Diabetes, Metabolic Syndrome and Obesity

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Estimated Pulse Wave Velocity as a Novel Non-Invasive Biomarker for Metabolic Syndrome Among People Living with HIV

Suling Chen[1,*], Yuanhui Jiang[1,*], Xiaoli Lin[1,*], Hongjie Chen[1], Xiaoxuan Wu[2], Zhe Qian[3], Xuwen Xu[1], Huiqun Zhong[1], Jie Peng[1], Shaohang Cai[1]

[1]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, People's Republic of China; [2]Department of Communicable and Endemic Disease Control and Prevention, Haizhu District Center for Disease Control and Prevention, Guangzhou, People's Republic of China; [3]Second Department of Elderly Respiratory, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Provincial Geriatrics Institute, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Huiqun Zhong; Jie Peng, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, 510515, People's Republic of China, Email lovely870821@163.com; pjie138@163.com

Purpose: This study aims to investigate the relationship between estimated pulse wave velocity (ePWV) and metabolic syndrome (MetS) in people living with HIV (PLWH), proposing a novel and convenient predictor for early detection of MetS in PLWH.

Patients and Methods: A total of 485 PLWH were enrolled. These participants were categorized into two groups based on the estimated pulse wave velocity (ePWV) level. Demographic and clinical data were collected to investigate the correlation between ePWV and MetS.

Results: The cohort of 485 PLWH was categorized into high-ePWV and low-ePWV groups based on ePWV cutoff value of 10 m/s. We observed significant differences in components of MetS including triglycerides (TG, $P < 0.05$), HDL cholesterol (HDL-C, $P < 0.01$), systolic blood pressure (SBP, $P < 0.001$), diastolic blood pressure (DBP, $P < 0.05$), and fasting plasma glucose (FPG, $P < 0.001$) between the two groups. Furthermore, we employed receiver operating characteristic (ROC) curves to demonstrate the effectiveness of ePWV as a predictive indicator for MetS in PLWH (AUC = 0.739, $P < 0.001$). According to the ROC curve, the optimal cut-off value of ePWV was 7.4 m/s, and its sensitivity and specificity in diagnosing MetS in PLWH were 79.03% and 64.07%, respectively. Although the 7.4 m/s cutoff increased the false positive rate compared to the traditional cutoff, it significantly reduced the rate of missed diagnoses, effectively identifying 79.03% of PLWH with MetS.

Conclusion: ePWV is a non-invasive and convenient novel biomarker with predictive capabilities for MetS in PLWH.

Keywords: HIV/AIDS, highly active antiretroviral therapy, metabolic syndrome, estimated pulse wave velocity

Introduction

The introduction and widespread utilization of highly active antiretroviral therapy (HAART) for acquired immunodeficiency syndrome (AIDS) redefined it as a manageable chronic disease and led to a significant extension in the life expectancy of people living with HIV (PLWH).[1] However, the incidence of various non-AIDS-defining diseases has been on the rise,[2] including metabolic syndrome (MetS), cardiovascular diseases (CVD), chronic liver and kidney disorders, skeletal issues and non-AIDS-defining cancers.[3] This emergent trend is becoming an increasingly significant concern, impacting both the quality of life and the long-term prognosis of PLWH in the post-HAART era.[4]

MetS comprises a series of risk factors that collectively contribute to CVD as a primary clinical outcome. These factors encompass centripetal obesity, impaired glucose metabolism, elevated blood pressure, elevated triglycerides (TG), and reduced levels of high-density lipoprotein cholesterol (HDL-C).[5] With the aging of this population in the post-HAART era, PLWH are at increased risk of MetS and the incidence of cardiovascular events is on the rise.[6] The

Received: 12 December 2023
Accepted: 4 May 2024
Published: 13 May 2024

underlying causes of the risk of MetS in PLWH are not fully clear. Complex interactions between persistent low-level immune activation, metabolic toxicity of HAART, and non-HIV-related risk factors in chronic HIV infection may contribute to an increased risk of MetS in PLWH.[7] Early prediction and primary prevention of MetS in PLWH is challenging and is becoming a critical public health concern.[8]

