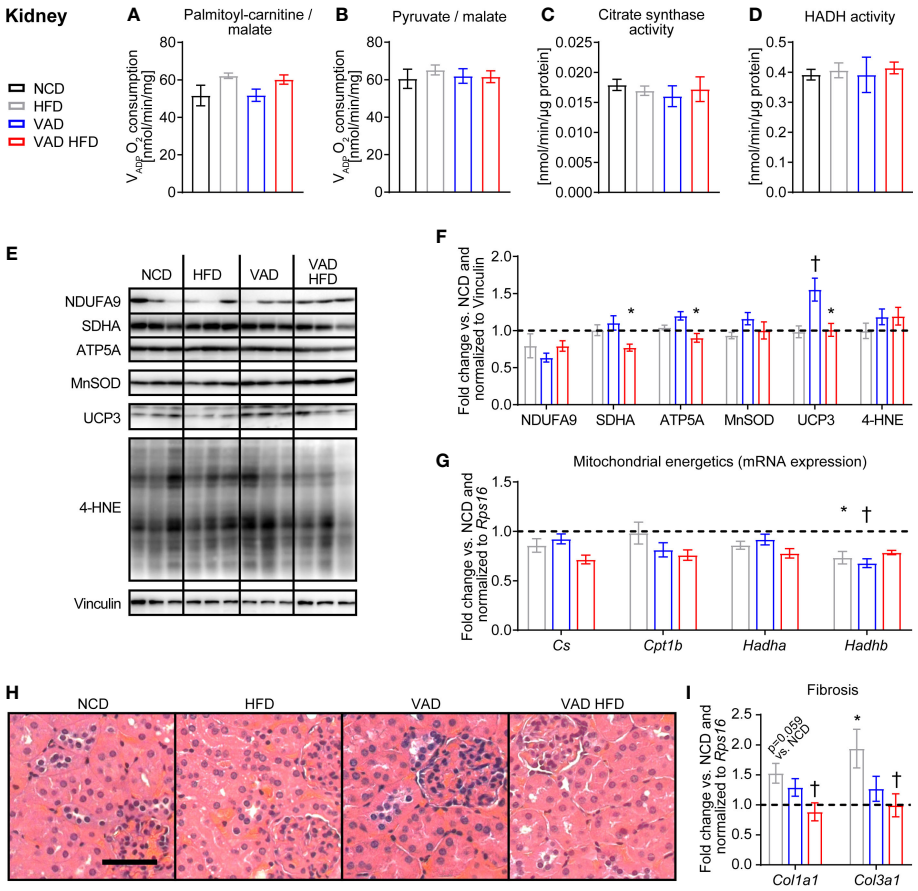

FIGURE 4
VitA mediates the pro-fibrotic transcriptional response in kidney tissue following HFD feeding independent of mitochondrial energetics. Data are reported as mean values ± SE. Two-way ANOVA was performed to analyze differences by HFD feeding and VitA. Results of *post-hoc* analyses for each comparison are summarized by symbols as defined: # p<0.05 for HFD feeding, $ p<0.05 for VitA, and & p<0.05 for the interaction between HFD feeding and VitA. V_{ADP} of isolated kidney mitochondria with **(A)** palmitoyl-carnitine (#) and **(B)** pyruvate each combined with malate as substrates (n=6-8). **(C)** Citrate synthase and **(D)** HADH activity in kidney tissue (n=7-8). **(E)** Representative immunoblots and **(F)** densitometric analysis of NDUFA, SDHA (&), ATP5A (&), MnSOD, UCP3 (#, $, &), and 4-HNE normalized to Vinculin. Data are presented as fold change relative to NCD (assigned as 1.0; dashed line), n=6. **(G)** mRNA expression of transcripts involved in mitochondrial energetics (*Cs:* #; *Cpt1b:* $; *Hadha:* #; *Hadhb:* $, &). Data are presented as fold change relative to NCD and normalized to *Rps16* (assigned as 1.0; dashed line), n=8. **(H)** Representative H&E stains of kidney sections (scale bar: 50 µm). **(I)** mRNA expression of transcripts involved in organ fibrosis (*Col1a1:* &; *Col3a1:* &). Data are presented as fold change relative to NCD and normalized to *Rps16* (assigned as 1.0; dashed line), n=8. *p < 0.05 vs. normocaloric diet same VitA availability, † p<0.05 vs. VitA sufficiency same caloric diet.

isoforms, i.e., *Col1a1* and *Col3a1*, in the VAD HFD group relative to the HFD group indicates that VitA signaling may contribute to a pro-fibrotic transcriptional program in DIO, which is like our observation in liver tissue (Figures 2H–L). This VitA-mediated transcriptional program may mediate subsequent kidney fibrosis and organ damage in DIO.

Numerous animal models investigated the relationship between dietary VitA intake and the pathophysiology and consequences of obesity and insulin resistance (32–36). VitA supplementation at a high dose of 129 mg/kg diet for the duration of two months, which corresponds to approximately 3 mg/kg body weight/day, attenuates body weight gain in obese WNIN/Ob rats relative to controls receiving diets containing 2.6 mg VitA/kg diet (32). Short-term retinoic acid supplementation decreases body weight and improves insulin sensitivity (34, 35), while feeding a VAD diet increases body weight and adiposity in mice (36). In the present study, the body weight increase following HFD feeding was not influenced by tissue levels of VitA (14). Moreover, mice subjected to VAD diets did not show characteristics of severe VAD, including alopecia, ataxia, or weight loss. All-*trans*-retinoic acid doses that are used in rodents studies to block or reverse accumulation of adipose tissue are typically very high and range up to 100 mg/kg body weight, which is equivalent to 6,000 mg/60 kg human being (37). All-*trans*-retinoic acid is used to treat patients with acute promyelocytic leukemia (APL) at a recommended dose of 45 mg/m^2/d for adult patients. This is equivalent to approximately 80 mg/dose administered (38) and therefore much lower compared to doses that block or reverse adiposity in rodents. Importantly, about 1 in 4 patients with APL receiving all-*trans*-retinoic acid induction therapy develop "Differentiation Syndrome" (formerly known as "Retinoic Acid Syndrome"). Characteristics of this potential life-threatening side effect comprise unexplained fever, acute respiratory distress, capillary leak syndrome, and renal failure (39). Moreover, treatment of skin disease with 13-*cis* retinoic acid increases the risk

of hyperlipidemia and metabolic syndrome (40). Patients with increased serum retinol levels exhibit an increased risk of hip fracture (41), which might be attributable to a crosstalk of VitA and vitamin D metabolism resulting in osteoporosis (42). Together, these serious effects defines the challenges inherent in using retinoic acid as a potential anti-obesity drug (37).

Previous studies investigated the impact of VitA on mitochondrial energetics and dynamics in different tissues. Dietary treatment of rats with VitA-deficient diets impairs function of mitochondria that were isolated from cardiac, but not from liver tissue (11, 12). Furthermore, the VitA metabolite all-trans retinoic acid (ATRA) increases dynamin-related protein (DRP1) levels and promotes mitochondrial fission in murine hearts (43). VitA mediates the expression of genes involved in oxidative phosphorylation as previously reported for the mitochondrial gene ATPase 6 in primary hepatocytes following stimulation with retinoic acid (44) and in cardiac tissue in DIO using the same experimental model used in the present study (14). Interestingly, mitochondrial gene expression was relatively preserved between groups in liver, skeletal muscle, and kidney in the present study. These data indicate that cardiac tissue is more susceptible to the loss of VitA on mitochondrial gene expression under HFD conditions. A potential mechanism for this observation is the mitochondrial content of cardiac tissue, which is the greatest across all tissues in mammals (15). Further studies are required to delineate the tissue-specific impact of VitA on mitochondrial energetics, both under basal conditions and in the context of superimposed stressors.

Limitations of our study include the use of adult mice at a relatively young age, which contrasts the onset of T2D-associated complications that are typically observed in older patients. Another limitation is that *Lrat*$^{-/-}$ mice were fed with VAD diets to study the relationship between VitA availability and manifestations of DIO (14). Therefore, we cannot dissociate the effect of the genetic modification of the mice investigated from the dietary treatment. It is important to note that hepatic all-*trans*-retinal and all-*trans*-retinol levels were nearly absent in *Lrat*$^{-/-}$ mice following feeding with VAD diets independent of dietary fat content (14). Hepatic retinoid levels represent whole body VitA status (45, 46). Even though not directly measured, these data indicate impaired tissue VitA availability in the VAD groups independent of dietary fat content, including skeletal muscle, and kidney. The profound impairment in VitA metabolite levels, which is accomplished by our combined transgenic and dietary approach, might only partially reflect the adaptations in patients following restricted dietary VitA intake and VitA levels. Mitochondrial capacity was determined by measuring V_{ADP}, CS and HADH enzymatic activity. This experimental approach might not detect defects in mitochondrial energetics that might exist, and which might only be detected by very sophisticated measurements, including the measurement of mitochondrial membrane potential and ATP production that is required to directly assess coupling of mitochondrial ATP production to mitochondrial oxygen consumption.

In the present study, mitochondrial oxygen consumption was determined in isolated mitochondria. Previous studies used saponin-permeabilized tissue preparations for the measurement of mitochondrial oxygen consumption in skeletal muscle (47) and liver tissue (48, 49). A potential limitation of the isolated mitochondria technique is the disruption of the mitochondrial network and the potential enrichment of a mitochondrial population during the isolation process. Since acute changes in liver metabolism might not be detected in saponin-permeabilized liver tissue (49), we used isolated mitochondria for the measurement of oxygen consumption. It is of interest for future studies to determine the impact of HFD feeding and VitA on mitochondrial respiratory capacity in isolated mitochondria and in saponin-permeabilized tissue using a complementary experimental approach. Previous studies reported profound and tissue-specific differences in the mitochondrial proteome of type 1 diabetic mice (50) and VitA is a master regulator of transcriptional regulation (51, 52). Thus, another limitation is that we measured abundance of a

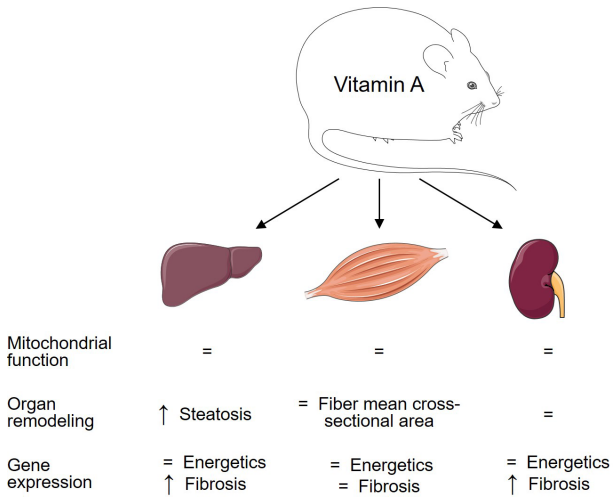

FIGURE 5
Tissue-specific impact of VitA on mitochondrial energetics and tissue remodeling in DIO. Changes in the HFD relative to VAD HFD group are summarized to visualize the relationship between VitA content and tissue responses to HFD feeding.

limited number of transcripts and proteins involved in mitochondrial energetics in the present study. Our previous studies using the same experimental protocol identified that VitA preserves cardiac energetic gene expression in DIO; however, has no impact on cardiac remodeling, mitochondrial and contractile function following HFD feeding (14). This previous report supports the present study, which identifies a tissue-specific impact for VitA on adverse organ remodeling in DIO independent of mitochondrial function.

In summary, the present study identifies an unexpected role for VitA that regulates the pro-fibrotic transcriptional response and pathological remodeling in a tissue-specific manner in DIO that is independent of mitochondrial function and mitochondrial energetic gene expression (Figure 5). In contrast, our previous studies using the same experimental protocol identified a VitA-mediated transcriptional program that preserves cardiac energetic gene expression in DIO and that might attenuate subsequent mitochondrial dysfunction and diabetic cardiomyopathy (14). Thus, VitA mediates both, protective and adverse, effects on organ damage in DIO and T2D. The present study extends our knowledge on the complex and tissue-specific aspects of VitA metabolism in metabolic disease and highlights the importance of additional studies in this area of research prior to the use of VitA metabolites as potential anti-obesity drugs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit.

Author contributions

CW, IS, LN, MS, and NF planned experiment, performed experiments and analyzed data. CR analyzed data. DJ, AW, EDA, JB, MK, and WB provided intellectual input for the project, interpreted data, and critically revised the manuscript. CR secured funding, conceived the study, prepared figures, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1118751/full#supplementary-material

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EDITED BY
Paola Di Pietro,
University of Salerno, Italy

REVIEWED BY
Rutao Wang,
Xijing Hospital, China
Jun Fang,
Fujian Medical University Union Hospital, China
Zhehao Piao,
Wenzhou Medical University, China

*CORRESPONDENCE
Chenghui Yan
yanch1029@163.com
Yaling Han
hanyaling@163.net

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Fibroblast growth factor 21 and prognosis of patients with cardiovascular disease: A meta-analysis

Bing Yan[1,2], Sicong Ma[1,2], Chenghui Yan[2]* and Yaling Han[1,2]*

[1]Department of Cardiology, The Second Hospital of Jilin University, Changchun, Jilin, China, [2]Department of Cardiology and Cardiovascular Research Institute, Chinese People's Liberation Army, General Hospital of Northern Theater Command, Shenyang, Liaoning, China

Background: The role of fibroblast growth factor 21 (FGF21) in predicting the long-term prognosis of patients with cardiovascular disease (CVD) remains unknown.

Methods: A comprehensive search in PubMed, Embase, and the Cochrane Library was performed to identify studies reporting the association between FGF21 and prognosis among patients with CVD. A meta-analysis was performed, with patients stratified by coronary artery disease (CAD) or heart failure (HF). The endpoint of CAD or HF was major adverse cardiovascular events defined by each study and a composite of death or HF readmission, respectively. The I^2 method and linear regression test of funnel plot asymmetry were used to test heterogeneity (I^2 > 50% indicates substantial heterogeneity) and publication bias (asymmetry P < 0.05, indicating publication bias).

Results: A total of 807 records were retrieved, and nine studies were finally included. Higher FGF21 levels were significantly associated with the risk of major adverse cardiovascular events in patients with CAD (multivariate hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 1.40–2.23, P < 0.05, I^2 = 0%, fixed-effect model). Increased FGF21 levels were also associated with the risk of all-cause death among patients with CAD (multivariate HR: 2.67, 95% CI: 1.25–5.72, P < 0.05, I^2 = 64%, random-effect model). No association was found between FGF21 and the endpoint among patients with HF (HR: 1.57, 95% CI: 0.99–2.48, P > 0.05, random-effect model), but a large heterogeneity (I^2 = 95%) and potential publication bias (Asymmetry P < 0.05) existed in the analysis.

Conclusion: Increased FGF21 levels were independently associated with poor prognosis of CAD, whereas the role of FGF21 in predicting clinical outcomes of HF requires further investigation.

KEYWORDS

death, prognosis, coronary artery disease, fibroblast growth factor (FGF 21), heart failure, major adverse cardiac event (MACE)

1 Introduction

Fibroblast growth factor 21 (FGF21), belonging to the FGF19 subclass of the FGF family, is a pleiotropic endocrine hormone (1) that acts in an autocrine/paracrine manner in multiple tissues (2, 3). FGF21 is induced in white adipose tissue (WAT) by fasting and refeeding and can stimulate glucose entry and increase lipolysis and mitochondrial oxidative capacity (2). FGF21 is a key regulator of energy homeostasis (4), which initiates fat mobilization and increases insulin sensitivity (5–7). Many studies have demonstrated that FGF21 protects against pancreatic damage and β-cell dysfunction and increases glucose transport *via* glucose transporter protein 1 (8). A series of studies have shown that FGF21 has beneficial effects on body weight and glucose and lipid metabolism under physiological conditions (9).

Considering the close association between metabolic syndrome and cardiovascular disease (10), an increasing number of studies have investigated the beneficial effects of FGF21 on the cardiovascular system. Bench et al. reported that FGF21 prevents atherosclerosis (11) and protects against cardiac hypertrophy (12). FGF21 protects against atherosclerosis *via* two independent mechanisms: regulation of adipocyte adiponectin production and suppression of hepatic expression of the transcription factor sterol regulatory element-binding protein-2 (10, 11). Endogenous FGF21 protects against cardiac hypertrophy *via* the sirtuin 1 (SIRT1)–peroxisome proliferator-activated receptor α (PPAR-α) pathway (13). Although a protective role of FGF21 in cardiac function and metabolism has been found, the link between FGF21 and cardiovascular disease is controversial. A series of clinical trials and meta-analyses reported that elevated serum FGF21 levels were associated with an increased incidence of cardiovascular diseases (CVD) (14) as well as cardiovascular mortality among patients with diabetes (15). Collectively, these results from bench research and clinical trials created a paradox in determining the predictive value of FGF21 in CVD. Moreover, most studies have focused on the association between FGF21 levels and the primary prevention of CVD, whereas clinical evidence evaluating the role of FGF21 in the prognosis of patients with CVD is limited. Therefore, we conducted a meta-analysis to explore the association between FGF21 and long-term prognosis of patients with established CVD to provide new evidence unveiling the prognostic role of FGF21 in CVD.

Abbreviations: FGF21, fibroblast growth factor 21; WAT, white adipose tissue; SIRT1, sirtuin 1; PPAR, peroxisome proliferator-activated receptor; CVD, cardiovascular disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis Protocols; MI, myocardial infarction; HF, heart failure; PICOS, patient, intervention, comparison, outcome, study type; CAD, coronary artery disease; MACE, major adverse cardiovascular event; CV, cardiovascular; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; RR, risk ratio; CI, confidence interval; FGFR, fibroblast growth factor receptor; ERK, extracellular signal regulated kinase; AMPK, adenosine monophosphate activated protein kinase; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

2 Materials and methods

2.1 Study eligibility and outcomes

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) (16). A comprehensive search was conducted in PubMed, Embase, and the Cochrane Library on June 9, 2022 to identify studies in English that reported the association between FGF21 and the clinical outcomes of patients with CVD. Studies meeting the following inclusion criteria were considered eligible: 1) study population comprising patients with established CVD; 2) studies reporting the relationship between FGF21 levels and CVD prognosis; 3) study endpoints with hard cardiovascular outcomes, such as all-cause or cardiac death, myocardial infarction (MI), and readmission for heart failure (HF); and 4) the follow-up period of studies was at least 6 months from discharge. Using these inclusion criteria and the PICOS (patient, intervention, comparison, outcomes, and study type) principle, we designed the following search terms: "cardiometabolic disease," "cardiovascular disease," "coronary artery disease," "heart failure," "cardiomyopathy," "fibroblast growth factor 21," and "FGF21." We did not retrieve terms regarding study outcome or type to ensure complete and comprehensive search results (refer to the search strategy in PubMed in the Supplemental Materials).

First, the titles and abstracts of the records were reviewed. If relevant, the full texts and references of each record were manually searched and reviewed to evaluate eligibility. No limitations of study type (cohort or case-control study) were included. Conference abstracts were excluded owing to insufficient information. For patients with coronary artery disease (CAD), the primary endpoint was major adverse cardiovascular events (MACE), defined as the composite of ischemic events from each included study, and secondary endpoints included all-cause death and cardiovascular death. For patients with HF, the endpoint was the composite of all-cause death and readmission for HF.

2.2 Data extraction and quality evaluation

The following items were extracted from each eligible study: first author, study type, year of publication, patient diagnosis and characteristics, sample size, cutoff value of FGF21 levels, endpoints, follow-up duration, and effect size (event and total numbers, univariate or multivariate hazard ratio [HR]). The authors of the included studies were contacted if key data were unavailable. Observational studies stratified by cohort and case-control studies were evaluated using two versions of the modified Newcastle–Ottawa Scale (NOS) (17, 18). Studies were regarded as high-, medium-, or low-quality if the NOS score was ≥ 7, 5–6, or ≤ 4 points, respectively. All processes of study selection, data extraction, and quality evaluation were performed by two independent reviewers (B. Yan and S. Ma), and discrepancies were finally judged by a third reviewer (C. Yan).

2.3 Statistical analyses

The event and total numbers were first calculated as unadjusted risk ratios (RR). Pooled RRs or HRs and 95% confidence intervals (CIs) were synthesized to estimate the impact of FGF21 levels on the observed endpoints using a fixed- or random-effect model if significant heterogeneity existed. Heterogeneity was determined using the Q statistic and I^2 method and considered significant for $P < 0.10$ for Q statistic or $I^2 > 50\%$. Publication bias was detected using funnel plots and a linear regression test for funnel plot asymmetry. Subgroup analysis for the primary endpoint of CAD was conducted among MI sub-populations, and sensitivity analyses were stratified by the effect size (RR derived from event and total numbers or HR) or by omitting each study. A two-sided $P < 0.05$ was considered statistically significant, except for the heterogeneity test ($P < 0.10$). All analyses were performed using RStudio (Version 1.2.1335) meta-packages.

3 Results

A total of 807 records were identified through a comprehensive retrieval. After removing 27 duplicate studies, titles and abstracts of 781 records were screened. A total of 157 records remained for full-text review, and one record was identified from the reference lists. Finally, nine observational studies that fully met the pre-specified reporting clinical outcomes were included in this meta-analysis (see selection flow diagram in Figure 1). During the full-test review, we found that a series of studies reported both FGF21 and cardiovascular prognosis but were finally excluded from our meta-analysis because they were not in accordance with at least one of the inclusion criteria. Representative excluded studies and their respective reasons for exclusion are presented in Supplemental Materials, Table S1.

The nine included studies contained five cohort (19–23) and four case-control studies (24–27). Seven studies reported the effect sizes of patients with CAD (19–25), and three studies specifically focused on patients with HF (23, 26, 27). A total of 2674 patients from four studies were included in the analysis of the primary endpoint MACE for CAD (20, 22, 24, 25). A total of 771 patients with HF from three studies were included in the analysis of a composite endpoint of death or readmission for HF (23, 26, 27). Details of the studies included in this meta-analysis are presented in Table 1. All included studies were considered medium or high quality with scores ≥ 5 points in the NOS, except for one case-control study (26) that scored 4 points owing to the potential bias of population selection (Table 2).

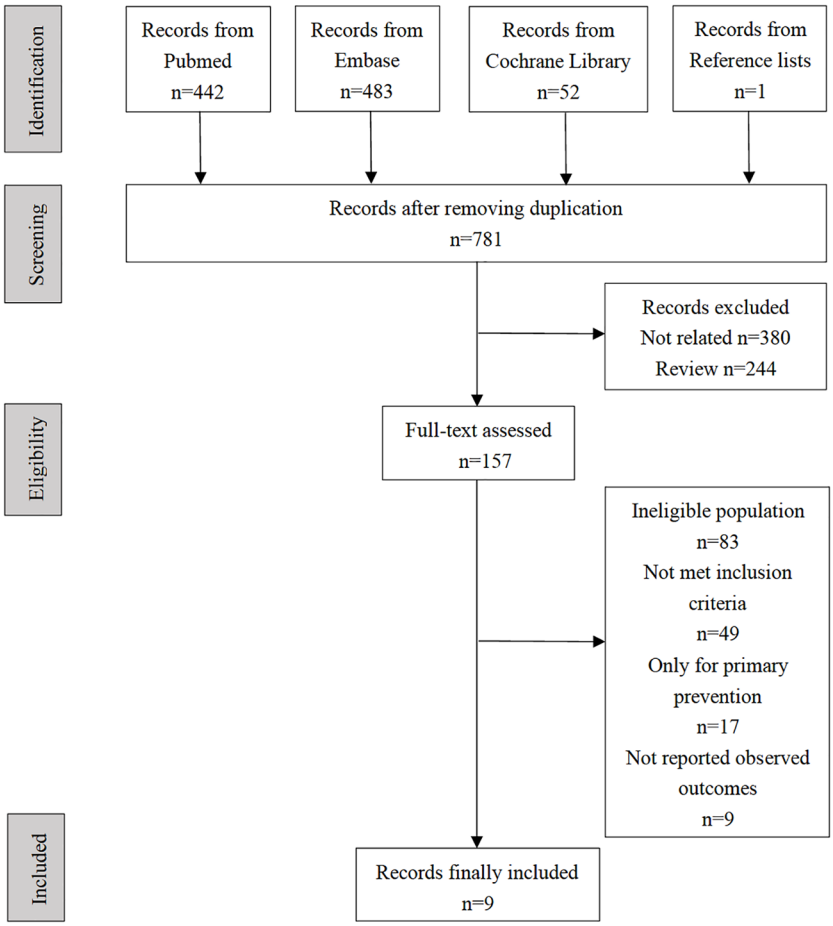

FIGURE 1
Flowchart of screening eligible studies.

3.1 Association between FGF21 and MACE in CAD

As mentioned previously, four studies including 2674 patients explored the association between FGF21 levels and long-term MACE among patients with CAD (20, 22, 24, 25). All four studies performed Cox regression analysis and reported multivariate HR as the effect size, and the median follow-up length was at least 24 months (Table 1). After effect size synthesis, higher FGF21 levels were independently and significantly associated with the long-term risk of MACE among patients with CAD (multivariate HR: 1.77, 95% CI: 1.40–2.23, $P < 0.05$, $I^2 = 0\%$, fixed-effect model; Figure 2A). For the subgroup analysis of patients with MI, two studies were included in the analysis (22, 25), and the results showed that higher FGF21 levels were also independently associated with an increased risk of MACE in patients with MI (multivariate HR: 1.82, 95% CI: 1.22–2.71, $P < 0.05$, $I^2 = 0\%$, fixed-effect model; Figure 2B). To test the stability of the results, sensitivity analysis was performed by omitting each study from the main analysis. The results demonstrated that higher FGF21 levels were consistently and significantly associated with the risk of MACE, irrespective of the removal of any single study ($P < 0.05$, Supplemental Materials, Figure S1). Funnel plots and asymmetry tests of the two analyses showed that no publication bias existed (Supplemental Materials, Figures S2A, B).

3.2 Association between FGF21 and death in CAD

Three studies including 2235 patients with CAD identified the relationship between FGF21 levels and all-cause death: two cohort studies reporting multivariate HR (19, 23) and one case-control

TABLE 1 Characteristics of studies included in the meta-analysis.

Study	Population	Sample size	Study design	Male, n (%)	Age, years (± SD)	FGF21 cut-off value (pg/ml)	Endpoints	Follow-up	Effect sizes
Li 2016	CAD	1668	Cohort study	1093 (65.5%)	–	Median (IQR): 643.2 (534.7-818.5) *vs* 229.0 (197.4-255.2)	All-cause death and CV death	Median: 4.9 years	Multivariate HR
Ong 2018	Stable CAD	1992	Cohort study	–	–	≥281.0 *vs* ≤ 155.0	MACE (CHD death, non-fatal MI, cardiac arrest and stroke)	Median: 4.9 years	Multivariate HR
Shen 2018	CAD	169	Case-control study	117 (69.2%)	–	Continuous variable (Logarithm transformation)	MACE (Cardiac death, non-fatal MI, readmission for angina, non-fatal stroke or TVR)	Median: 57 months	Multivariate HR
Chen 2018	AMI	165	Case-control study	–	–	≥123.0 *vs* < 123.0	MACE (CV death, recurrent MI, TVR and readmission for HF), all-cause death and CV death	24 months	Multivariate HR for MACE, event/total number for all-cause/CV death
Gu 2020	DCM with HFrEF	241	Case-control study	173 (71.8%)	68.8 ± 12.8	≥ 228.4 *vs* < 228.4	A composite of all-cause death and readmission	Mean: 16.1 months	Multivariate HR
Gan 2020	CAC	1132	Cohort study	712 (62.9%)	54.2 ± 13.7	≥ 276.1 *vs* < 108.6	SCD	12 months	Event/total number
Gu 2021	STEMI with PCI	348	Cohort study	280 (80.5%)	62.1 ± 13.1	≥ 229.8 *vs* < 229.8	MACE (all-cause death and readmission for angina, HF or AMI)	Median: 24 months	Multivariate HR
Wu 2022	AHF (including CAD subgroup)	402	Cohort study	234 (58.2%)	70.0 ± 12.0	≥262.0 *vs* < 262.0	All-cause death and a composite of all-cause death and readmission	Median: 193 days	Multivariate HR for all-cause death, event/total number for a composite of all-cause death or readmission
Fan 2022	HFrEF	128	Case-control study	86 (67.2%)	70.9 ± 12.4	≥ 231.4 *vs* < 231.4	A composite of all-cause death and HF readmission	Mean: 13.4 months	Univariate HR

SD, standard deviation; FGF21, fibroblast growth factor 21; CAD, coronary artery disease; IQR, interquartile range; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; CHD, coronary heart disease; MI, myocardial infarction; TVR, target vessel revascularization; AMI, acute myocardial infarction; HF, heart failure; CAC, coronary artery calcification; SCD, sudden cardiac death; ACS, acute coronary syndrome; DCM, dilated HFrEF, heart failure with reduced ejection fraction; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; AHF, acute heart failure; OR, odds ratio.

TABLE 2 NOS score of studies included in meta-analysis.

Cohort studies	Selection				Comparability of cohorts based on analysis	Outcome			Total
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow-up length	Follow-up adequacy	
Li 2016	1	0	1	1	1	1	1	1	7
Ong 2018	1	1	1	1	1	1	1	1	8
Gan 2020	0	1	1	1	1	0	1	1	6
Gu 2021	1	1	0	1	1	1	1	1	7
Wu 2022	1	1	1	1	1	1	0	1	7
Case-control studies	**Selection**				**Comparability of cases and controls based on analysis**	**Outcome**			**Total**
	Adequate definition of cases	**Representativeness of cases**	**Selection of controls**	**Definition of controls**		**Assessment of outcome**	**Follow-up length**	**Follow-up adequacy**	
Shen 2018	1	1	1	1	1	1	1	1	8
Chen 2018	0	0	1	1	1	1	1	1	6
Gu 2020	1	0	0	0	1	0	1	1	4
Fan 2022	1	1	0	0	1	0	1	1	5

Table 2 shows the NOS points of each included studies to evaluate the study quality. Studies were regarded as high quality if scored ≥ 7 points. NOS, Newcastle-Ottawa Scale.

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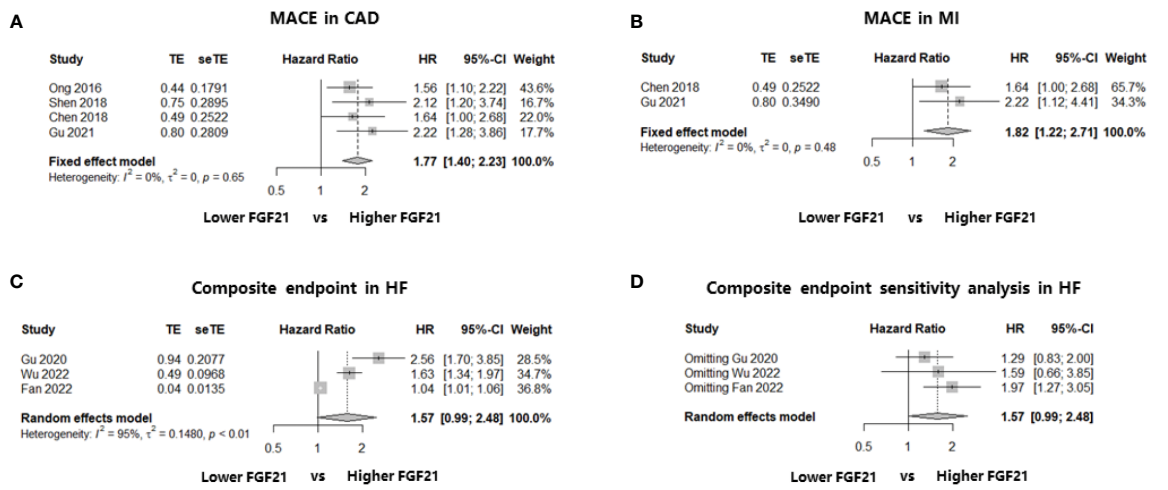

FIGURE 2
Forest plots of the association of FGF21 with endpoints in patients with CAD or HF. Figure 2 shows the synthesized effect sizes of FGF21 on predicting endpoints among either CAD or HF patients. The endpoint for CAD and HF was MACE and a composite of all-cause death or HF readmission, respectively. **(A)** FGF21 and MACE in CAD; **(B)** FGF21 and MACE in MI; **(C)** FGF21 and a composite of all-cause death or HF readmission in HF; **(D)** sensitivity analysis of endpoint in HF. FGF21, fibroblast growth factor 21; CAD, coronary artery disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction.

study reporting the event and total numbers (25). We first calculated the RR in this case-control study and then synthesized the RR using multivariate HRs. The results showed that higher FGF21 levels were not associated with the risk of all-cause death among patients with CAD (HR: 1.86, 95% CI: 0.89–3.87, P > 0.05, I^2 = 90%, random-effect model; Figure 3A). However, there was significant heterogeneity (I^2 = 90%), which may have been because of the mixture of HRs and RR. In addition, funnel plots and asymmetry tests revealed that publication bias may exist (asymmetry P = 0.02; Supplemental Materials, Figure S3A). Therefore, we performed a sensitivity analysis by excluding the case-control study without multivariate HR (25), and an independent and significant association between higher FGF21 levels and the risk of all-cause death was found in patients with CAD (HR: 2.67, 95% CI: 1.25–5.72, P < 0.05, I^2 = 64%, random-effect model; Figure 3B).

In terms of FGF21 and CV death, three studies that enrolled patients with CAD were included in the analysis. Two of the three studies reported the event and total numbers (21, 25), and only one cohort study reported the multivariate HR (19). No association was found between FGF21 levels and the risk of CV death among patients with CAD after the effect size synthesis with substantial heterogeneity (RR: 1.04, 95% CI: 0.93–1.17, P > 0.05, I^2 = 80%, random-effect model; Figure 3C). To eliminate the heterogeneity from the mixture of RR and HRs, a sensitivity analysis including the two studies (21, 25) reporting event and total numbers was

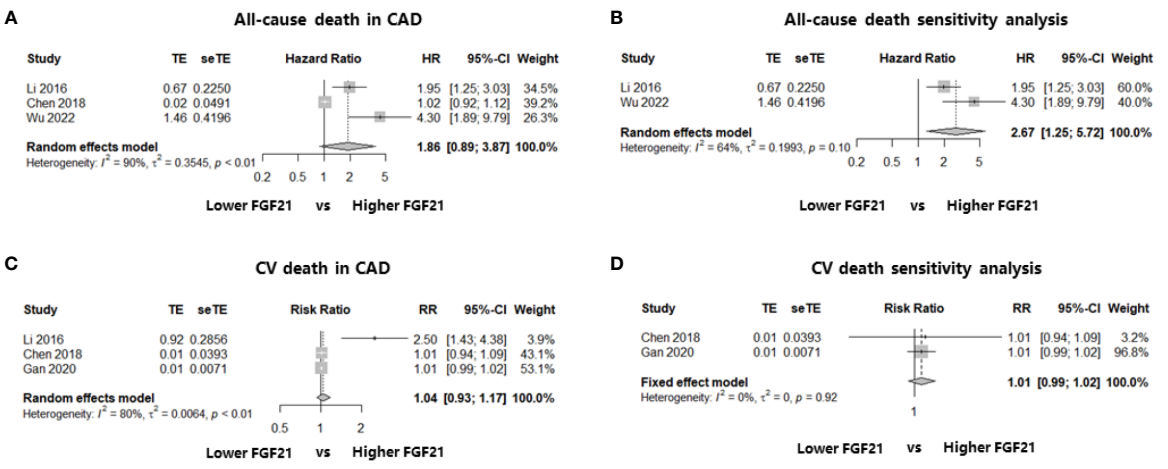

FIGURE 3
Forest plots of the association of FGF21 with all-cause death or CV death in patients with CAD. Figure 3 shows the synthesized effect sizes of FGF21 on predicting all-cause death or CV death among CAD patients. **(A)** FGF21 and all-cause death in CAD; **(B)** sensitivity analysis of all-cause death in CAD; **(C)** FGF21 and CV death in CAD; **(D)** sensitivity analysis of CV death in CAD. FGF21, fibroblast growth factor 21; CV death, cardiovascular death.

performed, which also found no significant association between FGF21 and the rate of CV death among patients with CAD (RR: 1.01, 95% CI: 0.99–1.02, P > 0.05, I^2 = 0%, fixed-effect model; Figure 3D). Funnel plots and asymmetry tests found no potential publication bias in the two meta-analyses of CV death (Supplemental Materials, Figures S3C, D).

3.3 Association between FGF21 and prognosis of HF

Three studies recruiting 771 patients with HF reported the composite endpoint of death or readmission for HF and were included in the meta-analysis (23, 26, 27). The effect sizes of these three studies were event and total numbers (23), univariate HR (27), and multivariate HR (26). The results showed that there was no association between higher FGF21 levels and a composite of death or HF readmission among patients with HF, although there was a statistically significant trend (HR: 1.57, 95% CI: 0.99–2.48, P > 0.05, I^2 = 95%, random-effect model; Figure 2C). We also found a large heterogeneity (I^2 = 95%) and potential publication bias in this effect size synthesis (asymmetry P < 0.05, funnel plots in Supplemental Materials, Figure S2C). A sensitivity analysis, omitting each study, did not significantly change the negative findings (Figure 2D).

4 Discussion

In this meta-analysis, we explored the association between FGF21 levels and long-term clinical outcomes in patients with CVD stratified by CAD and HF. The results show that higher FGF21 levels were independently associated with the incidence of MACE among patients with CAD. Although the main analysis found no association between FGF21 levels and the rate of all-cause death in CAD, sub-analysis including high-quality studies reporting multivariate HRs showed a significant association between higher FGF21 levels and the risk of all-cause death. In patients with HF, FGF21 was not associated with the rate of a composite of all-cause death or HF readmission, although this outcome should be considered with caution due to the substantial study heterogeneity and variability of effect sizes, including RR, univariate, and multivariate HR. To our knowledge, this is the first meta-analysis to evaluate the association between FGF21 and prognosis of patients with CVD.

FGF21 is a well-known key endocrine hormone that regulates lipolysis in WAT and increases fatty acid oxidation in the liver (28–30). FGF21 increases insulin-independent glucose uptake, improves glucose tolerance, and reduces serum triglyceride levels (31). It has also been recognized that FGF21 has a direct effect on the heart in an endocrine and autocrine manner, which is mediated by the FGFR and co-receptor β-Klotho (32). FGFR1 and FGFR3 are the main FGF21 receptors in the heart (33, 34). FGF21 binds to FGFR and the co-receptor β-Klotho in cardiomyocytes and activates downstream signaling pathways, including ERK, AMPK, and the SIRT1-PPAR-α pathway (35, 36). Among these receptors, FGF21 exerts cardioprotective effects, mainly through FGFR1 (37). A recent study also showed that sodium/glucose cotransporter-2 inhibitors (SGLT2i) can increase serum FGF21 levels, which is one of the mechanisms underlying the cardioprotective effects of SGLT2i (38). Several preclinical trials have also demonstrated that mimics and long-acting derivatives of FGF21 have beneficial effects on body weight, lipoprotein profiles, and metabolic homeostasis (39, 40). However, previous clinical trials have reported that elevated FGF21 levels are associated with increased cardiovascular risk and mortality (41–45). Obviously, a paradox between basic research and clinical studies exists regarding the definite role of FGF21 and CVD; therefore, further comprehensive studies are needed to resolve this issue.

One of the main findings of this meta-analysis was that high FGF21 levels were independently and significantly associated with an increased long-term risk of MACE in patients with CAD (multivariate HR: 1.77, 95% CI: 1.40–2.23, P < 0.05, I^2 = 0%, fixed-effect model). Even when focusing on the MI subgroup, the result was consistent (multivariate HR: 1.82, 95% CI: 1.22–2.71, P < 0.05, I^2 = 0%, fixed-effect model). No study heterogeneity or publication bias was found in the statistical analyses, indicating that these results were stable and reliable. In terms of all-cause death and FGF21 among patients with CAD, the meta-analysis did not find a significant association (HR: 1.86, 95% CI: 0.89–3.87, P > 0.05, I^2 = 90%, random-effect model). However, high study heterogeneity from a mixture of multivariate HRs and RR may discount credibility. Therefore, a sensitivity analysis including studies reporting multivariate HRs was conducted, and an independent and significant association was found between higher FGF21 levels and the risk of all-cause death in CAD. Similar meta-analyses were also performed to determine the relationship between FGF21 and CV death in patients with CAD, but no significant associations were found, irrespective of the main outcome, including three studies (RR: 1.04, 95% CI: 0.93–1.17, P > 0.05, I^2 = 80%, random-effect model) or the sensitivity analysis including two studies reporting RR (RR: 1.01, 95% CI: 0.99–1.02, P > 0.05, I^2 = 0%, fixed-effect model). Nevertheless, we should note that the study sample size involved in CV death was small; more importantly, two of the three studies only reported event and total numbers without adjusting for other multiple factors, which is inferior to the multivariate HR for authentically reflecting the effect size. Therefore, elevated FGF21 levels are independently associated with poor long-term prognosis in patients with CAD, although more high-level evidence is warranted.

For patients with HF, we pre-specified a composite of all-cause death and HF readmission as endpoints. After statistical analysis, there was no significant association between FGF21 and the long-term endpoint of patients with HF (HR: 1.57, 95% CI: 0.99–2.48, P > 0.05, I^2 = 95%, random-effect model). The sensitivity analysis showed that the result was positive only when a case-control study that reported a univariate HR was excluded. The study heterogeneity was also high owing to the effect size variability reported by the included studies (including RR, univariate HR, and multivariate HR). Hence, although a negative relationship was found between FGF21 and clinical outcomes in patients with HF, this result may be insufficient to determine the definite relationship between FGF21 and the prognosis of patients with HF and needs to

be reconfirmed by more clinical trials. Overall, our meta-analysis and previous findings (14, 15, 45) collectively identify that increased FGF21 levels may be an independent predictor of poor prognosis among patients with CVD, rather than a protective factor of the heart, which was found in mechanistic studies. The FGF21 paradox not only exists in primary prevention but also in the long-term prognosis of CVD. This paradox may be because of a compensatory response to metabolic stress in patients with CVD. FGF21 resistance may be another underlying mechanism, according to recent findings reporting that stress conditions can decrease FGF21 co-receptor β-Klotho expression in the heart, impair FGF21 signaling, and weaken the protective effect of FGF21 on cardiomyocytes (46). Both underlying mechanism studies and high-level clinical trials are needed to determine this uncertainty to provide potential drug targets.

The present meta-analysis had several limitations. First, although comprehensive retrieval was performed and nine studies were finally included, the study sample size was also relatively small. Second, the effect sizes reported by the included studies were varied and uneven, including event/total number, odds ratio, and univariate and multivariate HR. This diversity increases the study heterogeneity, which may influence data synthesis. Moreover, as shown in Table 1, the cutoff values of FGF21 used in the included studies varied without a uniform criterion. Therefore, a definite FGF21 cutoff value for predicting cardiovascular risk still needs to be explored. Finally, the study endpoints were not abundant because of limited data obtained from the included studies. These deficiencies require further clinical trials to fill the gap.

This meta-analysis demonstrated that increased FGF21 levels were independently associated with the long-term prognosis of patients with CAD. In patients with HF, no association was found between FGF21 levels and prognosis, and the role of FGF21 in predicting clinical outcomes remains unclear. The FGF21 paradox exists in the long-term prognosis of CVD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

BY designed this study. SM wrote the main manuscript and prepared figures. CY conducted the manuscript reviewing and editing. YH supervised all these procedures of this study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1108234/full#supplementary-material

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Hongwei Ji,
The Affiliated Hospital of Qingdao University, China
Yan-Feng Wu,
The Second Affiliated Hospital of Nanjing Medical University, China

*CORRESPONDENCE
Aihua Hu
✉ aihuacn@hotmail.com

†These authors have contributed equally to this work and share first authorship

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Keeping obesity status is a risk factor of hypertension onset: evidence from a community-based longitudinal cohort study in North China

Qiujing Cai[1†], Xiaolei Zhao[1†], Liguang Dong[2,3], Xinmin Zhang[1], Chenglong Wang[1], Shu Wang[3], Yi Zhou[4], Xianliang Zhou[4], Yanqi Li[3], Shuyu Wang[3], Lisheng Liu[3] and Aihua Hu[1*]

[1]Center for Non-communicable Disease Management, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China, [2]Center for Health Care Management, Peking University Shougang Hospital, Beijing, China, [3]Beijing Hypertension League, Beijing, China, [4]Department of Cardiology, Fuwai Hospital, Beijing, China

Objective: The purpose of our study was to investigate the association of obesity status change with hypertension onset based on a community-based longitudinal cohort study in North China.

Methods: This longitudinal study included 3,581 individuals free of hypertension at baseline in the first survey (2011–2012). All participants were followed up (2018–2019). According to the criteria, a total of 2,618 individuals were collected for analysis. We used adjusted Cox regression models and Kaplan–Meier survival analysis to estimate the association between obesity status change and hypertension onset. Additionally, we applied the forest plot to visualize the subgroup analysis including age, gender, and the differences in some variables between baseline and follow-up. Finally, we conducted a sensitivity analysis to examine the stability of our results.

Results: Over nearly 7 years of follow-up, a total of 811 (31%) developed hypertension. The new hypertension incidence was mostly observed in those who were obese all the time (P for trend < 0.01). In the fully adjusted Cox regression model, being obese all the time increased the risk of hypertension by 30.10% [HR 4.01 (95% CI 2.20–7.32)]. The Kaplan–Meier survival analysis revealed the change in obesity status as an important feature to predict the occurrence of hypertension. Sensitivity analysis shows a consistent trend between the change in obesity status and hypertension onset in all populations. Subgroup analysis showed that age above 60 years was an important risk factor for hypertension onset, that men were more likely than women to develop hypertension, and that weight control was beneficial in avoiding future hypertension in women. There were statistically significant differences in ΔBMI, ΔSBP, ΔDBP, and ΔbaPWV between the four groups, and all variables, except baPWV changes, increased the risk of future hypertension.

Conclusion: Our study shows that obese status was notably associated with a significant risk of hypertension onset among the Chinese community-based cohort.

KEYWORDS

obesity status change, hypertension onset, cardiovascular diseases, metabolic disorder, vascular injury and remodeling

1. Introduction

Hypertension has become a major health issue with the increasing aging population and unfavorable healthy behaviors, which contributes to 20% of mortality and 50% of morbidity related to cardiovascular diseases (CVDs) in China (1). Over the past few years, hypertension and obesity have increased worldwide, and hypertension often occurs concurrently with obesity. Moreover, hypertension and obesity are both the major components of metabolic syndrome (MS) that threaten public health, as it interacts with metabolic risk factors to dominate and accelerate the abnormal internal environment homeostasis progression. Despite the increasing global epidemic of obesity, mortality caused by coronary artery disease (CAD) and stroke has declined in the past 10 years, probably as a result of the improved public health management of other CVD risk factors (2). However, the prevalence of hypertension shows a consistently increasing trend among the overweight and obese population (3). The risk of CVD is higher in adults with an elevated body mass index (BMI), but there is little study on whether the obese status change has a relationship with hypertension onset based on the Chinese population since the majority of the earlier research was based on Western population (4).

The rising tendency of overweight and obesity is worrisome and becoming a worldwide challenge. It is widely established that obesity, defined as elevated BMI, has been proven to be associated with a higher risk of hypertension (5). Moreover, because obesity is occurring at increasingly younger ages, it is likely to translate into a high cumulative incidence of hypertension (6). Currently, individuals are experiencing a large cumulative exposure to excess adiposity obtained in their lifetime, thus, it is very important to understand the effect of obesity status change on hypertension onset. This raises the question of whether the obesity status change is more detrimental to future hypertension risk. A more in-depth perception of the relationship between obesity and hypertension would be critical to the better management of abdominal obesity-related cardiometabolic risk, thus offering an additional chance for the primary prevention of CVD (7).

Emerging evidence has demonstrated that obese individuals were at higher risk of hypertension later in life (8), though no information about how obesity status changes affect hypertension onset was provided in those studies. Hence, our study aimed to study the association between obesity status change and hypertension onset based on a community-based longitudinal cohort in North China. In this research, we analyzed longitudinal data to determine if there was an association between obesity status changes with the consequent risk of hypertension onset.

2. Methods

2.1. Study population and design

This longitudinal cohort study of the Shougang community in Beijing in North China is a prospective cohort, which was designed to assess the determinants and progression of CVD between 2011 and 2019 among 2,618 participants aged from 18 to 98 years. We recruited participants from the employee and retiree population of the community. Beginning from the study's inception, participants conducted healthy assessments and questionnaires for demographic features, lifestyle factors, anthropometric measurements, and blood tests. The baseline was conducted from 2011 to 2012, and the enrolled individuals were re-examined from 2018 to 2019. All participants were provided written informed consent for inclusion in this cohort.

Figure 1 illustrates the flow chart for screening eligible participants in 3581 subjects. The subjects who had complete follow-up records were included in our study. The exclusion criteria were as follows: (1) participants diagnosed with hypertension in baseline; (2) without blood pressure measure records; (3) with cancer or malignant tumor; (4) lost BMI records; (5) diagnosis of a history of stroke, myocardial infarction, or other CVD; (6) less than 18 years old; and (7) pregnant.

Finally, a total of 2,618 participants who had normal blood pressure were enrolled in our study. The survey protocols, instruments, and the process for obtaining informed consent were approved by the Ethics Committee of Beijing Hypertension League Institute (Ethical Approval No. 2017-102), and each participant provided written informed consent. Our study conformed with the principles of the Declaration of Helsinki and the following checklist in accordance with STROBE Statement 2019 (Supplementary Table 4).

2.2. Definition of obesity status change

The change in obesity status means that according to the BMI change from baseline to 2018, we divided the population into four groups: Group 1 (always having a normal weight, which means from baseline to follow-up, this group's weight kept in the normal range), Group 2 (from normal weight to becoming obesity, which means this group had normal weight at first, but being fat finally), Group 3 (from obesity to become normal weight, which means this group was obese at first, and then becoming normal), and Group 4 (keeping obesity all the time, which means this group had been obese during 7 years). Those four groups represented four obesity statuses in our study.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and subsequently categorized as low ($<$18.5 kg/m^2), normal (18.5–23.9 kg/m^2); overweight (24.0–27.9 kg/m^2), or obese ($\geq$28 kg/m^2) according to the criteria of the expert consensus on obesity prevention and treatment in China (9). In a personal assessment, weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were determined by standardized equipment, and BMI was then calculated as described above.

2.3. Definition of hypertension onset

According to multiple previous studies (10–12), we defined hypertension onset as follows. After the baseline examination without hypertension, individuals who were diagnosed with hypertension in follow-up examination were reported hypertension onset.

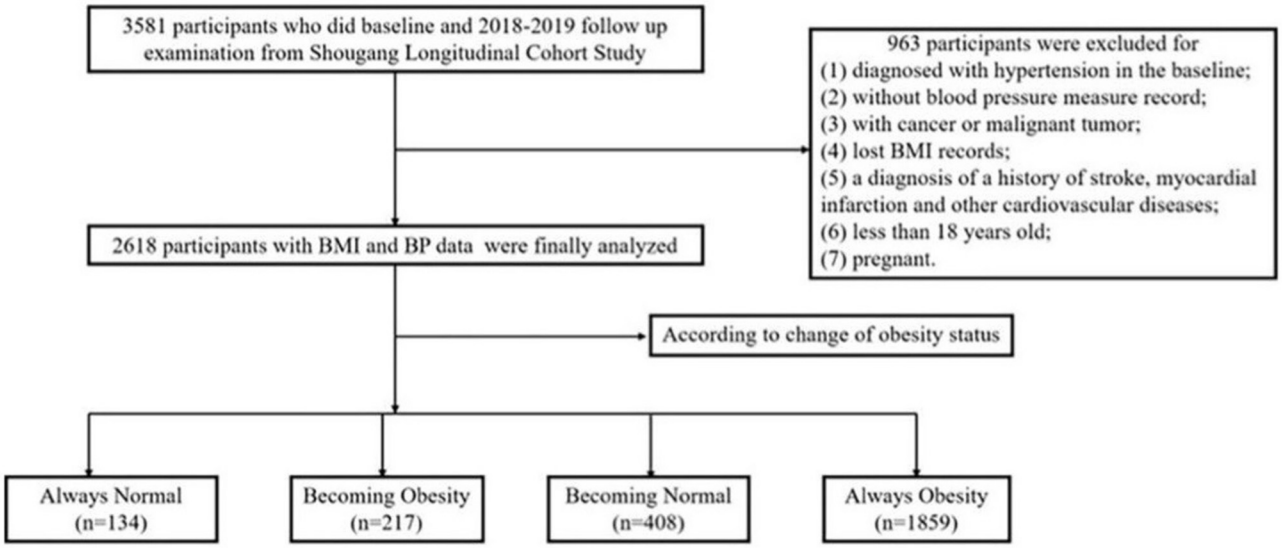

FIGURE 1
Flow chart of this cohort study.

Hypertension criteria (13) included: (1) average systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg; (2) self-reported hypertension; and (3) current administration of antihypertensive drugs within 2 weeks.

Systolic and diastolic blood pressures were measured three times by one trained examiner using an automatic blood pressure monitor (Omron HEM-7200 Monitor) in the right arm according to a standardized protocol. The average blood pressure was calculated accordingly.

2.4. Assessment of covariates

We used a validated questionnaire to obtain participants' information, including demographic information, metabolic biomarkers, and health behavioral factors to control the related bias. For smoking and drinking, we combined data on current and previous smoking and drinking status. Body height and weight were measured using a standard method by calibrated apparatus. Brachial-ankle pulse wave velocity (baPWV) was examined by the Omron non-invasive vascular screening device (BP-203RPEIII). Demographic information (age and gender) and health behaviors (smoking status and alcohol consumption) were accessed from face-to-face household interviews using structured questionnaires. After household interviews, venous blood was collected by trained staff. The blood samples were transported to the Peking University Shougang Hospital in Beijing and stored at −80°C refrigerator. Metabolic biomarkers were acquired following a standard protocol of biochemical detection, including triglycerides (TGs), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC).

2.5. Statistical analysis

The statistical analysis were performed according to the recommendation of the American Heart Association Scientific Publication Committee (14). The missing covariates were filled with mean to reduce selection bias. Normally distributed variables (decided by the Kolmogorov–Smirnov test) are presented as mean ± standard deviation (SD). Categorical variables were provided as frequencies with percentages. The baseline characteristics were compared among the obesity status change groups quartiles by one-way ANOVA test (normal distribution), and the difference of hypertension onset based on four groups was analyzed by chi-square test (categorical variables).

A multivariable Cox regression analysis was conducted to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association between obesity status change and hypertension onset. First, we adjusted for age and gender, and then in the minimally adjusted model, we adjusted age, sex, income, smoking status, alcohol status, outdoor activity status, and amount of adding salt in food. In the final Cox models, we adjusted for the following potential confounders: age, sex, income, smoking status, alcohol status, outdoor activity status, amount of adding salt in food, family history of hypertension, and family history of high cholesterol. Additionally, stratified analyses were performed to evaluate the possible effect modification of subgroups according to age, gender, and the change in BMI, SBP, DBP, and baPWV. Furthermore, a sensitivity analysis based on the exclusion of participants who had a family history of hypertension was performed to test the robustness of the findings. We conducted the *P* for interaction analysis as well to examine the sex-to-obesity status interaction in association with hypertension onset. Finally, we illustrated the outcomes of the Kaplan–Meier survival analysis to dig into the influence of obesity status change and hypertension onset. A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. All data analyses were performed using

TABLE 1 Baseline characteristics of the total participants according to different BMI change groups.

Characteristics		Total	Group 1	Group 2	Group 3	Group 4
Population	*n* (%)	2,618	134 (5.10%)	217 (8.30%)	408 (15.60%)	1,859 (71.00%)
Age	Mean ± SD	55.57 ± 7.37	52.08 ± 6.79	54.60 ± 8.06	55.48 ± 7.05	55.96 ± 7.32
Sex						
Male	*n* (%)	845 (32.30%)	3 (2.20%)	37 (17.10%)	69 (16.90%)	736 (39.60%)
Female	*n* (%)	1,773 (67.70%)	131 (97.80%)	180 (82.90%)	339 (83.10%)	1,123 (60.40%)
Diagnosis BMI	Mean ± SD	25.49 ± 3.32	21.48 ± 1.59	21.78 ± 1.55	23.13 ± 2.30	26.72 ± 2.91
WHR	Mean ± SD	0.89 ± 0.06	0.80 ± 0.03	0.81 ± 0.03	0.88 ± 0.04	0.91 ± 0.06
Smoking status						
Never	*n* (%)	2,224 (84.95%)	131 (97.76%)	204 (94.01%)	373 (91.42%)	1,515 (81.50%)
Yes	*n* (%)	394 (15.05%)	2 (1.49%)	13 (5.99%)	35 (8.58%)	344 (18.50%)
Blood pressure						
SBP	Mean ± SD	124.04 ± 9.72	118.11 ± 10.70	120.51 ± 11.28	121.93 ± 10.82	125.33 ± 8.82
DBP	Mean ± SD	72.06 ± 7.67	68.73 ± 7.38	69.79 ± 7.93	70.86 ± 7.82	72.83 ± 7.48
baPWV	Mean ± SD	1,513.72 ± 269.86	1,406.37 ± 244.91	1,465.39 ± 274.64	1,482.95 ± 252.69	1,533.85 ± 271.67
TC	Mean ± SD	5.32 ± 1.58	5.38 ± 1.04	5.15 ± 1.01	5.37 ± 0.92	5.32 ± 1.77
TG	Mean ± SD	1.51 ± 1.22	1.07 ± 0.51	1.11 ± 0.99	1.40 ± 1.36	1.61 ± 1.23
HDL	Mean ± SD	1.48 ± 0.48	1.81 ± 0.38	1.71 ± 0.41	1.60 ± 0.37	1.40 ± 0.49
LDL	Mean ± SD	3.21 ± 0.82	3.14 ± 0.86	2.98 ± 0.80	3.24 ± 0.77	3.24 ± 0.82

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; baPWV, brachial-ankle pulse wave velocity; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

SPSS 26.0 (SPSS Inc., Chicago, Illinois, United States), and all figures were performed by R software (version 4.2.1), GraphPad Prism 8, and Origin 2021.

3. Results

3.1. Clinical characteristics of the study population

The clinical characteristics of the study population are presented in Table 1 according to obesity status change. This cohort study consisted of 2,618 participants with a mean age of 55.57 years, and 32.3% of them were male participants. Four groups defined by BMI changes from baseline to the final follow-up are shown in Figure 2. In the baseline survey, although all individuals were without hypertension, the other three groups' SBP and DBP elevated when compared with Group 1's SBP and DBP (118.11 ± 10.70, 68.73 ± 7.38). Consistently, Group 2 (120.51 ± 11.28, 69.79 ± 7.93), Group 3 (121.93 ± 10.82, 70.86 ± 7.82), and Group 4 (125.33 ± 8.82, 72.83 ± 7.48) were also increasing by groups. Interestingly, Group 3 was the population that lost weight successfully, and their blood pressure was higher than Group 2 in which the participants were fatter than baseline. This interesting finding might illustrated that once people became obese, their blood pressure would increase. Moreover, compared with Group 1 and Group 2, individuals from Group 3 who were obese at baseline had superior TC, LDL, TG, waist–hip ratio (WHR), baPWV, and decreased HDL. The characteristics of Group 4 who were keeping obesity status were always at the supreme level.

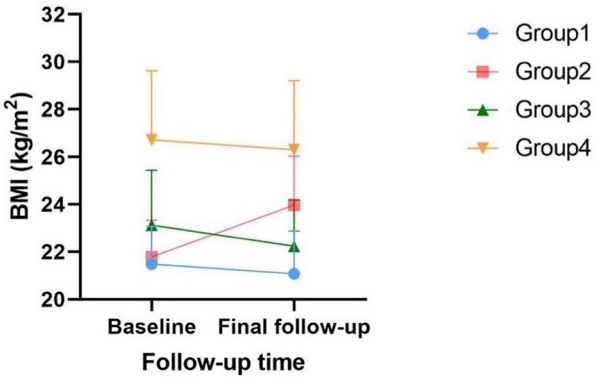

FIGURE 2
Visualization of four groups defined by BMI changes.

3.2. The crude prevalence of hypertension onset

During a 7-year follow-up, 811 participants (31%) developed hypertension. Table 2, Figure 3 summarize the hypertension onset situation of four groups. The hypertension onset was more

TABLE 2 Crude prevalence of hypertension onset in four groups.

Groups		Total	Group 1	Group 2	Group 3	Group 4	χ^2	*P*-value
Normal	*n* (%)	1,807 (69.00%)	123 (91.80%)	166 (76.50%)	324 (79.40%)	1,194 (64.20%)	78.74	<0.01
Hypertension onset	*n* (%)	811 (31.00%)	11 (8.20%)	51 (23.50%)	84 (20.60%)	665 (35.80%)		

Group 1: always normal weight; Group 2: becoming obesity; Group 3: becoming normal weight; and Group 4: always obesity.

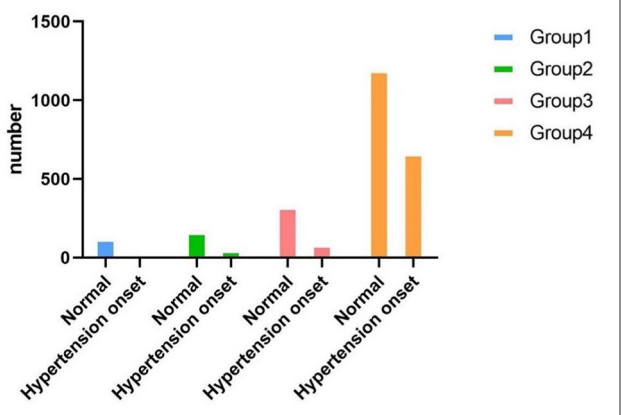

FIGURE 3
Bar plot shows the crude prevalence of hypertension onset situation in four groups.

frequently observed in Group 4 ($n = 665/N = 1,859$, 35.80%) where the participants were keeping obesity status all the time. The hypertension onset was seen in Group 2 ($n = 51/N = 217$, 23.50%) higher than in Group 3 ($n = 84/N = 408$, 20.60%). The hypertension onset was seen lowest in Group 1 ($n = 11/N = 134$, 8.20%). The chi-square test was adopted with a statistically significant difference (χ^2=78.74, $P < 0.01$). We found that keeping obese had a strong association with hypertension onset, and becoming fat was observed to have a higher risk for future hypertension than keeping a normal weight and becoming thin.

3.3. Risk of obesity status change and hypertension onset

Table 3 summarizes the Cox regression analysis of the association between obesity status change and hypertension onset. The other groups had an increased risk of developing hypertension in comparison to Group 1. In the fully adjusted model, participants in Group 2 [HR 2.82 (95%CI 1.47–5.42); $P < 0.01$] exhibited a 2.82-fold risk, Group 3 [HR 2.29 (95%CI 1.22–4.31); $P < 0.05$] exhibited a 2.29-fold risk, and Group 4 [HR 4.01 (95%CI 2.20–7.32); $P<0.01$] exhibited a 4.01-fold risk of developing hypertension when setting the Group 1 as reference. Moreover, the risk factors involved in model 3 (fully adjusted model) were shown by a forest plot (Figure 4). The results of the Kaplan–Meier survival analysis showing in Figure 5 revealed that the odds of cumulative risk of hypertension onset increased by years in participants from Groups 1 to Group 4, and the percentage of increase was not equal among groups. By calculating the cumulative risk probability of developing hypertension onset, the results showed that four groups were statistically significant compared to the other groups.

3.4. Subgroups analysis

3.4.1. Age subgroup analysis

As age was a significant variable in the Cox regression model, we divided the population into two subgroups based on age (<60 years and ≥60 years). Figure 6 shows that age over 60 years was a significant risk factor contributing to future hypertension, especially can be observed that the HR of age over 60 years was high in Group 2 (HR 3.69) and Group 4 (HR 4.67). Moreover, other variables analyzed above were shown in the next two forest plots with HRs and 95%CI (Figures 7A, B). Figure 7A shows the result of age under 60 years, and Figure 7B shows the result of age over 60 years.

3.4.2. Sex subgroup analysis

Because sex was a significant variable in the Cox regression model, female participants had a lower risk of developing future hypertension [HR 0.81 (95%CI 0.67–0.98)] than male participants. Therefore, we analyzed the risk of the female participants to have hypertension onset (Figures 8A, B), Figure 8A shows the HR of each group, Group 2 [HR 3.05 (95%CI 1.57–5.92)], Group 3 [HR 2.25 (95%CI 1.19–4.27)], and Group 4 [HR 3.60 (95%CI 1.97–6.58)] respectively. Figure 8B shows the association between female and hypertension onset based on Cox regression analysis. The outcomes displayed that when the female gender was taken into account, the risk of the decreased BMI (Group 3) with the hypertension onset was attenuated. Moreover, remaining obese (Group 4) and becoming obese (Group 2) in female participants might increase the risk of future hypertension. We also classified the participants into two subgroups according to gender based on the joint associations of sex and obesity status change with hypertension onset (P for interaction = 0.009) (Supplementary Table 1).

3.5. Association of the ΔBMI, ΔSBP, ΔDBP, and ΔbaPWV between baseline to final follow-up with hypertension onset within four groups

Table 4 showed the ΔBMI, Δ SBP, ΔDBP, and ΔbaPWV between four groups had significant statistical

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TABLE 3 Cox models indicate the association of obesity status changes with hypertension onset.

	Hypertension onset					
	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Group 1	1		1		1	
Group 2	2.79 (1.45, 5.46)	<0.01	2.80 (1.46, 5.39)	<0.01	2.82 (1.47, 5.42)	<0.01
Group 3	2.30 (1.23, 4.32)	<0.05	2.29 (1.22, 4.30)	<0.05	2.29 (1.22, 4.31)	<0.05
Group 4	4.05 (2.22, 7.38)	<0.01	4.05 (2.22, 7.38)	<0.01	4.01 (2.20, 7.32)	<0.01
Age	0.57 (0.55, 0.58)	<0.01	0.57 (0.55, 0.60)	<0.01	0.57 (0.55, 0.60)	<0.01
Sex, female	0.79 (0.69, 0.91)	<0.01	0.85 (0.71, 1.03)	0.09	0.81 (0.67, 0.98)	<0.05
Income	…	…	0.97 (0.91, 1.04)	0.36	0.97 (0.90, 1.03)	0.30
Smoking status	…	…	1.09 (0.98, 1.22)	0.10	1.09 (0.98, 1.21)	0.13
Alcohol status	…	…	1.04 (0.93, 1.17)	0.50	1.04 (0.93, 1.16)	0.54
Outdoor activity	…	…	0.98 (0.85, 1.13)	0.82	0.97 (0.84, 1.12)	0.65
Salt intake	…	…	0.95 (0.87, 1.05)	0.32	0.96 (0.88, 1.05)	0.41
Family history of hypertension	…	…	…	…	1.23 (1.07, 1.41)	<0.01
Family history of high cholesterol	…	…	…	…	1.17 (0.99, 1.37)	0.05

Model 1 (crude model) adjusted for age and sex.
Model 2 (minimally adjusted model) adjusted for age, sex, income, smoking status, alcohol status, outdoor activity, and salt intake.
Model 3 (fully adjusted model) fully adjusted, with the addition of adjustments for family history of hypertension and family history of high cholesterol.

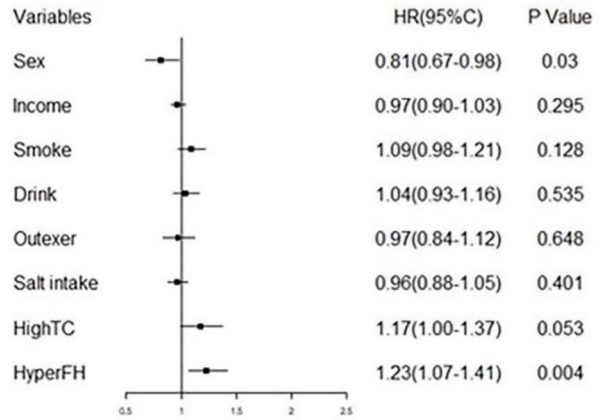

FIGURE 4
Forest plot of fully adjusted variables in COX regression analysis model (model 3) shows risk of different obesity status and hypertension.

differences ($P < 0.01$); however, after fully adjusting by age, sex, income, smoking, drinking, outdoor activity, salt intake, high cholesterol, and family history of hypertension, the HR (95%CI), 1.06 (1.02, 1.10), 1.05 (1.05, 1.06), 1.06 (1.06, 1.07), and 1.00 (1.00, 1.00), respectively, which indicated that there were no statistical significant that baPWV change made to hypertension onset. The variables adjusted contributed to the risk of future hypertension are shown in Supplementary material.

4. Discussion

Hypertension is an independent risk factor for cardiovascular events, and it is also the major modifiable risk factor for CVD and premature mortality. Current estimates suggest that there are 435.3 million people with prehypertension worldwide (15), accounting for 41.3% of the population aged over 18 years. Studies on hypertension have primarily focused on weight status during childhood and adulthood (16). However, to the best of our knowledge, there is little study on the association of obesity status change with hypertension onset among the adult population in the Chinese community.

In our community-based, longitudinal cohort study, we found that 811 participants were newly diagnosed with hypertension after nearly 7 years of follow-up. Notably, the most important outcome of our study is that maintaining obesity status (Group 4) was associated with the highest HR of future hypertension, whereas losing weight to become normal weight (Group 3) was associated with a slightly higher risk of hypertension onset than status from normal weight to obesity (Group 2). Our finding is in accordance with recent studies (17), indicating that keeping obesity status is an important risk factor for hypertension onset. A possible explanation for this might be that patients keeping obesity status are accompanied by sympathetic nerve excitation (18), which results in the amount of norepinephrine, angiotensin II, and adrenaline being released in their body causing vasoconstriction so that their blood pressure is rising over time. Previous studies (19, 20) have shown that there are many other internal mechanisms of obesity that affect the hypertension onset, such as renin–angiotensin–aldosterone system (RAAS) activation, water and sodium retention, vascular endothelial contraction, and even dysfunction through mediating oxidative stress and abnormal inflammatory response.

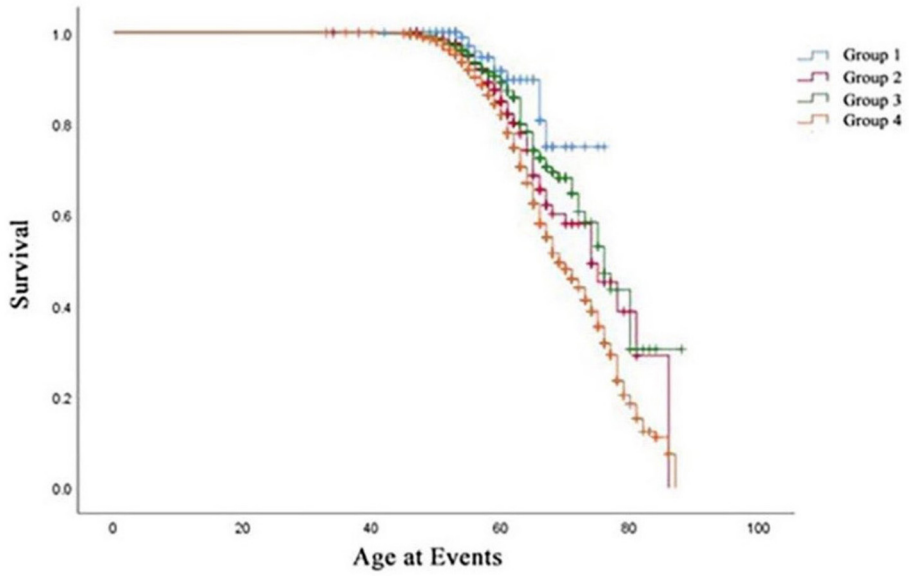

FIGURE 5
Kaplan-Meier estimates of survival in the four groups.

Whereas, taking the "obesity paradox" into account (21), which is that individuals with mildly higher BMI are associated with better survival and fewer cardiovascular events, our study's finding is in contrast to it. We thought obesity has a bad risk effect on hypertension onset. The reasons for differences between the contrast results might be the following aspects, such as limited studies on the relationship between obesity and hypertension onset, the ambiguous elucidated pathophysiological process of obesity-induced hypertension, and the co-pathogenesis under it. Hence, more case–control studies and cohort studies on more people are needed to evaluate the correlation between obesity and hypertension onset later.

Additionally, the risk of hypertension onset was continuously attenuated with each group according to female gender and age under 60 years. Interestingly, our results were opposite to Li's research (8), in which they observed that participants older than 60 were negatively associated with an increased incidence of hypertension. The various results between other studies and ours might be caused by the different study population composition. Our study had nearly 67.7% female participants, and they had 32.1% female participants involved in their study. The huge gender difference made our research outcomes contrary to their research. Nonetheless, these current findings are likely to be prone to bias caused by self-reporting or thinking of body weight, or they were limited to a finite age range that did not extend beyond middle age. In addition, our study indicated a gender difference in hypertension onset with different obesity status changes. In line with the previous report, Tara's study has shown that male participants were more likely than female participants to develop a variety of obesity-related diseases, such as diabetes, hypertension, and other CVD (22). The underlying pathogenic mechanism might be that the inflammation level in male participants is higher than in female participants (23), which causes the function of endothelial cells to decrease without any responses to vascular or immune stimulation. However, in female participants, the vascular endothelial cells show the sustainable ability to respond to the changing inflammation level even though keeping high-fat diet stress. Meanwhile, this evidence may expound the possible mechanism behind the influence of obesity on hypertension onset.

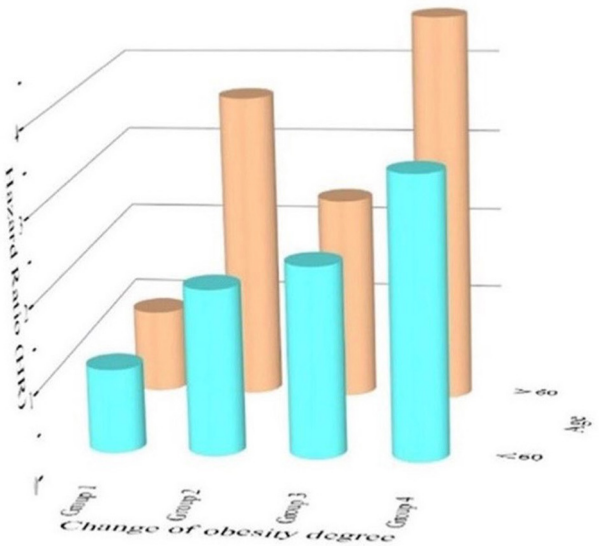

FIGURE 6
3D bar plot showing the cox regression analysis of age under 60 years old and age over 60 years old.

The most interesting founding of our research is that the population who has an obesity history, no matter how they lost weight by any means, their risk to develop future hypertension was higher than the population who was always keeping a normal weight, especially higher than the population who were normal at

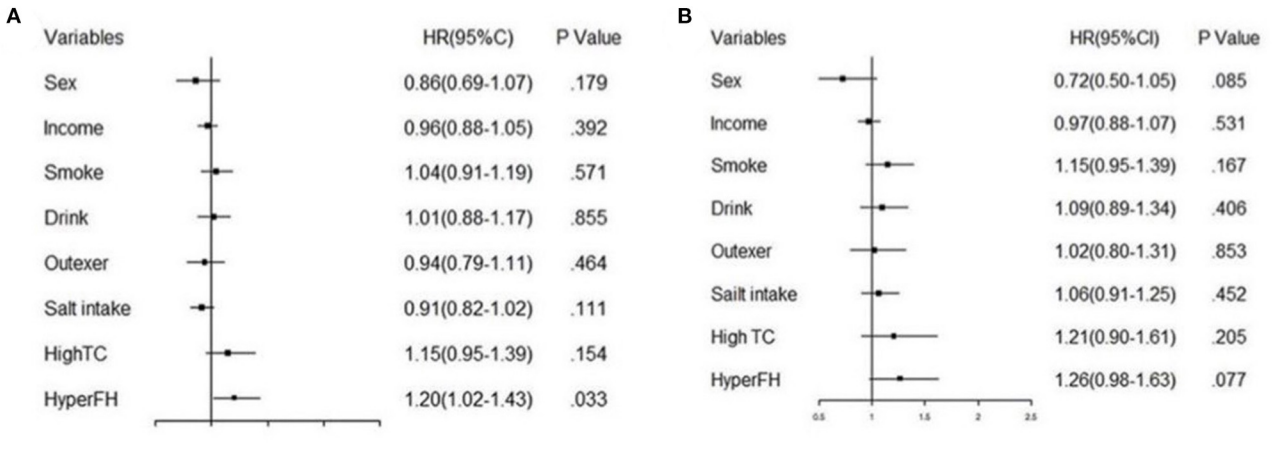

FIGURE 7
The forest plot of fully adjusted Cox model analysis of age subgroups. **(A)** shows the result of subgroup under 60 years old and **(B)** illustrates the result of subgroup over 60 years old.

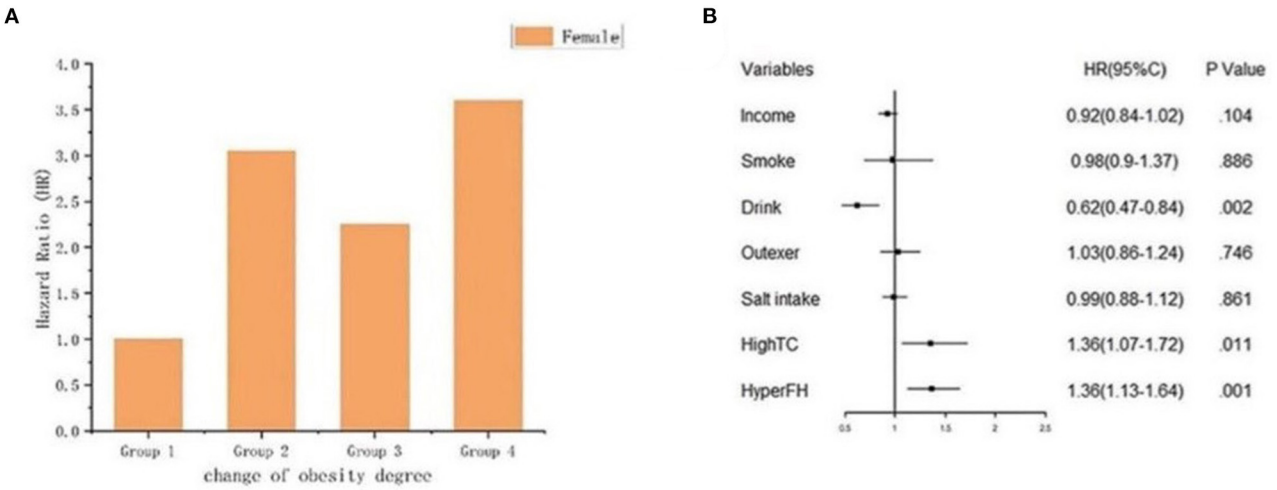

FIGURE 8
The graph indicated the risk of female with hypertension onset. **(A)** Bar plot; **(B)** Forest plot of the association between female and hypertension onset based on cox regression analysis. The association was adjusted for income, smoke, drink, outdoor activity, salt intake, high total cholesterol history and hypertension family history.

first with obesity status later. It indicated no matter developing into obesity status or from obesity to normal weight, as long as obesity had occurred in one's lifespan, blood pressure would be abnormal. Studies have found that this is caused by the hidden danger of immune cell abnormalities during the obesity period (24). We speculate that this might be due to a large amount of free fatty acids in the circulatory system of obese individuals, and these fatty acids can directly change the innate immune cells including monocytes and macrophages into inflammatory phenotypes, which are retained in the aging process of mice through "epigenetic memory" (25). These patterned macrophages then travel in the body, where they initiate inflammatory programs that promote age-related hypertension. One study analyzed adipose tissue from obese, lean, and normal mice, and the researchers found that after a while on a high-fat diet (HFD), adipose-related macrophages (ARMs) in adipose tissue were observed to develop toward a pro-inflammatory phenotype, with many inflammatory genes becoming significantly expressed in these cells (26), including tumor necrosis factor-α (TNF-a), interleukin-1b (IL-1b), and interleukin-6 (IL-6). The two studies above provide a deep insight into the mechanism of obesity incidence's effect on system metabolic change. In other words, adipose tissue macrophages produce cytokines due to a history of obesity and maintain a pro-inflammatory state after weight loss. Those studies may explain the reason why people who losing weight after being obesity still have high risks to deliver future hypertension.

Moreover, decreased physical activity, obesity genes, intrauterine epigenetics, environmental toxins, and high-fat and fructose diets lead to insulin resistance, obesity, hypertension,

TABLE 4 Association of the ΔBMI, ΔSBP, ΔDBP, and ΔbaPWV between baseline and follow-up with hypertension onset according to different obesity statuses.

Characteristics		Total	Group 1	Group 2	Group 3	Group 4
BMI 2012 (kg/m^2)	Mean ± SD	25.49 ± 3.32	21.48 ± 1.59	21.78 ± 1.55	23.13 ± 2.30	26.72 ± 2.91
BMI 2018 (kg/m^2)	Mean ± SD	25.04 ± 3.33	21.07 ± 1.80	23.97 ± 2.07	22.24 ± 1.95	26.30 ± 2.91
ΔBMI (kg/m^2)	Mean ± SD	−0.44 ± 1.73	−0.45 ± 1.21**	0.23 ± 1.57**	−0.89 ± 1.81**	−0.42 ± 1.73**
BP 2012						
SBP	Mean ± SD	124.04 ± 9.72	118.11 ± 10.70	120.51 ± 11.28	121.93 ± 10.82	125.33 ± 8.82
DBP	Mean ± SD	72.06 ± 7.67	68.73 ± 7.38	69.79 ± 7.93	70.86 ± 7.82	72.83 ± 7.48
BP 2018						
SBP	Mean ± SD	128.30 ± 15.04	118.27 ± 14.32	124.36 ± 14.20	124.44 ± 15.34	130.32 ± 14.58
DBP	Mean ± SD	77.95 ± 9.03	73.68 ± 8.16	75.63 ± 8.79	75.59 ± 8.82	79.04 ± 8.93
ΔBP						
ΔSBP	Mean ± SD	4.23 ± 13.15	0.15 ± 10.72**	3.91 ± 11.85**	2.46 ± 12.58**	4.94 ± 13.49**
ΔDBP	Mean ± SD	5.87 ± 7.99	4.94 ± 6.51**	5.86 ± 7.79**	4.76 ± 7.27**	6.18 ± 8.23**
baPWV 2012	Mean ± SD	1,513.72 ± 269.86	1,406.37 ± 244.91	1,465.39 ± 274.64	1,482.95 ± 252.69	1,533.85 ± 271.67
baPWV 2018	Mean ± SD	1, 619.48 ± 308.96	1,487.16 ± 259.25	1,582.41 ± 316.82	1,580.22 ± 296.94	1,641.97 ± 310.47
ΔbaPWV	Mean ± SD	105.76 ± 224.82	80.79 ± 184.45**	117.01 ± 197.99**	97.27 ± 200.29**	108.12 ± 235.22**

P-value < 0.05 is statistically significant.
*P < 0.05, **P < 0.01, and ***P < 0.001.

and vascular dysfunction, suggesting a vicious cycle throughout the lifespan. A complex interaction of endocrine factors (27), cytokines, vascular cellular components (28), extracellular matrix (28), perivascular adipose tissue (29), and immune cells (30) could be seen within the progression of hypertension. Diet-induced obesity creates conditions for impaired endothelial nitric oxide synthase activation (31), vascular cell-specific mineralocorticoid and increased aldosterone plasma level, and decreased nitric oxide bioavailability (32) leading to increased vascular permeability and inflammation, leukocyte adhesion, increased vascular constriction, tissue remodeling, and fibrosis (6). Those may indicate the communication behind obesity and hypertension. Diet-induced obesity in early life will trigger the continuous reprogramming of the innate immune system (33), which will persist long after the normalization of metabolic abnormalities and have a lasting impact on individual health status. Therefore, individuals who are not obese need to try their best to avoid obesity and reduce the possibility of leaving epigenetic abnormal cells.

Above all, obesity and hypertension are major global public health problems and disease burdens. Obesity has been recognized as an important risk factor for hypertension. Our study shows the association of obesity status change with hypertension onset. First, we found that keeping obesity status was the most important risk among the four statuses for delivering hypertension onset. Second, female gender and age under 60 years were two protective factors for different obesity status groups to have future hypertension, and losing weight was more significant in the female population. Last but not least, what is interesting is that once obesity happens in one's life, the blood pressure level could not recover to a normal state easily.

5. Limitation

There are several potential limitations to our study. The major limitation of our study is that we only used BMI as the standard to define obesity status change. BMI-defined obesity has heterogeneous to some extent because BMI could not reflect regional body fat distribution. Nevertheless, BMI is still the most frequently used metric for identifying obesity, which had a minimal influence on our results. Admittedly, the present study is also limited by the lack of variables that influence hypertension onset possibly in the cohort database (12, 34), such as heart rate, estimated glomerular filtration rate (eGFR), and fasting blood glucose (FBG). Further studies with those variables and multi standards defined obesity status change are still warranted.

6. Conclusion

In the present study, we observed a trend toward an association between obesity status change and hypertension onset. Keeping obese status was associated with the highest risk of hypertension onset. Losing weight after being obese was associated with a higher risk of hypertension onset than being at normal weight at first and then becoming fat. Moreover, keeping a normal weight is always the best choice to be away from future hypertension. Awareness of weight control and prevention from becoming obese may contribute to hypertension risk management in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QJC and XLZ designed the whole study and modified the manuscript. XMZ, CLW, SW, and YQL collected and tidied up the clinical information with data analysis. YZ, XLZ, LGD, SYW, LSL, and AHH revised the manuscript and gave professional advice. QJC wrote the manuscript. All authors reviewed this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1170334/full#supplementary-material

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EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Yijun Lin,
Xiamen University Affiliated Cardiovascular Hospital, China
Min Xu,
Chang Zhou No.1 Hospital, China

*CORRESPONDENCE
Honglin Hu
huhonglin@ahmu.edu.cn
Qiu Zhang
zhangqiu@ahmu.edu.cn

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Age at diagnosis, diabetes duration and the risk of cardiovascular disease in patients with diabetes mellitus: a cross-sectional study

Xuelin Yao, Jie Zhang, Xiaoqian Zhang, Tian Jiang, Yi Zhang, Fang Dai, Honglin Hu* and Qiu Zhang*

Department of Endocrinology, First Affiliated Hospital of Anhui Medical University, Hefei, China

Background: The purpose of the study was to evaluate characteristics and risk of cardiovascular disease (CVD) according to age at diagnosis and disease duration among adults with diabetes mellitus (DM).

Methods: The association between age at diagnosis, diabetes duration and CVD were examined in 1,765 patients with DM. High risk of estimated ten-year atherosclerotic cardiovascular disease (ASCVD) was performed by the Prediction for ASCVD Risk in China (China-PAR) project. Data were compared with analysis of variance and $\chi 2$ test, respectively. Multiple logistic regression was used to determine the risk factors of CVD.

Results: The mean age at diagnosis ($\pm$ standard deviation) was 52.91 $\pm$ 10.25 years and diabetes duration was 8.06 $\pm$ 5.66 years. Subjects were divided into early-onset DM group ($\leq$43 years), late-onset DM group (44 to 59 years), elderly-onset DM group ($\geq$60 years) according to age at diagnosis. Diabetes duration was classified by 5 years. Both early-onset and longest diabetes duration (>15 years) had prominent hyperglycaemia. Diabetes duration was associated with the risk of ischemic stroke (odds ratio (OR), 1.091) and coronary artery disease (OR, 1.080). Early-onset group (OR, 2.323), and late-onset group (OR, 5.199), and hypertension (OR, 2.729) were associated with the risk of ischemic stroke. Late-onset group (OR, 5.001), disease duration (OR, 1.080), and hypertension (OR, 2.015) and hyperlipidemia (OR, 1.527) might increase the risk of coronary artery disease. Aged over 65 (OR, 10.192), central obesity (OR, 1.992), hypertension (OR, 18.816), cardiovascular drugs (OR, 5.184), antihypertensive drugs (OR, 2.780), and participants with disease duration >15 years (OR, 1.976) were associated with the high risk of estimated ten-year ASCVD in participants with DM.

Conclusion: Age at diagnosis, diabetes duration, hypertension and hyperlipidemia were independent risks of CVD. Longest (>15 years) diabetes

duration increased the high risk of ten-year ASCVD prediction among Chinese patients with DM. It's urgent to emphasize the importance of age at diagnosis and diabetes duration to improve primary complication of diabetes.