Carotid-femoral pulse wave velocity (cfPWV) has long been acknowledged as the gold standard metric for the assessment of arterial stiffness (AS).[9] However, its clinical applicability has been constrained due to its intricacy and the associated high costs. In response, an alternative measure, known as estimated pulse wave velocity (ePWV), has emerged as a viable substitute for cfPWV in clinical practice and large-scale clinical investigations, as it has shown strong concordance with the conventional pulse wave velocity.[10–12] Elevated ePWV has been demonstrated to be associated with an increased incidence of new atrial fibrillation, and it independently augments the risk of stroke, thereby signifying a favorable predictive capacity of ePWV.[13,14] Subsequent research have proposed an independent association between elevated ePWV and an increased risk of diabetes in Chinese adults, suggesting ePWV's potential utility as a reliable indicator of early diabetes risk.[15] However, it is not known whether ePWV exhibits predictive power in MetS among PLWH.

Therefore, this study aimed to investigate the relationship between ePWV and MetS in PLWH and propose a novel and convenient predictor for the early detection and primary prevention of MetS in PLWH.

Materials and Methods

Study Design

This cross-sectional study was carried out at Nanfang Hospital affiliated with Southern Medical University. We included 508 participants diagnosed with HIV-1 infection who were followed up at Nanfang Hospital, and we ended up approaching 485 participants based on the inclusion and exclusion criteria (Supplementary Figure 1). We excluded (1) participants with malignancies, systemic infections, or those who were pregnant, (2) participants who declined to participate, and (3) participants lacking essential clinical data.

In accordance with the guidelines, a threshold of greater than 10 m/s for PWV was established to indicate clinically significant CVD risk.[16] As ePWV served as a proxy for PWV, we used the PWV standard for categorization. Consequently, we grouped participants according to ePWV $\leq$ 10 and $>$ 10 m/s to explore the relationship between ePWV and various clinical indicators in PLWH. Subsequently, to further explore the relationship between ePWV and MetS in PLWH, we classified participants based on the five components of the MetS contained, which are central obesity, impaired fasting glucose, elevated blood pressure, elevated TG level, and decreased HDL-C level.

Data Collection

For PLWH, clinical variables were collected, including age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HAART duration (measured in months), HAART regimen, CD4+T cell count, CD8+T cell count, CD4/CD8 ratio, HIV RNA (100 copies/mL as lower detection limit), TG, CHOL, HDL-C, low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartic aminotransferase (AST), fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), uric acid (UA) and estimated glomerular filtration rate (eGFR). Transient elastography examination was conducted and controlled attenuation parameter (CAP) measurement was made for the evaluation of hepatic steatosis while liver stiffness measurements (LSM) were conducted to assess hepatic fibrosis.[17]

Participants completed self-assessment questionnaires during each visit to gather information on traditional risk factors associated with MetS. These factors were as follows: (1) "Smoking" was defined as participants who had smoked more than 100 cigarettes and were still smoking. (2) "Alcoholism" was defined as participants who consumed 25 or more grams per day for men and 15 or more grams per day for women on average.[18] (3) "Sports" was defined as participants who engaged in at least 150 minutes of moderate-intensity aerobic activity, or at least 75 minutes of vigorous-intensity aerobic activity per week.[19] (4) "Sleep" was defined as participants who meet the recommended minimum of 7 hours of sleep per day.[20] (5) "Anxiety/depression" was defined as participants with a previous diagnosis of anxiety and depression.

(6) "CVD family history" was defined as participants with at least a blood-related relative who has been previously diagnosed with CVD.

Calculation of ePWV

In this study, age was measured in years, and mean blood pressure (MBP) was calculated as MBP = DBP + 0.4 × (SBP − DBP). The blood pressure used were the average of at least three measurements, and participants were asked to rest for five minutes in a quiet environment before taking the measurements. ePWV was calculated using the following equation:[12,21]

$$ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MBP + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$$

To compare instrumental pulse wave velocity (PWV) with calculated ePWV, brachial-ankle pulse wave velocity (baPWV) was also assessed in a subset of participants as part of this study. We performed correlation analysis and conducted a comparison of receiver operating characteristic (ROC) curves between baPWV and ePWV. Our findings indicated that the diagnostic efficiency of ePWV was quite similar to that of baPWV (Supplementary Figure 2).