KEYWORDS

diabetes mellitus, cardiovascular disease, diabetes duration, age at diagnosis, macrovascular complications

1 Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a chronic metabolic disorder caused by insufficient insulin production and/or insulin resistance resulting from both environmental and genetic components (1). Its prevalence increased dramatically over the last three decades. An estimated 536.6 million people in 20–79 year olds have DM in 2021, and this number is expected to reach 12.2% (783.2 million) by the year 2045 (1). Considering the health and economic consequences associated with DM (complications, obesity, mortality), there is huge interest in strategies to reduce DM prevalence (2, 3). Cardiovascular disease (CVD), including coronary artery disease, cerebrovascular disease, or peripheral arterial disease, is a macrovascular complication that mostly develops in patients with diabetes (4). The prevalence rate of CVD is higher in adults with diabetes than in those without diabetes (4). CVD mostly developed in the following cases: genetic predisposition, hypoglycaemia, during treatment, increased insulin resistance (4). Furthermore, CVD greatly contributes to morbidity and mortality among patients with DM. In addition, compared with patients without CVD, those diagnosed with the disease are particularly prominent among younger patients with hyperglycaemia and serious renal complications (5). Similar to the increase in DM prevalence, cerebrovascular disease prevalence has also increased globally and increasingly been recognised as cerebral macrovascular complications of type 2 diabetes mellitus (T2DM) (6). T2DM is associated with a 2.5-times increased risk of ischaemic stroke (7). Ischaemic stroke is also common among adults with prediabetes than among people with normoglycaemia, suggesting that cerebral infarcts processes start before the onset of diabetes (8, 9). In view of ageing populations and the growing prevalence of DM, DM prevention strategies are of paramount importance and identifying the mechanisms linking DM with CVD is key to reduce the macrovascular complications.

Previous data suggested that age, age at diagnosis and disease duration had varying effects on the risk of vascular complications in patients with DM (10–12). For example, Zoungas et al. reported that age or age-onset, and duration of diabetes were independently associated with macrovascular events and death, whereas only duration is independently associated with microvascular events (12). Subsequent studies confirmed age and duration of diabetes were strong risk factors for myocardial infarction, stroke, and heart failure (10). Furthermore, studies of people with T2DM using a propensity score-matched cohort analysis provide excellent insight into the early clinical course of diabetes, indicating the earlier onset of T2DM induce the higher risk of microvascular (11). Few studies evaluated clinical characteristics and macrovascular complications according to age at diagnosis and prolonged duration of diabetes among Chinese patients with DM (13). Therefore, the aim of our study is to investigate the relationship between onset age of diabetes and complications, and provide a better understanding of age at diagnosis on the risk of complications, and improved explanation of the modifiable risk factors to reduce the burden of macrovascular complications and T2DM.

2 Methods

2.1 Setting and study subjects

The current data analysis was based on the China National Diabetic Chronic Complications Study (China DiaChronic Study), which has been reported in detail previously (14). Briefly, a total of 53,401 Chinese adults with diagnosed diabetes ages 18–74 were recruited and completed baseline questionnaires and medical examinations between March 2018 and January 2020. The multistage sampling scheme (stratification, clustering, and random) was used to sample study participants based on the disease surveillance points (DSPs) started in 2013 from the China Chronic Disease and Risk Factors Surveillance (CCDRFS). The sampling details have been described elsewhere (15, 16). Stage 1, four DSPs were selected from 25 provinces, autonomous regions and municipalities, five DSPs were selected from Sichuan, Henan, Shandong, 2 to 3 DSPs were selected from Qinghai, Tibet, Xinjiang. In total, there are 122 study sites (65 urban and 57 rural DSPs) from the 2013 CCDRFS were invited to participate. Stage 2, four

Abbreviations: DM, Diabetes mellitus; CVD, Cardiovascular disease; ASCVD, Atherosclerotic cardiovascular disease; China-PAR, The Prediction for ASCVD Risk in China project; FPG, Fasting plasma glucose; HbA1c, Glycosylated hemoglobin; OR, odds ratio; 95% CI, 95 percent confidence interval; T2DM, Type 2 diabetes mellitus; China DiaChronic Study, The China National Diabetic Chronic Complications Study; DSPs, Disease surveillance points; CCDRFS, The China Chronic Disease and Risk Factors Surveillance; WC, Waist circumference; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

neighborhoods/villages were selected from each DSP, and a total of 260 neighborhoods and 228 villages were acquired. Stage 3, 58,560 Chinese adults with diagnosed diabetes ages 18-74 were recruited in the study after selecting 120 participants at each neighborhood/village by gender and age ratio.

In this study, a total of 1,765 participants were recruited from four cities (Huainan, Fuyang, Ma'anshan, Chuzhou) in Anhui province. Each participant received a series of medical examinations including a general physical examination and biochemical tests of blood and urine sample, as well as a standard self-administered questionnaire survey. Moreover, to avoid the influence of confounding factors, we restricted our analysis to those participants aged 18–74 years, and who had resided in the study sites for at least 6 months during the 12 months prior to the survey. We also excluded those who reported the following conditions: pregnant female, history of mental illness, the bedridden and the intellectually disabled, and missing information related to informed consent. Information on personal age at diabetes mellitus diagnosis and diabetes duration was obtained by a self-administrated questionnaire. Diabetes duration was calculated by subtracting age at diagnosis from age at study baseline. Duration of diabetes was classified into four ordinal groups (≤5, >5–10, >10–15 and >15 years). For age at diagnosis, they were asked "When did you first diagnose diabetes?" Age at diagnosis was classified into three groups: less than age 44 (early-onset DM), aged range of 44 to 59 (late-onset DM), aged from 60 and 74 (elderly-onset DM). Furthermore, the China-PAR project was used to predict 10-year atherosclerotic cardiovascular disease (ASCVD) risk among Chinese population, the details have been described elsewhere (17–19). The Chinese prediction models directly included age, SBP, total cholesterol, HDL-C, current smoking, and diabetes. Four additional covariates (waist circumference (WC), geographic region, urbanization, and family history of ASCVD) met the pre-defined inclusion criteria based on relative integrated discrimination improvement (IDI) of 6% or greater. This tool is applicable to people aged 20 and above without history of cardiovascular and cerebrovascular diseases. Therefore, 1423 participants were selected in our study. According to predicted ASCVD risk, participants were divided into three categories: low risk (<5%), median risk (5%–9.9%), high risk (≥10%). Details of the workflow chart are presented in Figure 1. Personal identification was removed and remained anonymous when the data were released for this research. All participants provided written informed consent, and Ethical Review Committee (Approval No: 2018-010) approved the study, which was registered in the Chinese Clinical Trial registry (ChiCTR1800014432).

2.2 Estimation of sample size

The sample size calculation was estimated by using following formula.

$$n = \frac{(1-p)Z_{1-\alpha/2}}{\varepsilon^2 p}$$

$Z_{1-\alpha/2} = 1.96$, the prevalence of diabetes mellitus was 11.2% (p), the desired level of relative precision was 0.15 (ε) (20). Then, considering multicenter design and drop-out rate of 10% total sample size, hence the minimum sample required for conducting this study was found to be 1540.

2.3 Assessment of covariates

Information on sociodemographic characteristics collected in the baseline was used in the current data analysis, including age, sex, medical insurrance, marital status (single, married, lived together, divorced, separated and widowed), total annual family income and education level (primary school or below, middle school, and college, and university or above). Lifestyle factors including alcohol drinking (never, former, and current), cigarette smoking (never, former, and current), and family medical histories (yes, no) was collected at baseline by trained interviewers using semi-structured questionnaires. The general health examinations were performed by qualified personnel. Hyperglycaemia was defined as a glycosylated hemoglobin (HbA1c) >7.0% and fasting plasma glucose (FPG) >7.0 mmol/L (1). Body mass index (BMI) was calculated as weight in kilograms divided by height in

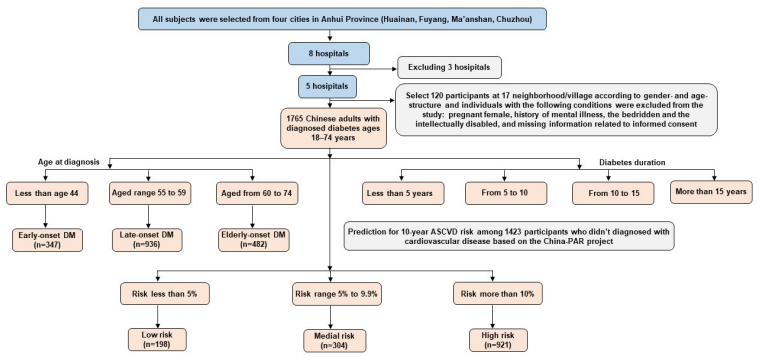

FIGURE 1
Flowchart of the subjects selecting in the study.

meters squared. Obesity was defined as a BMI of ≥28 kg/m^2 (21). WC was calculated by horizontal girth of waist through belly button. Central obesity was defined as WC ≥90 cm in men and WC ≥85 cm in women for Chinese (22). Resting blood pressure including systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured and fasting blood was drawn for laboratory assays of blood lipids, fasting glucose, glycosylated hemoglobin, hepatic function, renal function. Hypertension was defined as self-reported physiciandiagnosed hypertension or current use of antihypertensive medications or SBP ≥140mmHg/DBP ≥90 mmHg by the 2017 American College of Cardiology/American Heart Association guidelines (23). Myocardial infarction was defined as a history of physician-diagnosed myocardial infarction. Hyperlipidemia was defined as a history of physician-diagnosed hyperlipidemia or current usage of lipid-lowering medications or total cholesterol (TC) ≥5.20 mmol/L or triglycerides (TG) ≥1.70 mmol/L or high-density lipoprotein cholesterol (HDL-C)<1.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L by the 2019 China Cholesterol Education Program (CCEP) expert advice for the management of dyslipidaemias to reduce cardiovascular risk (24). Information on medications collected in the baseline was used in our study, including antihypertensive drugs, cardiovascular drugs, lipid lowering medication, glucose lowering medication.

2.4 Ascertainment of the outcome

The presence of diabetic macrovascular complications (coronary artery disease and cerebrovascular disease) was assessed from the questionnaire of each participants. To collect the information, the participants were asked: "Have you ever been diagnosed as cardiovascular disease or ischemic stroke by physicians in medical institutions at county/district level or above?" Those participants who answered "yes" were then defined as having a event of cardiovascular disease or ischemic stroke. Furthermore, these patients were asked two questions: "When did you first diagnose these diseases?" "Did you hospitalized after you suffer from above mentioned disease?" A total of 234 ischemic stroke cases and 145 coronary artery disease cases were observed in this study.

2.5 Statistical analysis

Data were presented as mean (standard deviation) for continuous variables and percentages for categorical variables, respectively. $\chi 2$ test was employed to compare categorical variables between groups. Statistical differences between groups for continuous variables were compared with Mann-Whitney U tests or analysis of variance. Binary logistic regression analysis with forward selection was performed to identify independent factors associated with the risk of ischemic stroke and coronary artery disease. The results were presented as odds ratio (OR) and 95 percent confidence interval (95% CI), taking age at diagnosis of 60 to 74 years as the reference groups, based on the previous studies suggesting that the onset age after 60 years was less likely to have macrovascular and microvascular complications (11). Potential covariates included in the adjusted model were age, BMI, WC, hypertension, hyperlipidemia, diabetes duration, family history of ischemic stroke and coronary artery disease, age at diagnosis, lipid lowering medication, cardiovascular drugs, antihypertensive drugs. Analysis of variance (ANOVA) with Tukey's test for multiple comparison was conducted to compare following values (BMI, HbA1c, FPG, LDL-C, TC, TG) and trends according to disease duration among the three age groups. Furthermore, Hosmer-Lemeshow test was performed to evaluate the goodness of fit of the logistic regression model. All analyses were conducted using SPSS version 25.0 (IBM Co., Armonk, NY, USA) All statistical tests were two-tailed and the significance level was set at $P<0.05$.

3 Results

3.1 Characteristics of study population

The baseline characteristics of the study population by strata of age at diagnosis and diabetes duration are shown in Tables 1, 2, respectively. Of a total of 1765 patients, the mean (± SD) age of the cohort was 56.96 ± 10.02 years and the age at diagnosis was 52.91 ± 10.25 years, with 19.7%, 53.0% and 27.3% of patients reporting their age at diagnosis as 18–43, >44–59 and >60–74 years, respectively (Table 1). The mean (± SD) diabetes duration was 8.06 ± 5.66 years, with 40.0%, 29.9%, 18.5% and 11.7% of patients reporting a diabetes duration of ≤5, >5–10, >10–15 and >15 years, respectively (Table 2). The mean age at diagnosis of the group with the longest diabetes duration (>15 years) was significnatly lower than of the groups with shorter diabetes duration ($P<0.001$, Table 2). Early-onset group (aged ≤43 years) and longest diabetes duration group (>15 years) were more likely to have higher level of FPG and HbA1c, and higher family history of diabetes, compared to those diagnosed at older age group (44 to 59 and 60 to 74 years) and shorter diabetes duration (≤ 15 years) ($P<0.001$, Tables 1, 2). Furthermore, compared with the younger onset age group, participants reporting diagnosed at elderly onset group were more likely to have hypertension and take antihypertensive drugs, to have coronary vascular disease and use cardiovascular drugs, to have ischemic stroke and take lipid lowering medication (P<0.001, Table 1). Besides, the longest diabetes duration (>15 years) were also more likely to have hypertension, ischemic stroke and coronary vascular disease compared with the shorter diabetes duration. However, participants reporting with the longer diabetes duration (10–15 years) were more likely to take antihypertensive drugs, and cardiovascular drugs ($P<0.001$, Table 2). Meanwhile, compared with participants reporting older age group and shorter diabetes duration, those reporting diagnosed at early-onset group and longest diabetes duration were more likely to have higher DBP level ($P<0.001$, Tables 1, 2). No interaction was observed between the age at diagnosis and diabetes duration on gender, WC, lipid abnormalities, medical insurance, family history of diseases (cardiovascular disease, ischemic stroke and hyperlipidemia),

10.3389/fendo.2023.1131395

TABLE 1 Characteristics of the participants with diabetes mellitus stratified by age at diagnosise.

Variables (mean (SD) or N (%))	Age at diagnosis, years			
	≤43 (n=347)	44-59 (n=936)	60-74(n=482)	*P* value
Age, years	44.43(8.05)	56.27(6.62)	67.30(3.90)	<0.001
Disease duration, years	10.38(7.42)	8.29(5.37)	5.93(3.64)	<0.001
Male	181(52.2)	442(47.2)	250(51.9)	0.135
BMI, kg/m2	26.17(4.39)	25.98(3.37)	26.00(3.62)	0.709
Weight, kg	69.18(13.45)	67.69(10.84)	66.06(11.07)	<0.001
Waist circumference, cm	89.42(11.35)	89.57(9.23)	90.18(10.00)	0.454
SBP, mmHg	143(20.70)	147(20.68)	150(22.55)	<0.001
DBP, mmHg	86(12.74)	84(11.65)	80(11.60)	<0.001
FPG, mmol/L	10.36(4.00)	9.49(3.16)	8.67(2.62)	<0.001
HbA1c, %	7.97(1.99)	7.58(1.72)	7.30(1.56)	<0.001
TC, mmol/L	5.19(1.24)	5.18(1.20)	5.18(1.17)	0.995
LDL-C, mmol/L	3.07(1.07)	3.06(0.95)	3.07(0.95)	0.975
HDL-C, mmol/L	1.42(0.49)	1.42(0.40)	1.47(0.42)	0.096
TG, mmol/L	2.55(3.29)	2.34(2.60)	3.14(2.13)	0.079
Obesity	108(31.1)	222(23.8)	119(24.7)	0.025
Medical insurance	335(96.5)	911(97.3)	466(96.7)	0.681
Marital status				<0.001
Single	13(3.7)	8(0.9)	9(1.9)	
Married or lived together	323(93.1)	879(93.9)	415(86.1)	
Divorced or separated	5(1.4)	13(1.4)	8(1.7)	
Windowed	6(1.7)	36(3.8)	50(10.4)	
Education level				<0.001
Primary school or below	165(47.6)	538(57.5)	359(74.5)	
Middle school	122(35.2)	267(28.5)	83(17.2)	
Highschool or beyond	60(17.3)	131(14.0)	40(8.3)	
Total annual family income, yuan				<0.001
≤18000	51(14.7)	173(18.5)	130(27.0)	
18000 to ≤40000	138(39.8)	387(41.3)	224(46.5)	
40000 to ≤70000	76(21.9)	193(20.6)	77(16.0)	
>70000	82(23.6)	183(19.6)	51(10.6)	
Current drinking	104(30.0)	284(30.3)	102(21.2)	0.001
Current smoking	79(22.8)	196(20.9)	73(15.1)	0.01
Family history of hypertension	230(66.3)	584(62.4)	274(56.8)	0.018
Family history of diabetes	190(54.8)	443(47.3)	152(41.5)	<0.001
Family history of obesity	137(39.5)	301(32.2)	133(27.6)	0.001
Family history of cardiovascular disease	69(19.9)	178(19.0)	107(22.2)	0.365
Family history of ischemic stroke	82(23.6)	210(22.4)	107(22.2)	0.874
Family history of hyperlipidemia	94(27.1)	232(24.8)	91(18.9)	0.011

(Continued)

TABLE 1 Continued

Variables (mean (SD) or N (%))	Age at diagnosis, years			
	≤43 (n=347)	44-59 (n=936)	60-74(n=482)	*P* value
Antihypertensive drugs	103(29.7)	405(43.3)	246(51.0)	<0.001
Cardiovascular drugs	9(2.6)	67(7.2)	58(12.0)	<0.001
Lipid lowering medication	35(10.1)	151(16.1)	65(13.5)	0.019
Glucose lowering medication				0.323
Insulin	30(8.6)	121(12.9)	57(11.8)	
Oral hypoglycemic drugs	265(76.4)	690(73.7)	358(74.3)	
Comorbidities				
Coronary vascular disease	17(4.9)	60(6.4)	68(14.1)	<0.001
Hypertension	124(35.7)	469(50.1)	282(58.5)	<0.001
Ischemic stroke	23(6.6)	111(11.9)	100(20.7)	<0.001
Hyperlipidemia	213(61.4)	618(66.0)	313(64.9)	0.302

Data are Number(%) for categorical variables, and mean (SD) for continuous variables.
P values were derived from analysis of variance or Mann-Whitney U tests for continuous variables according to data distribution and $\chi 2$ test for category variables.
BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin;TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol.

glucose lowering medication and comorbidities of hyperlipidemia (all P >0.05) (Tables 1, 2).

3.2 Different patterns of parameters and disease duration according to age at diagnosis

As shown in Figure 2, HbA1c and FPG increased with the duration of disease, which exceeding the maximum normal reference value (HbA1c<7.0%, FPG<7.0 mmol/L) (1). The HbA1c showed positively associated with the duration of diabetes and the degree of increase was more prominent in participants with late-onset group (R^2 = 0.066, 44 to 59 years) than those with early-onset group (R^2 = 0.058, P<0.001, ≤43 years) and elderly-onset group (R^2 = 0.026, P<0.001, 60 to 74 years). The significant association was also observed in FPG, and the degree of increase was more prominent in participants reporting late-onset group (R^2 = 0.065, P<0.001) than those with early-onset group (R^2 = 0.02, P<0.001), while no significant association with elderly-onset group (P =0.17). However, the trend of increasing BMI, TC, TG, LDL-C according to disease duration was incomparable among age groups (all P >0.05).

3.3 Risk factors of diabetic macrovascular complications (coronary artery disease and ischemic stroke) in participants with DM

The prevalence of ischemic stroke was different among the three age-onset groups and four diabetes duration groups (P<0.001) (Tables 1, 2). Coronary artery disease and ischemic stroke were significantly more common in elderly-onset group and longest diabetes duration (P<0.001) (Tables 1, 2). With regard to risk factors associated with ischemic stroke complications in patients with DM, disease duration (OR, 1.091; 95% CI, 1.060 to 1.124; P<0.001), hypertension (OR, 2.729; 95% CI, 1.968 to 3.785; P<0.001), early-onset group (≤43 years, OR, 2.323; 95% CI, 1.367 to 3.947; P = 0.002), and late-onset group (44 to 59 years, OR, 5.199; 95% CI, 2.602 to 10.386, P< 0.001) were independently associated with the risk of ischemic stroke. Meanwhile, diabetes duration (OR, 1.080; 95% CI, 1.043 to 1.118; P<0.001), hypertension (OR, 2.015; 95% CI, 1.363-2.979, P<0.001), hyperlipidemia (OR, 1.527; 95% CI, 1.014-2.298, P = 0.043), family history of coronary heart disease (OR, 2.315; 95% CI, 1.592-3.365, P<0.001), and late-onset group (44 to 59 years old; OR, 5.001, 95% CI, 2.280-10.969, P<0.001) were associated with coronary artery disease. No interactions was observed between age, BMI, central obesity, and the risk of macrovascular events (all P >0.05) (Table 3).

3.4 Characteristics of the participants stratified by estimated ten-year ASCVD risk (%)

The baseline characteristics of the 1,423 participants stratified by estimated ten-year ASCVD were shown in Table 4, respectively. Overall, the mean (± SD) age of the cohort was 55.68 ± 10.01 years, the age at diagnosis was 52.03 ± 10.15 years, and the mean (± SD) diabetes duration was 7.66 ± 5.36 years, respectively (Table 4). According to predicted ASCVD risk, participants who were identified with high risk (≥10%) were more likely to be male (51.8% vs. 50.3% vs. 38.9%; P = 0.004), older (59.40 years vs. 52.91 years vs. 42.58 years; P<0.001), current smoking (22.4% vs. 12.1% vs. 21.1%; P = 0.005) and higher central obesity (82.7% vs. 67.1% vs. 59.1%; P<0.001), higher BMI (26.38 kg/m^2 vs. 25.17 kg/m^2 vs. 24.87 kg/m^2; P<0.001) and WC (91.05 cm vs. 87.11cm vs. 85.25 cm; P<0.001), higher value of

10.3389/fendo.2023.1131395

TABLE 2 Baseline characteristics by strata of diabetes duration.

Variables (mean (SD) or N (%))	Diabetes duration, years				
	≤5 (n=706)	5-10 (n=527)	11-15 (n=326)	>15 (n=206)	*P* value
Age, years	54.57(10.56)	56.81(9.38)	60.02(8.91)	69.67(8.98)	<0.001
Age when diabetes first diagnosed, years	55.38(10.53)	53.35(9.36)	51.71(8.84)	45.21(9.47)	<0.001
Male	369(52.3)	254(48.2)	142(43.6)	108(52.4)	0.05
BMI, kg/m2	26.23(3.72)	26.10(3.64)	25.82(3.30)	25.45(3.96)	0.035
Weight, kg	68.54(11.96)	67.61(11.66)	66.38(10.18)	66.77(11.15)	0.004
Waist circumference, cm	89.99(10.36)	89.95(9.55)	89.69(9.29)	88.16(9.91)	0.113
SBP, mmHg	146(21.50)	148(21.90)	148(20.51)	148(21.35)	0.697
DBP, mmHg	85(12.03)	84(12.02)	82(11.02)	80(12.70)	<0.001
FPG, mmol/L	8.72(2.87)	9.65(3.28)	10.05(3.45)	10.37(3.64)	<0.001
HbA1c, %	7.06(1.51)	7.77(1.83)	8.03(1.78)	8.17(1.75)	<0.001
TC, mmol/L	5.18(1.18)	5.18(1.21)	5.24(1.22)	5.06(1.21)	0.421
LDL-C, mmol/L	3.06(0.97)	3.04(0.96)	3.15(0.98)	3.02(0.98)	0.346
HDL-C, mmol/L	1.44(0.41)	1.40(0.41)	1.45(0.44)	1.48(0.44)	0.08
TG, mmol/L	2.36(2.67)	2.52(2.89)	2.16(2.27)	1.97(2.32)	0.048
Obesity	176(24.9)	140(26.6)	83(25.5)	50(24.3)	0.897
Medical insurance	680(96.3)	513(97.3)	321(98.5)	198(96.1)	0.231
Current drinking	208(29.5)	147(27.9)	83(25.5)	52(25.2)	0.469
Current smoking	153(21.7)	99(18.8)	56(17.2)	40(19.4)	0.343
Family history of hypertension	423(59.9)	326(61.9)	207(63.5)	132(64.1)	0.595
Family history of diabetes	268(38.0)	233(44.2)	174(53.4)	110(53.4)	<0.001
Family history of obesity	231(32.7)	161(30.6)	104(31.9)	75(36.4)	0.493
Family history of cardiovascular disease	150(21.2)	100(19.0)	64(19.6)	40(19.4)	0.231
Family history of ischemic stroke	160(22.7)	121(23.0)	73(22.4)	45(21.8)	0.99
Family history of hyperlipidemia	171(24.2)	127(24.1)	71(21.8)	48(23.3)	0.842
Antihypertensive drugs	261(37.0)	223(42.3)	166(50.9)	104(50.5)	<0.001
Cardiovascular drugs	38(5.4)	37(7.0)	39(12.0)	20(9.7)	0.002
Lipid lowering medication	78(11.0)	75(14.2)	59(18.1)	39(18.9)	0.004
Glucose lowering medication					0.386
Insulin	88(12.5)	60(11.4)	30(9.2)	30(14.6)	
Oral hypoglycemic drugs	518(73.4)	403(76.5)	244(74.8)	148(71.8)	
Comorbidities					
Coronary vascular disease	49(6.9)	38(7.2)	33(10.1)	25(12.1)	0.046
Hypertension	325(46.0)	253(48.0)	180(55.2)	117(56.8)	0.006
Ischemic stroke	69(9.8)	61(11.6)	61(18.7)	43(20.9)	<0.001
Hyperlipidemia	451(63.9)	339(64.3)	228(69.9)	126(61.2)	0.152

Data are Number (%) for categorical variables, and mean (SD) for continuous variables.
P values were derived from analysis of variance or Mann-Whitney U tests for continuous variables according to data distribution and $\chi 2$ test for category variables.
BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol.

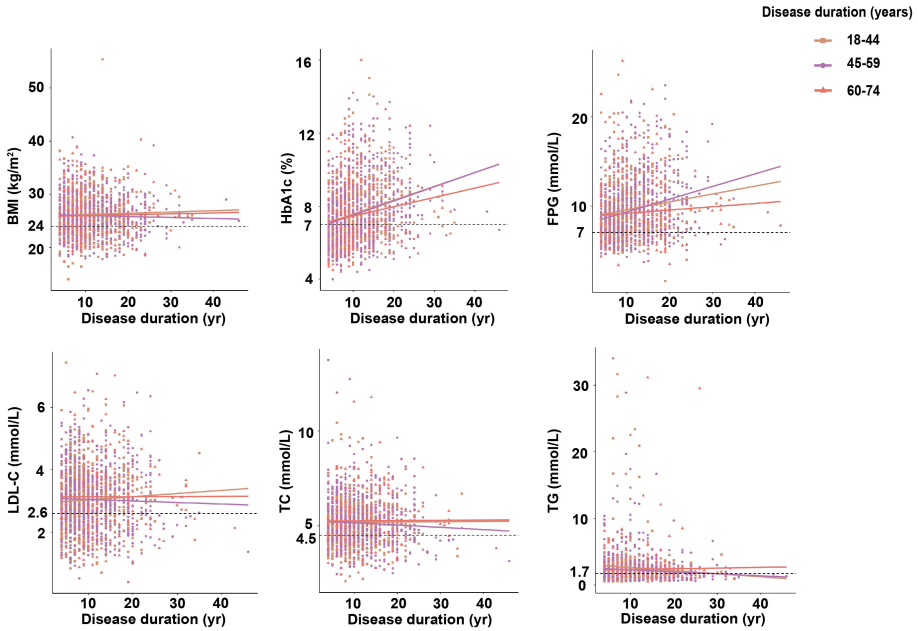

FIGURE 2
Relation between disease duration and clinical parameters according to age at diagnosis.

SBP (154.45 mmHg vs. 136.54 mmHg, vs. 126.90 mmHg; P<0.001) and DBP (85.42 mmHg vs. 81.30 mmHg vs. 78.68 mmHg; P<0.001), higher TC (5.28 mmol/L vs. 5.21 mmol/L vs. 4.95 mmol/L; P = 0.002) and TG level (2.63 mmol/L vs. 2.01 mmol/L vs. 1.92 mmol/L; P<0.001) compared with the lower risk groups (low risk and median risk). In addition, compared with the lower risk groups, participants who were identified with high risk were more likely to diagnose at elderly-onset group (60-74 years, 23.7% vs. 1.0% vs. 9.9%; *P*<0.001) and less likely to diagnose at early-onset group (11.5% vs. 66.7% vs. 23.4%; *P*<0.001), and more likely to have lower family history of diabetes (42.1% vs. 48.0% vs. 42.1%; *P* = 0.002) and have hypertension (59.8% vs. 5.6% vs. 22.0%; *P*<0.001) and hyperlipidemia (66.3% vs. 47.5% vs. 60.0%; P<0.001). Furthermore, compared with the lower risk groups, participants who were identified with high risk were more likely to take blood pressure medicine (50.6% vs. 20.4% vs. 5.1%; *P*<0.001), lipid lowering medication (12.9% vs. 8.9% vs. 3.5%; *P*<0.001) Besides, participants who were identified with medial risk were more likely to take cardiovascular drugs (4.6% vs. 2.0% vs. 0.5%; *P* = 0.005). Compared to those with a diabetes duration of<5 years, a diabetes duration of ≥10 years,was associated with increased estimated risk of

TABLE 3 Risks factors associated with ischemic stroke and coronary disease.

Variables	Ischemic stroke		Coronary artery disease	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Age, years	1.165(0.775-1.751)	0.463	0.903(0.555-1.468)	0.681
BMI, kg/m2	0.780(0.527-1.152)	0.212	1.066(0.660-1.720)	0.794
Central obesity	1.216(0.821-1.800)	0.329	0.974(0.604-1.570)	0.913
Hypertension	2.729(1.968-3.785)	<0.001	2.015(1.363-2.979)	<0.001
Hyperlipidemia	1.612(0.821-1.800)	0.329	1.527(1.014-2.298)	0.043
diabetes duration, years	1.091(1.060-1.124)	<0.001	1.080(1.043-1.118)	<0.001
Family history of ischemic stroke	1.286(0.923-1.793)	0.137	–	–
Family history of coronary heart disease	–	–	2.315(1.592-3.365)	<0.001
Age at DM diagnosis, years		<0.001		<0.001
≤43	2.323(1.367-3.947)	0.002	1.650(0.893-3.049)	0.11
44-59	5.199(2.602-10.386)	<0.001	5.001(2.280-10.969)	<0.001
60-74	1(reference)	–	1(reference)	–

OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus.

10.3389/fendo.2023.1131395

TABLE 4 Characteristics of the participants with diabetes mellitus stratified by estimated 10-year ASCVD risk (%).

Variables (mean (SD) or N (%))	Estimated 10-year ASCVD risk			
	low risk (<5%)	(medial risk (5-9.9%)	high risk (≥10%)	*P* value
Age, years	42.58(7.72)	52.91(7.53)	59.40(8.37)	<0.001
Disease duration, years	6.18(4.41)	7.18(5.06)	8.13(5.57)	<0.001
Weight, kg	64.43(12.59)	66.16(11.66)	68.53(11.31)	<0.001
Waist circumference, cm	85.25(11.52)	87.11(9.63)	91.05(9.16)	<0.001
BMI, kg/m2	24.87(3.84)	25.17(3.62)	26.38(3.53)	<0.001
SBP, mmHg	126.90(13.62)	136.54(14.01)	154.45(19.85)	<0.001
DBP, mmHg	78.68(10.19)	81.30(10.15)	85.42(12.30)	<0.001
FPG, mmol/L	9.58(3.95)	9.79(3.53)	9.42(3.10)	0.231
HbA1c, %	7.57(2.01)	7.61(1.93)	7.60(1.67)	0.959
TC, mmol/L	4.95(1.04)	5.21(1.13)	5.28(1.21)	0.002
LDL-C, mmol/L	2.94(0.90)	3.14(0.97)	3.08(0.96)	0.074
HDL-C, mmol/L	1.50(0.50)	1.51(0.42)	1.41(0.42)	<0.001
TG, mmol/L	1.92(1.73)	2.01(2.06)	2.63(3.25)	<0.001
Male	77(38.9)	153(50.3)	477(51.8)	0.004
Medical insurance	191(96.5)	293(96.4)	893(97.0)	0.856
Education level				<0.001
Primary school or below	90(45.5)	169(155.6)	576(62.5)	
Middle school	59(34.8)	85(28.0)	240(26.1)	
Highschool or beyond	39(19.7)	50(16.4)	105(11.4)	
Total annual family income, yuan				<0.001
≤18000	17(8.6)	40(13.2)	214(23.2)	
18000 to ≤40000	75(37.9)	109(35.9)	410(44.5)	
40000 to ≤70000	52(26.3)	85(28.0)	156(16.9)	
>70000	54(27.3)	70(23.0)	141(15.3)	
Current drinking	47(23.7)	99(32.6)	276(30.0)	0.1
Current smoking	24(12.1)	64(21.1)	206(22.4)	0.005
Family history of hypertension	108(54.5)	179(58.9)	581(63.1)	0.057
Family history of diabetes	95(48.0)	163(53.6)	388(42.1)	0.002
Family history of obesity	70(35.4)	91(29.9)	294(31.9)	0.444
Family history of cardiovascular disease	25(12.6)	52(17.1)	184(20.0)	0.043
Family history of ischemic stroke	38(19.2)	74(24.3)	195(20.0)	0.345
Family history of hyperlipidemia	50(25.3)	71(23.4)	201(21.8)	0.546
Central obesity	117(59.1)	204(67.1)	762(82.7)	<0.001
Antihypertensive drugs	10(5.1)	62(20.4)	466(50.6)	<0.001
Cardiovascular drugs	1(0.5)	14(4.6)	18(2.0)	0.005
Lipid lowering medication	7(3.5)	27(8.9)	119(12.9)	<0.001

(Continued)

TABLE 4 Continued

Variables (mean (SD) or N (%))	Estimated 10-year ASCVD risk			
	low risk (<5%)	(medial risk (5-9.9%)	high risk (≥10%)	*P* value
Glucose lowering medication				0.366
Insulin	18(9.1)	43(14.1)	112(12.2)	
Oral hypoglycemic drugs	158(79.8)	221(72.7)	682(74.0)	
Disease duration, years				<0.001
<5	107(54.0)	137(45.1)	356(38.7)	
5-10	53(26.8)	96(31.6)	287(31.2)	
10-15	27(13.6)	47(15.5)	167(18.1)	
>15	11(5.6)	24(7.9)	111(12.1)	
Age at diagnosis with DM				<0.001
20-43	132(66.7)	71(23.4)	106(11.5)	
44-59	64(32.3)	203(66.8)	510(55.4)	
60-74	2(1.0)	30(9.9)	337(23.7)	
Hypertension	11(5.6)	67(22.0)	551(59.8)	<0.001
Hyperlipidemia	11(5.6)	67(22.0)	551(59.8)	<0.001

Data are Number (%) for categorical variables, and mean (SD) for continuous variables.
P values were derived from analysis of variance or Mann-Whitney U tests for continuous variables according to data distribution and $\chi 2$ test for category variables.
BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; TC, total cholesterol.
Estimated 10-year ASCVD risk.

10-year ASCVD risk (P = 0.001). However, there was no evidence for FPG, HbA1c, LDL-C, current drinking, medical insurance, family history of a series of diseases (hypertension, obesity, cardiovascular disease, ischemic stroke and hyperlipidemia) and glucose lowering medication between three groups (all P >0.05) (Table 4).

3.5 Risk factors of the high risk of estimated ten-year ASCVD in participants with DM

The risk of estimated 10-year ASCVD was different among the three groups (<5%, 5%-9.9%, ≥10%: 13.9% vs. 21.4% vs. 64.7%, P<0.001). With regard to risk factors associated with high risk of 10-year ASCVD in participants with DM, aged over 65 (OR, 10.192; 95% CI, 6.188 to 16.788; P<0.001), central obesity (OR,1.992; 95% CI, 1.361 to 2.914; P<0.001), hypertension (OR, 18.816; 95% CI, 7.286 to 48.592; P<0.001), hyperlipidemia (OR, 1.366; 95% CI, 1.007 to 1.852; P = 0.045) were independently associated with the high risk of estimated ten-year ASCVD in participants with DM. Compared to those with a diabetes duration of ≤15 years, a diabetes duration of >15 years was associated with increased high risk of estimated ten-year ASCVD in in participants with DM (OR, 1.976; 95% CI, 1.156 to 3.377; P = 0.013). Compared to those without using cardiovascular and antihypertensive drugs, treatment with using above drugs were associated with increased high risk of estimated ten-year ASCVD (OR, 5.184, 95% CI, 1.976 to 13.601; P = 0.001; OR 2.780; 95%CI, 1.047 to 7.384; P = 0.040). No interactions was observed between BMI, family history of ASCVD, age at diagnosis, and patients with diabetes duration 5–10 years, 10–15 years and the age at diagnosis (all P >0.05) (Table 5).

4 Discussions

In this population-based study, we have described the risks for diabetes related complications, and how this varies by attained age, BMI, WC, hypertension, hyperlipidemia, duration of diabetes, age at diagnosis, and family history of ischemic stroke and coronary heart disease. Several factors increase the risk of heart attack, such as hyperglycaemia, obesity, abnormal cholesterol levels, hypertension, and smoking (20).

Participants who were diagnosed with early-onset (age ≤43 years) had higher FPG and HbA1c level than those diagnosed at older ages (aged 44 to 74 years). Most complications in patients with DM are associated with hyperglycaemia, which are important components of metabolic syndrome and may be the early manifestations of insulin resistance (25). Hyperglycaemia can induce oxidative stress in the vasculature, leading to disruption of the normal endothelial function and impaired relaxation of the arterial vascular smooth muscle cells (26). Hyperglycaemia also leads to excessive production of advanced glycation end products

TABLE 5 Risk factors of the high risk of estimated 10-year ASCVD in participants with DM.

Variables	High risk of estimated 10-year ASCVD		
	OR	95%CI	P value
Age, years	10.192	6.188-16.788	<0.001
BMI, kg/m2	1.29	0.926-1.796	0.132
Central obeity	1.992	1.361-2.914	<0.001
Hypertension	18.816	7.286-48.592	<0.001
Hyperlipidemia	1.366	1.007-1.852	0.045
Diabetes duration, years			0.061
<5	1	reference	–
5-10	1.368	0.978-1.912	0.067
10-15	1.361	0.895-2.071	0.150
>15	1.976	1.156-3.377	0.013
Lipid lowering medication	1.028	0.606-1.746	0.917
Cardiovascular drugs	5.184	1.976-13.601	0.001
Antihypertensive drugs	2.780	1.047-7.384	0.04
Family history of ASCVD	1.025	0.752-1.396	0.876
Age at diagnosis, years			0.985
20-43	1	reference	–
44-59	1.053	0.729-1.520	0.784
60-74	1.046	0.681-1.606	0.838

ASCVD, atherosclerotic cardiovascular disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus.
P < 0.05.

and cytokines, which cause activation of adhesion molecules and thickening of intima media (27). Vascular endothelial dysfunction and adhesion activation are also related to hypertension (28), dyslipidemia and diabetic cardiomyopathy (29). Individuals with early-onset diabetes have accompanying metabolic risk factors similar to, or even worse than, those of individuals with late-onset diabetes. For early-onset patients with diabetes, effective glycemic control may contribute to hyperglycaemic episodes, treatment of dyslipidemia, hypertension, obesity, therefore, counteract both microvascular and macrovascular complications of diabetes. Although glucose levels can be controlled through diet, exercise and medications including insulin and oral hypoglycemic agents, many patients continue to undergo numerous life-threatening complications following glucose normalization, suggesting the persistent detrimental effects of high glucose exposure through metabolic memory even after glycaemic control has been established (30, 31). Moreover, the landmark Diabetes Control and Complications Trial (DCCT) confirmed that the damage of hyperglycaemia to microvessels can be delayed for a long time after intensive glycaemic control (32).

Several studies have shown that diabetes duration leads to atherosclerotic lesions, including intimal thickness and thin cap fibroatheromas, which contribute to the deleterious effects on small and large vessels and lead to the development of cardiovascular disease and mortality (12, 33, 34). Further study suggested that diabetes duration during adulthood was associated with coronary artery calcified plaque and left ventricular systolic and diastolic dysfunction in later life, suggesting that the cumulative exposure to chronic hyperglycemia may lead to increased risk of atherosclerosis and impaired cardiac function (35). Our study identified that increasing duration increased the high risk of estimated ten-year ASCVD. These studies are backed up by data from a large population based study from the UK Biobank, which identified that duration of diabetes was independently associated with a greater risk of CVD, myocardial infarction and stroke (36). Further study takes the findings to a broader population based scale where they showed that increasing duration and late-stage complications of DM increase the associated risk of infective endocarditis (37).

We also observed hypertension and hyperdemia were independent risk factors for high risk of estimated 10-year ASCVD in patients with diabetes. As highlighted in the study, ASCVD was prone to occur in the patients with the agedness, central obesity, longer diabetes duration, hypertension and hyperlipidemia. Previous study found that diabetic dyslipidemia precedes T2DM by several years, and lipid abnormalities were associated with an increased risk of CVD (38). Some scholars emphasized that diabetes patients are commonly accompanied by lipid metabolism disorder and hyperlipidemia due to the dysfunction of insulin biological regulation (39). On the one

hand, insulin resistance can lead to blood glucose fluctuation and chronic hyperglycemia, which in turn triggers oxidative stress and increases the expression of pro-inflammatory factors and pro-coagulant factors that leads to cell damage (40). On the other hand, insulin resistance can induce an imbalance in lipoproteins profle alterations that contributes to the development of dyslipidemia and the lipid triad (41). The abnormal association between insulin resistance and endothelial signal conduction disorder leads to inflammation, which further disrupts the balance between endothelial vasodilator and vasoconstrictor mechanisms, and leads to the formation of atherosclerotic plaque (40, 42). New therapies focused on decreasing insulin resistance may be investigated as a potential future therapeutic target for mitigating both CVD and atherosclerotic plaque generation.

Compared to those patients with DM who have't been diagnosed as ASCVD, the high risk of estimated 10-year ASCVD in DM patients treatment with antihypertensive drugs is estimated to increase up to 3-times, and the high risk level is 5-times higher than without using cardiovascular drugs. It's well known that both antihypertensive drugs and cardiovascular drugs are perfect preventive medications for ASCVD in high-risk patients with DM. Obviously, we may arrive at a conclusion that high-risk population are more willing to take antihypertensive drugs and cardiovascular drugs under medical advice. These findings advance the arguments for wider and earlier use of China-PAR model in this population and provide important practical value for the prevention of cardiovascular diseases in diabetic patients. However, the data of patients using cardiovascular drugs in the analysis model is so small that can't reflect the real world impact of all diabetes patients after receiving cardiovascular drug treatment.

The patients with early-onset DM were characterized by a higher level of BMI and weight, and were more likely to have obesity than older-onset DM. As an important indicator to reflect the obesity, BMI can evaluate the severity of insulin resistance in obese DM patients. Obesity increased the risk for development of DM and may lead to an earlier age of diagnosis (43, 44). Our analysis is consistent with these findings. The significant proportion of metabolic disorders and insulin resistance among patients with early-onset DM, and the risk for development of macrovascular complications from diabetes is increased among obese individuals with DM (43). Therefore, it is suggested that early-onset DM patients should repair metabolic disorders and ameliorate insulin resistance by reducing weight and BMI as soon as possible.

The results of the present study show that early-onset age of DM increases the risk of macrovascular complications later in life. Compared with late-onset DM, people with early-onset DM have a significantly higher risk of developing macrovascular complications, especially ischemic stroke. Our findings are consistent with those of two previous studies (4, 45). It was found in previous studies that patients diagnosed with early-onset (20-39 years) T2DM had a higher risk of developing cardiovascular disease and a higher cardiac 10-year expected risk than patients with late-onset T2DM (46). These studies all suggested that the impending increase in average duration of diabetes in people with T2DM is likely to increase the burden of coronary artery disease and ischemic stroke. The groups with younger age at diagnosis (age ≤59 years) was independently associated with the risk of macrovascular complications compared to the elderly-onset group (60 to 74 years). These results were similar to other studies. Observational studies showed that patients with younger age at diabetes diagnosis was associated with higher risk of vascular disease (47). And cardiovascular complications were more common in patients with early-onset T2DM at any given age (48). Therefore, early and sustained interventions are essential to delay T2DM onset, and improve blood glucose levels, and cardiovascular risk profiles of those already diagnosed. However, other studies argued that patients with early-onset diabetes are more likely to have microvascular complications than macrovascular complications (11). In the study, the increase in comorbidities of coronary vascular disease and ischemic stroke with age at diagnosis was more pronounced in the elderly-onset (60 to 74 years) than those with younger onset (age ≤59 years). Both age at diagnosis and duration of diabetes affected the risk for coronary artery disease and ischemic stroke, but the relative impact was different for each. For ischemic stroke, the incidence risk was primarily driven by disease duration and age at diagnosis, which led to the relative risk of people with different diabetes duration at a given age. However, these relative risks were smaller for coronary artery disease, indicating less of an effect of duration of diabetes and more so of age at diagnosis than for ischemic stroke.

Our findings should be interpreted in light of the strengths and limitations of our study. The strengths of this work include that data were derived from a large, multi-center and multi-level design cohort of patients with diabetes, and had comprehensive clinical implications for diabetes complications. our study found that people with early-onset diabetes had a high risk of complications, indicating diabetes-related complications will increasingly occur in people of working age, which may result in substantial healthcare burden. It is essential to intensified efforts to prevent these complications. We first used the China-PAR project to predict the ten-year ASCVD in the study, which will help to improve primary prevention of macrovascular complications. The China-PAR project developed based on the recent epidemics of CVD and risk factors will be better to identify high risk individuals with appropriately predicted risk probability, and to evaluate ASCVD outcome with standardized review process, using the same diagnosis criteria across cohorts.

The present study had some limitations. First, information on coronary heart disease and cerebrovascular disease was collected from the questionnaire, which is similar to most other epidemiological studies (49). However, it is not practical to measure coronary heart disease and cerebrovascular disease by equipment in a large-scale study. Second, previous studies show that younger age at diabetes diagnosis was associated with high risk of macrovascular and microvascular disease (47). The diabetes duration has been thought to be an noteworthy factor, absent of the ability to quantify the effects of duration of diabetes after the diagnosis of diabetes. Longer periods of follow-up may be need to be carried out among participants. It is a great pity that numbers of clinical events and kinds of complications were present in small amounts. Patients were grouped according to their age at onset, but for asymptomatic patients, the age onset and disease duration might

be underestimated. However, in view of the similarity between our cohort and the cohort of patients with diabetes observed by other teams, we still believe that our findings are somewhat universal and comparable among onset-age groups (10, 12, 47). Furthermore, this was a cross-sectional study in four cities that does not represent broad sections of the people with diabetes at different region cross the country. In addition, several limitations should be addressed in our study when using the China-PAR modeling. Firstly, the project is aimed to develop and validate 10-year risk prediction equations for ASCVD from all Chinese participants, not diabetes patients. Thus, cautions should be used and training among physicians is required to communicate predicted 10-year risk of ASCVD to patients when the modeling are applied in prevention practice. Secondly, further investigation is warranted to examine whether the 10-year risk prediction modeling could have good performance in large-scale cohorts with short durations of follow-up.

5 Conclusions

The present study demonstrated that higher FPG and HbA1c according to disease duration were observed in patients diagnosed at early-onset age than those diagnosed at older age. Age at diagnosis and diabetes duration, hypertension and hyperlipidemia were associated with an increased risk of macrovascular events and high risk of ten-year ASCVD prediction. Further prospective cohort studies are necessary to examine our findings in large-scale populations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee (Approval No: 2018-010). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QZ, HH, and FD designed and proposed the study. XY, JZ, XZ, TJ, and YZ collected the patients' data. XY prepared and drafted the manuscript. JZ and XZ analyzed and illustrated the data. YZ and TJ revised the paper. All authors have read and approved the manuscript. In addition, we confirm that all listed authors meet the authorship criteria and that all authors are in agreement with the content of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Albino Carrizzo,
University of Salerno, Italy

REVIEWED BY
Carmine Izzo,
University of Salerno, Italy
David Bradley,
Penn State Milton S. Hershey Medical Center, United States

*CORRESPONDENCE
Guifang Liu
guifangliu2023@163.com

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Weight cycling and risk of clinical adverse events in patients with heart failure with preserved ejection fraction: a *post-hoc* analysis of TOPCAT

Yi Tan[1], Hang Guo[2], Ning Zhang[3], Keyang Zheng[2] and Guifang Liu[4]*

[1]Department of Education, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China, [2]Department of Education, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [3]Department of Education, Beijing Stomatological Hospital, Capital Medical University, Beijing, China, [4]Department of Radiology, Qingdao Central Hospital, Qingdao, Shandong, China

Background: Previous studies hardly evaluated the association of variability of body mass index (BMI) or waist circumference with clinical adverse events and investigated whether weight cycling had an effect on the prognosis of patients with heart failure with preserved ejection fraction (HFpEF).

Methods: This study was a *post-hoc* analysis of TOPCAT. Three outcomes were evaluated: the primary endpoint, cardiovascular disease (CVD) death, and heart failure hospitalization. Among them, CVD death and hospitalization were outcomes of heart failure. Kaplan–Meier curves were used to describe the cumulative risk of outcome and were tested using the log-rank test. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95%CIs for outcomes. We also performed a subgroup analysis, and several subgroups were compared.

Results: A total of 3,146 patients were included. In the Kaplan–Meier curves, the coefficients of variation of both BMI and waist circumference were grouped according to quartiles, with the Q4 group having the highest cumulative risk (log-rank $P < 0.001$). In the coefficient of BMI variation and the outcomes, the HRs for group Q4 of coefficient of variation of BMI were 2.35 (95%CI: 1.82, 3.03) for the primary endpoint, 2.40 (95%CI: 1.69, 3.40) for death, and 2.33 (95%CI: 1.68, 3.22) for HF hospitalization in model 3 (fully adjusted model) compared with group Q1. In the coefficient of waist circumference variation and the outcomes, group Q4 had increased hazard of the primary endpoint [HR: 2.39 (95%CI: 1.84, 3.12)], CVD death [HR: 3.29 (95%CI: 2.28, 4.77)], and HF hospitalization [HR: 1.98 (95%CI 1.43, 2.75)] in model 3 (fully adjusted model) compared with group Q1. In the subgroup analysis, there was a significant interaction in the diabetes mellitus subgroup (P for interaction = 0.0234).

Conclusion: Weight cycling had a negative effect on the prognosis of patients with HFpEF. The presence of comorbid diabetes weakened the relationship between waist circumference variability and clinical adverse events.

KEYWORDS

body mass index, waist circumference, heart failure with preserved ejection fraction, weight cycling, diabetes mellitus

1 Introduction

Obesity is common in heart failure with preserved ejection fraction (HFpEF) patients and is considered as an independent risk factor for the development of HFpEF (1). Thus, weight management is important for HFpEF patients with obesity. A single central trial showed that a modest weight loss could improve the exercise capacity and quality of life for obesity and HFpEF patients (2). There is also evidence that weight loss in obesity can improve left ventricular concentric remodeling in patients with heart failure (3).

However, overweight and obese individuals are likely to result in an equal or greater weight gain after the resultant weight loss with a poor weight loss method, which is called weight cycling (4). Weight cycling has been shown to correlate with adverse events in diabetic populations (5) and coronary artery disease (CAD) (6) populations. Moreover, recent studies have identified weight cycling as a risk factor for cardiometabolic diseases independent of body weight (7).

The variability of body mass index (BMI) and waist circumference are two indicators that show the fluctuation in body weight and can reflect the process of weight cycling. Since BMI is a parameter reflecting overall body weight and waist circumference, as another parameter reflecting abdominal obesity, it may be more associated with adverse cardiovascular disease (CVD) outcomes (8, 9). Many studies have focused on the relationship between changes in BMI and a poor prognosis of CVD. However, in patients with HFpEF, no clinical studies have focused on the prognostic impact of variability in BMI or waist circumference. Thus, we conducted a *post-hoc* analysis of TOPCAT to evaluate the relationship of the variability of BMI or waist circumference on the prognosis of HFpEF. This study aimed to investigate whether such weight cycling has an effect on the prognosis of patients with HFpEF.

2 Method

2.1 Study design and population

This study is a *post-hoc* analysis of TOPCAT. The data was obtained from the BioLINCC website (https://biolincc.nhlbi.nih.gov/), and we were licensed to use this data. TOPCAT is a randomized, double-blind trial of patients with symptomatic heart failure and ejection fraction of 45% or greater. Adverse events such as death and hospitalization due to heart failure were compared between treatment with spironolactone (15 to 45 mg per day) and placebo (10). The study enrolled 3,445 patients who met the criteria and were followed for 3.3 years (mean follow-up time). The original study found no significant difference in outcomes between the two groups of patients receiving different treatments.

In the analysis of this study, patients were included according to the following steps: In the first step, three patients who were not followed up for weight and waist circumference were excluded; secondly, among the patients who completed the follow-up, 296 patients with fewer than four follow-up records of weight or waist circumference were excluded. Finally, 3,146 patients were included in this study (Figure 1).

2.2 Assessment of variability of BMI and waist circumference and outcome

Height data were collected at baseline to calculate the BMI. The patients were followed up for weight and waist circumference at 4 weeks, 8 weeks, 4 months, and every 4 months thereafter after enrollment. Considering that the traditional description variable standard deviation (SD) excluded the influence of mean value, the variability of BMI and waist circumference is thus described by coefficients of variation (CV).

Three outcomes were evaluated in this study (1): primary endpoint of the original study, (2) CVD death, and (3) heart failure

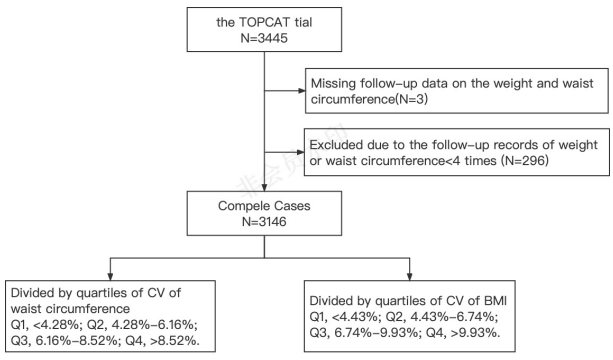

FIGURE 1
Flow chart for enrolling patients in this study.

(HF) hospitalization. The definition of the primary endpoint is cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure as a composite. More definitions of outcomes can be found in the original study (10).

2.3 Statistical analysis

The patients' characteristics were presented in quartiles of the CV of waist circumference. Continuous variables were expressed as mean (SD) or median (IQR), and ANOVA or Kruskal–Wallis test was used to compare differences between groups; categorical variables were expressed as proportions, and χ^2 test was used for comparison between groups.

Kaplan–Meier (KM) curves were used to describe the cumulative risk of outcome between different BMI or waist circumference variability groups and were tested using log-rank test.

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95%CIs for outcomes (primary endpoint, death, and HF hospitalization). The CV of waist circumference or BMI was assessed as categorical variables. In this study, three models were used for waist circumference or BMI: model 1 adjusted for none; model 2 adjusted for age, sex, and race; and model 3 included model 2 plus adjustment for current smoking, intervention, NYHA class, diabetes mellitus, glucose, eGFR, and baseline medication.

The subgroup analysis was performed using model 3 (covariates that were tested for interactions were excluded), and we treated the CV of BMI or waist circumference as a continuous variable (per group). The following subgroups were compared: male vs. female; age <69 vs. age ≥69; White vs. Black vs. others; visit-to-visit mean BMI <30 vs. visit-to-visit mean BMI ≥30; visit-to-visit mean waist circumference <101.3 vs. visit-to-visit mean waist circumference ≥101.3; and with diabetes mellitus vs. without diabetes mellitus.

All statistical analyses were performed using R version 4.2.2 (Vienna, Austria, https://www.r-project.org/). Bilateral P <0.05 was considered statistically significant.

3 Results

3.1 Characteristics of the enrolled patients

A total of 3,146 patients were included, with a mean age of 68.4 ± 9.5 years old and with 1,536 (48.8%) being male patients. The patients were divided into four groups according to the quartiles of CV of waist circumference, and the characteristics of the patients are shown in Table 1. Compared with group Q1, group Q4 was older, more likely to be female patients, less likely to be White, and less likely to smoke. Regarding medical history, group Q1 had the highest prevalence of DM and angina, and group Q2 had the highest history of past myocardial infarction. Regarding laboratory tests, Q4 group had the lowest blood glucose levels and EGFR. At baseline, the utilization rate of ACEI/ARB and beta receptor antagonist in group Q4 was the lowest. The visit-to-visit mean BMI and waist circumference of the Q4 group were both the lowest. Regarding outcomes, Q4 group had the highest rate of the primary endpoint, CVD death, and HF hospitalization.

TABLE 1 Characteristics of 3,146 patients by quartiles of coefficient of variation of waist circumference.

Characteristics	Q1, <4.28% N = 787	Q2,4.28%–6.16% N = 786	Q3, 6.16%–8.52% N = 786	Q4, >8.52% N = 787	P-value
Age, years	64.88 ± 8.50	67.23 ± 9.15	69.00 ± 9.27	72.41 ± 9.53	<0.001
Sex					<0.001
Male, *n* (%)	506 (64.29%)	428 (54.45%)	368 (46.82%)	234 (29.73%)	
Female, *n* (%)	281 (35.71%)	358 (45.55%)	418 (53.18%)	553 (70.27%)	
Race					<0.001
White, *n* (%)	721 (91.61%)	723 (91.98%)	719 (91.48%)	685 (87.04%)	
Black, *n* (%)	58 (7.37%)	57 (7.25%)	47 (5.98%)	66 (8.39%)	
Others, *n* (%)	8 (1.02%)	6 (0.76%)	20 (2.54%)	36 (4.57%)	
Current smoking, *n* (%)	96 (12.20%)	85 (10.81%)	87 (11.07%)	63 (8.01%)	0.047
Visit-to-visit mean BMI, kg/m^2	34.78 ± 7.25	32.82 ± 6.14	31.92 ± 6.35	30.40 ± 6.10	<0.001
Visit-to-visit mean waist circumference, cm	108.35 ± 18.81	104.37 ± 16.08	101.96 ± 14.55	97.03 ± 14.64	<0.001
Intervention, *n* (%)	394 (50.06%)	379 (48.22%)	409 (52.04%)	396 (50.32%)	0.512
Medical history					
Hypertension, *n* (%)	729 (92.63%)	724 (92.11%)	716 (91.09%)	710 (90.22%)	0.319

(Continued)

TABLE 1 Continued

Characteristics	Q1, <4.28% N = 787	Q2,4.28%–6.16% N = 786	Q3, 6.16%–8.52% N = 786	Q4, >8.52% N = 787	*P*-value
Diabetes mellitus, *n* (%)	296 (37.61%)	234 (29.77%)	223 (28.37%)	242 (30.75%)	<0.001
Angina, *n* (%)	433 (55.02%)	407 (51.78%)	362 (46.06%)	317 (40.28%)	<0.001
History of myocardial infarction, *n* (%)	198 (25.16%)	248 (31.55%)	194 (24.68%)	193 (24.52%)	0.003
History of stroke, *n* (%)	53 (6.73%)	66 (8.40%)	60 (7.63%)	58 (7.37%)	0.658
NYHA class					0.669
I–II class, *n* (%)	534 (67.85%)	537 (68.32%)	554 (70.48%)	537 (68.23%)	
III–IV class, *n* (%)	253 (32.15%)	249 (31.68%)	232 (29.52%)	250 (31.77%)	
Laboratory tests					
Glucose, mg/dl, median (Q1–Q3)					
Class 1	98.18 (89.09–109.09)	98.00 (89.09–107.27)	97.00 (88.00–109.00)	98.18 (89.09–107.27)	0.608
Class 2	120.00 (100.00–140.45)	114.55 (105.09–125.91)	114.55 (101.82–144.00)	121.00 (100.00–129.02)	0.624
Class 3	144.00 (109.09–181.00)	128.00 (103.32–170.45)	134.55 (109.00–185.45)	130.50 (102.41–177.00)	0.463
eGFR, ml/(min·1.73m^2)	69.71 ± 19.54	68.83 ± 19.47	67.65 ± 19.82	65.48 ± 19.70	<0.001
Baseline medication					
ACEI/ARB, *n* (%)	712 (90.47%)	654 (83.21%)	656 (83.46%)	643 (81.81%)	<0.001
Beta receptor antagonist, *n* (%)	619 (78.65%)	638 (81.17%)	603 (76.72%)	594 (75.57%)	0.041
Calcium channel blockers, *n* (%)	296 (37.61%)	283 (36.01%)	312 (39.69%)	290 (36.90%)	0.478
Diuretic agent, *n* (%)	663 (84.24%)	639 (81.30%)	639 (81.30%)	627 (79.77%)	0.138
Outcomes					
Primary endpoint, *n* (%)	104 (13.21%)	128 (16.28%)	149 (18.96%)	187 (23.76%)	<0.001
CVD death, *n* (%)	70 (8.89%)	91 (11.58%)	107 (13.61%)	171 (21.73%)	<0.001
Heart failure hospitalization, *n* (%)	289 (36.72%)	347 (44.15%)	356 (45.29%)	401 (50.95%)	<0.001

Class 1 means glucose for patients without diabetes mellitus (DM), class 2 means glucose for DM patients without anti-diabetic medications, and class 3 means glucose for DM patients with anti-diabetic medications.

3.2 KM curves of BMI or waist circumference variability and outcomes

As shown in Figure 2A, after grouping according to quartiles of CV of waist circumference, the cumulative risk of the primary endpoint was significantly different among the four groups, with the highest cumulative risk in the Q4 group (log-rank $P < 0.001$).

As shown in Figure 2B, the CV of BMI was also grouped according to quartiles, with the Q4 group having the highest cumulative risk (log-rank $P < 0.001$).

3.3 Coefficient of variation of waist circumference and outcomes

Hazard ratios for outcomes by CV of waist circumference are shown in Table 2. Group Q4 had increased hazard of the primary endpoint [HR: 2.39 (95%CI: 1.84, 3.12)], CVD death [HR: 3.29 (95%CI: 2.28, 4.77)], and HF hospitalization [HR 1.98 (95%CI: 1.43, 2.75)] in model 3 (fully adjusted model) compared with group Q1. *P* for trend was also calculated in all outcomes, and the trend was all significant in model 3.

3.4 Coefficient of variation of BMI and outcomes

Hazard ratios for outcomes by BMI of waist circumference are shown in Table 3. The HRs for group Q4 of coefficient of variation of BMI were 2.35 (95%CI: 1.82, 3.03) for the primary endpoint, 2.40 (95%CI: 1.69, 3.40) for death, and 2.33 (95%CI: 1.68, 3.22) for HF hospitalization in model 3 (fully adjusted model) compared with group Q1. *P* for trend was <0.001 in all outcomes in the fully adjusted model (model 3).

3.5 Subgroup analysis of variability of BMI or waist circumference and outcomes

The results of the subgroup analysis of variability of waist circumference and primary endpoint are shown in Figure 3. No

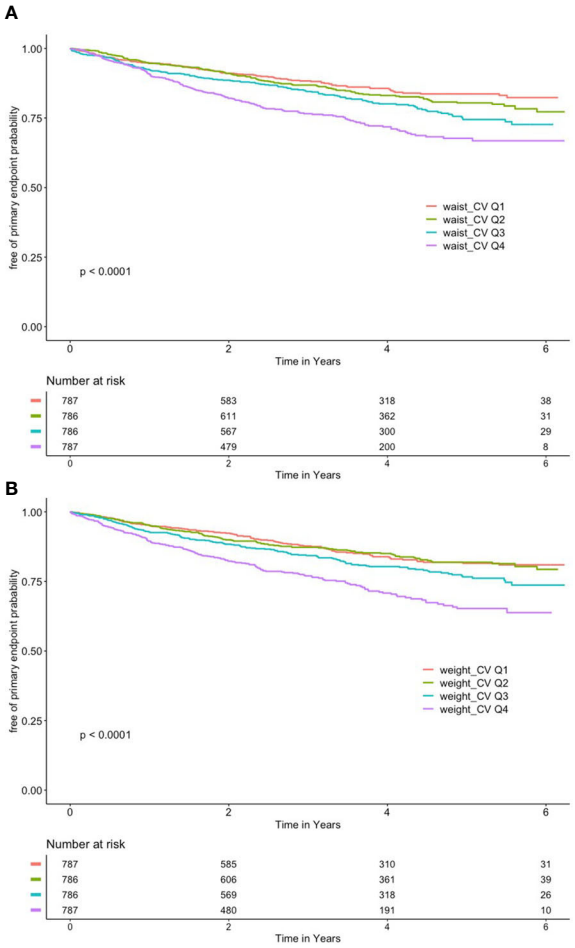

FIGURE 2
(A) Kaplan–Meier curve of different coefficient variations of waist and primary outcome. **(B)** Kaplan–Meier curve of different coefficient variations of body mass index and primary outcome.

significant interactions were found in sex, age, race, mean BMI, and mean waist circumference subgroups (all *P* for interaction >0.05). However, this study found a significant interaction in the diabetes mellitus subgroup (*P* for interaction = 0.0234). In the diabetic population, the HR per group increase in the CV of waist circumference was 1.24 (95%CI: 1.11, 1.39) for the primary endpoint. In the population without diabetes mellitus, the HR per group increase in the CV of waist circumference was 1.49 (95%CI: 1.32, 1.67) for the primary endpoint.

Figure 4 presents the variability of BMI and the results of the subgroup analysis of the primary endpoint. No significant interactions were found in sex, age, race, mean BMI, mean waist circumference, and diabetes mellitus subgroups (all *P* for interaction >0.05).

4 Discussion

This study evaluated the relationship between weight cycling and clinical outcomes in HFpEF patients. Both BMI variability and waist circumference variability were found to be significantly associated with clinical adverse events, and the risk of clinical adverse events increased with increasing variability. In the subgroup analysis, we found that the presence or absence of comorbid diabetes affected the relationship between waist circumference variability and clinical adverse events.

Previous studies have also discussed the association between weight cycling and clinical adverse events in people with type 2 diabetes. Arnaud D. Kaze conducted a prospective cohort study and found a positive and consistent correlation between weight cycling and CVD outcomes and deaths in people with type 2 diabetes (5). Moreover, the study also researched whether an intensive lifestyle intervention can affect this association. An intensive lifestyle intervention had the purpose of 7% weight loss or greater via more physical activity and less caloric intake compared with the standard of care (diabetes support and education). The outcomes showed that an intensive lifestyle intervention could alter the association of weight cycling with cardiovascular outcomes and deaths, which provided a possible opportunity for people with type 2 diabetes to eliminate the impacts of weight cycling when losing weight. However, a report from the NHLBI-sponsored WISE Study found an opposite outcome about the association between weight cycling and clinical adverse events in people with suspected ischemia (6). In their research, weight cycling was associated with a lower cardiovascular outcome rate in women with suspected ischemia despite the influence of HDL-cholesterol. The findings were not consistent with prior studies in men (11). The possible reason might be the sex differences in metabolism, fat storage, diabetes, and CVD.

The mechanisms underlying the association between variability in BMI or waist circumference and poor prognosis are not yet fully understood. One possible mechanism is that fluctuations in body weight lead to changes in fat metabolism. It has been found that when the body loses weight (especially when dieting to lose weight), the participating lipocytes will grow and proliferate more rapidly if the body gains weight again afterwards, probably because the metabolic shift tends to be more favorable for lipid accumulation (12, 13). It has also been found that repeated weight loss and then recovery preferentially promotes the gain of abdominal fat and is associated with a poor prognosis of cardiovascular disease (13, 14). This is also similar to our finding that the variability of waist circumference, which better represents abdominal fat, was associated with a higher risk of death from CVD than the variability of BMI. Another possible mechanism is the adipocyte-associated inflammatory response. The rapid remodeling of adipose tissue associated with weight fluctuations may lead to the abnormal production of pro-inflammatory factors (15), and weight fluctuations have been found to be associated with elevated circulating C-reactive protein concentrations which had adverse effects on the cardiovascular system. Animal studies have also found an overproduction of lymphocytes and a large increase in cytokines in the adipose tissue of weight-cycling mice, which may be a possible mechanism by which the inflammatory response mediates weight cycling and poor prognosis (14).

TABLE 2 Hazard ratios for outcomes by coefficient of variation of waist circumference.

Outcomes	Q1, <4.28%	Q2, 4.28%–6.16%	Q3, 6.16%–8.52%	Q4, >8.52%	*P* for trend
Primary endpoint Hazard ratios (95%CI), *P*-value					
Model 1	Reference	1.17 (0.90, 1.51) 0.2369	1.47 (1.15, 1.89) 0.0024	1.17 (0.90, 1.51) 0.1613	<0.0001
Model 2	Reference	1.17 (0.90, 1.52) 0.2358	1.50 (1.16, 1.94) 0.0018	2.10 (1.62, 2.73) 0.0002	<0.0001
Model 3	Reference	1.21 (0.93, 1.57) 0.1613	1.64 (1.26, 2.12) 0.0002	2.39 (1.84, 3.12) <0.0001	<0.0001
CVD death Hazard ratios (95%CI), *P*-value					
Model 1	Reference	0.99 (0.66, 1.46) 0.9430	1.53 (1.06, 2.21) 0.0217	3.00 (2.14, 4.21) <0.0001	<0.0001
Model 2	Reference	1.00 (0.67, 1.48) 0.9911	1.54 (1.06, 2.24) 0.0224	3.17 (2.20, 4.57) <0.0001	<0.0001
Model 3	Reference	1.02 (0.69, 1.53) 0.9040	1.60 (1.10, 2.33) 0.0136	3.29 (2.28, 4.77) <0.0001	<0.0001
Heart failure hospitalization Hazard ratios (95%CI), *P*-value					
Model 1	Reference	1.31 (0.96, 1.79) 0.0833	1.45 (1.07, 1.97) 0.0177	1.84 (1.36, 2.48) <0.0001	<0.0001
Model 2	Reference	1.28 (0.94, 1.75) 0.1182	1.42 (1.04, 1.95) 0.0267	1.64 (1.19, 2.26) 0.0027	<0.0001
Model 3	Reference	1.31 (0.95, 1.79) 0.0958	1.60 (1.17, 2.20) 0.0035	1.98 (1.43, 2.75) <0.0001	<0.0001

Model 1 adjusted for none. Model 2 adjusted for age, sex, and race. Model 3 adjusted for age, sex, race, current smoking, intervention, NYHA class, diabetes mellitus, glucose, eGFR, and baseline medication.

Our study also found that the presence or absence of diabetes affected the relationship between waist circumference variability and the primary endpoint, with the relationship between the two attenuated by the presence of diabetes. Based on previous studies, one of the possible mechanisms for the relationship was the altered metabolism of adipocytes. Previous studies have found that fat metabolism is abnormal in DM patients, with reduced glucose uptake and lipolysis in adipocytes from DM patients, and the extracellular matrix from DM patients has been found to impair glucose uptake in adipocytes from non-DM patients (16). It has also been suggested that it may be that adipocytes promote the formation of insulin resistance in patients with DM, thus affecting

TABLE 3 Hazard ratios for outcomes by coefficient of variation of body mass index.

Outcomes	Q1, <4.43%	Q2, 4.43%–6.73%	Q3, 6.73%–9.93%	Q4, >9.93%	*P* for trend
Primary endpoint Hazard ratios (95%CI), *P*-value					
Model 1	Reference	1.02 (0.79, 1.33) 0.8569	1.33 (1.04, 1.71) 0.0222	2.07 (1.64, 2.61) <0.0001	<0.0001
Model 2	Reference	1.06 (0.82, 1.37) 0.6682	1.32 (1.03, 1.70) 0.0286	2.05 (1.59, 2.63) <0.0001	<0.0001
Model 3	Reference	1.12 (0.86, 1.46) 0.3813	1.41 (1.10, 1.83) 0.0078	2.35 (1.82, 3.03) <0.0001	<0.0001
CVD death Hazard ratios (95%CI), *P*-value					
Model 1	Reference	0.82 (0.56, 1.19) 0.2875	1.09 (0.77, 1.56) 0.6181	2.37 (1.72, 3.26) <0.0001	<0.0001
Model 2	Reference	0.82 (0.56, 1.20) 0.3092	1.05 (0.73, 1.51) 0.7841	2.28 (1.62, 3.21) <0.0001	<0.0001
Model 3	Reference	0.84 (0.57, 1.23) 0.3682	1.09 (0.76, 1.57) 0.6481	2.40 (1.69, 3.40) <0.0001	<0.0001
Heart failure hospitalization Hazard ratios (95%CI), *P*-value					
Model 1	Reference	1.22 (0.89, 1.68) 0.2227	1.51 (1.11, 2.05) 0.0086	2.07 (1.54, 2.79) <0.0001	<0.0001
Model 2	Reference	1.27 (0.92, 1.74) 0.1474	1.46 (1.07, 2.00) 0.0173	1.94 (1.42, 2.66) <0.0001	<0.0001
Model 3	Reference	1.33 (0.96, 1.83) 0.0864	1.56 (1.14, 2.15) 0.0058	2.33 (1.68, 3.22) <0.0001	<0.0001

Model 1 adjusted for none. Model 2 adjusted for age, sex, and race. Model 3 adjusted for age, sex, race, current smoking, intervention, NYHA class, diabetes mellitus, glucose, eGFR, and baseline medication.

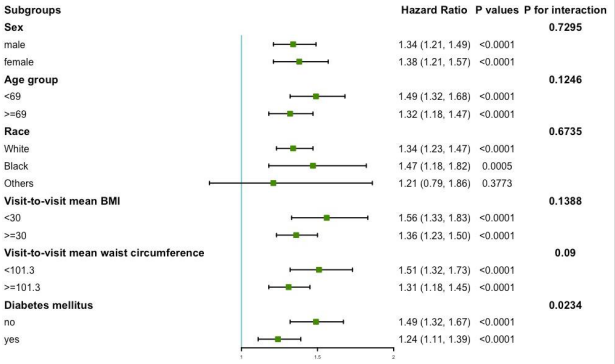

FIGURE 3
Subgroup analysis for the risk of primary endpoint by coefficient of variation of waist circumference (per group). Model 3 was used, but the covariates that were tested for interactions were excluded.

the metabolism of the organism (17). In addition to the mechanisms mentioned above, more metabolic disorders were also found in patients with DM (18), which may attenuate the relationship between variability in waist circumference and adverse events.

Our study has strength in such a way that we introduced the concept of weight cycling into the evaluation of the prognosis of HFpEF since previous studies paid little attention to the variability of the BMI and waist circumference. Moreover, the TOPCAT study had a long follow-up time of 3.3 years which helped to observe the fluctuation of such two slowly changing indicators.

We acknowledged that there were some limitations to our study. Since it was a *post-hoc* analysis of a trial, it could not conform to the population and the randomization model of statistical inference. The explicit mechanisms of the effect of weight cycling on the poor prognosis of cardiovascular disease are also unclear and remain to be verified.

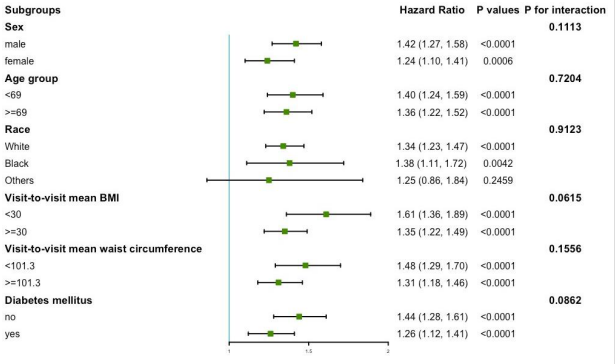

FIGURE 4
Subgroup analysis for the risk of primary endpoint by coefficient of variation of body mass index (per group). Model 3 was used, but the covariates that were tested for interactions were excluded.

5 Conclusion

In this *post-hoc* analysis of TOPCAT, we found that weight cycling had a negative effect on the prognosis of patients with HFpEF. The presence of comorbid diabetes weakened the relationship between waist circumference variability and clinical adverse events. These findings indicated BMI and waist circumference as independent risk factors for clinical adverse events. When losing weight, it is important for patients with HFpEF to pay attention to weight cycling and take action to smoothen the fluctuations of BMI and waist circumference. We look forward to more effective weight loss methods to prevent weight cycling and maintain a long-term effect of weight loss, which could further reduce the risk of patients with heart failure with preserved ejection fraction.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: the BioLINCC website (https://biolincc.nhlbi.nih.gov/).

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Committee of Beijing Chaoyang Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YT wrote the manuscript. YT, HG, and KZ applied for the database and performed the statistical analysis. NZ and GL revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Shuyu Zhang,
Sichuan University, China
Shuangxi Wang,
Shandong University, China
Huachen Jiao,
Affiliated Hospital of Shandong University of Traditional Chinese Medicine, China
Junhui Xing,
The First Affiliated Hospital of Zhengzhou University, China
Jiamming Pei, Air Force Medical University, China

*CORRESPONDENCE
Yinglong Hou
yinglonghou@hotmail.com

†These authors have contributed equally to this work and share first authorship

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Serum uric acid: creatinine ratio (UCR) is associated with recurrence of atrial fibrillation after catheter ablation

Yujiao Zhang[1†], Yanxin Wang[2†], Xuesong Yang[2], Zhan Li[1], Luxiang Shang[1] and Yinglong Hou[1,2*]

[1]Department of Cardiology, Shandong First Medical University, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Medicine and Health Key Laboratory of Cardiac Electrophysiology and Arrhythmia, Jinan, China, [2]Department of Cardiology, Shandong Provincial Qianfoshan Hospital, Shandong Medicine and Health Key Laboratory of Cardiac Electrophysiology and Arrhythmia, Cheeloo College of Medicine, Shandong University, Jinan, China

Background and aims: Studies showed that elevated preoperative serum uric acid(SUA) levels are associated with recurrence of atrial fibrillation(AF) after catheter ablation. UA:creatinine ratio(UCR - UA normalised for renal function) has appeared as a new biomarker and is considered to reflect endogenous UA levels preferably because it eliminates the influence of renal function. This study aimed to investigate the correlation between UCR and recurrence of AF after catheter ablation.

Methods and results: A total of 233 consecutive patients with symptomatic, drug-refractory AF underwent catheter ablation. All participants underwent history-taking, physical examination and blood biochemistry analysis at baseline. After a mean follow-up of 23.99 $\pm$ 0.76 months, recurrence ratios for each UCR quartile (from lowest quartile to highest) were 10.9%, 23.6%, 23.6%, and 41.8%, respectively (P = 0.005). Multivariate Cox regression analysis revealed that UCR was an independent predictor of AF recurrence (HR 1.217, 95%CI 1.008-1.468; P = 0.041). Subgroup analysis showed that UCR was associated with AF recurrence in paroxysmal AF (HR 1.426, 95% CI 1.092-1.8608; P = 0.009) and in male patients (HR 1.407, 95% CI 1.015-1.950; P = 0.04). A cut-off point of 4.475 for the UCR had sensitivity of 65.5% and specificity of 59.6% in predicting AF recurrence (P = 0.001).

Conclusion: Our results demonstrate that elevated preoperative UCR is associated with recurrence of AF after catheter ablation, and it indicate UCR maybe a predictive factor for the recurrence of AF.

KEYWORDS

atrial fibrillation, catheter ablation, recurrence, uric acid: creatinine ratio (UCR), arrhythmia

1 Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality (1). Over the past 20 years, catheter ablation has become an increasingly popular means of procuring rhythm control for patients with symptomatic and drug-refractory AF. However, there is still a risk of recurrence after ablation, occurring in approximately 25-50% of patients (2). It is important to explore the risk factors related to recurrence of AF and carry out intervention to prevent recurrence.

At present, the risk factors known to be associated with recurrence of AF include hypertension, coronary heart disease, obesity, obstructive sleep apnoea (OSA), and other inflammatory or metabolic diseases. However, there is limited evidence to support the view that these serum biomarkers could be used to detect pathogenesis of AF recurrence. Serum uric acid (SUA), an important indicator of metabolism, has been associated with recurrence of AF (3). Nevertheless, renal function is also an influential factor for AF. Given the fact that renal clearance of SUA is often impaired during kidney injury, renal function is the major confounder in studies for the association between serum UA levels and CVD (4, 5).

A study suggested that serum UA to creatinine (Cr) ratio (UA : Cr, UCR) might be a better predictor excluding factors of kidney injury than serum UA alone. Higher serum UCR levels correlated with an increased risk of all metabolic syndrome components (4). Recently, the components of metabolic syndrome were also found to be associated with high serum Cr levels. Notably, the subjects with higher levels of serum UCR have more cardiometabolic risk factors and hence the serum UCR may be useful in determining prognosis for metabolic syndrome. In addition, previous studies have shown that this biomarker was closely related to metabolic syndrome, renal disease progression, as well as total and cause specific mortality (6–8). However, its relationship with AF recurrence still required investigation. Therefore, we tried to generate a new index using renal function-normalised UA and tested whether it is superior to UA as the predictor of AF recurrence after catheter ablation.

2 Methods

2.1 Study design and population

For this retrospective study, we included consecutive Chinese patients with drug-refractory AF who had undergone radiofrequency (RF) catheter ablation for the first time between January 2018 and May 2021 at Department of Cardiology, the first affiliated hospital of Shandong First Medical University. According to the guidelines for the diagnosis and management of AF, a standard 12-lead ECG recording or a single-lead ECG tracing of ≥ 30 s showing heart rhythm with no discernible P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF (9). The exclusion criteria were as follows: (i) left ventricular ejection fraction (LVEF) < 50% and left atrium (LA) diameter > 55 mm; (ii) estimated Glomerular Filtration Rate (eGFR) < 15 mL/min. Written informed consent had been obtained before participation and the study was approved by the institutional ethical review committee. Prior to the procedure, informed consent was obtained from all patients, in accordance with our hospital guidelines. The study was approved by the Ethics Committee of the First Affiliated Hospital of Shandong First Medical University.

2.2 Baseline data collection

Detailed medical histories related to cardiovascular and systemic conditions of all the patients were collected. Baseline characteristics, including age, sex, height, weight, smoking history, alcohol consumption, and drug history, were assessed. Complications related to cardiovascular disease, including diabetes, hypertension, hyperlipidaemia and coronary atherosclerotic heart disease were evaluated. The CHA2DS2-VASc scores were calculated for each patient according to 2020 ESC Guidelines for the diagnosis and management of AF (9). Fasting blood samples were collected from all participants before catheter ablation. Hematological indicators were measured using standard laboratory procedures. SUA, creatinine, triglyceride (TG) and superoxide dismutase (SOD) concentration were measured by the colorimetric method. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and glycated hemoglobin A1c (HbA1c) were measured by enzyme colorimetry, the direct method of the catalase clear method, selective elimination and high efficiency liquid chromatography, respectively.

2.3 Preoperative preparation

All patients underwent transthoracic echocardiography and transoesophageal echocardiography to examine left atrium diameter (LAD), LVEF, valve parameters and to define no left atrial thrombus within 48 hours before the procedure. Pulmonary vein (PV) CT was used to assess the structure of the PVs. Novel oral anticoagulants were continued until 12h before the procedure. Vitamin K antagonist (VKA) was stopped 2 days before the intervention to achieve an international normalised ratio between 1.5 and 2.0, and subcutaneous low-molecular weight heparin twice per day was administered as bridge therapy. Antiarrhythmic drugs except amiodarone were stopped five half-lives before the procedure, and restarted on the following day.

2.4 Ablation procedure

Procedures were performed under modest sedation with fentanyl. The dose of heparin used was 70-100U/kg body weight. The left atrial structure was reconstructed under the guidance of three-dimensional mapping system (CARTO-3, Biosense Webster Inc., Irvine, CA, USA). Using trans-septal access, the Lasso or PentaRay mapping catheter was placed sequentially within each PV to record baseline PV potentials. Circumferential PV isolation was performed using an irrigated-tip contact-force sensing RF ablation

catheter (Thermocool SmartTouch, Biosense Webster) for patients undergoing radiofrequency ablation. Point by point ablation along the PV vestibule (power mode, 30-40 W, maximum 43°C, infusion rate 15 mL/min) was performed. The contact force applied prior to lesion delivery was 20 g (acceptable range 10-30g), with a minimum individual target lesion duration of 400 gram-seconds force-time integral. The ablation points were connected into a ring line around the left and right PVs, and complete electrical isolation of the PVs was verified. Bidirectional conduction block from the atrium to the PVs was judged as the successful ablation endpoint identified by a mapping catheter (10). Electrical cardioversion was used to restore sinus rhythm when necessary.

2.5 Post-procedural follow-up

Antiarrhythmic and oral anticoagulant drugs were continued for 3 months if there was no recurrence of arrhythmia. All patients were followed up with continuous electrocardiogram monitoring for 24 h before discharge. A 12-lead electrocardiogram (ECG) and 24-hour Holter recording were undertaken before discharge, at three months after the ablation procedure, and twice every year subsequently. In addition, telephone interviews were conducted by a referring physician every 6 months. If a patient became symptomatic, a new ECG or 24-hour Holter recording was performed. Recurrence was defined as an episode of AF, atrial flutter or atrial tachycardia of at least 30 seconds duration confirmed by ECG or Holter recording more than 3 months after the AF ablation. The follow-up time was at least 6 months.

2.6 Statistical analysis

Continuous data were presented as means ± standard deviation and compared using Student's t-test. Categorical data were presented as percentages of the total in each category and were compared using the chi-squared test. Participants were stratified by serum UCR quartiles. Cox proportional hazard regression analysis was used to test the effect of the variables on AF recurrence, adjusted for other variables. Kaplan–Meier analysis was used to analyse time to recurrence of AF after ablation. The risk was presented as hazard ratio (HR) at 95% confidence interval (95% CI). Correlations were assessed using Spearman's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of UCR and AF subtype for incident AF recurrence. All tests were two-sided, and P-values < 0.05 were considered statistically significant. Data analysis was performed using SPSS software, version 24.0 (SPSS, Inc.).

3 Results

3.1 Patient baseline clinical characteristics

The study population consisted of 233 consecutive patients (mean age 61.44 ± 9.43 years, 128 males) with either paroxysmal (n = 171) or persistent (n = 62) AF according to the exclusion criteria. The mean SUA and Cr of this cohort were 310.1 ± 80.35 mmol/L and 71.94 ± 16.01 mmol/L, respectively. PV isolation was achieved in all patients. After a mean follow-up of 20.74 ± 12.01months, 55 (23.60%) patients had AF recurrence. The mean UCR values had a higher level of AF recurrence than AF non-recurrence (4.868 ± 1.191 vs 4.291 ± 1.246, P = 0.003). Hypertension and diabetes were present in 27/55 (49.09%) and 7/55 (12.73%) of individuals with recurrence, 88/178 (49.43%) and 32/178 (17.98%) of non-recurrence patients, respectively. Patients with AF recurrence had a greater prevalence of persistent AF (PeAF) (41.82% vs 21.91%, P < 0.01) than those without AF recurrence. Baseline characteristics and demographic features of the study population are given in Table 1.

The baseline clinical characteristics of patients classified by pre-ablation UCR quartile are listed in Table 2. Patients in Q4 had higher UCR (P < 0.001). From the lowest to the highest UCR quartile, participants had increasing levels of UA (P < 0.01), TG (P < 0.01), LDL-C (P < 0.01), WBC (P < 0.05) and neutrophils (P < 0.01). Meanwhile, there were no statistically significant differences in age, sex, BMI, D-dimer, Fib, HbA1c, SOD, LAD, or LVEF among the UCR quartiles.

3.2 UCR correlation with AF recurrence after ablation

Univariate Cox regression analysis revealed that UCR (HR 1.299, 95% CI 1.092-1.545, P = 0.003), AF subtype (HR 2.19, 95% CI 1.274-3.763, P = 0.005), TG (HR 1.424, 95% CI 1.064-1.905, P = 0.017) and HbA1c (HR 1.373. 95% CI 1.016-1.856, P = 0.039) were associated with AF recurrence during the follow-up period (Table 3). Multivariate Cox regression analysis revealed that UCR (HR 1.217, 95% CI 1.008-1.468, P = 0.041), AF subtype (HR 2.711, 95% CI 1.414-5.199, P = 0.003), and TG (HR 1.437, 95% CI 1.054-1.960, P = 0.022) were associated with AF recurrence. The higher values of UCR were significantly associated with the incidence of AF recurrence. Considering UCR as a categorical variable, after adjustment for age, sex and LAD, there was an increased risk of recurrence in subjects in the highest quartile of UCR compared with subjects in the lowest quartile (HR 4.099, 95% CI 1.636-10.268, P = 0.003).

3.3 Predictive value of UCR in AF recurrence

Kaplan–Meier curves showed time to recurrence of AF in patients within different quartiles of UCR (P = 0.002, Figure 1). According to the results of ROC analysis, as shown in Figure 2, the area under the curve (AUC) for UCR was 0.651 (95% CI: 0.568-0.733, P = 0.001). UCR exhibited a larger AUC than the SUA (AUC:0.601, 95% CI: 0.516-0.686, P = 0.024) and AF subtype (AUC: 0.59, 95% CI: 0.501-0.680, P = 0.046). A cut-off point of 4.475 for UCR had sensitivity of 65.5% and specificity of 59.6% in predicting AF recurrence (P = 0.001). Kaplan–Meier curves showed time to recurrence of AF in patients with UCR above and below the cut-off level of 4.475 (P = 0.003, Figure 2).