Diagnosis of Metabolic Disorders

MetS was defined according to the International Diabetes Federation (IDF) criteria,[22] which require the presence of central obesity (waist circumference ≥ 90cm in men and 80cm in women) along with at least two of the following components: (1) TG levels ≥ 1.70 mmol/L or being on treatment for dyslipidemia. (2) Low HDL-C levels were defined as ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women, or if the participant was receiving treatment for dyslipidemia. (3) Elevated blood pressure was defined as ≥ 130 mmHg, and/or DBP ≥ 85 mmHg or if the participant was using antihypertensive medication. (4) FBG levels ≥ 5.6 mmol/L, a diagnosis of type 2 diabetes, or treatment with oral hypoglycemic agents. It is worth noting that the IDF guidelines mention that central obesity can be assumed if the criteria for obesity are met.[22] In this analysis, we utilized the Chinese obesity threshold, defined as BMI > 27.5 kg/m^2 according to the World Health Organization guidelines for the Asian population.[23]

In addition, metabolic disorders associated with MetS were defined as follows: hypertriglyceridemia was defined as TG ≥ 1.7mmol/L.[24] Low level of high-density lipoprotein, also known as hypoalphalipoproteinemia (HA), was defined as HDL-C ≤ 1.03 mmol/L in men and ≤ 1.29 mmol/L in women.[25] Hypertension was defined as ≥ 130 mmHg, and/or DBP ≥ 80 mmHg or if the participant was using antihypertensive medication.[26] Elevated fasting glucose includes diagnostic criteria for impaired fasting glucose and diabetes, defined as FPG ≥ 5.6mmol/L.[27,28]

Statistical Analysis

Measurement units were reported as mean ± standard deviation for datasets displaying normal distribution, while datasets with non-normal distribution were represented as median (interquartile range). Categorical data were presented as percentages. This study uses the Kolmogorov–Smirnov test to assess data normality. For the comparison of continuous variables between two groups, Student's *t*-test or Mann–Whitney *U*-test was used according to whether data met normal distribution. Multivariate continuous variables were compared using one-way ANOVA or Kruskal–Wallis test according to data normality. Chi-square test or Fisher exact test was utilized to compare categorical variables. We used Pearson correlation to analyze the association between ePWV with clinical variables, and the predictive capacity of ePWV for disease was evaluated using ROC curves. Logistic regression was utilized to evaluate the association between clinical variables and the outcome. Odds ratios and 95% confidence intervals were calculated to gauge the strength of these relationships. All statistical analyses were conducted using SPSS software (version 26.0), and statistical significance was defined by a two-sided p-value of less than 0.05. To develop the nomogram, the nomogram function included in the R 4.2.2. rms package was used. The "nomogram" function was used to build a suitable model and draw a nomogram by these risk genes. Figures were generated using R Version 4.2.2.

Results

Demographics and Clinical Characteristics of Participants Enrolled

A total of 485 PLWH were classified into two groups based on their ePWV being <10 m/s or ≥10 m/s (low-ePWV group and high-ePWV group). As shown in Table 1, age (P < 0.001), MBP (P < 0.001), CAP (P = 0.009) and HbA1c (P <

Table 1 Demographics and Clinical Characteristics of Participants Enrolled

Characteristics	Overall (N = 485)	Low-ePWV (N = 454)	High-ePWV (N = 31)	P value
Age, years	32.00 [26.00, 43.00]	32.00 [26.00, 40.00]	59.00 [55.00, 71.00]	**<0.001**
Sex, male	447 (92.16%)	422 (92.95%)	25 (80.65%)	**0.026**
BMI, kg/m^2	22.23 [19.75, 24.49]	22.19 [19.65, 24.44]	23.00 [20.86, 24.97]	0.210
MBP, mmHg	102.02 ± 10.03	101.21 ± 9.03	113.92 ± 15.32	**<0.001**
Smoking	150 (36.14%)	139 (35.46%)	11 (47.83%)	0.230
Alcoholism	77 (18.51%)	71 (18.11%)	6 (25.00%)	0.417
Regularly exercise	159 (38.22%)	151 (38.52%)	8 (33.33%)	0.612
Sleep deprivation	68 (16.35%)	63 (16.07%)	5 (20.83%)	0.568
Anxiety/depression	91 (21.88%)	81 (20.66%)	10 (41.67%)	**0.016**
CVD Family history	152 (36.54%)	139 (35.46%)	13 (54.17%)	0.065
CAP, dB/m	213.00 [190.00, 250.00]	210.50 [190.00, 248.00]	230.00 [212.50, 263.00]	**0.009**
LSM, kPa	5.00 [4.40, 5.70]	5.00 [4.40, 5.70]	5.40 [4.35, 5.80]	0.675
ALT, U/L	23.00 [16.00, 34.00]	23.00 [16.00, 35.00]	23.00 [16.00, 27.00]	0.793
AST, U/L	21.00 [18.00, 26.00]	20.00 [18.00, 26.00]	23.00 [20.00, 29.50]	0.073
HbA1c, %	5.40 [5.10, 5.70]	5.40 [5.10, 5.60]	5.70 [5.55, 6.20]	**<0.001**
UA, μmmol/L	365.00 [305.00, 432.00]	368.50 [310.25, 434.75]	299.00 [250.00, 358.00]	**<0.001**
eGFR, mL/min/1.73m^2	106.23 [93.28, 117.06]	107.69 [95.34, 118.21]	82.02 [65.46, 91.92]	**<0.001**

Notes: Continuous variables are expressed as mean ± standard deviation or median [interquartile range], and categorical variables are expressed as n (%). Bold text indicates P value < 0.05.

Abbreviations: ePWV, estimated pulse wave velocity; BMI, body mass index; MBP, mean blood pressure; CVD, cardiovascular disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; ALT, alanine aminotransferase; AST, aspartic aminotransferase; HbA1c, glycated hemoglobin A1c; UA, uric acid; eGFR, estimated glomerular filtration rate.

0.001) in the high-ePWV group were significantly higher than in the low-ePWV group. Moreover, a higher proportion of female PLWH (P = 0.026) and PLWH with anxiety or depression (P = 0.016) was observed in high-ePWV group. In contrast, UA (P < 0.001) and eGFR (P < 0.001) were significantly higher in low-ePWV group.

Components of MetS Grouped by ePWV Among PLWH

Our analysis revealed significant difference between the low-ePWV and high-ePWV groups concerning the components associated with MetS. We observed that TG (Figure 1A, P < 0.05), HDL-C (Figure 1B, P < 0.01), SBP (Figure 1C, P < 0.001), DBP (Figure 1D, P < 0.05) and FPG (Figure 1E, P < 0.001) were significantly higher in high-ePWV group than in low-ePWV group. To further validate this observation, we compared ePWV in PLWH with different numbers of components of MetS, and the result indicated that ePWV increased with the increase of components of MetS. (Figure 1F, P < 0.05).

Correlation Between ePWV with Clinical Variables Among PLWH

In order to further evaluate the relationship between clinical data and ePWV in PLWH, Pearson's correlation analysis was conducted. We found that BMI (r = 0.235, P < 0.001), FPG level (r = 0.307, P < 0.001), CAP level (r = 0.232, P < 0.001), TG level (r = 0.198, P < 0.001), CHOL level (r = 0.217, P < 0.001) and LDL-C level (r = 0.226, P < 0.001) exhibited positive correlations with ePWV level (Figure 2A-F). On the other hand, the HDL-C level (r = −0.172, P < 0.001) and