10.3389/fendo.2023.1110102

TABLE 1 Baseline characteristics of the study population(n=233).

	Total (n=233)	Recurrence (n=55)	No recurrence (n=178)	P
Clinical data				
Age(years)	61.44 ± 9.43	60.56 ± 8.92	61.71 ± 9.60	P=0.423
Gender, male; n (%)	128(54.9%)	26(47.3%)	102(57.3%)	P=0.191
BMI	26.01 ± 3.54	25.87 ± 3.42	26.05 ± 3.58	P=0.786
Smoking, n (%)	66(28.3%)	11(20.0%)	55(30.9%)	P=0.117
Alcohol, n (%)	66(22.75%)	11(20.0%)	42(23.60%)	P=0.578
Hypertension, n (%)	115/233(49.36%)	27/55(49.09%)	88/178(49.43%)	P=0.964
Diabetes mellitus, n (%)	39/233(16.74%)	7/55(12.73%)	32/178(17.98%)	P=0.362
CAD, n (%)	82/233(35.19%)	20(36.36%)	62(34.83%)	P=0.835
CHA2DS2-vasc Score	2.318 ± 1.641	2.33 ± 1.846	2.32 ± 1.577	P=0.96
Echocardiographic parameters				
LA, mm	38.83 ± 5.26	39.21 ± 5.69	38.71 ± 5.13	P=0.553
LVEF, %	63.45 ± 5.65	64.0 ± 5.94	63.28 ± 5.56	P=0.423
Laboratory parameters				
D-dimer, mg/L	0.360 ± 0.45	0.288 ± 0.47	0.381 ± 0.44	P=0.195
WBC, ×10^9	6.04 ± 1.56	5.98 ± 1.41	6.06 ± 1.61	P=0.731
Neutrophil,×10^9	3.56 ± 1.34	3.38 ± 1.05	3.62 ± 1.41	P=0.261
TG, mmol/L	1.33 ± 0.72	1.50 ± 0.80	1.28 ± 0.69	P=0.058
TC, mmol/L	4.05 ± 0.95	4.05 ± 0.91	4.05 ± 0.97	P=0.998
LDL-C, mmol/L	2.31 ± 0.73	2.32 ± 0.67	2.31 ± 0.75	P=0.913
HbA1c, %	6.116 ± 0.795	6.270 ± 0.932	6.041 ± 0.709	P=0.067
BNP, pg/mL	147.7 ± 185.1	149.9 ± 198.1	147.0 ± 178.6	P=0.922
creatinine, mmol/L	71.94 ± 16.01	68.80 ± 13.79	72.92 ± 16.56	P=0.096
UA, mmol/L	310.1 ± 80.35	328.8 ± 78.71	304.3 ± 80.19	P=0.047
SOD, U/mL	162.2 ± 20.44	165.6 ± 25.82	161.2 ± 18.43	P=0.18
UA : SOD	1.914 ± 0.543	1.93 ± 0.508	1.908 ± 0.555	P-0.803
UCR	4.427 ± 1.255	4.868 ± 1.191	4.291 ± 1.246	P=0.003
UCR (%) P=0.0048				
Q1(≤3.56)	58(24.9%)	6(10.9%)	52(29.2%)	
Q2(3.57-4.31)	58(24.9%)	13(23.6%)	45(25.3%)	
Q3(4.32-5.09)	57(24.5%)	13(23.6%)	44(24.7%)	
Q4(≥5.10)	60(25.7%)	23(41.8%)	37(20.8%)	
PeAF	62(26.61%)	23(41.82%)	39(21.91%)	P=0.004

BMI, body mass index; CAD, coronary artery disease; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; WBC, white blood cells; TG, triglyceride; TC, total cholesterol; LDL-C; low-density lipoprotein cholesterol; HbA1c, glycosylated haemoglobin; BNP, B-type natriuretic peptide; SOD, superoxide dismutase; UA, uric acid; UCR, uric acid:creatinine; PeAF, persistent atrial fibrillation.

3.4 UCR in different AF types and genders

Subgroup analysis was conducted according to the different AF type and genders. Patients with PeAF had higher levels of UCR (4.81 ± 1.44 vs. 4.29 ± 1.15, P < 0.001) than PAF. Univariate Cox regression analysis showed that UCR was associated with AF recurrence in PAF (HR 1.426, 95% CI 1.092-1.8608, P = 0.009), but not in PeAF (HR 1.104, 95% CI 0.854-1.426, P = 0.451).

In terms of gender, female patients had higher levels of UCR (4.669 ± 1.375 vs. 4.228 ± 1.113, P < 0.001) than male patients.

TABLE 2 Clinical characteristics according to quartiles of UCR level.

	Q1(<3.57) (n=58)	Q2(3.58-4.31) (n=58)	Q3(4.32-5.09) (n=57)	Q4(>5.10) (n=60)	P
Clinical data					
Age(years)	62.43 ± 10.60	63.03 ± 8.21	60.32 ± 8.52	60.00 ± 10.02	P=0.084
Gender, male; n (%)	40(69.0%)	30(51.7%)	30(52.6%)	28(46.7%)	P=0.085
BMI	24.91 ± 3.5	25.6 ± 5.22	26.28 ± 3.34	26.74 ± 3.66	P=0.174
Smoking, n (%)	22(37.9%)	17(29.3%)	13(22.8%)	15(25.0%)	P=0.285
Alcohol, n (%)	25(43.1%)	20(34.5%)	21(36.8%)	17(28.3%)	P=0.411
Hypertension, n (%)	23(39.7%)	29(50.0%)	30(52.6%)	33(55.0%)	P=0.361
Diabetes mellitus, n (%)	13(22.4%)	12(20.7%)	7(12.3%)	8(13.3%)	P=0.361
CAD, n (%)	23(39.7%)	17(29.3%)	20(35.1%)	22(36.7%)	P=0.695
CHA2DS2-vasc Score	2.19 ± 1.88	2.40 ± 1.44	2.35 ± 1.61	2.33 ± 1.64	P=0.916
Echocardiographic parameters					
LAD(mm)	38.40 ± 5.21	39.17 ± 5.45	38.62 ± 5.02	39.13 ± 5.43	P=0.842
LVEF, %	63.04 ± 5.95	63.46 ± 5.39	63.94 ± 5.55	63.38 ± 5.80	P=0.874
Laboratory parameters					
D-dimer, mg/L	0.422 ± 0.460	0.328 ± 0.253	0.314 ± 0.448	0.376 ± 0.571	P=0.586
WBC, ×10^9	6.171 ± 1.819	6.511 ± 1.658	5.659 ± 1.277	5.818 ± 1.335	P=0.018
neutrophil,×10^9	3.771 ± 1.443	4.0 ± 1.553	3.208 ± 1.068	3.27 ± 1.069	P=0.002
lymphocyte,×10^9	1.753 ± 0.530	1.856 ± 0.639	1.863 ± 0.488	1.923 ± 0.564	P=0.430
Fibrinogen, g/L	2.626 ± 0.708	2.589 ± 0.511	2.62 ± 0.654	2.70 ± 0.421	P=0.739
TG, mmol/L	1.068 ± 0.497	1.322 ± 0.635	1.405 ± 0.942	1.515 ± 0.698	P=0.009
TC, mmol/L	3.78 ± 0.917	4.036 ± 0.959	4.108 ± 0.943	4.268 ± 0.953	P=0.056
LDL-C, mmol/L	2.061 ± 0.685	2.297 ± 0.723	2.348 ± 0.689	2.527 ± 0.771	P=0.009
HbA1c,%	6.012 ± 0.853	6.206 ± 0.776	6.067 ± 0.759	6.096 ± 0.710	P=0.641
creatinine, mmol/L	80.66 ± 19.65	74.31 ± 15.20	69.39 ± 11.75	63.66 ± 11.19	P<0.001
UA, mmol/L	242.9 ± 62.39	290.7 ± 62.23	322.7 ± 56.17	381.7 ± 68.60	P<0.001
SOD, U/mL	159.8 ± 17.54	159.0 ± 27.35	161.8 ± 19.89	167.8 ± 15.63	P=0.119
UCR	3.032 ± 0.414	3.909 ± 0.205	4.651 ± 0.190	6.063 ± 1.000	P<0.001

Abbreviations as in Table 1.

Univariate Cox regression analysis showed that higher UCR was associated with AF recurrence in male patients (HR 1.407, 95% CI 1.015-1.950, P = 0.04), but there was no significant association in female patients (HR 1.226, 95% CI 0.979-1.535, P = 0.077).

3.5 Correlation analysis of UCR with TG, LDL-C and BMI

Calculation of Spearman's correlation coefficient showed that there was a positive correlation of pre-procedural UCR with TG (r = 0.276, P < 0.001), LDL-C (r = 0.251, P < 0.001) and BMI (r = 0.160, P = 0.037) (Figure 3).

4 Discussion

The study revealed that an increase in UCR was positively associated with AF recurrence after radiofrequency catheter ablation. Participants in the highest UCR quartile (Q4) had a significantly elevated risk of AF recurrence than those in the lowest quartile. This increase of UCR in AF recurrence was also statistically significant in PAF and in male patients. Moreover, UCR might be a better predictor of AF recurrence than UA.

AF poses a significant burden on patients, physicians, and healthcare systems globally; however, the effectiveness of therapeutic measures has been unsatisfactory. Catheter ablation of AF appears to be a promising treatment, but recurrence rates are

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TABLE 3 Correlation Between UCR and recurrence of AF.

	Model 1		Model 2		Model 3	
	HR(95% CI)	P value	HR(95% CI)	P value	HR(95% CI)	P value
UCR (continuous)	1.299(1.092-1.545)	0.003*	1.271(1.062-1.521)	0.009*	1.217(1.008-1.468)	0.041*
UCR quartiles						
Q1	Reference		Reference		Reference	
Q2	2.117(0.805-5.572)	0.129	2.054(0.777-5.430)	0.147	2.022(0.764-5.352)	0.156
Q3	2.302(0.875-6.057)	0.091	2.222(0.839-5.885)	0.108	2.204(0.832-5.839)	0.112
Q4	4.424(1.800-10.874)	0.001*	4.203(1.684-10.491)	0.002*	4.099(1.636-10.268)	0.003*
AF subtype	2.190(1.274-3.763)	0.005*	2.344(1.359-4.043)	0.002*	2.711(1.414-5.199)	0.003*
TG, mmol/L	1.424(1.064-1.905)	0.017*	1.418(1.051-1.913)	0.022*	1.437(1.054-1.960)	0.022*
HbA1c, %	1.373(1.016-1.856)	0.039*	1.399(1.02-1.917)	0.037*	1.292(0.904-1.847)	0.159
Age	0.989(0.961-1.017)	0.42				
Sex	0.731(0.43-1.241)	0.246				
LAD, mm	1.021(0.97-1.075)	0.433				

Model 1, Unadjusted; Model 2, Adjusted for age,sex; Model 3, Adjusted for age, sex, LAD. Abbreviations as in Table 1.

still relatively high. The risk factors influencing the outcome of catheter ablation of AF include not only the type and duration of AF, but also hypertension, obesity, diabetes, hyperlipidaemia, smoking, alcohol consumption, OSA, and physical inactivity. In a retrospective study of 330 patients with paroxysmal AF who underwent catheter ablation, elevated preoperative SUA was associated with a higher rate of recurrence of AF (11). In another prospective study, Canpolat et al. enrolled 363 patients with paroxysmal AF. They demonstrated that SUA level is a powerful and independent predictor of AF recurrence in patients who have undergone successful cryoballoon-based AF ablation (12). Previous studies have shown that, SUA levels were positively correlated with recurrence of AF (11–14). SUA is a metabolic product of purine metabolism. Xanthine oxidase(XO) is a key enzyme in the breakdown of purines and pyrimidines to UA, and is also a critical source of reactive oxygen species (ROS), free radicals responsible for oxidative damage in AF (15). One study found that febuxostat could inhibit atrial electrical and structural remodelling of AF by suppressing XO (16). UA activates NF-KB and MAPK signalling pathways and induces the expression of inflammatory factors and chemokines, which have been connected with AF (17). Inflammation and oxidative stress, both of which promote the progression of the electrical and structural remodelling of AF, also accelerate the recurrence of AF (12).

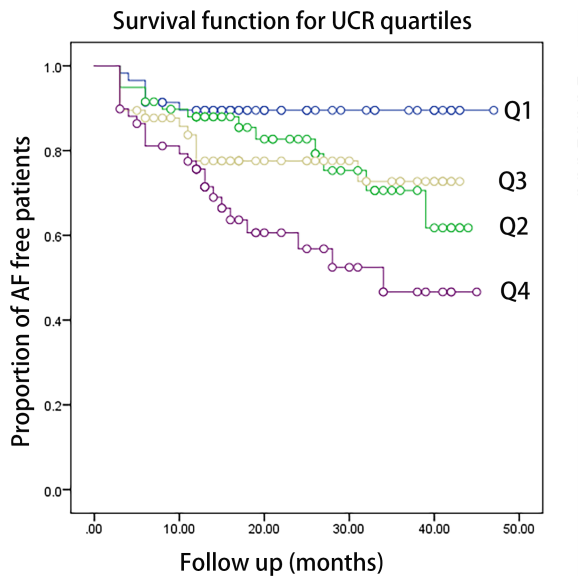

FIGURE 1
The Kaplan-Meier analysis of the AF free rate during the follow-up period according to UCR quartiles (log-rank P=0.002. Q1: <3.57,Q2: 3.58-4.31, Q3: 4.32-5.09, Q4: >5.10). AF, atrial fibrillation; UCR, uric acid/creatinine ratio.

SUA is increased in acute and chronic renal insufficiency, and renal dysfunction increases the risk of AF recurrence after catheter ablation (18, 19). Recently, renal function-normalised serum UA level has appeared as a new biomarker and is believed to reflect endogenous UA levels more precisely than SUA. Several studies have suggested that serum UCR is significantly associated with chronic obstructive pulmonary disease, chronic kidney disease, and B-Cell function in type 2 diabetes mellitus (20–22). The serum UCR, which represents renal function-normalized SUA, is associated with diverse adverse outcomes. Furthermore, this association was partially mediated through blood lipids, BMI, blood pressure, hs-CRP, and blood glucose (23). In a prospective cohort study, baseline UCR was significantly associated with incident metabolic syndrome (MetS), and UCR may be a better biomarker of incident MetS than SUA by stepwise multiple linear regression analysis, among community-dwelling women (6). A recent longitudinal study on Chinese communities found that

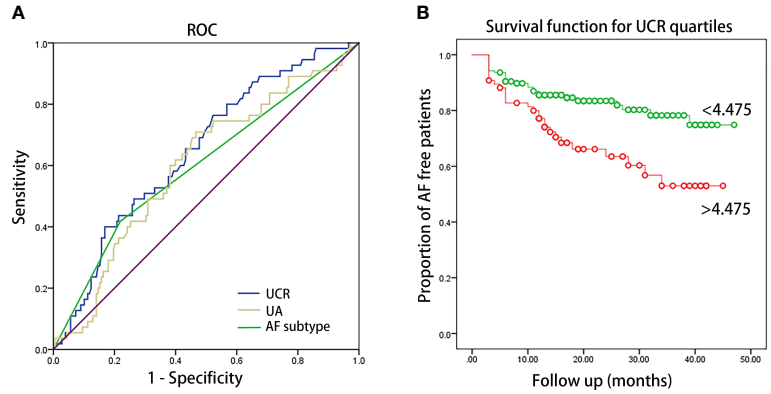

FIGURE 2
(A) ROC curve of UCR, UA and AF subtype for predicting AF recurrence after catheter ablation. The AUC were 0.651 (95% CI: 0.568-0.733, P = 0.001), 0.601 (95% CI: 0.516-0.686, P = 0.024) and 0.59 (95% CI: 0.501-0.680, P = 0.046) for UCR, UA and AF subtype, respectively. AUC: area under the curve. **(B)** Kaplan–Meier survival estimates of AF recurrence in patients with AF undergoing catheter ablation stratified by the pre-ablation UCR level of 4.475.

renal function-normalised UA was associated with renal disease progression in a cohort of T2DM patients. In addition to predicting metabolism and renal function, UCR also predicts all-cause mortality (8, 24). In the middle age and older population in China, elevated values of UCR were strongly associated with an increased risk of MetS, and this positive relationship remained in those individuals with normal uric acid levels (25). In common with previous studies, the present study showed that UCR is significantly associated with AF recurrence and predicted recurrence with greater sensitivity than UA. This might be because UCR is a global index of SUA and creatinine metabolism, so that it is a better indicator than a single index. In our study, in addition to pre-ablation UCR level, we also found that AF subtype, TG, HbA1c, and UA levels were independent predictors of AF recurrence. Correlation analysis showed that there was a positive correlation of pre-procedural UCR with TG, LDL-C and BMI. In a chinese study, serum UCR are strongly associated with the risk of MetS in postmenopausal Chinese women (26). In addition, a significant increase was observed in the prevalence of overweight/obesity, hypertension, and dyslipidemia across the SUA quartiles in Patients With Type 2 Diabetes Mellitus (27).

The study results corroborated those of previous studies and strengthened the relationship of SUA and creatinine in AF recurrence after catheter ablation. In this study, LAD was not found to be a predictor of AF recurrence. A possible reason is that the LA of the population we included had relatively small diameter. This is one of the reasons for the low AF recurrence rate in this study. In subgroup analysis, this study suggests that UCR is a valuable predictive biomarker in AF recurrence in patients with PAF and in male patients. In female patients and those with PeAF, UCR has no predictive value for AF recurrence. We speculated on the possible reasons. Several studies also reported that there are sex-related differences in clinical characteristics in the section of the AF population who are free of valvular disease. Women with AF are older than their male counterpart, and have a higher heart rate, more symptoms, more complications, a poorer quality of life, worse prognosis, and increased prevalence of PeAF, stroke and death (28–30). Our data showed a tendency for female patients to have an increased risk of recurrence after catheter ablation, which was in agreement with previous findings. In addition, the reason for the finding that UCR level does not predict recurrence of PeAF is elusive. It is widely known that the recurrence rate in patients with PeAF is significantly higher than that in patients with PAF. The reasons may be the longer duration of episodes of AF, larger atrial volume and severe atrial fibrosis in PeAF, which are the more important risks for the recurrence of PeAF.

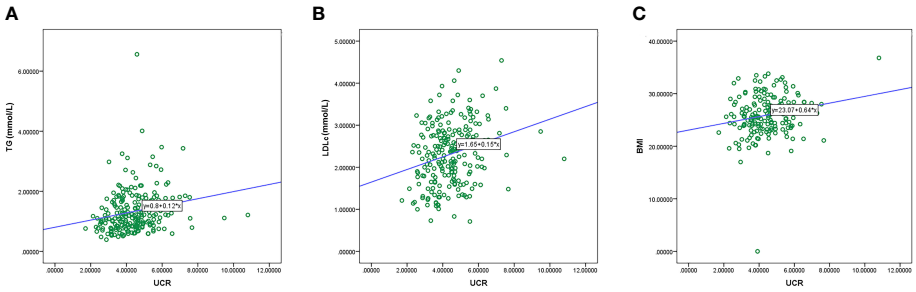

FIGURE 3
Correlation between the UCR level and duration of TG **(A)**, LDL-C **(B)**, and BMI **(C)**. TG, triglyceride.

Our study had several limitations. First, the diagnosis of AF recurrence was based on the occurrence of palpitations symptoms, periodic phone calls, ECG and Holter recordings. But ECG and Holter were done every three or six months, it might not catch the rhythm of a patient with PAF, or it might not be done in time for an AF attack. Therefore, we underestimated the true incidence of AF relapse in our study possibly. Second, we did not measure other markers of specific oxidative stress and inflammation, such as IL-6, TNF-α and ROS. Finally, this study was a retrospective study performed with data from a single centre with a relatively small sample size and short follow-up period. Therefore, further prospective studies with a larger number of patients and longer follow-up period may be needed to confirm and enhance our results.

5 Conclusion

UCR was significantly associated with AF recurrence after catheter ablation. However, further studies are required to identify the appropriate parameters of SUA or MetS for predicting recurrence of AF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of Shandong First Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ was responsible for data collection, statistical analysis and paper writing. YW was responsible for data collection and follow-up. XY was responsible for the follow-up of some patients. ZL was responsible for informed consent signing and preoperative data collection. LS is responsible for the writing and guidance of the thesis. YH is responsible for the project design and paper revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Paola Di Pietro,
University of Salerno, Italy

REVIEWED BY
Guido Zavatta,
University of Bologna, Italy
Luigi Petramala,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Charbel Abi Khalil
cha2022@med.cornell.edu

†These authors have contributed equally to this work

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Primary hyperaldosteronism is associated with increased mortality and morbidity in patients with hypertension and diabetes

Krishnadev Pillai[1†], Ahmed Fares[1†], Soha Dargham[2], Jassim Al Suwaidi[3], Amin Jayyousi[4] and Charbel Abi Khalil[1,3,5*]

[1]Department of Medicine, Weill Cornell Medicine–Qatar, Doha, Qatar, [2]Biostatistics Core, Weill Cornell Medicine–Qatar, Doha, Qatar, [3]Heart Hospital, Hamad Medical Corporation, Doha, Qatar, [4]Department of Endocrinology, Hamad Medical Corporation, Doha, Qatar, [5]Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine, New York, NY, United States

Aims: Primary hyperaldosteronism (PA) is a common cause of hypertension. It is more prevalent in patients with diabetes. We assessed the cardiovascular impact of PA in patients with established hypertension and diabetes.

Methods: Data from the National Inpatient Sample (2008-2016) was used to identify adults with PA with hypertension and diabetes comorbidities and then compared to non-PA patients. The primary outcome was in-hospital death. Secondary outcomes included ischemic stroke, hemorrhagic stroke, acute renal failure, atrial fibrillation, and acute heart failure.

Results: A total of 48,434,503 patients with hypertension and diabetes were included in the analysis, of whom 12,850 (0.03%) were diagnosed with primary hyperaldosteronism (PA). Compared to patients with hypertension and diabetes but no PA, those with PA were more likely to be younger [63(13) vs. 67 (14), male (57.1% vs. 48.3%), and African-Americans (32% vs. 18.5%) (p<0.001 for all). PA was associated with a higher risk of mortality (adjusted OR 1.076 [1.076-1.077]), ischemic stroke [adjusted OR 1.049 (1.049-1.05)], hemorrhagic stroke [adjusted OR 1.05 (1.05-1.051)], acute renal failure [adjusted OR 1.058 (1.058-1.058)], acute heart failure [OR 1.104 (1.104-1.104)], and atrial fibrillation [adjusted OR 1.034 (1.033-1.034)]. As expected, older age and underlying cardiovascular disease were the strongest predictors of mortality. However, the female gender conferred protection [OR 0.889 (0.886-0.892].

Conclusion: Primary hyperaldosteronism in patients with hypertension and diabetes is associated with increased mortality and morbidity.

KEYWORDS

hypertension, cardiovascular disease, diabetes, National Inpatient Database (NIS), primary hyperaldosteronism (PA)

1 Introduction

The autonomous production of aldosterone by an aldosterone-producing adenoma in a single adrenal gland or by bilateral adrenal lesions in hyperaldosteronism. Primary hyperaldosteronism (PA) commonly presents with hypertension and hypokalemia attributed to the effect of aldosterone on the mineralocorticoid receptors resulting in renal reabsorption of sodium and excretion of potassium (1). PA was previously considered a rare cause of hypertension and was estimated to be prevalent in 0.5-2% of hypertensive patients (2, 3). However, with increased use of plasma aldosterone concentration to plasma renin activity ratio or aldosterone/renin ratio as screening tests.

PA is estimated to be present in 5-10% of hypertensive patients (4–8). Hypertension in PA is associated with left ventricular hypertrophy (LVH), stroke, renal dysfunction (9), and impaired glucose metabolism (10). Further, those complications correlate with plasma aldosterone levels. However, there is limited evidence on the co-existence of PA and hypertension in patients with established diabetes. Our study aims to characterize the outcomes of PA in hypertension patients with diabetes using a large database, the National (Nationwide) Inpatient Database (NIS).

2 Methods

2.1 Data source

We analyzed data from the National Inpatient Sample (NIS) from 2008 to 2016. The NIS is an administrative and de-identified database designed by the Healthcare Cost and Utilization Project (HCUP) to produce US regional and national estimates of inpatient utilization, access, charges, quality, and outcomes, excluding outpatients or readmissions. It accounts for 20% of all US community hospitals. Each entry in the database entails demographic details such as age, gender, race, etiology of admissions, and outcomes while using safeguards to protect the privacy of patients, physicians, and hospitals (11). The study did not require institutional review board approval but an exempt determination (number 18-00017).

2.2 Study population and outcomes

We included in our analysis hospitalized patients with both hypertension and diabetes. We then stratified them into two groups according to the presence of PA. The primary outcome was in-hospital death. Secondary outcomes included ischemic stroke, hemorrhagic stroke, acute renal failure, atrial fibrillation, and acute heart failure. Diagnosis, comorbidities, and outcomes were extracted using the ICD-9-CM and ICD-10-CM codes.

2.3 Statistical analysis

Data were weighted per the recommendation of the HCUP to generate national estimates of admissions each year (12). Patients were divided into two groups according to the presence of PA and compared in terms of baseline characteristics and outcomes. Finally, we assessed the predictors of mortality in hypertensive patients with diabetes and PA. Data are presented as mean (SD), median (IQR), number (%), or OR (95% CI). A Chi-squared test, student T-test, or ANOVA was used to compare groups, as appropriate. Binary logistic regression was used to calculate the unadjusted odds ratios of outcomes, which were further adjusted for all baseline characteristics that were different among both groups. Multivariate logistic regression was performed to determine predictors of mortality. The significance level was set at 5%; all analyses were done using SPSS version 26 (IBM SPSS Statistics, IBM, Armonk, New York).

3 Results

3.1 Population

A total of 9,746,732 patients with diabetes and hypertension were hospitalized between 2008 and 2016. After excluding patients under 18 and those with incomplete or missing records, 9,741,009 patients were included in the analysis. After the application of weights, the data set included 48,434,503 patients. Of these, 12,850 (0.03%) were diagnosed with PA (Figure 1).

3.2 Baseline characteristics

Patients in the PA group were more likely to be younger [63(13) vs. 67 (14) years], male (57.1% vs. 48.3%), and African-American (32% vs. 18.5%) (p<0.001 for all) (Table 1). They were also more likely to have comorbidities such as obesity, dyslipidemia, and renal failure but less likely to smoke or have comorbidities including valvular heart disease, peripheral vascular disease, and coronary artery disease (p < 0.001). As expected, patients with PA had a significantly higher prevalence of hypokalemia than their non-PA counterparts (39.3% vs 9.2%, respectively; p<0.001).

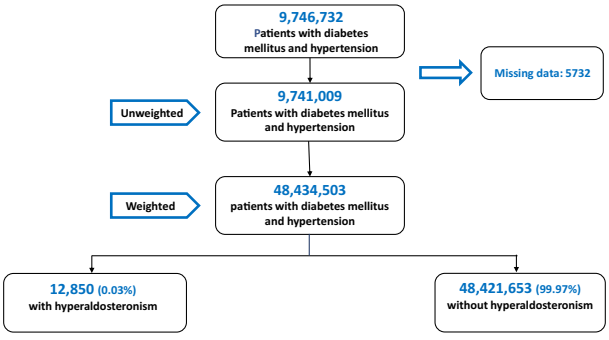

FIGURE 1
Flow chart of the study.

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TABLE 1 Comparison of baseline characteristics of patients with diabetes and hypertension, with and without primary hyperaldosteronism (PA).

	With PA	Without PA	P-value
Age			
Mean (SD)	63 (13)	67 (14)	<0.001
<55	3, 322 (25.8%)	8,936,376 (18.5%)	<0.001
55 - 64	3,729 (29.0%)	10,827,343 (22.4%)	<0.001
65 - 74	3,370 (26.2%)	13,073,773 (27.0%)	<0.001
75 - 84	1,974 (15.4%)	10,798,557 (22.3%)	<0.001
>85	457 (3.6%)	4,785,605 (9.9%)	<0.001
Sex			
Male	7,335 (57.1%)	23,367,934 (48.3%)	<0.001
Female	5,515 (42.9%)	25,053,720 (51.7%)	<0.001
Race			
Caucasians	6,343 (54.3%)	28,791,851 (64.6%)	<0.001
African Americans	3,742 (32.0%)	8,232,450 (18.5%)	<0.001
Asians	289 (2.5%)	1074203 (2.4%)	0.114
Hispanics	972 (8.3%)	4,808,929 (10.8%)	<0.001
Comorbidities			
Obesity	3,590 (27.9%)	10,760,842 (22.2%)	<0.001
Dyslipidemia	7,005 (54.5%)	25,360,416 (52.4%)	<0.001
Valvular Heart Disease	633 (4.9%)	2,507,445 (5.2%)	0.007
Peripheral Vascular Disease	1,107 (8.6%)	5,249,702 (10.8%)	<0.001
Chronic kidney disease	5,274 (41.0%)	13,559,885 (28.0%)	<0.001
Coronary Artery Disease	2,830 (22.0%)	13,661,526 (28.2%)	<0.001
Aortic aneurysm	139 (1.1%)	494,591 (1.0%)	0.497
Hypokalemia	5,046 (39.3%)	4,476,475 (9.2%)	<0.001

3.3 Comparison of PA and non-PA Groups

Patients with PA were more likely to die in hospital [adjusted OR = 1.076 (1.076-1.077)] and experience adverse outcomes, including atrial fibrillation [adjusted OR = 1.034 (1.033-1.034)], ischemic stroke [adjusted OR = 1.049 (1.049-1.05)], hemorrhagic stroke [adjusted OR = 1.05 (1.05-1.051)], acute renal failure [adjusted OR = 1.058 (1.058-1.058)], and acute heart failure [adjusted OR = 1.104 (1.104-1.104) (Table 2).

3.4 Predictors of mortality

As expected, the mortality risk in patients with PA increases with age [OR = 1.039 (1.027-1.046)] (Table 3). Compared to Caucasians, Asians have a higher mortality risk [OR = 1.375 (1.361-1.389)]. Interestingly, African American and Hispanic patients had a lower risk of mortality [ORs = 0.874 (0.869-0.878) and 0.93 (0.924-0.936), respectively]. The female gender conferred protection [OR 0.889 (0.886-0.892]. Among comorbidities, valvular heart disease, peripheral vascular disease, chronic kidney disease, coronary artery disease, and hypokalemia were associated with increased mortality. Interestingly, obesity and dyslipidemia were shown to be protective.

4 Discussion

Our study showed that PA among hospitalized patients with hypertension and diabetes was associated with increased mortality risk, atrial fibrillation, stroke, acute heart failure, and acute renal failure. Comorbidities, including valvular heart disease, peripheral vascular disease, chronic kidney disease, and hypokalemia, independently increased mortality risk. It is already known that hypertension in the presence of PA is associated with higher cardiovascular event rates. Milliez et al. reported an increased risk of stroke, myocardial infarction, and atrial fibrillation in patients with PA compared to patients with essential hypertension (13).

10.3389/fendo.2023.1147225

TABLE 2 Comparison of outcomes of patients with diabetes and hypertension with and without primary aldosteronism (PA).

	Number of Events (OR; 95% CI)			
Outcome	With PA	Without PA	Adjusted OR (95% CI)	P-value
Mortality	1,211,127	125	1.076 (1.076-1.077)	<0.001
	(OR = 1)	(OR = 0.38; 0.256-0.564)		
Atrial Fibrillation	7,853,993	1,902	1.034 (1.033-1.034)	<0.001
	(OR = 1)	(OR = 0.892; 0.800-0.994)		
Ischemic Stroke	278,901	89	1.049 (1.049-1.05)	<0.001
	(OR = 1)	(OR = 1.208; 0.760-1.921)		
Hemorrhagic Stroke	87,865	54	1.05 (1.05-1.051)	<0.001
	(OR = 1)	(OR = 2.349; 1.299-4.248)		
Acute renal failure	7494,970	2,863	1.058 (1.058-1.058)	<0.001
	(OR = 1)	(OR = 1.563; 1.425-1.715)		
Acute Heart Failure	12,024,478	3,108	1.104 (1.104-1.104)	<0.001
	(OR = 1)	(OR = 0.962; 0.879-1.052)		

HA is more frequent in females than in females. However, we observed a greater prevalence of the disease in males. One plausible explanation for this discordance is that we only assessed in-hospital patients with diabetes and PA; therefore, the male/female ratio could differ from the one observed in cohorts from outpatient clinics. Further, data pertinent to the gender difference in primary HA with diabetes are lacking. A recent Taiwanese analysis estimated the male proportion of diabetes patients with PA to be 50.8% (14). In an analysis of 256 outpatients with new-onset T2D and hypertension patients, a higher number of males with PA was reported (15).

In our study, PA patients had a higher rate of hypokalemia, increasing their mortality risk. This finding was recently reported in a 10-year follow-up of a cohort of PA patients (16). However, we did not find any difference in the prevalence of aortal aneurysms. Previous data indicated that PA patients had larger ascending aorta diameters and increased abdominal aortic calcification (17, 18), facts that, unfortunately, we can't check in the NIS database since those data are lacking. In experimental models, excessive aldosterone levels were related to myocardial and vascular inflammation, injury, and fibrosis (19–21). Aldosterone-mediated fibrosis of the human myocardium has also been reported in cardiac imaging studies and is associated with systolic and diastolic dysfunction (22, 23). The structural changes of the heart in the setting of PA serve as a substrate for cardiac arrhythmias such as atrial fibrillation. Hypokalemia, one of the hallmarks of PA, causes prolongation of the atrioventricular conduction time and increases the likelihood of atrioventricular reentry mechanisms, increasing the risk of atrial fibrillation (24). Furthermore, aldosterone directly contributes to cardiac electrophysiologic remodeling, increasing the risk of atrial fibrillation (25). Aldosterone also induces inflammation, fibrosis, and necrosis of various other organs, including the kidneys (26), which may explain the increased risk of acute renal failure.

The pathophysiology of diabetes in PA is multifactorial. In 1964, Conn et al. reported an increased incidence of impaired glucose tolerance in a review of 145 patients with PA (1). The higher prevalence of diabetes in PA can be explained by impaired pancreatic insulin secretion and reduced insulin sensitivity in the setting of high levels of aldosterone (27). Garg et al. demonstrated that elevated aldosterone levels were associated with insulin resistance in normotensive healthy subjects (28). In a 10-year prospective study, high plasma aldosterone levels predicted the development of insulin resistance, suggesting that hyperaldosteronism may induce diabetes (29). Aldosterone also induces clonal β-cell failure through the glucocorticoid receptor (30).

The exact mechanisms by which PA increases cardiovascular mortality and morbidity are unclear. It might be possible that PA-related inflammation mediated by higher aldosterone levels accelerates atherosclerosis in diabetes since aldosterone promotes the production of inflammatory cytokines and decreases beneficial adipokines such as adiponectin (31). Further, high aldosterone levels are associated with increased reactive oxygen species (32–34), one of the hallmarks of the development of cardiovascular complications of diabetes.

The results of our study must be interpreted within its limitations. We used ICD-9-CM and ICD-10-CM codes to extract data from the NIS database; reporting and coding errors may be present. Further, the methodology and criteria used to diagnose PA are unclear. The retrospective nature of the database prevents us from establishing causality, and only correlations can be made. Due to the unavailability of patient-level data, information related to medications, biochemical parameters, echocardiography data, diabetes control and duration, and severity of comorbidities were not included. Our analysis only included hospitalized patients, which may represent a sicker cohort with an increased prevalence

TABLE 3 Predictors of mortality in patients with diabetes, hypertension, and primary aldosteronism.

		OR (95% CI)	P-value
Age	*Mean*	1.039 (1.027-1.046)	<0.001
	<55	Ref	Ref
	55 - 64	1.631 (1.619-1.644)	<0.001
	65 - 74	2.231 (2.214-2.247)	<0.001
	75 - 84	3.221 (3.198-3.244)	<0.001
	>85	4.872 (4.836-4.909)	<0.001
Sex	Male	Ref	Ref
	Female	0.889 (0.886-0.892)	<0.001
Race	Caucasian	Ref	Ref
	African American	0.874 (0.869-0.878)	<0.001
	Hispanic	0.93 (0.924-0.936)	<0.001
	Asian	1.375 (1.361-1.389)	<0.001
Obesity	No	Ref	Ref
	Yes	0.645 (0.641-0.648)	<0.001
Dyslipidemia	No	Ref	Ref
	Yes	0.617 (0.615-0.619)	<0.001
Valvular Heart Disease	No	Ref	Ref
	Yes	1.658 (1.647-1.669)	<0.001
Peripheral Vascular Disease	No	Ref	Ref
	Yes	1.474 (1.467-1.482)	<0.001
Chronic kidney disease	No	Ref	Ref
	Yes	2.004 (1.996-2.011)	<0.001
Coronary Artery Disease	No	Ref	Ref
	Yes	1.218 (1.214-1.223)	<0.001
Hypokalemia	No	Ref	Ref
	Yes	1.20 (1.01-1.31)	<0.001

of adverse outcomes compared to the general population. Lastly, data following patient discharge or readmission data were unavailable, so follow-up of patients was not possible. Despite these limitations, our results are derived from a large sample representative of the US population.

5 Conclusion

In conclusion, we showed that primary hyperaldosteronism is associated with worse outcomes in hospitalized patients with hypertension and diabetes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The study did not require institutional review board approval but an exempt determination (number 18-00017). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CAK conceived the study concept and design. KP and AF acquired data and performed statistical analyses with SD. KP, AF, JA, AJ, and CAK analyzed and interpreted data. KP and AF wrote the first draft and conducted the literature search. CAK is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and

the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Stephen Fitzgerald,
Royal Adelaide Hospital, Australia
Akira Sugawara,
Tohoku University, Japan
Anthony Martin Gerdes,
New York Institute of Technology, United States

*CORRESPONDENCE
Shaohua Wang
gyjwsh@126.com

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The severity of valvular heart disease in euthyroid individuals is associated with thyroid hormone levels but not with TSH levels

Pin Wang [1,2], Sen Lu [3], Yan Yang [2], Limei Liu [2], Guangpeng Zhou [2], Jieling Zhu [4], Diejing Niu [5], Yi Wang [3] and Shaohua Wang [5]*

[1]Department of Endocrinology, Medical School of Southeast University, Nanjing, China, [2]Department of Endocrinology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China, [3]Department of Intensive Care Unit, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China, [4]Department of Nursing, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital, Chengdu, China, [5]Department of Endocrinology, Affiliated ZhongDa Hospital of Southeast University, Nanjing, China

Background: Abnormal thyroid function is a metabolic disorder and can lead to several complications, including cardiovascular diseases. In this study, we aimed to examine the relationship between clinical traits and outcomes and the thyroid hormone level of euthyroid individuals with valvular heart disease (VHD).

Method: The thyroid function was evaluated in 526 euthyroid VHD patients and 155 healthy control people. As well as clinical indicators were collected and analyzed.

Results: No difference in TSH levels ($p>0.05$) was recorded; however, fT3, TT3, and TT4 levels were lower in the euthyroid VHD patients than in healthy control(4.3 vs 4.63; 1.37 vs 1.48; 97.7 vs 102.09, respectively, all $p<0.05$), while the fT4 level was higher (12.91 vs 12.35, $p<0.05$). Moreover, all showed a continuous trend with the change of NYHA grade which does not consist of the incidence of euthyroid sick syndrome(ESS). Further analysis showed that for every 10-fold increase in BNP, fT4 increases by 83%, fT3 decreases by 30%, and TT3 decreases by 12% after being adjusted for other influencing factors. Meanwhile, adjusted fT4 was correlated with multiple worse clinical indicators, which were influenced by age.

Conclusion: Thyroid hormones are widely regulated in VHD patients even with acceptable cardiac function, except for TSH level. And the adjusted fT4 is related to worse clinical indicators and outcomes which are only recorded in patients under 53 years old.

KEYWORDS

thyroid hormone, valvular heart disease, euthyroid sick syndrome, NYHA grades, age

Introduction

Thyroid hormone impacts on the body can have a positive impact on the heart and vascular system (1). The active cellular form of thyroid hormones, triiodothyronine (T3), profoundly alters cardiovascular hemodynamics through a number of mechanisms, including direct genomic effects, extra-nuclear, nongenomic effects on the ion channels, and other effects on the peripheral circulation (2, 3). By influencing tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility, and heart rate, triiodothyronine can boost cardiac output in various ways (1). Faster heart rates, ejection fractions, cardiac outputs, and blood volumes in hyperthyroidism patients indicate enhanced cardiac pump performance with lower afterloads. They also have lower systemic vascular resistance and isovolumic relaxation times (1, 2). Contrary to hyperthyroidism, hypothyroidism considerably decreases cardiac preload and increases afterload, resulting in a decrease in stroke volume and cardiac output. Even in the condition's preclinical manifestations, this is true. Adults with hypothyroidism are more likely than euthyroid people to experience heart failure, decreased cardiac function, coronary heart disease, and all-cause mortality (4–6).

In addition to the considerable effects thyroid hormones have on the circulatory system, heart diseases are distinct pathophysiological disorders that may also have an effect on the level of thyroid hormones (7). In the past, euthyroid sick syndrome (ESS) was blamed for the irregular thyroid functions in people with cardiac disorders. However, individuals with heart disorders, in particular those with valvular heart diseases unrelated to metabolic factors, have a distinct cardiac function (8). As opposed to ESS, which is controlled by a variety of peripheral thyroid hormone regulation systems, the status of thyroid hormones in this state is more complex. Numerous studies have examined the connection between thyroid hormones and heart failure, but the most widely used indicator of thyroid function was the TSH (thyroid-stimulating hormone) level, which may not be a reliable indicator of thyroid function in heart failure because TSH levels are not correlated with triiodothyronine levels (9–12). Meanwhile, it is worth to noting that several studies have identified intriguing associations between FT4 and the heart. For instance, the Penn Heart Failure Study discovered a positive correlation between atrial fibrillation and higher levels of FT4 (not FT3 or TT3) (9). Additionally, other studies have revealed higher FT4 levels are linked to an increased risk of heart failure and sudden cardiac death (13, 14). As a result, TSH may not be the most significant indicator of thyroid function in euthyroid people with valvular heart disease due to their thyroid hormone status. However, the connection between thyroid hormone levels and the clinical signs and prognosis of valvular heart disease is not yet fully understood.

Thus, studying the thyroid hormone levels in euthyroid patients with valvular heart disease and analyzing their correlation with clinical traits and outcomes are the goals of this clinical study.

Materials and methods

Patients

From January 2019 to June 2021, the Sichuan Provincial People's Hospital's Department of Endocrinology, cardiac surgery, intensive care unit, and health examination center conducted this retrospective study. It was accepted by the Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital Research Ethics Committee, and all trials were carried out in accordance with the necessary standards and laws.

The thyroid function profile, which comprises TT3, TT4, fT3, fT4, TSH, TgAb, and TPOAb (thyroid peroxidase antibody), was assessed in 526 euthyroid patients with valvular heart disease who were hospitalized for cardiac surgery department from January 2019 to June 2021. At the same time, data on 155 healthy individuals' thyroid function and demographics, such as their age and gender, were gathered from the Sichuan Provincial People's Hospital's Health Examination Center. The primary first exclusion requirements were: 1) A TPOAb level of greater than 30 IU/ml or a TgAb level of greater than 75 IU/ml; 2) A history of thyroid disease; 3) A history of thyroid-related drug use, including lithium, amiodarone, interferon-alpha, interleukin-2, tyrosine kinase inhibitors, phenytoin, phenobarbiturates, iodine contrast, and carbamazepine; and 4) A history of pituitary disease.

Clinical data collection

Patients with valvular heart disease demographic data were gathered, including their age, sex, weight, height, smoking, alcohol consumption, history of chronic illness, and drug use. Heart rate, blood pressure, pulse rate, and respiration rate were recorded as baseline clinical features. On the first day of admission, blood samples were taken and examined concurrently. Lymphocyte count, CRP, alanine transaminase, aspartate aminotransferase, total bilirubin, direct bilirubin, glucose, creatinine, blood urea nitrogen, cardiac troponin I, creatine kinase (CK), creatine kinase (CK), creatine kinase (CK), creatine kinase (CK), and creatine kinase, muscle and brain (CK-MB). The level of heart failure was also determined by looking at the brain natriuretic peptide (BNP). Heart surgery indicators such as cardiopulmonary bypass time (CPBT) and aortic occlusion time were gathered (AOT). Patients recovering from heart surgery in our cardiac surgery center are frequently transferred to the intensive care unit (ICU) for post-operative observation. For the severity assessment of the post-cardiac surgery patients, we additionally recorded ICU characteristics such as the sequential organ failure assessment (SOFA) score and acute physiology and chronic health illness categorization system II (APACHE II). The use of invasive and non-invasive ventilators, endotracheal intubation time, the likelihood of re-tracheal intubation, lung infections, intra-aortic

balloon pumps (IABP), continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and ICU time was also noted. After being released, the outcome of the hospital stay and deaths were also recorded. During or after data collection, none of the authors had access to information that may identify specific participants.