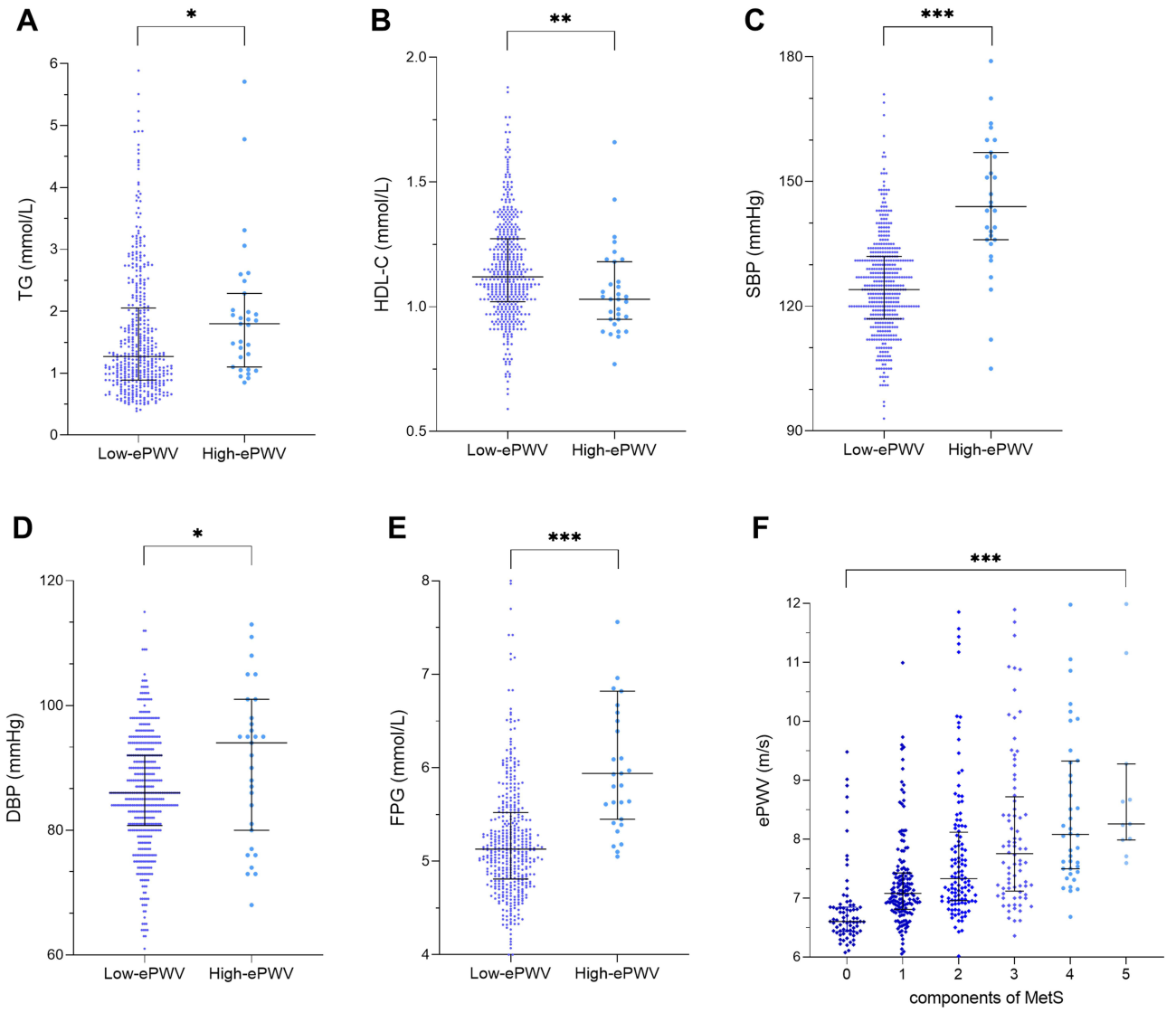

Figure 1 Risk components of MetS between low-ePWV group and high-ePWV group among PLWH. (**A**) TG level in PLWH between low-ePWV group and high-ePWV group (1.27 [0.89, 2.04] versus 1.80 [1.18, 2.16]; P < 0.05). (**B**) HDL-C level in PLWH between low-ePWV group and high-ePWV group (1.12 [1.02, 1.27] versus 1.03 [0.95, 1.14]; P < 0.01). (**C**) SBP level in PLWH between low-ePWV group and high-ePWV group (124.00 [117.00, 131.75] versus 144.00 [136.00, 156.50]; P < 0.001). (**D**) DBP level in PLWH between low-ePWV group and high-ePWV group (86.06 ± 9.17 versus 92.00 ± 14.79; P < 0.05). (**E**) FPG level in PLWH between low-ePWV group and high-ePWV group (5.13 [4.81, 5.52] versus 5.94 [5.53, 6.75]; P < 0.001). (**F**) ePWV level in groups containing different amounts of components of MetS (P < 0.001).
Notes: *Indicates P value < 0.05; **Indicates P value < 0.01; ***Indicates P value < 0.001.
Abbreviations: ePWV, estimated pulse wave velocity; TG, total triglycerides; HDL-C, High-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, Fasting plasma glucose; MetS, metabolic syndrome.

eGFR level (r = −0.553, P < 0.001) displayed significant negative associations with ePWV level (Figure 2G and H). These findings collectively underscore the close relationship between ePWV and MetS.