As patients were admitted, doctors and patients graded the NYHA class (New York Heart Association functional classification) scores following the NYHA functional classification (15).

Thyroid hormone sampling

An automated chemiluminescence assay (Immulite 2000sr; Abbott, Shanghai, China) was used to evaluate the thyroid function profile, including TT3, TT4, fT3, fT4, TSH, TgAb, and TPOAb, immediately after sampling at the central laboratory of the Sichuan Provincial People's hospital under routine external quality control. Based on data showing an analytical sensitivity of 0.0025 IU/ml for TSH, 1.5 pg/ml for fT3, and 0.22 ng/dl for fT4, the test was given regulatory approval. The intra- and inter-assay coefficients of variance were 5% and 10%, respectively, across all assays. TSH 0.35-4.94 mIU/l, fT3 2.43-6.01 pmol/l, fT4 9.01-19.05 pmol/l, TT3 (0.88-2.44nmol/L), and TT4 (62.68-150.8nmol/L) are the reference ranges used in our lab. TPOAb has a 30 IU/mL upper limit, while TgAb has a 75 IU/mL upper limit.

The presence of both a normal serum TSH level (0.35–4.94 mIU/L) and a serum T3 level below the lowest laboratory normal limit (0.88nmol/L) was used to diagnose ESS (16).

Statistical analysis

Statistical evaluations were carried out utilizing SPSS version 23. (SPSS Inc., Chicago, IL, USA). Statistical significance was set at p 0.05 for all two-sided analyses. Depending on the situation, data are reported as mean ± SD (standard deviation), median (quartile range), or n(%). ANOVA and the student's t-test were used for normally distributed variables, and the Mann-Whitney U and Kruskal-Wallis tests were used for nonparametric variables. Bonferroni's *post hoc* comparison procedure, Dunnett's unequal variance procedure, and Kruskal-Wallis one-way ANOVA were employed, respectively, for *post hoc* comparisons. For categorical variables, the Chi-squared test and Fisher exact probability approach were employed. In parametric statistical analysis, log-transformed was used for variables with known lognormal distributions (such as TSH and BNP). To investigate the correlations between the thyroid function and continuous variables, Pearson or Spearman rank correlation analysis and linear regression analysis were carried out. Analysis of covariance was used to examine how various effect modifiers interacted with one another. Also, the extent to which age influences the association between thyroid function and the clinical features of valvular heart disease was investigated using hierarchical analysis.

Results

Characteristics of thyroid function in patients with valvular heart disease

Differences in thyroid function between euthyroid patients with valvular heart disease and normal population

Table 1 summarizes the sex, age, and thyroid function data for euthyroid patients with valvular heart disease and the general population. There was no clinically meaningful difference in TSH levels between the two patient groups ($p>0.05$). However, euthyroid individuals with valvular heart disease had lower levels of fT3, TT3, and TT4 than healthy patients (4.3 vs. 4.63; 1.37 vs. 1.48; 97.7 vs. 102.09, respectively; all $p<0.05$). On the other hand, patients with euthyroid valvular heart disease had higher fT4 levels (12.91 vs. 12.35, $p<0.05$).

TABLE 1 Differences in thyroid function between patients with valvular heart disease and normal population.

	Healthy control	VHD patients	P value
Number	155	526	
Male	76 (49%)	242 (46%)	
Age	49 ± 12	52 ± 12.5	
fT3	4.63 ± 0.6	4.3 ± 0.8	0.000*
fT4	12.35 (11.61-13.03)	12.91 (11.90-14.22)	0.000†
TT3	1.48 ± 0.2	1.37 ± 0.28	0.000*
TT4	102.09 ± 16.7	97.7 ± 19	0.000*
TSH	1.88 ± 1.8	2.0 ± 2.0	0.32 ※*

The data are presented as the n(%), mean ± SD or median(interquartile range) unless otherwise specified. VHD, valvular heart disease; fT3, Free Triiodothyronine; fT4, Free Thyroxine; TT3, Total Triiodothyronine; TT4, Total Thyroxine; TSH, Thyroid stimulation Hormone. Unit: fT3(pmol/L), fT4(pmol/L), TT3(nmol/L), TT4(nmol/L), TSH(mIU/L).
*Student`s t test was employed for normal distributed variables.
†The Mann-Whitney U test was employed for asymmetrically distributed variables.
※Log transform was use in parametric statistical analyses.

Differences in thyroid function according to NYHA grades in euthyroid patients with valvular heart disease and normal population

To further explore the connection between thyroid function and heart function, we divided the VHD patients into subgroups using the NYHA classification (Table 2). ANOVA analysis revealed that there were statistically significant differences in the levels of fT3, fT4, TT3, and TT4 between the groups (all $p<0.05$), except for the TSH level. In particular, the levels of fT3, fT4, and TT3 all showed decreased trends in the various NYHA groups (Figure 1), but the level of TT4 did not show a clear trend. The subsequent hoc study revealed that there was no difference in thyroid function between valvular heart disease of NYHA grades 1 and 2 and healthy controls, but that there was a significant difference between the thyroid functions of valvular heart disease of NYHA grades 3 and 4 and healthy controls.

The incidence of ESS in different NYHA grades in euthyroid patients with valvular heart disease

Meanwhile, we compared several cardiac functions to describe the prevalence of ESS in valvular heart disease (Table 3). Patients with valvular heart disease and NYHA 1-3 grades did not have a substantially different incidence of ESS (all $p>0.05$); however, patients with NYHA 4 grades had a significantly greater incidence of ESS (16%, $p<0.05$).

Influencing factors of thyroid function in euthyroid patients with valvular heart disease

Age, sex, body mass index (BMI), and β-blocker therapy were investigated as variables impacting thyroid function in euthyroid patients with valvular heart disease. There was no gender-related difference in thyroid function ($p>0.05$). The findings indicated that older age was related to lower TSH levels (r -0.101, p <0.05). The relationship between fT3 and TT3 levels and BMI was found to be minimal ($p< 0.05$). Lower fT3 and TT3 levels were discovered to be related to treatment with β-blockers (r -0.135, p0.05; r -0.063, $p<0.05$, respectively). fT3 decreased by 30%, fT4 increased by 83%, and TT3 decreased by 12% for every 10-fold rise in BNP level, demonstrating the close relationship between thyroid function and BNP (Table 4 and Figure 2).

Relationships between fT4 level and clinical characteristics of valvular heart disease

To conduct a hierarchical analysis, we divided all patients with valvular heart disease into three equal groups based on fT4 levels, using 53 as the age cutoff (Table 5 and Figure 3). In the subgroup of patients under the age of 53, higher fT4 levels were associated with increased heart rate, elevated diastolic BP, higher total bilirubin, higher direct bilirubin, and elevated BNP levels (all $p<0.05$) upon admission to the hospital. Simultaneously, as fT4 levels increased, the SOFA score gradually increased in the ICU ($p<0.05$). In terms of outcome measures, increased F4 levels were closely correlated with longer ICU stay and overall length of stay (all $p<0.05$). Although in the subgroup of patients above the age of 53, higher fT4 levels were associated with an increased prevalence of hypertension, heart rate, systolic blood pressure, AST, total bilirubin, and BNP levels (all $p<0.05$), there was no strong association between higher fT4 levels and postoperative outcome measures in VHD patients. Although there was a statistical difference in intubation time, no increasing trend in intubation time was observed with increasing fT4 levels.

Discussion

Our study revealed that, even with acceptable cardiac function, with an increase in NYHA grade, euthyroid patients with valvular heart disease exhibited a continuous trend of decreased fT3, TT3, and TT4 levels and increased fT4 levels compared to healthy people,

TABLE 2 Differences in thyroid function according to NYHA class in patients with valvular heart disease and normal population.

		VHD(NYHA class)				
	Healthy control	I level	II level	III level	IV level	P Value
Number	155	32	114	295	85	
Male (%)	76 (49)	20 (63)	47 (41.2)	140 (47.5)	35 (41.2)	
age	49 ± 12	39.7 ± 15.4	47.5 ± 13.7	54.1 ± 10.5	54.4 ± 11.85	
fT3	$4.63 \pm 0.6^{3,4}$	4.7 ± 0.74^{4}	4.43 ± 0.78^{4}	4.31 ± 0.68^{0}	$4.02 \pm 0.95^{0,1,2}$	0.000*
fT4	$12.4\ (11.6,13.0)^{3,4}$	12.5 (12,14)	$12.7\ (11.9,13.9)^{4}$	$12.9\ (11.8,14.2)^{0}$	$13.4\ (12.2,15.2)^{0,2}$	0.000†
TT3	$1.48 \pm 0.2^{3,4}$	$1.53 \pm 0.28^{3,4}$	1.42 ± 0.27^{4}	$1.37 \pm 0.26^{0,1,4}$	$1.25 \pm 0.32^{0,1,2,3}$	0.000*
TT4	102.09 ± 16.7^{3}	96.98 ± 15.1	97.88 ± 18.8	94.3 ± 18.8^{0}	101.7 ± 20.2	0.008*
TSH	1.88 ± 1.8	2.01 ± 2.01	2.08 ± 1.98	2.0 ± 2.0	1.89 ± 2.14	0.720※*

The data are presented as the n (%), mean ± SD or median (interquartile range) unless otherwise specified. VHD, valvular heart disease; fT3, Free Triiodothyronine; fT4, Free Thyroxine; TT3, Total Triiodothyronine; TT4, Total Thyroxine; TSH, Thyroid stimulation Hormone. Unit: fT3(pmol/L), fT4(pmol/L), TT3(nmol/L), TT4(nmol/L), TSH(mIU/L).
*ANOVA test was employed for normal distributed variables. Post hoc comparisons were made using Bonferroni's method for equal variances, and Dunnett's method was used for unequal variances.
†The Kruskal-Wallis tests test was employed for asymmetrically distributed variables, and one-way ANOVA for post hoc comparison.
※Log transform was use in parametric statistical analyses.
Number: 0-4 respectively represent healthy control, I level, II level, III level, IV level, and superscript number means statistically significant with relevant group in post hoc comparisons.

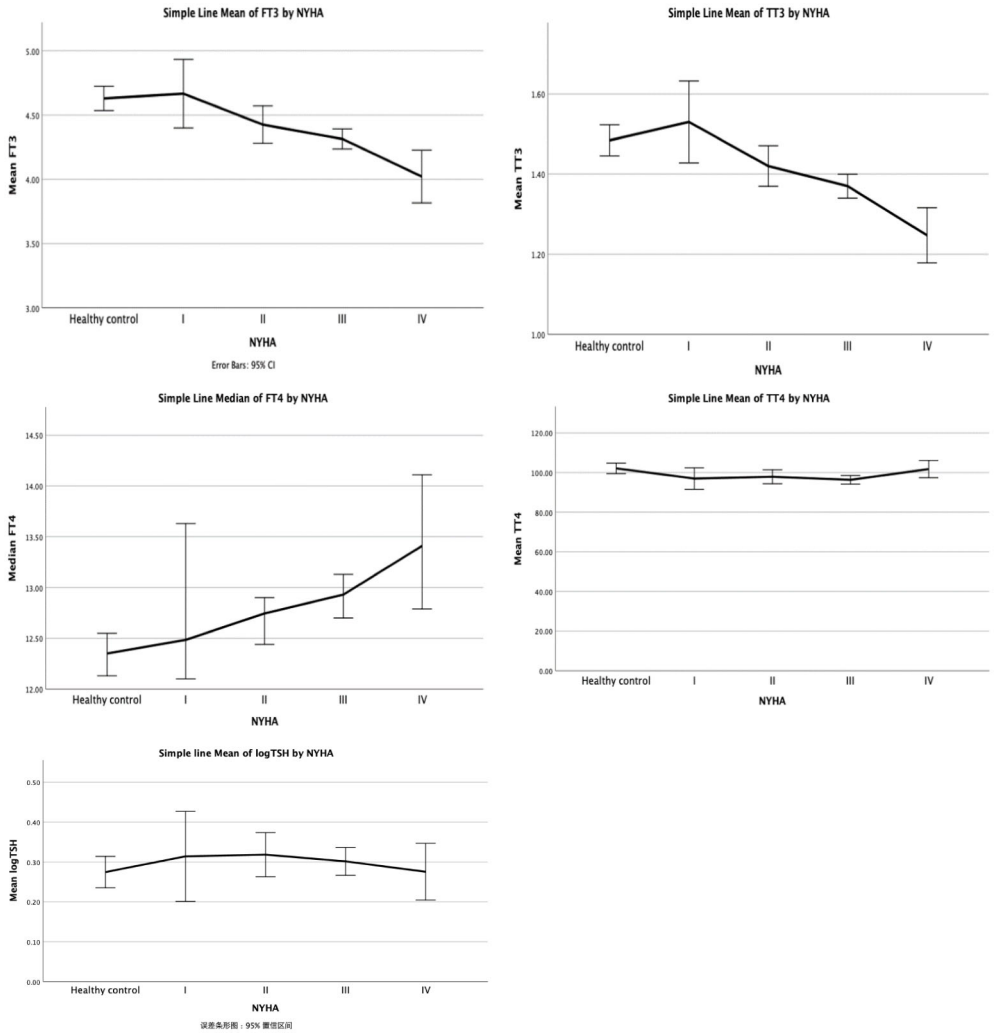

FIGURE 1
Thyroid function in patients with different NYHA grades of VHD.

except for TSH levels, which is inconsistent with the typical profile of patients with the ESS. Further investigation revealed that even after adjusting for other contributing factors (such as BMI and use of β-blockers), there was an 83% increase in fT4, a 30% decrease in fT3, and a 12% decrease in TT3 for every 10-fold increase in BNP. Also, other clinical signs are worse when fT3 levels are altered, but age is a significant influencing factor. Higher fT4 levels, higher heart rate, increased heart rate, elevated diastolic BP, higher total bilirubin, higher direct bilirubin, and elevated BNP levels, higher SOFA scores, are associated with longer ICU stay and overall length of stay in individuals under the age of 53 years. Many of the connections; however, were not present in patients over the age of 53 years.

The present study was a significant retrospective inquiry that targeted individuals with valvular heart disease who did not have any other metabolic disorders other coronary heart disease (17, 18). To minimize the effect on thyroid function, we also eliminated patients with thyroid illnesses (9, 19–21). In addition to examining

TABLE 3 Incidence of euthyroid sick syndrome in patients with valvular heart disease by different NYHA classes.

NYHA class	VHD				
	I level	II level	III level	IV level	P Value
Total number	32	114	295	85	
Euthyroid sick syndrome	2	5	22	14*	0.016
Percentage (%)	6.25	4.39	7.46	16.47	

The Chi-squared test was used for categorical variables.
* Statistically significant with other groups in post hoc comparisons.

TABLE 4 Effect of BNP on thyroid function.

BNP	Regression coefficient	Crude OR	Adjusted OR*
fT3	-0.361 (-0.47- -0.25)	0.67 (0.63-0.78)	0.70 (0.62-0.78)
fT4	0.685 (0.428 - 0.942)	1.98 (1.53-2.57)	1.83 (1.41-2.38)
TT3	-0.132 (-0.172 - -0.092)	0.88 (0.84-0.91)	0.88 (0.84-1.09)

* Adjusted for BMI (body mass index) and usage of β-blocker.

thyroid function in patients with valvular heart disease, we also investigated how thyroid function related to other clinical indicators, such as baseline characteristics, indicators related to surgery and the intensive care unit, as well as outcome measures such as hospital stay and death. In euthyroid individuals with valvular heart disease, our study provides the first comprehensive description of the thyroid profile, including TSH, fT3, fT4, TT3, and TT4, with specific attention to the various NYHA classes and their relationships to clinical indicators.

The ESS has been implicated in numerous earlier investigations as the cause of aberrant thyroid functioning in patients with cardiac insufficiency (22). In patients with either acute or chronic systemic diseases, the ESS is characterized by a typical laboratory values, notably low T3 levels with normal or low T4 and TSH levels, in patients with acute or chronic systemic diseases (23). In contrast to previous trials, our study revealed that the incidence of ESS was, 6.25%, 4.39%, and 7.46% in patients with NYHA classes I through III, respectively. The incidence of ESS did not differ statistically across the three groups. However, there was a downward trend observed in fT3 and TT3 levels among the valvular heart disease population compared to the healthy population. It is noteworthy that fT3 and TT3 levels may be affected in patients with NYHA I-III levels, even though the incidence of the ESS is not higher than that of the healthy population. While the ESS may contribute to these findings, individuals with valvular heart disease did exhibit relatively low T3 levels, and higher T4 levels, particularly, fT4. The ranges of T3 and T4 levels observed are wider than what would typically be expected in euthyroid sick syndrome.

Traditionally, studies on thyroid function have primarily focused on TSH levels, which have been associated with a higher risk of heart failure, changes in cardiac function, and even mortality. However, the CORONA experiment found no association between TSH levels and heart failure with a lower ejection fraction (3, 6, 7, 11, 24). Despite this, TSH has remained a crucial guiding signal for thyroid therapeutic intervention trials. In individuals with valvular heart disease, TSH levels, and T3 and T4 levels may not align consistently, potentially due to abnormal conversion of T4 to T3 in peripheral tissues (20, 25, 26). Importantly, T3 or T4 levels may have greater clinical significance in these patients. Therefore, in certain trials, particularly those involving patients with abnormal cardiac function, TSH, T3, and T4 levels should be considered, and T3 and T4 levels could potentially be used as a management target.

Additionally, to the changes in T3 levels, patients with valvular heart diseases also experienced different changes in fT4 levels when

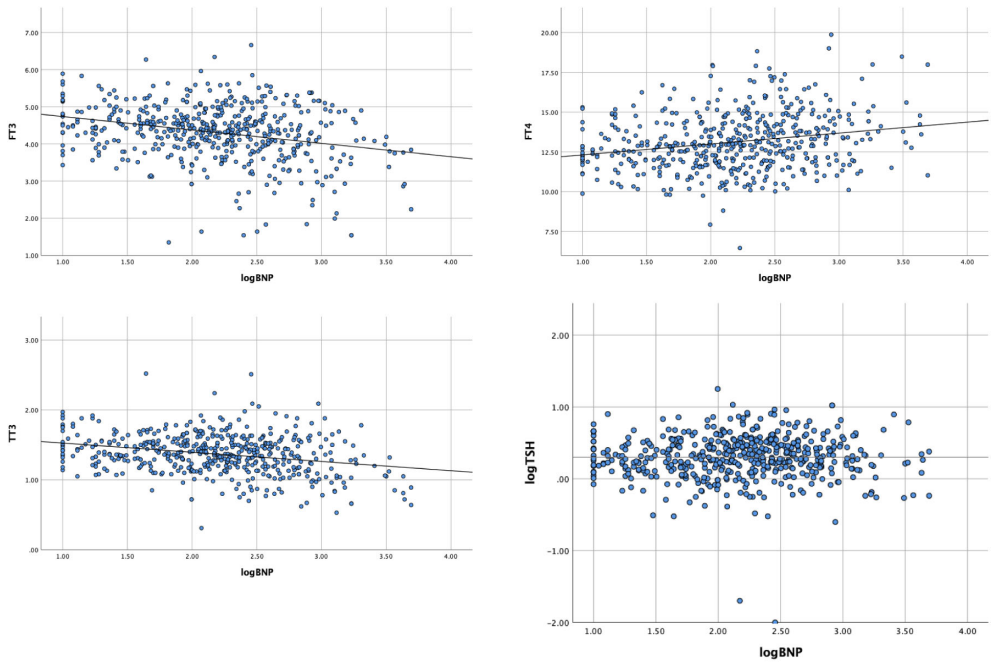

FIGURE 2
Simple scatter of thyroid function index by log BNP.

TABLE 5 Relationships between FT4 and clinical characteristics of patients with VHD at different ages.

Age (year)		≤53					>53				
fT4 Level(pmol/L)		ALL	<12.2	≥12.2 <13.7	≥13.7	P	ALL	<12.2	≥12.2 <13.7	≥13.7	P
Number		283	88	102	93		242	90	69	83	
Baseline Characteristics	BMI (kg/m^2)	23 (3)	23 (3)	23 (4)	23 (3)		23 (4)	23 (3)	24 (4)	24 (4)	
	Hypertension	25	10	9	6		65	30	12	23	p<0.05
	Heart rate	82 (16)	77 (15)^3	82 (14)^3	88 (16)^{1,2}	p<0.05	82 (17)	78 (13)^3	80 (12)^3	87 (22)^{1,2}	p<0.05
	Systolic BP	116 (16)	116 (17)	117 (17)	114 (14)		122 (19)	125 (19)^3	124 (18)^3	116 (18)^{1,2}	p<0.05
	Diastolic BP	69 (12)	67 (13)^{23}	70 (11)^1	71 (13)^1	p<0.05	70 (15)	70 (17)	69 (12)	72 (14)	
	Lymphocyte	1.7 (0.6)	1.7 (0.5)	1.7 (0.6)	1.6 (0.7)		1.5 (0.5)	1.5 (0.5)^3	1.6 (0.5)	1.5 (0.6)^1	
	ALT(U/L)	24 (15-40)	21 (15-33)	24 (15-35)	28 (16-53)		23 (16-38)	22 (15-35)	21 (14-35)	26 (18-45)	
	AST(U/L)	41 (102)	34 (42)	45 (145)	43 (86)		32 (18)	30 (12)^3	28 (11)^3	38 (25)^{1,2}	p<0.05
	TBIL (μmol/L)	18 (13-24)	16 (12-22)	18 (13-22)	20 (14-29)	p<0.05	17 (13-21)	16 (12-19)	16 (13-22)	18 (15-23)	p<0.05
	DBIL (μmol/L)	5.7 (4-8)	5.3 (4-7)	5.4 (4-7)	6.6 (4.9-8.4)	p<0.05	5.4 (4.4-7.2)	5.0 (3.9-6.5)	5.4 (4.3-7.0)	6.2 (5.0-8.4)	
	Glucose(mmol/L)	5.2 (2.9)	5.1 (1.0)	5.4 (4.5)	5.2 (1.3)		5.8 (2.1)	5.6 (2.0)	5.8 (1.6)	6.0 (2.7)	
	BNP (pg/mL) *	124 ± 4.0	,105 ± 4.0^3	91 ± 3.8^3	201 ± 3.7^{1,3}	p<0.05	194 ± 3.8	138 ± 3.8^3	204 ± 3.4	270 ± 3.9^1	p<0.05
Surgery related Indicators	CPBT (min)	127 (50)	131 (59)^3	125 (52)	125 (39)^1		138 (52)	132 (50)	140 (56)	141 (50)	
	AOT (min)	86 (40)	86 (43)^3	84 (40)	88 (36)^1		92 (36)	89 (37)	91 (35)	97 (36)	
ICU related indicators	SOFA	5.8 (1.8)	5.4 (1.6)^3	5.9 (1.8)	6.1 (1.9)^1	p<0.05	6.2 (1.9)	6.5 (1.8)	6.3 (1.9)	5.9 (1.8)	
	APCHE II	10 (3.4)	11 (4.0)	10 (3.0)	10 (3.3)		12 (4.0)	12 (3.2)	12 (4.0)	11 (4.9)	
	Intubation time (hr.)	26 (45)	34 (69)	21 (30)	23 (25)		28 (40)	21 (19)^3	38 (60)^3	28 (34)^{1,2}	p<0.05
	Re-tracheal intubation	5	1	1	3		11	3	5	3	
	IABP	14	6	1	7		14	6	4	4	
	CRRT	8	1	3	4		11	2	4	5	
	ICU time (day)	2 (1-4)	2 (1-4)	1 (1-3)	3 (1-4)	p<0.05	3 (1-5)	2 (2-5)	3 (2-5)	3 (1-4)	
Outcomes	Hospitalization time (day)	19 (15-24)	18 (15-22)	19 (14-23)	21 (17-26)	p<0.05	20 (17-26)	21 (17-26)	20 (17-27)	20 (17-25)	
	Death	3	0	2	1		13	4	5	4	

The data are presented as the n (%), mean ± SD or median (interquartile range) unless otherwise specified. VHD, valvular heart disease; fT3, Free Triiodothyronine; BP, blood pressure(mmHg); ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, Direct Bilirubin; BNP, brain natriuretic peptide; CPBT, cardiopulmonary bypass time; AOT, aortic occlusion time; SOFA, sequential organ failure assessment score; APCHE II, acute physiology and chronic health disease classification system II; IABP, intra-aortic balloon pump; CRRT, continuous renal replacement therapy.

ANOVA test was employed for normal distributed variables. Post hoc comparisons were made using Bonferroni's method for equal variances, and Dunnett's method was used for unequal variances.

The Kruskal-Wallis tests test was employed for asymmetrically distributed variables.

The Chi-squared test was used for categorical variables.

*Log transform was use in parametric statistical analyses.

Number: 1-3 respectively represent tripartite grouping of fT3, and superscript number means statistically significant with relevant group in post hoc comparisons.

p<0.05 was defined as statistical significance.

compared to healthy individuals and the fT4 level increased with the increase of NYHA grade and BNP level. While T3 is recognized as the active cellular form of thyroid hormones, it`s important not to underestimate the role of T4. The Penn Heart Failure Study found that atrial fibrillation was positively associated with higher levels not fT3 or TT3, meanwhile, higher fT4 levels were also linked to incident heart failure, and sudden cardiac death (9, 13, 14). Although our cross-sectional study does not establish a cause-and-

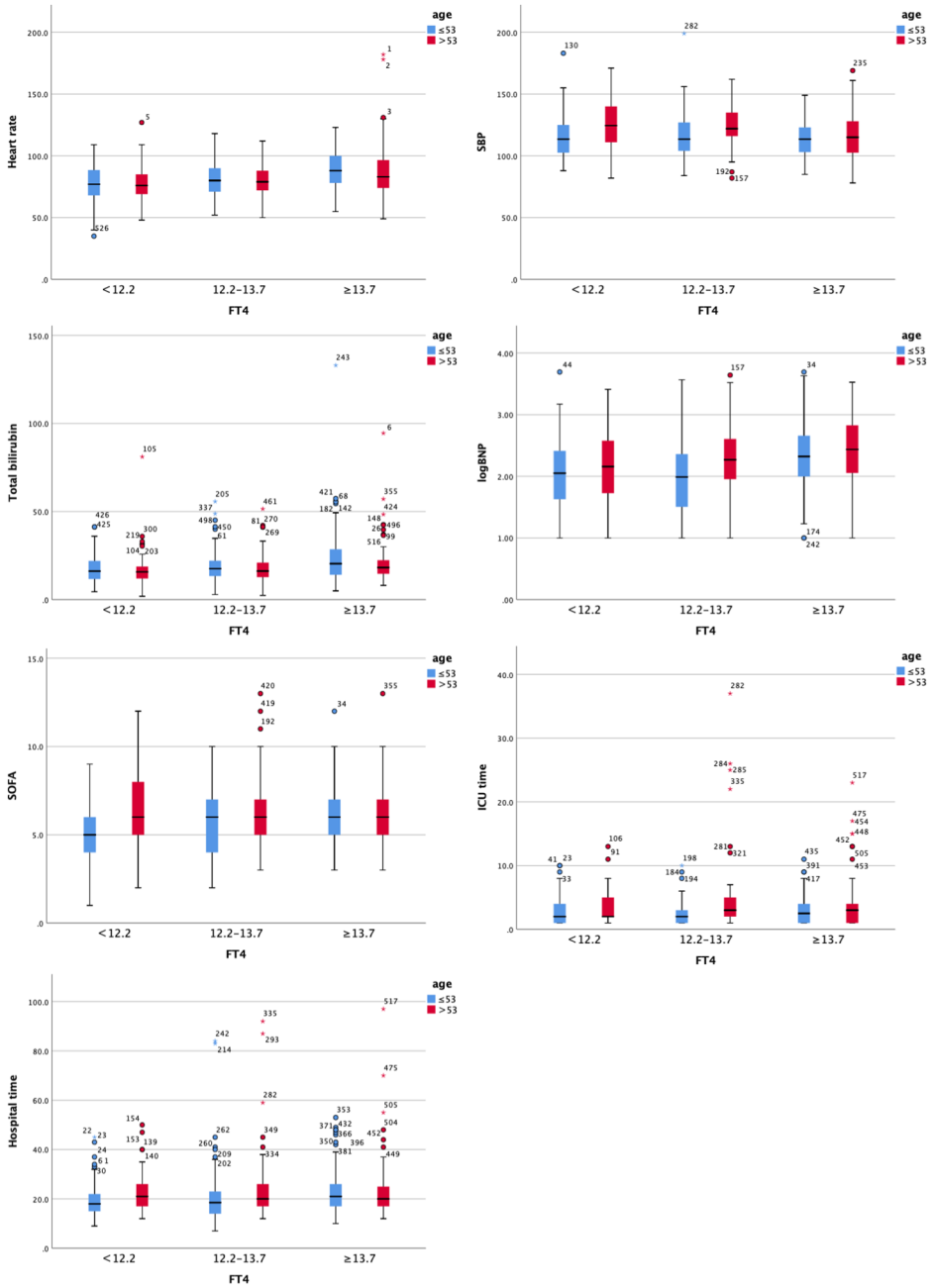

FIGURE 3
Clustered Boxplot of clinical index by fT3. The * represents outliers, which is a way of visualizing them in a box plot.

effect relationship, the close relationship between fT4 levels and NYHA levels, and BNP levels further underscores the crucial role of fT4 levels in patients with cardiac insufficiency. The peripheral deiodination of T4 to T3 may be affected by an increase in cytokines, free fatty acids, and cortisol, resulting in higher fT4 levels that reflect the worsening condition of heart failure.

The analysis of thyroid function and clinical features yielded intriguing results, indicating a connection between fT4 levels and several clinical parameters, with age playing a significant role in this association. The strength of the association between fT4 levels and clinical characteristics appears to be more pronounced in younger patients, while it is less prominent in older patients. This could be attributed to the fact that cardiac performance and clinical indicators in older patients are influenced by multiple uncorrected factors, making it more challenging to achieve favorable outcomes. These findings suggest the potential use of certain interventions, such as administering thyroxine to younger patients, to improve clinical outcomes. By targeting fT4 levels and addressing thyroid function in younger patients, it may be possible to enhance their overall prognosis.

The absence of the rT3 level due to technical limitations in our center's laboratory is the study's limitation; however, this does not

affect our analysis of the results, and in addition, most laboratories are unable to detect the level of rT3, so there are some restrictions on its potential clinical applications. At the same time, it was impossible to completely rule out the potential of central hypothyroidism. The second drawback is that patient mortality and death outcomes cannot be studied due to the low mortality rate before discharge and the short follow-up period. Monitoring thyroid function at multiple time points may provide a better understanding of the changes in thyroid hormone levels throughout the process. However, due to the retrospective design of the study, this may be considered a limitation of the current trial. Meanwhile, due to limited resources, we were unable to obtain sufficient imaging-based indicators before and after cardiac surgery, which may partially limit the scope of our study. In the future, more research can be done to get beyond these restrictions.

Conclusions

In conclusion, our study showed that euthyroid patients with valvular heart diseases had decreased fT3, TT3, and TT4 levels compared to healthy individuals, but increased levels of fT4 even with acceptable cardiac function. Additionally, they showed a continuous trend with the change in NYHA grade, which is inconsistent with the profile of ESS. Further research showed that for every 10-fold rise in BNP, fT4 increases by 83%, fT3 decreases by 30%, and TT3 lowers by 12%, even after accounting for other influencing variables. Additionally, there are various clinical indications that are connected to the adjusted level of fT4 that are associated with worse outcomes; however, age is a crucial influencing factor since many of the associations between the adjusted level of fT3 and clinical indicators are only evident in individuals under the age of 53. As a result, not only TSH but also T3, and T4 levels should be of concern in some trials, especially in patients with abnormal cardiac function, and T4 levels can even be used as a management target other than TSH. Further research is required to explore the use of thyroxine to improve clinical outcomes in abnormal thyroid function of valvular heart disease at a younger age.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: PW, SW, SL,YW. Data collection: PW, SL, YY, LL. Analysis and interpretation of results: PW, SL, GZ. Draft manuscript preparation: PW, JZ, DN. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1193557/full#supplementary-material

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EDITED BY
Carmine Izzo,
University of Salerno, Italy

REVIEWED BY
Elke Marjolein Muntjewerff,
Uppsala University, Sweden
Yalin Wu,
University of Alabama at Birmingham,
United States

*CORRESPONDENCE
Piotr Kmieć
piotrkmiec@gumed.edu.pl

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Low catestatin as a risk factor for cardiovascular disease – assessment in patients with adrenal incidentalomas

Ewa Zalewska[1], Piotr Kmieć[1]*, Jakub Sobolewski[2], Andrzej Koprowski[2] and Krzysztof Sworczak[1]

[1]Department of Endocrinology and Internal Medicine, Medical University of Gdańsk, Gdańsk, Poland, [2]First Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland

Background: Catestatin (Cts) is a peptide derived from proteolytic cleavage of chromogranin A, which exhibits cardioprotective and anti-inflammatory properties. Cts has been proposed as a potential biomarker for cardiovascular (CV) disease.

Objectives: examining Cts in patients with incidentally discovered adrenocortical adenomas (AI), and its associations with CV risk factors and blood pressure (BP).

Materials and methods: In this cross-sectional study, 64 AI patients without overt CV disease other than primary hypertension were recruited along with 24 age-, sex-, and body-mass-index (BMI)-matched controls with normal adrenal morphology. Laboratory, 24-h ambulatory BP monitoring, echocardiography, and common carotid artery sonography examinations were performed.

Results: Unadjusted Cts was higher in AI patients (median 6.5, interquartile range: 4.9-37 ng/ml) versus controls (4.5 (3.5 – 28)), p=0.048, however, the difference was insignificant after adjusting for confounding variables. Cts was lower in subjects with metabolic syndrome than in those without it (5.2 (3.9- 6.9) vs. 25.7 (5.8-115) ng/ml, p<0.01), and in men compared to women (4.9 (4-7.4) ng/ml vs. 7 (4.8-100), p=0.015). AI patients in the lower half of Cts levels compared to those in the upper had a higher prevalence of hypertension (OR 0.15, 95% CI: 0.041-0.5, p<0.001) and metabolic syndrome (OR 0.15, 95% CI 0.041-0.5, p<0.001). In AI patients Cts correlated positively with high-density lipoprotein cholesterol (Spearman's r=0.31), negatively with BMI (r=-0.31), and 10-year atherosclerotic CV disease risk (r=-0.42).

Conclusions: Our data indicate associations between CV risk factors and Cts. More clinical research is needed to apply serum Cts as a biomarker.

KEYWORDS

catestatin, adrenal incidentaloma (AI), cardiovascular disease(s), risk predictor, metabolic syndrome

1 Introduction

Risk factors for atherosclerotic cardiovascular disease (ASCVD) can be divided into nonmodifiable (e.g. age or sex) and modifiable (smoking, elevated blood pressure (BP), dyslipidemia, diabetes (DM), and obesity). Apart from established risk factors, new are sought (e.g. uric acid (UA) (1) and high-sensitivity C-reactive protein [hs-CRP) (2)]) to help distinguish persons at higher risk of developing cardiovascular disease (CVD), who would benefit more from medical interventions such as low-density lipoprotein cholesterol (LDL-C) reduction (3).

The sympathetic nervous system plays a pivotal role in CVD development. Chromogranin A (CgA) is co-stored and co-released with catecholaminec from sympathetic neuronal vesicles and the adrenall medulla. One of CgA's proteolytic cleavage products is catestatin (Cts), a cardioprotective, anti-hypertensive, and anti-inflammatory peptide (4, 5). *In vitro*, Cts was shown to bind to nicotinic acetylcholine receptors, which inhibits membrane depolarization and blocks calcium influx, and, consequently, suppresses catecholamine release and activation of the sympathetic nervous system (6). Studies with animal models demonstrated Cts exerts anti-inflammatory effects, cardioprotection, and reduces obesity and insulin resistance (7–9). Clinical studies indicate Cts is involved in the course of hypertension (HT), coronary artery diseases (CAD), and heart failure (HF) (10–12). Adolescents with metabolic syndrome (MetS) had decreased Cts, which was postulated as a novel CVD risk factor (12–14).

In the current study we aimed at 1) determining Cts levels in patients with an incidentally-discovered adrenocortical adenoma/hyperplasia (AI) and without overt CVD other than HT, as well as 2) investigating associations between Cts and ASCVD risk modifiers, and asymptomatic HT-mediated organ damage (15). The presence of an AI *per se*, and particularly mild autonomous cortisol secretion (MACS) in its course, have been associated with metabolic disorders, elevated CV risk and mortality (16). So far, Cts has not been investigated in this patient population.

2 Subjects and methods

2.1 Study population

Study participants with an AI were recruited among 376 consecutive adult patients hospitalized in the Department of Endocrinology and Internal Medicine of the University Clinical Center of the Medical University of Gdańsk between November 2018 through February 2020 due to an adrenal lesion. We included 64 patients with radiological features of an adrenal adenoma/hyperplasia revealed by computed tomography (CT) or magnetic resonance (MR), who agreed to participate in the study, and met none of the following exclusion criteria: 1) age over 75 or under 40; 2) obesity grade III (BMI >40 kg/m^2); 3) premenopausal period; 4) adrenal hormone excess other than MACS, i.e. cortisolemia between 50 and 138 nmol/l in the overnight 1-mg dexamethasone suppression test (DST) and no phenotypic features of Cushing's syndrome (17); 5) kidney disease with eGFR<60 ml/min/1.73m^2 and/or proteinuria >0.25 g/24h); 6) treatment with a mineralocorticoid receptor antagonist; 7) established and/or overt CVD other than primary HT, including: a) ASCVD (CAD, stroke, transient ischemic attack, peripheral artery disease), b) significant cardiac disease (e.g. pathological arrhythmia, severe valvular heart disease, cardiac tamponade, cardiomyopathy, congenital heart disease, HF), c) vascular diseases (among others venous thromboembolism and vasculitis); 8) active malignancy; 9) decompensated autoimmune disease or immune disease associated with CV and/or renal complications; 10) infectious diseases; 11) current or past addiction to alcohol and/or illicit drugs. Study participants were recruited based on anamnesis, physical examination, additional examinations available for review prior to enrollment and performed in the course of the study. Initially, 73 patients were included, however, three withdrew their consent to participate due to the COVID-19 pandemic, in four patients transthoracic echocardiography (TTE) revealed cardiac post-ischemic lesions, and two were diagnosed with primary aldosteronism.

Based on medical records of our hospital, which included examinations ordered in outpatient clinics and the emergency department, we identified 153 persons with normal adrenal morphology in a CT/MRI scan performed within five years preceding this study. There were 129 who met at least one of the above-listed exclusion criteria, declined participation or were unreachable, therefore, 24 subjects without an AI were enrolled as controls.

The research complied with the Declaration of Helsinki and was approved by the Independent Bioethics Committee for Research of our University. Informed consent for inclusion in the study was obtained in writing from each participant.

2.2 Study design

Both AI patients and controls underwent the following evaluation: 1) medical interview; 2) physical examination; 3) antecubital venous blood sampling for laboratory analyses; 4) resting 12-lead electrocardiography (ECG); 5) TTE; 6) common carotid artery (CCA) ultrasonography (USG) including CIMT determination, 7) 24-hour ambulatory blood pressure monitoring (ABPM).

Body-mass-index (BMI) was calculated by dividing body weight (W) in kg by the square of height (H) in meters. 2009 International Diabetes Federation criteria were used to diagnose MetS (18). Subjects with HT received hypotensive medications at the time of enrollment or were diagnosed by ABPM based on mean systolic and diastolic BP (SBP and DBP, respectively) of at least 135/85 mmHg for daytime, 120/75 mmHg for nighttime, and/or 130/80 mmHg for the 24-h period (15). Atherogenic dyslipidemia was defined as triglycerides (TGL) ≥150 mg/dL and serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dL for men and <45 mg/dL for women.

In all study participants, 10-year ACSVD risk was estimated using the 2018 calculator provided online by the American Heart Association and the American College of Cardiology based on Framingham Heart Study (FHS-ASCVD Risk) (19, 20). The calculator estimates 10-year risk of developing ASCVD including coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke,

hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and HF for individuals aged 30 to 74 and without CVD at baseline based on the following predictors: age, type 2 DM (DMt2), smoking, treated and untreated SBP, total cholesterol (TC), HDL-C, and LDL-C.

For nondiabetic subjects, 10-year CVD risk was also calculated using Systematic Coronary Risk Estimation 2 (SCORE2) for subjects aged 40-69 and SCORE2-Older People (SCORE2-OP) for those aged 70-75 for high CV risk countries, which include Poland (21). Predictors used in SCORE2/-OP are: age, sex, smoking, SBP, and non-HDL-C. We are aware SCORE2/-OP was developed to estimate risk in treatment-naïve persons, and that a significant portion of our subjects received lipid- and BP-lowering therapy. Nevertheless, we concluded applying this estimation tool along with FHS-ASCVD Risk calculation is of value.

2.3 Laboratory examinations

Blood was drawn between 8 and 10 a.m. after a fasting period of at least 8 hours from an antecubital vein, and used for regular examinations in the laboratory of our hospital apart from samples preserved for the determination of plasma Cts in all subjects, serum aldosterone and plasma direct renin concentration (DRC) in controls. These were centrifuged at 2,000 rpms for 20 minutes at 4 degrees C, aliquoted and stored at -80 degrees C until analysis.

Samples were analyzed in Central Clinical Laboratory in Gdańsk using standard laboratory methods (with a Siemens IMMULITE 1000 Immunoassay System for most biochemical tests, and an Abbott Architect analyzer, which applies the spectrophotometric method). Serum Cts was determined by an enzyme-linked immunosorbent assay (ELISA) by using a commercially-available diagnostic kit (SunRedBio, catalogue no: 201-12-8276; sensitivity: 0.268 ng/mL; assay range: 0.3-90 ng/mL). Cts concentrations above 90 ng/ml (n=15) were extrapolated based on ELISA standard curve.

Serum Cts, creatinine, sodium, potassium, aldosterone, renin, lipid profile (TC, HDL-C, LDL-C, and TGL), UA, hs-CRP, 24-h urinary protein and albumin excretion were determined both in AI patients and controls. Morning serum cortisol, dehydroepiandrosterone sulphate (DHEA-S), overnight 1 mg-DST cortisol and 24-h urinary cortisol were determined in AI patients. In most (n=50) AI patients, 24-h urinary meta- and normetanephrine excretion was determined, in others it had been performed prior to hospitalization. Screening for primary hyperaldosteronism based on aldosterone-to-renin ratio (ADRR) was performed without modifying antihypertensive medications in both AI patients and controls; there were no study participants with both HT and an ADRR above 2 ng/dL:μIU/mL.

2.4 Ambulatory blood pressure monitoring

24h ABPM was conducted using a Spacelabs Ontrak 90227 monitor on the non-dominant arm. During the day BP was recorded every 20 minutes, while during nighttime rest every 30 minutes. ABPM was repeated or not considered in the analysis if more than 30% of measurements were invalid. Normal results were adopted according to the European Society of Cardiology/European Society of Hypertension 2018 guideline: <130/80 mmHg for the 24-h period, <135/85 mmHg for daytime, and <120/70 mmHg for nighttime (22). Patients were classified as 'non-dippers' if their mean diurnal SBP and DBP were not at least 10% higher than nocturnal (22).

2.5 Transthoracic echocardiography

All measurements were performed in accordance with the recommendations endorsed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (23). Three on-site cardiology consultants with an expertise in ultrasonography performed TTE using the GE Vivid E9/E95 ultrasound system.

Measurements included left-ventricular (LV) internal dimension in diastole (LVIDd) and systole (LVIDs), LV ejection fraction (LVEF) according to modified Simpson's rule (24), posterior LV wall thickness (LVPWd), and interventricular septal thickness (IVSd). LV mass (LVM) was calculated with the cube formula: LVM (g)=0.8×1.04 ×[(LVEDd+IVSd+LVPWd)^3–LVEDd^3]+0.6. LVM was indexed to body surface area (BSA) calculated using the DuBois formula (BSA=0.007184×H$^{0.725}$×W$^{0.425}$): LVM index (LVMI)=LVM/BSA. Relative wall thickness (RWT) was calculated with the formula: RWT=(2×LVPWd)/LVEDd. Left ventricular hypertrophy (LVH) was defined as LVMI >95 g/m^2 for females and >115 g/m^2 for males. RWT was used to further classify LVH as either concentric (RWT >0.42) or eccentric (RWT ≤ 0.42).

Disk summation technique from apical four and two-chamber views was used to determine left atrial volume (LAV), which was indexed to BSA: LAV index (LAVI) (ml/m^2) = LAV/BSA (15). Apical four-chamber view was used to record peak blood flow velocity from LV relaxation in early diastole (E) and peak velocity flow in late diastole (A). Since LVEF was normal in all study participants, four criteria were applied to assess diastolic function: (1) LAVI ≥34 ml/m^2, (2) tricuspid regurgitation velocity (TR) ≥2.8 m/s, (3) ratio of E to average early mitral annular velocity (e') ≥14, (4) septal e'<7 cm/s or lateral e'<10 cm/s. Indeterminate diastolic function was stated if two criteria were met, and dysfunction if three or four (15).

2.6 Common carotid artery USG

Maximum carotid intima-media thickness (CIMT) measurements were recorded using echo-tracking technology on the distal wall of the right carotid artery, 1 to 3 cm below the carotid artery bifurcation. The presence of atherosclerotic plaques (ASP) defined as a CIMT ≥1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding CIMT value was also recorded.

2.7 Statistical analysis

Data were analyzed using R-studio. Discrete variables were presented as number (n) or n (percentage). Continuous

quantitative data with a normal distribution were presented as mean ± standard deviation (SD), and in the case of a non-normal distribution as median (interquartile range, IQR). We used the Shapiro-Wilk test to determine if a data set was well-modeled by a normal distribution. To compare differences between two independent groups Welch's t-test was used when variables were normally distributed or the Mann-Whitney U test in the case of non-normal distribution. One-way ANOVA and Tukey's honestly significant difference (HSD) tests were used to compare three or more independent groups. Simple (bivariate) correlations were computed with the non-parametric Spearman rank-order method (correlation coefficient r is given). Associations between dichotomous categorical variables were examined with Fisher's exact test, and Benjamini-Hochberg Method was applied to correct for multiple testing.

Multiple regression models were applied to adjust for differences in Cts concentrations depending on potential confounding variables including gender, age, BMI, smoking status, comorbidities (HT, DMt2, MetS), and medications (ACEI/ARB, CCB, BB, diuretics, statins, and PPIs). An exhaustive search method was used to select factors that had the strongest relationship with Cts, i.e.: 1) gender, presence of 2) MetS, 3) HT, therapy with 4) statins, and 5) PPIs. The final multivariate model had a R-squared of 0.1831. Out of five variables included in the model only the presence of MetS (ß=-30, p=0.005) was significantly and negatively associated with Cts. For dichotomous dependent variables (Cts halves, HT, DMt2, and MetS) binary logistic regression was used to adjust for gender, age, and BMI. Significance was set at 0.05.

3 Results

3.1 Comparison of examined parameters between AI patients and controls

To assess whether the presence of an AI affected Cts levels, verification of matching between AI patients and controls was undertaken. These groups did not differ in regard to age, sex, BMI, smoking status, and comorbidities (incidence of HT, DM t.2, ASP, and dyslipidemia), see Table 1. Concerning subjects with HT, the number of patients on mono-, dual- and triple-drug therapy (including betablockers) was also comparable (Supplementary Table 1).

Among AI patients, there were 14 with MACS and 31 classified as NFAI; analyses for AI patients and these two subgroups were performed separately.

Ten-year FHS-ASCVD Risk was comparable between patients with an AI/NFAI/MACS and controls, while in nondiabetic subjects, SCORE2/-OP was significantly higher in patients with MACS than in controls and patients with NFAI: 14% (11-18) vs. 8% (4.5-14), p = 0.021, and 8% (6-12), p = 0.005, respectively (Table 1). Still, this CVD risk index was comparable between controls and all AI patients (p=0.31), which illustrates effective matching between these groups.

Cts distribution was bimodal both in AI patients and controls. Unadjusted Cts was slightly higher in AI patients: 6.45 (4.9-37) vs. 4.5 (3.5-28) ng/ml, p=0.047 (Figure 1). However, after adjusting for potential confounding variables (gender, age, and BMI), solely BMI and male gender were significantly (negatively) associated with Cts (ß=-28.3, p=0.01 and ß=-2.3, p=0.04, respectively) but not the presence of an AI (ß=-8.1, p=0.44).

Lipid profile, hs-CRP, as well as UA were comparable between controls and AI patients, be it with a NFAI or MACS. Proteinuria and albuminuria were normal in all study participants (respectively below 150 and 30 mg/24h). ABPM parameters (SBP, DBP, and pulse rate, PR) were comparable between AI patients and controls (Table 1 and Supplementary Table 1).

Concerning TTE, there were significant differences in IVSd, LVPWd, and LVMI between AI patients and controls (respectively 11 (10-12) vs. 10 (9-10) mm, p=0.003; 10 (9-11) vs. 9 (8-9.5) mm, p=0.007; 86.4 ± 119.2 vs. 84.7 ± 18.5 g/m^2, p=0.001). Moreover, LVH was more prevalent in MACS patients than controls (42.9% vs. 4.4%, p=0.007) and NFAI patients (42.9% vs. 14%, p=0.028).

Maximum CIMT was higher in patients with an AI, be it with a NFAI or MACS, than in controls: 1 (0.9-1.1) vs. 0.8 (0.8-0.9) mm, p<0.01. However, there were no differences in maximum CIMT between patients with a NFAI and MACS (Table 1). A trend toward a higher prevalence of an ASP in AI, NFAI, and MACS patients (29.7%, 32%, 21.43%, respectively) than controls (9.5%) could be observed (p=0.12) (Table 1).

3.2 Catestatin in clinically-specified patient groups

Upon comparing Cts levels between controls with normal adrenal morphology and AI patients, peptide's levels were tested in different patient groups. Cts was higher in women than in men: 7 (4.8-100) vs. 4.9 (4-7.4) ng/ml, p=0.015, and the difference between sexes was significant in both AI patients (7.3 (5.5-103) vs. 6 (4.26-7.6) ng/ml, p=0.03) and controls (5.1 (3.8 - 62.6) vs. 2.8 (1.7 - 3.5) ng/ml, p = 0.043), see Figure 2.

Further, in AI patients and controls analyzed together Cts was lower in hyper- versus normotensive subjects: 5.6 (4-7.1) vs. 15.8 (5.2-103) ng/ml, p=0.003, which was also found for AI patients alone: 5.6 (4.36-6.82) vs. 21.7 (6.85-107), p < 0.001) (Figure 3). Cts was also significantly lower in subjects with MetsS than in those without it: 25.7 (5.8-115) vs. 5.2 (3.9- 6.9) ng/ml, p<0.01 (Figure 4), regardless of potential confounders (gender, age, BMI, presence of an AI and/or HT, statin and PPI use). We confirmed these differences (normo- versus hypertensive subjects as well as those without and with MetS) in women but not men (probably due to their low number). Cts in hypertensive AI females was lower than in normotensive ones: 5.6 (4.7 – 11.6) vs. 45.2 (8.2 – 118) ng/ml, p <0.01, and also lower in those with MetS than without it, both among AI patients: 5.6 (4.8-6.9) vs. 34.3 (7.7 - 121) ng/ml, p= <0.01 and controls: 3.8 (3.7-5.1) vs. 61.2 (8.4-112) ng/ml, p = 0.025 (Supplementary Figures 1, 2).

There were no differences in Cts between obese and non-obese subjects, smokers and non-smokers, or, among subjects with HT, 'dippers' and 'non-dippers'.

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TABLE 1 Clinical, laboratory, ABPM, echocardiographic, and CCA sonography parameters in AI patients and controls.

	Controls	AI patients			p	adjusted p		
		all	NFAI	MACS	Cont. vs. AI	Cont.vs. NFAI	Cont. vs. MACS	NFAI vs. MACS
n	24	64	50	14	–	–	–	–
F:M ratio	19:5	45:19	35:15	10:4	0.592	1	1	1
Age [years]	62.2 ± 7.4	60.9 ± 8.8	60.1 ± 8.8	63.7 ± 9.3	0.487	0.575	0.854	0.334
BMI [kg/m^2]	27.9 ± 4.6	28.6 ± 4.1	28.8 ± 4.2	28.3 ± 3.9	0.48	0.685	0.968	0.911
Obesity [n (%)]	8 (33.33%)	24 (37.5%)	20 (40%)	4 (28.6%)	0.807	0.928	1	0.928
HT [n (%)]	10 (41.7%)	36 (56.3%)	27 (54%)	9 (64.3%)	0.327	0.555	0.555	0.555
DMt2 [n (%)]	1 (4.17%)	12 (18.8%)	11 (22%)	1 (7.1%)	0.103	0.266	1	0.411
MetS [n (%)	11 (45.8%)	36 (56.3%)	27 (54%)	9 (64.3%)	0.527	0.621	0.621	0.621
Smokers [n (%)]	24 (33.3%)	28 (43.8%)	20 (40%)	8 (57.1%)	0.521	0.619	0.543	0.543
SCORE2/-OP [%] *	8 (4.5-14)	9 (7-13)	8 (6-12)	14 (11-18)	0.31	0.978	**0.021**	**0.005**
FHS-ASCVD score [%]	5.9 (2.8-12)	10.1 (4.8-16.4)	9.3 (4.6-16.4)	12.5 (8.4-15.6)	0.085	0.338	0.253	0.813
Catestatin [ng/ml]	4.5 (3.5-28)	6.5 (4.9-37)	7.2 (5-101)	6.1 (5-7.8)	**0.048**	0.71	0.7	0.274
HDL-C [mg/dl]	58.7 ± 12.1	54.0 ± 14.7	52.7 ± 14	58.7 ± 17	0.13	0.196	1	0.33
LDL-C [mg/dl]	120 ± 36.6	129 ± 48.2	130 ± 49.1	129 ± 46.8	0.32	0.663	0.828	0.998
TC [mg/dl]	202 ± 42.4	211 ± 53.1	210 ± 53.4	213 ± 53.8	0.45	0.813	0.803	0.978
TGL [<150 mg/dl]	106 (96.8-126)	130 (87-162)	130 (88.5-160)	129 (86.2-162)	0.25	0.414	0.965	0.727
UA [2.5-7 mg/dl]	5.3 (4.8-5.8)	5.1 (4.2-6.1)	5.1 (4.4 -6.1)	4.8 (4.2-5.8)	0.97	0.87	0.983	0.817
hs-CRP [<5 mg/l]	1.4 (1.1-2.5)	1.2 (0.7 - 1.7)	1.2 (0.7-1.6)	1.3 (0.6-2)	0.14	0.811	0.443	0.155
DST cortisol [<50 nmol/L]	–	26.9 ± 34	11.3 ± 17	79.1 ± 22.3	–	–	–	**<0.001**
24h SBP [mmHg]	118 ± 8.4	121 ± 9.7	120 ± 9.3	118 ± 7.7	0.5	0.62	0.982	0.612
24h DBP [mmHg]	70.6 ± 5.9	71.4 ± 7.8	71.7 ± 8.1	70.3 ± 6.5	0.61	0.818	0. 994	0.82
Non-dipper status [n (%)]†	6 (40%)	9 (28.1%)	9 (37.5%)	0	0.442	0.61	0.447	0.46
IVSd [mm]	10 (9-10)	11 (10-12)	11 (10-12)	12 (10.2-12)	**0.003**	**0.045**	**0.006**	0.295
LVIDd [mm]	46.1 ± 4.1	44.8 ± 4.5	45.2 ± 4.7	43.5 ± 3.7	0.193	0.651	0.183	0.427
LVIDs [mm]	29.9 ± 3.3	27.3 ± 3.1	27.3 ± 3.2	27.2 ± 3	**0.002**	**0.005**	**0.036**	0.991
LVPWd [mm]	9 (8-9.5)	10 (9-11)	10 (9-11)	11 (10-11.8)	**0.007**	0.08	**0.009**	0.268
LVM [g]	149 ± 27.2	165 ± 41.8	164 ± 42	169 ± 42.6	**0.047**	0.307	0.289	0.887
LVMI [g/m^2]	86.4 ± 19.2	84.7 ± 18.5	92.7 ± 21	77.9 ± 8.7	**0.006**	**0.037**	**0.023**	0.21
LVH [n (%)] #	1 (4.4%)	13 (20.3%)	7 (14%)	6 (42.9%)	0.101	0.421	**0.007**	**0.028**
LAVI [ml/m^2]	24.6 (15.1-31.9)	24.9 (15.9-31.6)	23.8 (13.1-31.8)	25.5 (20.5-30)	0.29	0.639	0.498	0.864
CIMT max [mm]	0.8 (0.7 -0.8)	1 (0.9 - 1.1)	1 (0.9 - 1.1)	0.9 (0.9 - 1)	< **0.01**	**<0.01**	**0.007**	0.996
ASP [n (%)]	2 (9.5%)	19 (29.7%)	16 (32%)	3 (21.4%)	0.117	0.215	0.526	0.526

Data are presented as number, n, (percentage, %), mean ± standard deviation or median (interquartile range) depending on distribution; p values were adjusted for multiple comparisons with Benjamini-Hochberg adjustment (for qualitative variables) and TukeyHSD test (for quantitative variables); bold font denotes significant (<0.05) p values; *only nondiabetic patients were included in SCORE2/-OP risk estimation (n= 23, 52, 39, and 13, respectively for Cont., AI, NFAI and MACS patients); #LVH was defined as values of LVMI exceeding 95 or 115 g/m2 in females and males respectively; † dipper status was considered only in patients with HT. ASP, atherosclerotic plaques; BMI, body mass index; CIMT, carotid intima media thickness; con., controls; DBP, diastolic blood pressure; DMt2, diabetes mellitus t2; DST, dexamethasone suppression test; FHS-ASCVD Risk – 10-year atherosclerotic cardiovascular disease risk calculated based on the Framingham Heart Study; HDL-C, high density lipoprotein cholesterol; HT, hypertension; hs-CRP, high sensitivity C-reactive protein; IVSd, interventricular septal end diastole; LAVI, left atrial volume index; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVIDd, left ventricular internal diameter end-diastole; LVIDs, left ventricular internal diameter end systole; LVM, left ventricular mass; LVMI, LVM index; LVPWd, left ventricular posterior wall end diastole; MetS, metabolic syndrome; SBP, systolic blood pressure; SCORE2/-OP, Systematic Coronary Risk Estimation 2/-Older People; TC, total cholesterol; TGL, triglycerides, UA, uric acid.

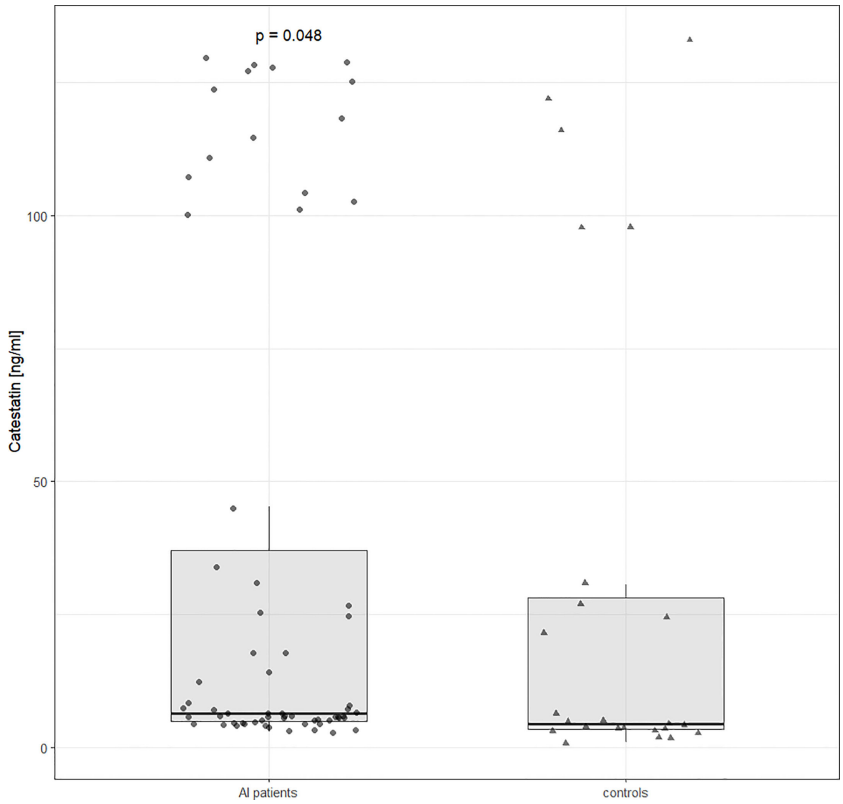

FIGURE 1
Catestatin distribution in controls and AI patients. Boxplot and data distribution with dots (AI patients) and triangles (controls) indicating individual datapoints. Unadjusted p value was determined using the Mann Whitney U test. AI, adrenal incidentaloma.

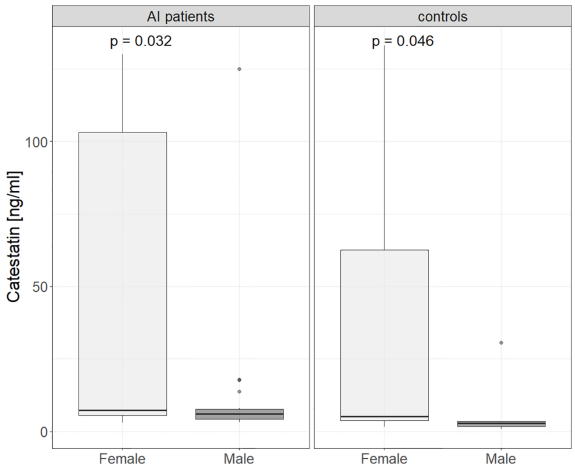

FIGURE 2
Catestatin in male and female controls and AI patients. Boxplot chart. P-value was determined using the Mann-Whitney U test. AI, adrenal incidentaloma.

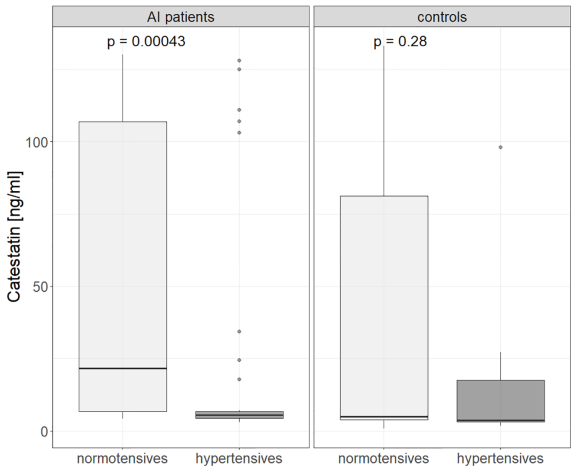

FIGURE 3
Catestatin in normotensive and hypertensive in controls and AI patients. Boxplot chart. P-values were determined using the Mann-Whitney U test. AI, adrenal incidentaloma.

3.3 Correlations between catestatin and laboratory, TTE, and CCA USG parameters

To further investigate associations between Cts and CVD risk, correlations were tested between peptide's levels and other parameters. In AI patients, weak correlations were found between Cts and: BMI (r=-0.31) (Figure 5A), FHS-ASCVD Risk (r=-0.42) (Figure 5B), and HDL-C (r=0.32) regardless of statin therapy (Figure 5C). Interestingly, among participants without it, there were also positive correlations between Cts and: TC and LDL-C

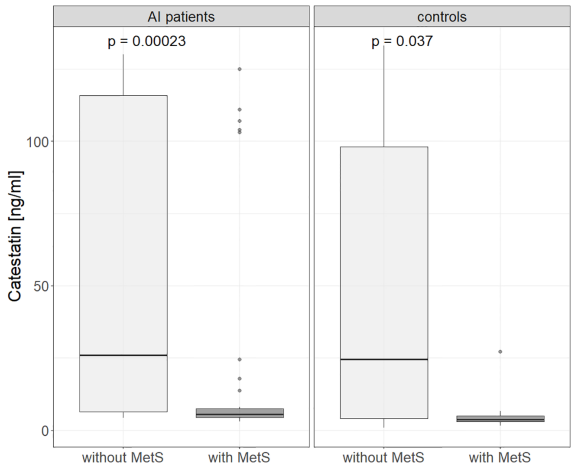

FIGURE 4
Catestatin in subjects without and with metabolic syndrome in controls and AI patients. AI, adrenal incidentaloma; MetS, metabolic syndrome. P-values determined using the Mann-Whitney U test.

(r=0.36 for both) (Table 2 and Supplementary Figures 3, 4). In AI patients and controls analyzed as a whole a negative correlation between Cts and UA was also observed (r=-0.27, p=0.01), while for each group analyzed separately, significance has not been reached probably due to sample size.

Analyses in subjects of each sex revealed Cts correlated with HDL (r=0.31, p=0.014), BMI (r=-0.29, p=0.019), and UA (r=-0.27, p=0.031) in women, but not in men (respectively r=0.13, p=0.53; r=-0.06, p=0.78; r=-0.12, p=0.56). A negative correlation between Cts and FHS-ASCVD Risk was also recorded in women with an AI (r=-0.3, p=0.049) but not in female controls (r =0.025, p=0.92), nor men with an AI (n=19, r=- 0.37, p=0.12). Correlations for male controls were not tested due to a low number of these subjects (n=5).

Concerning hormonal tests, only a weak correlation between Cts and DRC was observed, but not with aldosterone, nor ADRR (Supplementary Table 2). Cts did not correlate with ABPM, CCA USG, nor TTE parameters (LVPWd, IVSd, LVMI, LAVI) (Table 2 and Supplementary Table 2).

3.4 Clinical, laboratory, and TTE parameters according to catestatin categories

Further analyses were performed among AI patients based on Cts categories. First, adjustment for gender, age and BMI in binary logistic regression analysis revealed AI patients in the lower half of Cts concentrations (median 6.5, IQR 4.9-37 ng/ml) compared to those in the upper had a higher prevalence of HT (OR 0.17, CI 0.05-5.37, p=0.003), and MetS (OR 0.21, CI 0.06-7.51, p=0.018). Moreover, BMI, 24-SBP, and FHS-ASCVD Risk were also higher in the former (respectively 30.1 ± 4 vs. 27.2 ± 3.6 kg/m^2, p=0.004; 123 ± 7.4 vs. 117 ± 9.5 mmHg, p=0.022; 13.2%(8.9-19.2) vs. 6.3% (4.2-10.8), p=0.002), as summarized in Table 3.

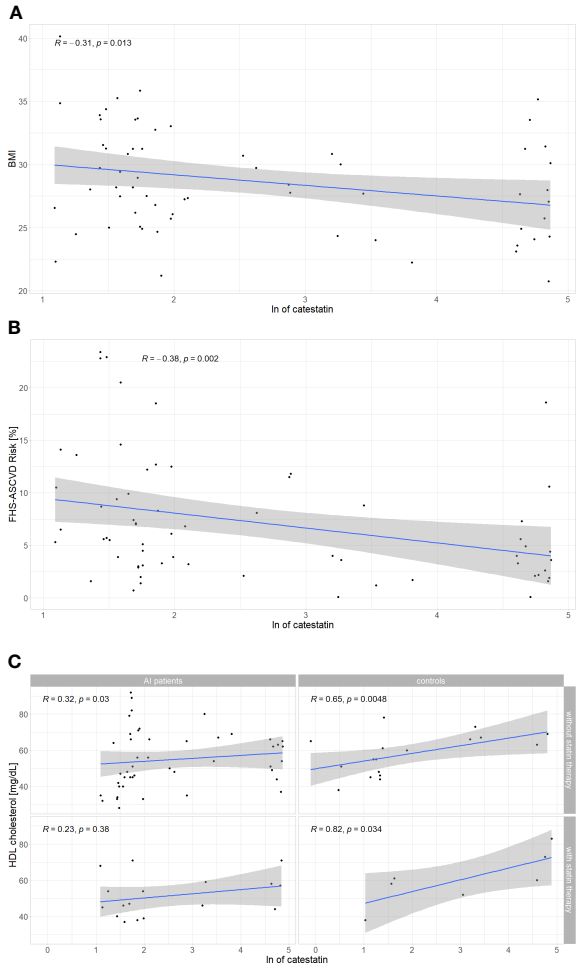

FIGURE 5
Correlations between catestatin and: **(A)** BMI in AI patients; **(B)** FHS-ASCVD Risk in AI patients; **(C)** HDL-C in AI patients and controls. Correlations were computed by the Spearman rank-order method. For HDL-C, correlations were tested separately in subjects with and without statin therapy. AI, adrenal incidentaloma, BMI, body mass index, FHS-ASCVD Risk - 10-year atherosclerotic cardiovascular disease risk calculated based on the Framingham Heart Study; HDL-C, high density lipoprotein cholesterol, ln, natural logarithm.

Second, based on Cts distribution, we divided AI participants into four subgroups, i.e. with: 'very low' (Cts <4.9 ng/ml, n=17), 'low' (≥4.9 and <6.5 ng/ml, n=15), 'intermediate' (≥6.5 and ≤45.2 ng/ml, n=17), and 'high' (≥100 ng/ml, n=15) Cts levels (Table 3). The first two comprised subjects from two lower quarters, while the 'high Cts' subgroup corresponded to almost all patients in the fourth quarter (15 instead of 16 patients were included since there were none in the 45.2 - 100 ng/ml range, see Figure 1).

These four Cts subgroups differed significantly in male-to-female ratio, prevalence of HT and MetS, mean/median BMI, HDL-C, 24h SBP, and FHS-ASCVD Risk (Table 3). *Post hoc* analysis revealed male gender was more prevalent in the 'very low' versus 'high' Cts subgroup (53% vs. 6.7%), while HT and MetS in the 'very low' versus 'intermediate' (82.4% vs. 35.3%, p=0.04 for both) and 'high' Cts subgroups (82.4% vs. 33.3%, p=0.04 for both). HDL-C was lower in the 'very low' than in the three remaining Cts subgroups (42.9 ± 42.9 vs. 61.6 ± 17.8, 56.7 ±

TABLE 2 Correlations between catestatin and examined parameters.

Correlation between Cts and	Control group (n = 24)		AI patients (n = 64)		Both groups (n = 88)	
	r	p	r	p	r	p
Age	0.246	0.247	-0.142	0.262	-0.016	0.7
BMI	-0.293	0.164	**-0.308**	**0.013**	**-0.27**	**0.009**
HDL-C	**0.704**	**< 0.001**	**0.306**	**0.014**	**0.344**	**0.001**
HDL-C *	**0.649**	**0.005**	**0.317**	**0.03**	**0.317**	**0.011**
LDL-C	0.102	0.634	0.15	0.236	0.153	0.15
LDL-C *	**0.573**	**0.016**	**0.361**	**0.003**	**0.361**	**0.003**
TC	0.215	0.313	0.118	0.353	0.16	0.137
TC *	**0.568**	**0.017**	**0.295**	**0.044**	**0.364**	**0.003**
TGL	-0.216	0.145	-0.19	0.131	-0.143	0.183
TGL *	-0.085	0.746	0.215	0.313	-0.142	0.263
UA $	-0.37	0.07	-0.209	0.1	**-0.27**	**0.01**
hs-CRP	0.191	0.407	0.005	0.97	-0.045	0.68
LVMI	0.149	0.488	-0.009	0.942	0.05	0.645
LAVI	0.13	0.545	-0.202	0.109	-0.121	0.263
Maximum CIMT	-0.09	0.697	-0.136	0.286	-0.03	0.774
SCORE2/-OP #	0.127	0.563	- 0.064	0.652	0.05	0.651
FHS-ASCVD Risk [%]	-0.237	0.265	**-0.42**	**< 0.001**	**-0.24**	**0.022**

Correlations were computed by the Spearman rank-order method; bold font denotes statistically significant correlations; *denotes scorrelations in participants without statin therapy: n=17 and 47, respectively for controls and AI patients; $ patients with and without medications that could lower uric acid (allopurinol, n = 1) were analyzed separately and the results were the same; # denotes correlations in nondiabetics only: n= 23 and 52, respectively for controls and AI patients; BMI, body mass index; CIMT, carotid intima media thickness; FHS-CVD, 10-year atherosclerotic cardiovascular disease risk calculated based on the Framingham Heart Study; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LAVI, left atrial volume index; LDL-C, low density lipoprotein cholesterol; LVMI, left ventricular mass index; r, correlation coefficient; SCORE2/-OP, Systematic Coronary Risk Estimation 2/-Older People; TC, total cholesterol; TGL, triglycerides; UA, uric acid.

13.7, and 55.8 ± 9.5 mg/dL, adjusted p=0.001, 0.01, and 0.03, respectively). What is more, 24h SBP in the 'low' Cts subgroup was higher than in the 'intermediate' (124.7 ± 6.7 vs. 114.5 ± 8.5 mmHg, adj. p=0.008).

Ten-year FHS-ASCVD Risk in the 'very low' Cts subgroup was higher than in the 'intermediate' and 'high': 14.3% (19.2-24.5) vs. 7.1% (4.7-14.2) and 5.6% (3.8-9.8), respective adjusted p=0.014 and 0.005, in line with differences in gender proportions, prevalence of metabolic disorders and HT between the subgroups.

Fisher's exact test revealed differences in LVH prevalence between four Cts subgroups, yet, without significance in pairwise comparisons with correction for multiple testing (Holm–Bonferroni method). No other significant differences were recorded between Cts halves and subgroups in TTE and CCA USG parameters (Table 3). Finally, clinical, laboratory and TTE parameters were also analyzed in the same Cts subgroups for females only (Supplementary Table 3). Significant differences were recorded for: HT and MetS prevalence, HDL-C and hs-CRP concentrations, mean 24h DBP, and FHS-ASCVD Risk. Calculations for male AI subjects were not performed due to their low number.

4 Discussion

Clinical research on Cts is scarce, even though it deserves attention due to its protective effects on the CV system demonstrated *in vitro* and *in vivo*. To our knowledge, our study is the first to examine Cts in patients with an AI, and to show lower Cts in adult patients with MetS than those without it, as well as correlations between Cts and FHS ASCVD risk index.

A thorough assessment was undertaken to investigate associations between Cts and CV risk factors. It must be highlighted that Cts changes dynamically in response to sympathetic nervous system activation in a negative feedback mechanism (25). Also, multiple diseases and drugs lead to CgA secretion, which may affect the concentration of its derivatives, including Cts. For these reasons, we excluded patients with established CVD, stage 3-5 chronic kidney disease, cancer, etc., and controlled the use of PPIs (10, 12, 26, 27). Limitations of our study include a small, heterogeneous patient sample, lack of CgA determination (Cts : CgA ratios may have provided further insights) and hormonal work-up in controls.

Since CgA is not expressed in the adrenocortical adenoma tissue, Cts levels are unlikely to differ between subjects with and

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TABLE 3 Clinical, laboratory, ABPM, echocardiographic, and CCA sonography parameters in AI patients according to catestatin category.

Cts half [ng/ml]	Lower (Cts < 6.5)		Upper (Cts ≥6.5)		p subgroups	p halves
Cts subgroup [ng/ml]	Very low (< 5)	Low (5 ≤ Cts < 6.5)	Intermediate (6.5 ≤ Cts ≤ 45.2)	High (Cts ≥ 100)		
n	17	15	17	15	-	-
F:M ratio	8:9	12:3	11:6	14:1 *	**0.027**	0.274
Age [years]	61.9 ± 9.4	61.7 ± 5.9	60.7 ± 11.5	59.2 ± 7.2	0.827	0.412
BMI [kg/m²]	30.4 ± 4.6	29.9 ± 3.4	27.1 ± 3.2	27.4 ± 4.2	**0.034**	**0.004**
Obesity [n (%)]	8 (47.1%)	8 (53.3%)	3 (17.7%)	5 (33.3%)	0.158	0.07
Smokers [n (%)]	7 (41.2%)	9 (40%)	5 (29.4%)	7 (46.7%)	0.378	0.45
PPI therapy [n (%)]	4 (23.5%)	4 (26.7%)	2 (11.8%)	3 (20%)	0.793	0.536
HT [n (%)]	14 (82.4%)	11 (73.3%)	6 (35.3%) *	5 (33.3%) *	**0.005**	< **0.001**
>1 hypotensive drug [n(%)] †	7 (50%)	7 (63.6%)	3 (50%)	1 (20%)	0.495	0.470
DMt2 [n (%)]	6 (35.3%)	4 (26.7%)	1 (5.9%)	1 (6.7%)	0.09	**0.022**
MetS [n (%)]	14 (82.4%)	11 (73.3%)	6 (35.3%) *	5 (33.3%) *	**0.005**	< **0.001**
Statin use [n (%)]	6 (35.3%)	3 (20%)	4 (23.5%)	4 (26.7%)	0.837	1
HDL-C [mg/dL]	42.9 ± 10.8	61.6 ± 17.8 *	56.7 ± 13.7 *	55.8 ± 9.5 *	**0.001**	0.076
LDL-C [mg/dL]	124 ± 49.4	121 ± 41.6	127 ± 36.3	146 ± 63.6	0.491	0.27
TC [mg/dL]	202 ± 52.6	206 ± 51	211 ± 41	225 ± 68.4	0.677	0.31
TGL [mg/dL]	143 (98 - 198)	133 (118 - 141)	121 (87 - 168)	105 (87.5 - 142)	0.159	0.36
Uric acid [mg/dL]	5.8 (4.9 - 6.8)	4.8 (4.1 - 5.8)	5.1 (4.2 - 6.1)	4.9 (4.3 - 5.8)	0.112	0.36
MACS [n (%)]	4 (23.5%)	4 (26.7%)	5 (29.4%)	1 (6.7%)	0.417	0.763
Hs-CRP [mg/L]	1.2 (0.8 - 3.9)	1.5 (1 - 2.1)	0.8 (0.6 - 1.5)	1.2 (0.8 - 2)	0.243	0.16
24h SBP [mmHg]	120.8 ± 7.8	124.7 ± 6.7	114.5 ± 8.5 #	119.2 ± 10.5	**0.01**	**0.009**
24h DBP [mmHg]	71.1 ± 9.6	74.9 ± 5.9	68.2 ± 6.1	72 ± 7.9	0.126	0.13
24h PR [bpm]	71.2 ± 9.8	72.9 ± 7.5	71.2 ± 6.5	72 ± 8.3	0.929	0.84
Non-dipper status [n (%)] †	4 (28.6%)	2 (18.2%)	1 (16.7%)	2 (40%)	0.723	0.685
LVMI [g/m^2]	86.1 ± 18.1	84.2 ± 17	86.6 ± 19	88.9 (± 24.0)	0.931	0.61
LVH [n (%)]	1 (5.9%)	3 (20%)	2 (11.76%)	7 (46.7%)	**0.036**	0.213
LAVI [ml/m^2]	26.6 ± 9.6	24 ± 8.6	24 ± 9.44	20.3 ± 7.1	0.258	0.2
Maximum CIMT [mm]	1 (0.9 - 1.2)	1 (0.9 - 1.1)	1 (0.9 - 1.1)	0.9 (0.9 -1.1)	0.685	0.393
ASP [n(%)]	7 (41.2%)	4 (26.7%)	4 (23.5%)	4 (26.7%)	0.709	0.585
SCORE2/-OP [%] ‡	8 (7 - 12)	12 (8 - 15.5)	7 (5 - 14.5)	8.5 (8 - 11.5)	0.572	0.29
FHS-ASCVD Risk [%]	14.3 (9.2 - 24.5)	11.2 (7.8 - 16.2)	7.1 (4.7 - 14.2)*	5.6 (3.8 - 10)*	**0.003**	**0.002**

AI patients were categorized based on catestatin concentrations into those in the lower and upper half, and further into four subgroups (two lowest were identical with first and second quartiles). Data are presented as number (percentage), mean ± standard deviation or median(interquartile range) depending on distribution; p-values were calculated with one-way ANOVA and Tukey's HSD tests (quantitative variables) or Fisher's exact test (categorical variables) with Benjamini-Hochberg correction for multiple testing. Bold font denotes significant (<0.05) p values; * denotes datapoints significantly different versus those for the 'very low' Cts subgroup in post hoc test; # denotes datapoints significantly different versus those for the 'low Cts' subgroup in post hoc test; † dipper status was considered only in patients with HT. ‡ Only nondiabetic patients were included in SCORE2/–OP risk estimation (n=11, 11, 16, and 14, for consecutive subgroups). ABPM, ambulatory blood pressure monitoring; ASP, atherosclerotic plaques; BMI, body mass index; bpm, beats per minute; CCA, common carotid artery; CIMT, carotid intima media thickness; DBP, diastolic blood pressure; DMt2, diabetes mellitus type 2; FHS-ASCVD Risk, 10–year atherosclerotic cardiovascular disease risk calculated based on data from the Framingham Heart Study; HDL-C, high density lipoprotein cholesterol; HT, hypertension; hs–CRP, high sensitivity C–reactive protein; LDL-C, low density lipoprotein cholesterol; LVH, left–ventricular hypertrophy; LVMI, left ventricular mass index; max, maximum; MACS, mild autonomous cortisol secretion; MetS, metabolic syndrome; PPI, proton pump inhibitor; PR, pulse rate; SCORE2/–OP, Systematic Coronary Risk Estimation 2/–Older People; SBP, systolic blood pressure; TC, Total cholesterol; TGL, triglycerides.

without an adrenal adenoma (28, 29), which is what we found here for AI patients compared to age-, sex-, and BMI-matched controls after adjusting for confounding factors. Other researchers showed higher plasma CgA in patients with an adrenal adenoma than in subjects without one, which may underlie a slightly higher unadjusted Cts in our AI patients than controls (24, 25). What should be noticed is a similar distribution of Cts levels in controls and AI patients, including the proportion of subjects with high (>97 ng/ml) Cts: 21% in the former and 23% in the latter. This further suggests that the presence of an AI does not affect Cts. Regarding hormonal activity, we found no differences in Cts between patients with MACS and NFAI, nor correlations between Cts and UFC or 1-mg DST cortisol, possibly due to small sample size.

Despite comparable age, BMI, male-to-female ratio, smoking status and comorbidities, IVSd, LVPWd, LVM, and LVMI were higher in AI patients than controls, which was driven by values recorded in subjects with MACS. Iacobellis et al. reported similar results (higher LVM in AI subjects versus controls, the difference depended on patients with MACS) (30). In our study, SCORE2/-OP was higher in MACS compared to NFAI patients and controls, which indicates increased CV risk associated with subclinical hypercortisolemia. The data support the hypothesis that chronic mild elevation of cortisol levels in AI patients adversely affect the CV system rather than the presence of an adrenal adenoma *per se*. Low Cts was associated here with a higher prevalence of male gender, HT, MetS, as well as BMI, 24h SBP, UA and lower HDL-C. Consequently, an association between Cts and ASCVD risk was recorded (Figure 6). In line with our results, Cts was lower in obese children with MetS than in those without it, and in normal-weight controls (13); O'Connor et al. showed Cts correlated negatively with BMI (12), and Durakoğlugil et al. reported a positive correlation between Cts and HDL-C (14). In the latter study, a negative correlation between plasma Cts and TGL concentration was also observed (14), which was not confirmed here. Surprisingly, among participants without statins, we recorded weak positive correlations between Cts and TC as well as LDL-C. The former may be connected with a positive correlation between Cts and HDL-C, however, the latter is difficult to explain, and requires further clarification.

To date, there are controversies regarding Cts in HT; lower Cts levels have been associated with this disease (12, 14, 31–35) (Figure 6). Here, Cts in AI subjects with HT was lower than in normotensive ones, however, the difference was not significant in the controls and we recorded no correlations between Cts and ABPM results. Our data add important facts to the discussion: low Cts levels are more common in HT, however, some patients do exhibit intermediate and high concentrations of the peptide. This was observed in individuals with effective hypotensive treatment revealed by 24-h monitoring.

Further, no significant associations were recorded here between Cts and TTE as well as CCA USG parameters. Small sample size clearly limits conclusions that can be drawn from these data. More sensitive methods (e.g. global longitudinal strain and microvasculature assessment) may have yielded different results.

Possibly, the most intriguing question is the clinical significance of high versus very low/low Cts in individuals with similar established CV risk factors. For instance, non-smoking females aged ca. 60, with overweight and HT (FHS-ASCVD Risk between 10 and 20%) were recorded both in the first half and highest quarter of Cts levels among AI patients. Longitudinal assessment of much larger populations is required to determine whether Cts provides protection against CVD. If so, determining therapeutic strategies that stimulate Cts would be beneficial.

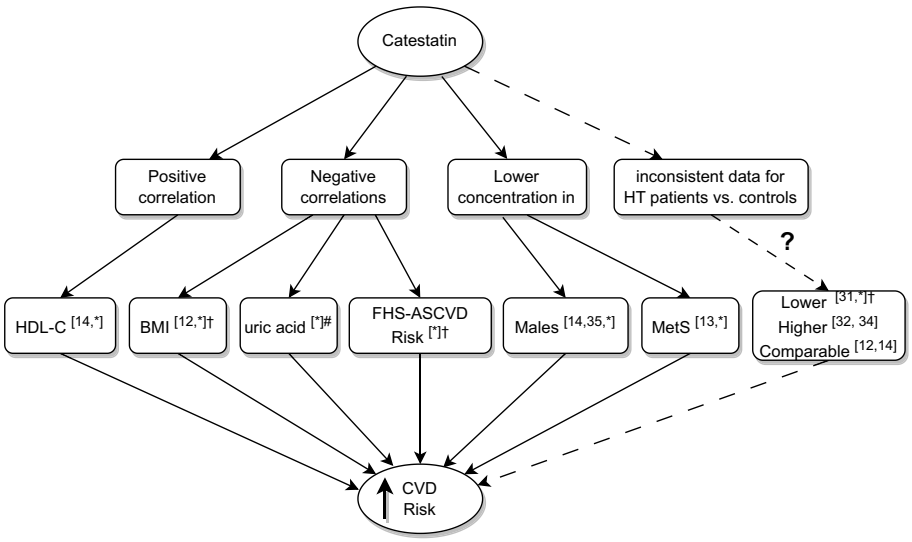

FIGURE 6
Summary of research on associations between low catestatin and cardiovascular risk. Superscript numbers indicate references to previous studies; *indicate results of the current study; #correlation between uric acid and Cts did not reach significance in AI patients analyzed here, it did upon analyzing AI patients and controls together; †significance achieved in AI patients. AI, adrenal incidentaloma, BMI, body mass index; Cts, catestatin; CVD, cardiovascular disease; FHS-ASCVD Risk, 10-year atherosclerotic cardiovascular disease risk calculated based on the Framingham Heart Study; HDL-C, high density lipoprotein cholesterol; HT, hypertension; MetS, Metabolic Syndrome.

5 Conclusions

We are the first to report that among persons without overt CVD other than primary HT, plasma Cts concentrations in patients with an AI are comparable to those of matched controls with normal adrenal morphology. Correlations between Cts and: HDL-C (positive) as well as BMI, UA and FHS-ASCVD Risk (negative) point at cardioprotective effects of the peptide. Data from ABPM, TTE and CCA intima-media assessment did not yield associations between Cts and BP or HT-mediated organ damage. It must be highlighted that many factors influence Cts, and further research is necessary to apply it as a biomarker.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (NKBB/659/2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

EZ secured ethical approval for the study, analyzed the data, and reviewed the literature. EZ and PK collected the data and wrote the manuscript. JS and AK performed echocardiography and ultrasound examination of the common carotid artery. PK and KS carried out critical interpretations. All authors contributed to the article, approved the submitted version, and are accountable for the content of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1198911/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Catestatin in normotensive and hypertensive AI patients and controls - analyses in subjects of each sex. Boxplot chart. P-values determined using the Mann-Whitney U test. AI – adrenal incidentaloma.

SUPPLEMENTARY FIGURE 2
Catestatin in subjects without and with metabolic syndrome in controls and AI patients - analyses in subjects of each sex. Boxplot chart. P-values determined using the Mann-Whitney U test. AI – adrenal incidentaloma; MetS – metabolic syndrome.

SUPPLEMENTARY FIGURE 3
Correlations between catestatin and LDL-C level in AI patients and controls. Correlations were computed by the Spearman rank-order method and were tested separately in subjects with and without statin therapy. AI – adrenal incidentaloma, LDL-C – low density lipoprotein cholesterol, ln – natural logarithm.

SUPPLEMENTARY FIGURE 4
Correlations between catestatin and total cholesterol level in AI patients and controls. Correlations were computed by the Spearman rank-order method and were tested separately in subjects with and without statin therapy. AI – adrenal incidentaloma, ln – natural logarithm.

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EDITED BY
Paola Di Pietro,
University of Salerno, Italy

REVIEWED BY
Aleksandra Klisic,
Primary Health Care Center Podgorica, Montenegro
Akshyaya Pradhan,
King George Medical Univeirsty, India

*CORRESPONDENCE
Jian-Jun Mu
mujjun@163.com
Yang Wang
wangyangxxk@126.com

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Associations of lipid accumulation product, visceral adiposity index, and triglyceride-glucose index with subclinical organ damage in healthy Chinese adults

Ming-Fei Du[1,2], Xi Zhang[1], Gui-Lin Hu[1,2], Jian-Jun Mu[1,2]*, Chao Chu[1,2], Yue-Yuan Liao[1,2], Chen Chen[1,2], Dan Wang[1,2], Qiong Ma[1,2], Yu Yan[1,2], Hao Jia[1,2], Ke-Ke Wang[1,2], Yue Sun[1,2], Ze-Jiaxin Niu[1], Zi-Yue Man[1], Lan Wang[3], Xiao-Yu Zhang[4], Wen-Jing Luo[1], Wei-Hua Gao[5], Hao Li[6], Guan-Ji Wu[7], Ke Gao[1], Jie Zhang[8] and Yang Wang[1,2]*

[1]Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Key Laboratory of Molecular Cardiology of Shaanxi Province, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3]Department of Cardiology, Xi'an International Medical Center Hospital, Xi'an, China, [4]Department of Cardiology, Northwest Women's and Children's Hospital of Xi'an Jiaotong University Health Science Center, Xi'an, China, [5]Department of Cardiology, Xi'an No.1 Hospital, Xi'an, China, [6]Department of Critical Care Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [7]Department of Cardiology, Xi'an Central Hospital of Xi'an Jiaotong University, Xi'an, China, [8]Department of Cardiology, Xi'an People's Hospital, Xi'an, China

Background and aims: Obesity is an independent risk factor for cardiovascular disease development. Here, we aimed to examine and compare the predictive values of three novel obesity indices, lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride-glucose (TyG) index, for cardiovascular subclinical organ damage.

Methods: A total of 1,773 healthy individuals from the Hanzhong Adolescent Hypertension Study cohort were enrolled. Anthropometric, biochemical, urinary albumin-to-creatinine ratio (uACR), brachial-ankle pulse wave velocity (baPWV), and Cornell voltage-duration product data were collected. Furthermore, the potential risk factors for subclinical organ damage were investigated, with particular emphasis on examining the predictive value of the LAP, VAI, and TyG index for detecting subclinical organ damage.

Results: LAP, VAI, and TyG index exhibited a significant positive association with baPWV and uACR. However, only LAP and VAI were found to have a positive correlation with Cornell product. While the three indices did not show an association with electrocardiographic left ventricular hypertrophy, higher values of LAP and TyG index were significantly associated with an increased risk of arterial stiffness and albuminuria. Furthermore, after dividing the population into quartiles, the fourth quartiles of LAP and TyG index showed a significant association with arterial stiffness and albuminuria when compared

with the first quartiles, in both unadjusted and fully adjusted models. Additionally, the concordance index (C-index) values for LAP, VAI, and TyG index were reasonably high for arterial stiffness (0.856, 0.856, and 0.857, respectively) and albuminuria (0.739, 0.737, and 0.746, respectively). Lastly, the analyses of continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) demonstrated that the TyG index exhibited significantly higher predictive values for arterial stiffness and albuminuria compared with LAP and VAI.

Conclusion: LAP, VAI, and, especially, TyG index demonstrated utility in screening cardiovascular subclinical organ damage among Chinese adults in this community-based sample. These indices have the potential to function as markers for early detection of cardiovascular disease in otherwise healthy individuals.

KEYWORDS

lipid accumulation product, visceral adiposity index, triglyceride-glucose index, albuminuria, arterial stiffness, left ventricular hypertrophy, subclinical organ damage

1 Introduction

Cardiovascular disease is a growing public health burden on the global population because of its increasing morbidity and mortality (1). Furthermore, metabolic abnormalities, which are prevalent in obesity, serve as independent risk factors for cardiovascular disease. Studies have reported that obesity at any time in life is independently associated with increased albuminuria risk, irrespective of obesity-related comorbidities, including hypertension, dyslipidemia, and impaired glucose tolerance (2, 3). Moreover, obesity is an established risk factor for developing arterial stiffness and left ventricular hypertrophy (LVH), which in turn have been suggested as early detectable measures of cardiovascular disease and are associated with related long-term adverse outcomes, such as coronary heart disease, stroke, and sudden cardiac death (4, 5).

The obesity-related adverse outcomes are not simply concerned with the extent but also the distribution (6). Previous evidence has demonstrated that visceral adipose tissue rather than subcutaneous adipose tissue may play an important role in systemic injuries, such as those in blood vessels, heart, and kidneys, making it an independent marker of cardiovascular and metabolic morbidity and mortality (7, 8). Although body mass index (BMI) is a powerful predictor of obesity, visceral fat accumulation may vary among people with the same BMI. Waist circumference (WC) is the easiest and the most common index used for evaluating central obesity in clinical practice, replacing BMI in the clinical diagnosis of metabolic syndrome (9). However, WC cannot efficiently distinguish visceral fat from subcutaneous fat, and subcutaneous fat is a much weaker indicator of cardiovascular risk (10). Additionally, computed tomography and magnetic resonance imaging are the gold methods for evaluating and quantifying fat distribution and have developed rapidly and tended to maturely (11, 12). However, they are not routinely applied in clinical settings and community screening due to their high cost, radiation exposure, and operation complexity.

Three reliable markers of visceral adiposity were proposed based on anthropometric and metabolic parameters. First, lipid accumulation product (LAP) is an index that combines WC and fasting triglyceride (TG) values (13). LAP has shown potential for predicting the risk of hypertension, renal function decline, impaired fasting glucose, and even diabetes and cardiovascular disease, while outperforming BMI (14–18). Second, visceral adiposity index (VAI) is a measurement estimated using TG and high-density lipoprotein cholesterol (HDL-C) levels as well as BMI and WC values (19). Finally, the triglyceride-glucose (TyG) index is calculated by incorporating TG and fasting blood glucose (FBG) levels. The TyG index has exhibited associations with insulin resistance, arterial stiffness, and cardiovascular disease (20, 21). Previous studies have primarily focused on evaluating the value of single surrogate markers of visceral adiposity, such as LAP, VAI, and TyG index, to identify the risk for single cardiovascular subclinical organ damage and even cardiovascular disease. However, the performance of all three markers in predicting subclinical organ damage (SOD) remains unclear.

Therefore, in this study, we conducted a cross-sectional analysis based on our previously established Hanzhong cohort to investigate and compare the associations of LAP, VAI, and TyG index with SOD, including albuminuria, arterial stiffness, and LVH, in Chinese adults. We further aimed to examine the predictive capacity of the three indices for SOD in the general population.

2 Materials and methods

2.1 Study cohort

The study population was derived from the Hanzhong Adolescent Hypertension Study cohort, established in 1987. A total of 4,623 children and adolescents were enrolled from 26 rural areas in three towns in Hanzhong City, Shaanxi Province, China. The ongoing prospective, population-based cohort study included regular screenings to monitor the development of cardiovascular risk factors. The study protocol details have been published elsewhere (22, 23).

Here, we explored the association of LAP, VAI, and TyG index with the risk of SOD using the cross-sectional analysis of the latest follow-up data in 2017. The flowchart of the participant selection process is outlined in Figure S1. A total of 2,780 participants were followed up in 2017, yielding a response rate of 60.9%. Participants with missing data on serum or urinary biochemistry (n = 147 and 390, respectively), anthropometric data (n = 29), and brachial-ankle pulse wave velocity (baPWV) and LVH data (n = 474) or a self-identified history of coronary heart disease, severe arrhythmia, renal failure, or stroke (n = 7) were excluded, leaving 1,733 participants available for our primary analysis.

2.2 Clinical and anthropometric measurements

Participants completed on-site questionnaires that collected general information on their smoking habits, alcohol consumption, physical activity, medical conditions, and medication history. Physical examinations included body height, weight, and WC. BMI was calculated as weight (kg) divided by the square of height (m^2). Blood pressure (BP) was measured in the sitting position using a standard mercury sphygmomanometer. The average of three BP readings was recorded. The baPWV was assessed using an automatic arteriosclerosis diagnostic device (BP-203RPEII; Nihon Colin, Tokyo, Japan). Briefly, four cuffs were wrapped around the upper arms and ankles of the supine participants and connected to plethysmographic and oscillometric pressure sensors. The highest baPWV value obtained was included in the analysis. Further details of the baPWV measurement process have been described previously (24). A routine 12-lead electrocardiogram (ECG) examination was conducted, as reported earlier (23), with a paper speed of 25 mm/s and a gain of 10 mm/mV.

2.3 Biochemical assays

Blood samples were acquired in the morning after at least 8 h of fasting. The blood samples were immediately centrifuged to separate the serum, which was stored at −80°C. Spot urine samples were obtained from the first urine in the morning and frozen at −40°C. Biochemical parameters, including FBG, TG, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, creatinine, uric acid, and albumin, were measured as reported previously (24). The estimated glomerular filtration rate (eGFR) was calculated as follows: eGFR (mL/min per 1.73 m^2) = 175 × serum creatinine (mg/dL)$^{-1.234}$ × age (years)$^{-0.179}$ (× 0.79 for women) (25). Furthermore, the three visceral adiposity parameters were calculated using the following formulas (26, 27): LAP = (WC [cm] − 65 for men [58 for women]) × TG (mmol/L), TyG index = ln (TG [mg/dL] × FBG [mg/dL]/2), VAI for men = (WC [cm]/[39.68 + 1.88 × BMI {kg/m^2}]) × (TG [mmol/L]/1.03) × (1.31/HDL-C [mmol/L]), VAI for women = (WC [cm]/[36.58 + 1.89 × BMI {kg/m^2}]) × (TG [mmol/L]/0.81) × (1.52/HDL-C [mmol/L]).

2.4 Definitions

Hypertension was defined as systolic blood pressure (SBP) of ≥140 mmHg, diastolic blood pressure (DBP) of ≥90 mmHg, or the present use of antihypertensive drugs (28). Diabetes was described as FBG of ≥7.0 mmol/L, the current use of antidiabetic medication, or a previous history of diabetes (29). Hyperlipidemia was considered as the occurrence of hypertriglyceridemia (TG ≥2.26 mmol/L), hypercholesterolemia (total cholesterol ≥6.22 mmol/L), high LDL-C level (≥4.14 mmol/L), or low HDL-C level (≤1.04 mmol/L) (30). Participants were classified as having hyperuricemia if their serum uric acid levels were >420 μmol/L (in both men and women) (31). Albuminuria was defined as a urinary albumin-to-creatinine ratio (uACR) of ≥30 mg/g (32). Furthermore, increased baPWV has been reported to be a good indicator of arterial stiffness development, with a baPWV value of ≥1,400 cm/s considered a high-risk marker (33). ECG is a screening method for LVH, wherein the Cornell voltage-duration product ("Cornell product") is one of the common parameters employed (28). The Cornell product (mV·ms) is calculated as follows: RaVL + SV3 (with 0.8 mV added in women) × QRS duration, with a Cornell product of ≥244 mV·ms indicating ECG-LVH (34).

2.5 Statistical analyses

According to their distribution, continuous variates were presented as means ± standard deviations (SDs) or medians (25^{th} and 75^{th} percentiles). Statistically significant differences among groups were calculated using one-way analysis of variance, Mann–Whitney U test, Kruskal–Wallis H test, and *post-hoc* test as appropriate. Linear trends were tested by the Jonckheere–Terpstra test. The Spearman correlation coefficient was employed to analyze the association between two variates. Categorical variates were expressed as frequencies (n) or percentages (%). The χ^2 test was applied to assess the differences, whereas the linear-by-linear association test was performed to estimate the linear trends. Multivariable linear and logistic regression analyses were conducted to determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the predictive effect of the risk

factors on SOD, with adjustments for age, sex, SBP, serum creatinine, physical activity, smoking habit, and alcohol consumption. Three logistic regression models were constructed to evaluate the association of LAP, VAI, and TyG index with SOD risk. After the initial unadjusted analysis, age and sex were used as adjustment covariates in model 1. Next, SBP, serum creatinine, physical activity, smoking habit, and alcohol drinking were included as covariates in model 2. Additionally, all covariates were examined for multicollinearity before multivariate analysis. We further conducted subgroup analysis to assess the robustness of the associations of LAP, VAI, and TyG index with the risk for SOD. The predictive values of the three indices for SOD were estimated by calculating their concordance index (C-index) based on the fully adjusted model. According to this metric, C-index values over 0.7 indicate a good model (35). To further evaluate the discriminative ability of the indices, we performed pairwise comparisons of the fully adjusted models with LAP, VAI, or TyG index, along with continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses. Statistical analyses were conducted using R software 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 25.0 (SPSS Inc., IL, USA). Statistical significance was set at a two-tailed *P* value of <0.05.

3 Results

3.1 Association of LAP, VAI, and TyG index with arterial stiffness risk

The characteristics of the participants (n = 1,733) grouped according to the presence or absence of arterial stiffness are shown in Table 1. Participants with arterial stiffness (n = 456) were more likely to be male and displayed higher LAP, VAI, TyG index, uACR, and Cornell product values than those without arterial stiffness ($P < 0.05$). Overall, participants with arterial stiffness had a more adverse metabolic and cardiovascular risk profile (Table 1).

In terms of baPWV, LAP, VAI, and TyG index values were positively correlated with baPWV values ($P < 0.001$ for all). We further assessed these associations by categorizing the distribution of the three parameters of visceral adiposity into quartiles (Figure 1). The values of baPWV in the third and fourth quartiles of LAP, VAI, and TyG index were significantly higher compared with the first and second quartiles. After adjusting for traditional cardiovascular risk factors and potential confounders, LAP (OR [95% CI] = 1.004 [1.001–1.007], $P = 0.026$) and TyG index (OR [95% CI] = 1.461 [1.165–1.831], $P = 0.001$) were independently

TABLE 1 Characteristics of participants categorized by arterial stiffness status in 2017 (n = 1,733).

Characteristics	All (n = 1,733)	Non-AS (n = 1,277)	AS (n = 456)	*P* value
Gender (male, %)	980 (56.55%)	643 (50.35%)	337 (73.90%)	**<0.001**
Age (years)	43 (40-45)	43 (40-45)	44 (41-45)	**<0.001**
Diabetes mellitus (%)	395 (22.79%)	260 (20.36%)	135 (29.61%)	**<0.001**
Hypertension (%)	312 (18.00%)	140 (10.96%)	172 (37.72%)	**<0.001**
Hyperuricemia (%)	89 (5.14%)	49 (3.84%)	40 (8.77%)	**<0.001**
Hyperlipidemia (%)	694 (40.05%)	459 (35.94%)	235 (51.54%)	**<0.001**
Alcohol consumption (%)	509 (29.37%)	332 (26.00%)	177 (38.82%)	**<0.001**
Current smoking (%)	757 (43.68%)	495 (38.76%)	262 (57.46%)	**<0.001**
Obesity indices				
BMI (kg/m^2)	23.78 (21.85-26.02)	23.38 (21.55-25.43)	24.98 (22.99-26.88)	**<0.001**
WC (cm)	84.20 (78.00-91.40)	82.90 (76.95-89.70)	88.36 ± 9.62	**<0.001**
LAP	29.77 (17.22-50.69)	26.38 (15.63-45.29)	41.35 (23.92-65.66)	**<0.001**
VAI	1.80 (1.17-2.76)	1.68 (1.10-2.57)	2.09 (1.40-3.17)	**<0.001**
TyG index	8.49 (8.14-8.90)	8.42 (8.09-8.80)	8.71 (8.34-9.10)	**<0.001**
Measurement indicators				
Heart rate (beats/min)	73 (66-80)	72 (69-79)	75 (69-83)	**<0.001**
SBP (mmHg)	121 (112-131)	117 (110-125)	134 (126-148)	**<0.001**
DBP (mmHg)	76 (69-84)	73 (67-79)	86 (80-94)	**<0.001**
FBG (mmol/L)	4.57 (4.28-4.90)	4.54 (4.26-4.85)	4.65 (4.33-5.06)	**<0.001**
ALT (U/L)	19 (14-27)	18 (13-26)	22 (15-33)	**<0.001**

(Continued)

TABLE 1 Continued

Characteristics	All (n = 1,733)	Non-AS (n = 1,277)	AS (n = 456)	*P* value
AST (U/L)	16 (13-20)	16 (13-20)	17 (14-22)	**<0.001**
Total cholesterol (mmol/L)	4.50 (4.04-5.01)	4.47 (4.01-4.96)	4.64 (4.17-5.18)	**<0.001**
Triglycerides (mmol/L)	1.34 (0.95-1.94)	1.24 (0.91-1.80)	1.63 (1.15-2.30)	**<0.001**
LDL-C (mmol/L)	2.46 (2.11-2.84)	2.46 (2.10-2.84)	2.64 ± 0.67	**<0.001**
HDL-C (mmol/L)	1.15 (0.99-1.33)	1.17 (1.01-1.35)	1.09 (0.96-1.26)	**<0.001**
Serum UA (μmol/L)	279.90 (225.00-336.10)	268.60 (218.85-322.95)	314.19 ± 82.01	**<0.001**
Serum creatinine (μmol/L)	75.60 (66.45-85.90)	73.90 (65.30-84.75)	80.00 (71.13-87.65)	**<0.001**
eGFR (mL/min/1.73m^2)	97.76 (87.60-110.77)	98.76 (88.19-111.75)	95.11 (85.48-108.09)	**0.006**
uACR (mg/g)	8.45 (5.52-14.72)	7.73 (5.09-12.95)	11.36 (6.85-24.86)	**<0.001**
baPWV (cm/s)	1,263.00 (1,126.00-1415.50)	1,190.00 (1,086.50-1,289.00)	1,543.00 (1,466.00-1,656.50)	**<0.001**
Cornell product (mV·ms)	138.60 (106.62-174.88)	137.50 (106.34-170.74)	149.00 ± 59.12	**0.014**

Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD or n (%). AS, arterial stiffness; BMI, body mass index; WC, waist circumference; LAP, lipid accumulation product; VAI, visceral adiposity index; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, urine acid; eGFR, estimated glomerular filtration rate; uACR, urine albumin-to creatinine ratio.
Statistically values are presented in bold.

associated with a higher risk for arterial stiffness (Table 2). Furthermore, the prevalence of arterial stiffness was significantly positive with the quartile of LAP, VAI, and TyG index ($P < 0.001$). As presented in Table 3, the third and fourth quartiles of LAP, VAI, and TyG index demonstrated notable associations with the presence of arterial stiffness, both before and after adjusting for age and sex, when compared with the first quartiles (model 1). After further adjustment (model 2), the fourth quartiles of LAP, VAI, and TyG index retained their high predictive values for the presence of arterial stiffness compared with the corresponding first quartiles (OR [95% CI] = 1.538 [1.032–2.291], $P = 0.034$; OR [95% CI] = 1.639 [1.111–2.417], $P = 0.013$; and OR [95% CI] = 1.778 [1.192–2.653], $P = 0.005$, respectively).

In addition, the adjusted ORs for arterial stiffness associated with LAP, VAI, and TyG index according to the various subgroups are shown in Figure 2. LAP, VAI, and TyG index had better predictive values for arterial stiffness risk in men than in women. Moreover, the relationship between TyG index and the risk of arterial stiffness was consistently observed across all BMI groups, regardless of the presence of cardiometabolic risk factors (diabetes and hypertension) and drug medication (antihypertensive, hypoglycemic, and lipid-lowering drugs).

LAP, VAI, and TyG index had considerable discriminative and calibrating abilities for predicting arterial stiffness, with individual C-index values of 0.856, 0.856, and 0.857, respectively (all $P < 0.001$). According to the IDI analysis, replacing LAP or VAI with the TyG index improved the risk prediction in the fully adjusted model (TyG index *vs.* LAP: IDI [95% CI] = 0.003 [−0.0001 to 0.005], $P = 0.038$; VAI *vs.* TyG index: IDI [95% CI] = −0.003 [−0.006 to 0.0005], P=0.019). However, continuous NRI analysis did not show any significant improvement in the prediction (Table 4).

3.2 Association of LAP, VAI, and TyG index with albuminuria risk

A total of 184 individuals had albuminuria, and with a uACR value of 63.05 (38.77–138.60) mg/g (Table S1). Furthermore, participants with albuminuria had higher LAP, VAI, TyG index, heart rate, SBP, DBP, FBG, TG, baPWV, and Cornell product values

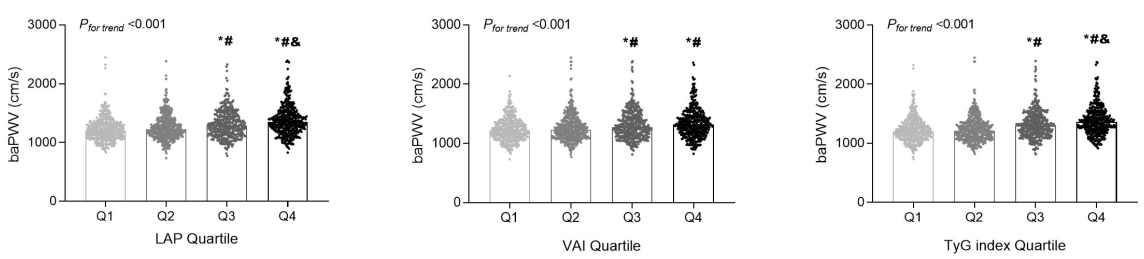

FIGURE 1
The distributions of the brachial-ankle pulse wave velocity (baPWV) values among the quartile (Q) groups according to the lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride-glucose (TyG) index. *$P < 0.05$ compared with the Q1 group; $^{\#}P < 0.05$ compared with the Q2 group; $^{\&}P < 0.05$ compared with the Q3 group.

TABLE 2 Associations between various characteristics and subclinical organ damage in 2017 (n=1,733).

	Arterial stiffness		Albuminuria		ECG-LVH	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender (male, %)	1.888 (1.241-2.872)	**0.003**	0.401 (0.228-0.706)	**0.002**	0.292 (0.160-0.531)	**<0.001**
Age (years)	1.065 (1.019-1.113)	**0.005**	0.926 (0.878-0.977)	**0.005**	0.958 (0.908-1.011)	0.120
Current smoking (%)	0.942 (0.655-1.354)	0.746	1.673 (0.970-2.866)	0.064	1.179 (0.647-1.721)	0.591
Alcohol consumption (%)	1.069 (0.783-1.460)	0.673	0.604 (0.389-0.939)	**0.025**	1.061 (0.654-1.721)	0.811
BMI (kg/m^2)	0.976 (0.933-1.022)	0.299	1.097 (1.043-1.155)	**<0.001**	1.041 (0.986-1.099)	0.145
WC (cm)	1.000 (0.985-1.015)	0.988	1.033 (1.014-1.052)	**0.001**	1.015 (0.996-1.034)	0.129
SBP (mmHg)	1.106 (1.094-1.119)	**<0.001**	1.051 (1.042-1.061)	**<0.001**	1.019 (1.009-1.028)	**<0.001**
Heart rate (bpm/s)	1.033 (1.019-1.046)	**<0.001**	1.025 (1.010-1.041)	**0.001**	0.984 (0.967-1.001)	0.059
ALT (U/L)	1.008 (0.999-1.018)	0.083	1.014 (1.003-1.025)	**0.011**	1.010 (0.998-1.022)	0.108
Serum UA (μmol/L)	0.449 (0.068-2.951)	**0.040**	1.001 (0.998-1.003)	0.588	1.002 (1.000-1.005)	0.088
Serum creatinine (μmol/L)	1.005 (0.994-1.016)	0.355	1.002 (0.989-1.014)	0.787	0.986 (0.973-1.000)	0.055
FBG (mmol/L)	1.094 (0.997-1.200)	0.058	1.415 (1.275-1.571)	**<0.001**	1.041 (0.923-1.175)	0.510
Triglycerides (mmol/L)	1.136 (1.029-1.254)	**0.011**	1.160 (1.041-1.292)	**0.007**	1.006 (0.864-1.172)	0.935
Total cholesterol (mmol/L)	1.188 (1.004-1.406)	**0.045**	1.089 (0.890-1.333)	0.407	0.990 (0.804-1.220)	0.928
LDL-C (mmol/L)	1.182 (0.957-1.460)	0.121	0.964 (0.741-1.255)	0.786	1.029 (0.786-1.345)	0.837
HDL-C (mmol/L)	0.902 (0.524-1.550)	0.708	0.651(0.328-1.292)	0.219	0.984 (0.510-1.901)	0.963
LAP	1.004 (1.001-1.007)	**0.026**	1.006 (1.003-1.010)	**<0.001**	1.002 (0.998-1.006)	0.337
VAI	1.047 (0.998-1.099)	0.062	1.068 (1.015-1.124)	**0.012**	1.010 (0.943-1.082)	0.768
TyG index	1.461 (1.165-1.831)	**0.001**	1.861(1.427-2.426)	**<0.001**	1.011 (0.757-1.350)	0.940

Models were adjusted for age, sex, smoking, alcohol consumption, physical activity, SBP, and serum creatinine. OR, odds ratio; 95% CI, 95% confidence intervals; ECG-LVH, electrocardiogram-left ventricular hypertrophy; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; ALT, alanine aminotransferase; UA, urine acid; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LAP, lipid accumulation product; VAI, visceral adiposity index; TyG index, triglyceride-glucose index. Statistically values are presented in bold.

and higher proportion of hypertension than those without albuminuria (P <0.05).

LAP, VAI, and TyG index demonstrated significant positive correlations with uACR value (all $P < 0.001$). As shown in Figure 3, the fourth quartiles of LAP, VAI, and TyG index exhibited significantly higher uACRs than the first quartiles ($P < 0.05$). Additionally, LAP (OR [95% CI] = 1.006 [1.003–1.010], $P < 0.001$), VAI (OR [95% CI] = 1.068 [1.015–1.124], $P = 0.012$), and TyG index (OR [95% CI] = 1.861 [1.427–2.426], $P < 0.001$) were independently associated with a higher risk for albuminuria, after adjusting for age, sex, SBP, serum creatinine, physical activity, smoking habit, and alcohol consumption (Table 2). Moreover, the high predictive values of the fourth quartiles of LAP and TyG index for the presence of albuminuria were maintained when compared with the first quartiles of LAP and TyG index (OR [95% CI] =1.889 [1.143–3.122], $P = 0.013$; OR [95% CI] = 2.091 [1.302–3.357], $P = 0.002$), respectively, after full adjustment (Table 3).

Further examination of albuminuria risk by the three indices according to the various subgroups demonstrated results similar to those for arterial stiffness (Figure S2). In all subgroups, the relationship between TyG index and albuminuria risk was significantly stronger than that between LAP and VAI and the risk of albuminuria ($P < 0.05$ for both).

As displayed in Table 4, further predictive performance evaluation revealed that LAP, VAI, and TyG index had C-index values of 0.739, 0.737, and 0.746 (all $P < 0.001$), respectively, indicating good discrimination by all three indices. Based on the IDI analysis, the TyG index significantly improved the discrimination of albuminuria risk (TyG index *vs.* LAP: IDI [95% CI] = 0.006 [0.0002–0.013], $P = 0.043$ and VAI *vs.* TyG index: IDI [95% CI] = −0.015 [−0.022 to −0.007], $P < 0.001$). Furthermore, continuous NRI analysis revealed that the TyG index significantly improved the discrimination of albuminuria risk compared with VAI.

3.3 Association of LAP, VAI, and TyG index with LVH risk

The characteristics of participants with and without ECG-LVH are presented in Table S2, with a median Cornell product value of 136.56 mV·ms (without ECG-LVG) and 280.24 mV·ms (with ECG-LVG). Participants with ECG-LVH (n = 84) had a higher prevalence of hypertension and higher BMI, WC, SBP, DBP, and uACR values than those without ECG-LVH ($P < 0.05$). However, LAP, VAI, and TyG index values were not significantly different

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TABLE 3 Association between various characteristics and arterial stiffness and albuminuria by multiple logistic regression analysis.

	Arterial stiffness				Albuminuria			
	n (%)	Odds ratios (95% confidence interval)			n (%)	Odds ratios (95% confidence interval)		
		Unadjusted	Model 1	Model 2		Unadjusted	Model 1	Model 2
LAP								
Quartile 1	66 (14.5%)	1 (reference)	1 (reference)	1 (reference)	28 (15.2%)	1 (reference)	1 (reference)	1 (reference)
Quartile 2	89 (19.5%)	**1.439 (1.013-2.043)**#	**1.536 (1.072-2.200)**#	1.163 (0.768-1.761)	39 (21.2%)	1.432 (0.864-2.372)	1.392 (0.839-2.311)	1.206 (0.712-2.044)
Quartile 3	128 (28.1%)	**2.326 (1.666-3.247)***	**2.235 (1.589-3.143)***	1.284 (0.859-1.920)	44 (23.9%)	1.632 (0.996-2.674)	**1.713 (1.043-2.813)**#	1.210 (0.715-2.049)
Quartile 4	173 (37.9%)	**3.700 (2.673-5.121)***	**3.424 (2.455-4.776)***	**1.538 (1.032-2.291)**#	73 (39.7%)	**2.933 (1.855-4.638)***	**3.204 (2.015-5.096)***	**1.889 (1.143-3.122)**#
P for trend	**<0.001**	**<0.001**	**<0.001**	**0.015**	**<0.001**	**<0.001**	**<0.001**	**0.017**
VAI								
Quartile 1	77 (16.9%)	1 (reference)	1 (reference)	1 (reference)	31 (16.8%)	1 (reference)	1 (reference)	1 (reference)
Quartile 2	99 (21.7%)	1.370 (0.982-1.912)	**1.483 (1.052-2.089)**#	1.330 (0.889-1.991)	39 (21.2%)	1.284 (0.785-2.099)	1.255 (0.766-2.054)	1.018 (0.607-1.706)
Quartile 3	129 (28.3%)	**1.955 (1.419-2.696)***	**2.079 (1.494-2.892)***	1.469 (0.990-2.181)	48 (26.1%)	**1.613 (1.005-2.587)**#	**1.607 (1.001-2.581)**#	1.179 (0.715-1.943)
Quartile 4	151 (33.1%)	**2.476 (1.805-3.395)***	**2.604 (1.881-3.604)***	**1.639 (1.111-2.417)**#	66 (35.9%)	**2.332 (1.488-3.656)***	**2.352 (1.499-3.691)**#	1.555 (0.966-2.505)
P for trend	**<0.001**	**<0.001**	**<0.001**	0.079	**<0.001**	**<0.001**	**<0.001**	0.093
TyG index								
Quartile 1	70 (15.4%)	1 (reference)	1 (reference)	1 (reference)	34 (18.5%)	1 (reference)	1 (reference)	1 (reference)
Quartile 2	79 (17.3%)	1.157 (0.813-1.648)	1.084 (0.756-1.555)	1.011 (0.659-1.550)	35 (19.0%)	1.032 (0.631-1.688)	1.074 (0.655-1.759)	1.023 (0.610-1.717)
Quartile 3	132 (28.9%)	**2.267 (1.634-3.145)***	**1.877 (1.340-2.629)***	1.401 (0.938-2.094)	40 (21.7%)	1.191 (0.739-1.921)	1.368 (0.842-2.224)	1.090 (0.652-1.820)
Quartile 4	175 (38.4%)	**3.517 (2.555-4.843)***	**2.901 (2.083-4.040)***	**1.778 (1.192-2.653)**#	75 (40.8%)	**2.459 (1.600-3.778)***	**2.929 (1.876-4.573)***	**2.091 (1.302-3.357)**#
P for trend	**<0.001**	**<0.001**	**<0.001**	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Logistic regression analyses were used to test the risk of albuminuria, model 1 adjusted for age and sex; model 2 is model 1 further plus exercise, smoking, alcohol consumption. SBP, serum creatinine. *$P < 0.001$; #$P<0.05$. SBP, systolic blood pressure; LAP, lipid accumulation product; VAI, visceral adiposity index; TyG index, triglyceride-glucose index.
Statistically values are presented in bold.

between the two groups. In addition, LAP and VAI values were positively correlated with Cornell product ($P < 0.05$ for both), but these associations were not detected when the LAP and VAI index values were divided into quartiles (Figure S3).

4 Discussion

In this study, we found that elevated values of LAP, VAI, and TyG index were independently associated with a higher risk of arterial stiffness and albuminuria but not with the risk of ECG-LVH. Additionally, the TyG index exhibited superior performance in identifying arterial stiffness and albuminuria compared with the other two indices. Thus, our findings suggest that these three markers of visceral adiposity, especially the TyG index, may serve as simple and noninvasive indicators to predict cardiovascular SOD in clinical practice.

Prior literature has suggested that the novel parameters of visceral adiposity, namely, LAP, VAI, and TyG index, are associated with baPWV. In a study involving Chinese hypertensive patients with a mean age of 64.42 years, a positive association was found between LAP and elevated baPWV (>75th percentile) (36). Another study reported that older Chinese participants (>60 years) in the higher VAI tertiles had a higher odds ratio (OR) for arterial stiffness (defined

10.3389/fendo.2023.1164592

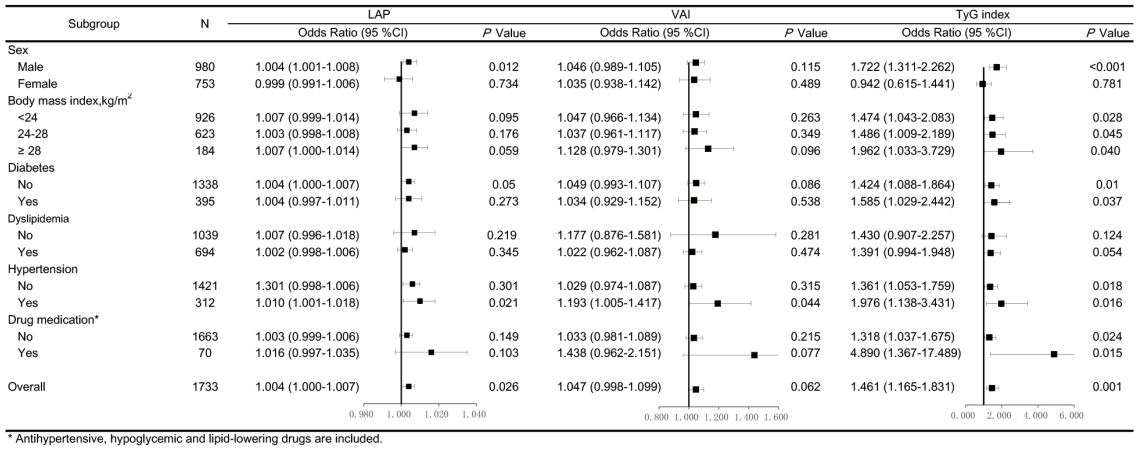

FIGURE 2
Forest plots of odds ratios (ORs) for the lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride-glucose (TyG) index and risk of arterial stiffness after adjustment. The adjustment model includes age, sex, SBP, serum creatinine, physical activity, smoking and alcohol consumption in participants stratified by sex, body mass index, diabetes, dyslipidemia, hypertension, and drug medication. Values are the ORs (95% confidence intervals [95% CIs]).

as baPWV ≥1,400 cm/s) compared with those in the lowest VAI tertile (37). In the Kailuan study, a significant dose–response relationship between the TyG index and the risk of arterial stiffness, measured by baPWV, was observed (38). However, the comparative predictive capabilities of LAP, VAI, and TyG index for arterial stiffness in the general population remain unclear. Our study revealed that all high quartiles of LAP, VAI, and TyG index were significantly associated with an increased risk of arterial stiffness after adjusting for confounding factors. Furthermore, our findings demonstrated that the TyG index outperformed the other two indices in all subgroup analyses. Therefore, our results indicate that the three parameters, especially the TyG index, possess considerable potential as simple and effective markers for identifying individuals with a high risk of vascular dysfunction.

Our study is the first to evaluate and compare the associations between all three parameters, namely, LAP, VAI, and TyG index, and albuminuria in the general Chinese population. Although previous studies have shown strong associations between obesity-related indices and chronic kidney disease (39), the findings are inconsistent. A cohort study involving 1,872 patients with type 2 diabetes reported a higher risk of albuminuria associated with elevated LAP, VAI, and TyG index (40). However, a community cohort study of 3,868 participants followed up for over 3.1 years revealed that albuminuria incidence increased proportionally with TyG index quartiles, but the TyG index itself was not identified as an independent risk factor for albuminuria (41). In our study, LAP, VAI, and TyG index were independently associated with an increased risk of albuminuria. Furthermore, our findings indicate that the TyG index outperformed the other two indices in all subgroup analyses, regardless of the presence of cardiometabolic risk factors and drug medication.

Albuminuria is a systemic vascular disturbance that is potentially associated with increased cardiovascular morbidity and mortality in obese individuals (42). The distribution of fat in

TABLE 4 The incremental predictive value of LAP, VAI, and TyG index the for subclinical organ damage in 2017 (n=1,733).

	C-index (95%CI)	*P*	Continuous NRI (95% CI)	*P*	IDI (95% CI)	*P*
Arterial stiffness						
LAP	0.856 (0.837-0.875)	0.983*	0.042 (0.016-0.067) *	0.051*	0.006 (-0.0007 to 0.002) *	0.346*
VAI	0.856 (0.836-0.875)	0.916#	-0.037 (-0.094 to 0.024) #	0.087#	-0.003 (-0.006 to 0.0005) #	**0.019#**
TyG index	0.857 (0.838-0.876)	0.941&	0.018 (-0.035 to 0.070) &	0.486&	0.003 (-0.0001 to 0.005) &	**0.038&**
Albuminuria						
LAP	0.739 (0.698-0.781)	0.946*	0.103 (0.037-0.176) *	**0.021***	0.008 (-0.000 to -0.014) *	**0.001***
VAI	0.737 (0.696-0.778)	0.759#	-0.109 (-0.211 to 0.000) #	**0.039#**	-0.015 (-0.022 to -0.007) #	**<0.001#**
TyG index	0.746 (0.706-0.787)	0.811&	0.005 (-0.091 to 0.097) &	0.902&	0.006 (0.0002-0.013) &	**0.043&**

Models were adjusted for age, sex, smoking, alcohol consumption, physical activity, systolic blood pressure, and serum creatinine. **vs.* VAI, #*vs.* TyG index, &*vs.* LAP. 95% CI, 95% confidence intervals; C-index, concordance index; NRI, net reclassification improvement; IDI, integrated discrimination improvement; LAP, lipid accumulation product; VAI, visceral adiposity index; TyG index, triglyceride-glucose index.
Statistically values are presented in bold.

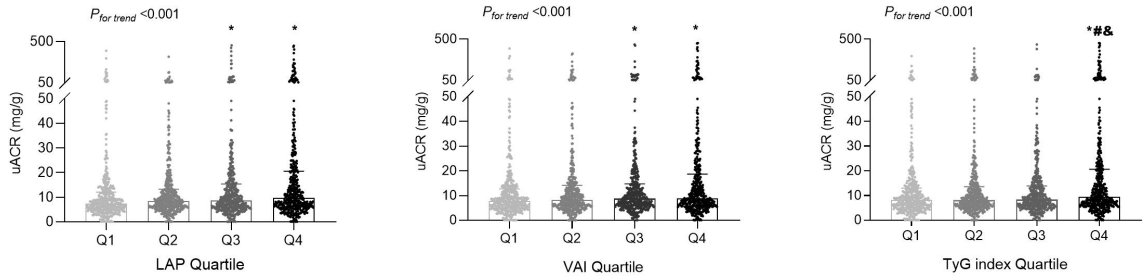

FIGURE 3
The distributions of the urinary albumin-to-creatinine ratio (uACR) values among the quartile (Q) groups according to the lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride-glucose (TyG) index. *$P < 0.05$ compared with the Q1 group; $^{\#}P < 0.05$ compared with the Q2 group; $^{\&}P < 0.05$ compared with the Q3 group.

the body may influence the health of arteries and kidneys (43). In particular, visceral adipose tissue can regulate pro-inflammatory cytokines, such as interleukin 6, and reduce the production of adiponectin, a cardiovascular protective protein. This contributes to inflammation, oxidative stress, insulin resistance, and podocyte dysfunction. These alterations can result in arterial stiffness, albuminuria, and other cardiovascular risks (44, 45). Additionally, excessive fat infiltration in the kidneys can further worsen renal damage (46).

Visceral adiposity can also influence cardiac remodeling via underlying mechanisms described above. A cohort study of 229 participants with suspected metabolic syndrome aged 56.4 ± 4.5 years demonstrated that visceral obesity, but not central obesity measured by WC, was independently associated with structural and functional cardiac remodeling (47). However, our current study of the general population, with a mean age of 43 (40–45) years, did not find any association between adiposity indices (LAP, VAI, and TyG index) and ECG-LVH. It would be necessary to observe long-term cardiac structural changes, since a large number of older individuals in the outcome group of the general population could help clarify the association between obesity indices and subclinical heart damage. However, we did confirm the findings of a previous investigation reporting an association between obesity phenotypes and LVH (48). Obesity is increasingly recognized as a heterogeneous condition with a cluster of metabolic derangements postulated to explain its association with cardiovascular organ dysfunction (27, 46). Therefore, we hypothesize that visceral adipose tissue and ectopic fat depots may play a significant role in the prevalence and progression of SOD.

The main advantages of this study were that it explored and compared the associations between three obesity-related indices and SOD in a general Chinese population. Additionally, the study aimed to investigate a wide range of subclinical organ outcomes, including blood vessels, kidneys, and the heart, instead of focusing on just one aspect. This comprehensive approach allows for a holistic evaluation of the cardiovascular high-risk group within this population. Furthermore, SOD outcomes were collected by a panel of physicians using detailed evaluation criteria, and the standardized data collection protocols and rigorous quality control. Nonetheless, some limitations merit consideration. First, our study was a cross-sectional analysis; therefore, a causal relationship between the three obesity indices and SOD outcomes could not be established. Second, the formula to calculate LAP was obtained by Kahn based on the data of the National Nutrition Survey of the United States (13). The parameter settings are accordingly derived from the Western population. Therefore, the formula's applicability to the Chinese population requires further exploration. Similar validations are necessary for VAI and TyG index as well. Notably, there is growing evidence of the value of the three markers in East Asians. Third, our study results should be confirmed by epidemiological data from other regions and larger populations.

In conclusion, LAP, VAI, and particularly TyG index can help identify SOD in clinical settings and stratify the high-risk group requiring early prevention strategies. Individuals with a higher TyG index have an elevated risk for vascular failure and early kidney damage in Chinese Han adults. These findings will help implement early detection approaches and preventive measures against cardiovascular SOD progression and adverse cardiovascular outcomes.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to YW, wangyangxxk@126.com.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2015LSL-047). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YW and M-FD conceived and designed the experiments; J-JM was responsible for participant recruitment; M-FD, XZ, G-LH, CChu, Y-YL, CChen, DW, QM, YY, HJ, K-KW, YS, Z-JN, Z-YM, LW, X-YZ, W-JL, W-HG, HL, G-JW, KG, and JZ performed the experiments; M-FD and YW analyzed the data; M-FD drafted the manuscript; and YW and J-JM edited and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1164592/full#supplementary-material

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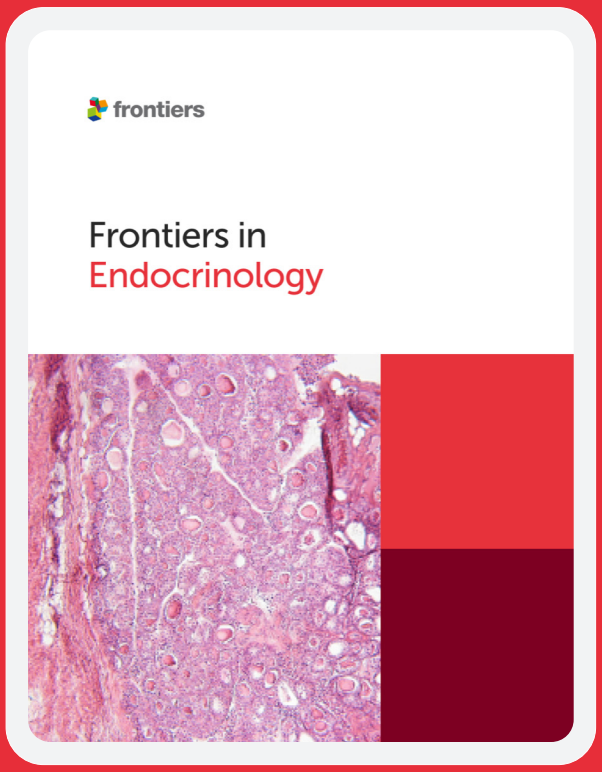

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