The Diagnostic Ability of ePWV on Metabolic Disorders

Given the observed strong association between ePWV and MetS, we constructed a ROC curve for ePWV to predict MetS, and the results demonstrated that ePWV could effectively predict MetS in PLWH (Figure 3A, AUC = 0.739, P < 0.001). We found the optimal cut-off value of ePWV was 7.4 m/s according to the ROC curve. At this threshold, the sensitivity and specificity in diagnosing MetS in PLWH were 79.03% and 64.07%, respectively. Subsequently, we evaluated the predictive ability of ePWV for metabolic disorders associated with MetS through ROC analysis, we found that ePWV exhibited excellent predictive accuracy for hypertension (Figure 3B, AUC = 0.815, P < 0.001), potentially

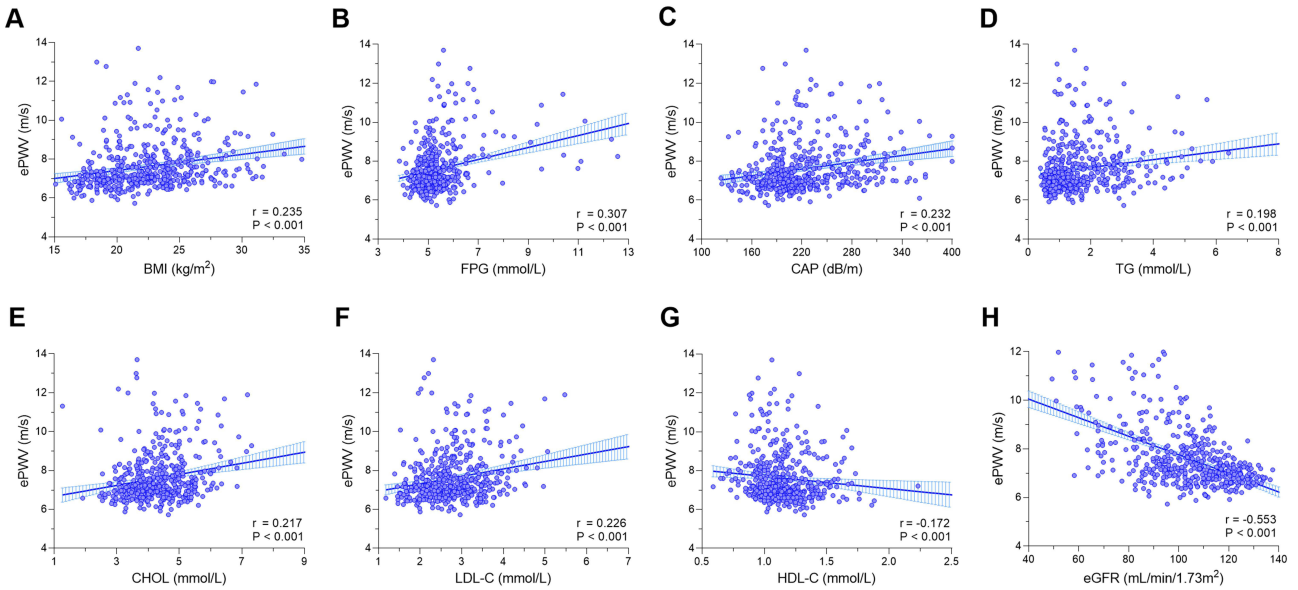

Figure 2 Correlation between ePWV with clinical variables among PLWH. The Scatter plots of ePWV and BMI (**A**), FPG level (**B**), CAP level (**C**), TG level (**D**), CHOL level (**E**), LDL-C level (**F**), HDL-C level (**G**) and eGFR level (**H**).

Notes: r means Pearson correlation coefficient.

Abbreviations: ePWV, estimated pulse wave velocity; BMI, body mass index; FPG, Fasting plasma glucose; CAP, controlled attenuation parameter; TG, total triglycerides; CHOL, total cholesterol; LDL-C, Low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

attributed to the inclusion of MBP in the ePWV calculation formula. Besides, ePWV also demonstrated robust predictive power for other MetS components (Figure 3C-F) of MetS including obesity (AUC = 0.649, P < 0.001), hypertriglyceridemia (AUC = 0.653, P < 0.001), declined HDL-C level (AUC = 0.595, P < 0.001) and elevated FPG level (AUC = 0.698, P < 0.001).

A More Suitable Cut-off Value of ePWV for PLWH

Consequently, the entire cohort of 485 participants was reassigned into two distinct groups (defined as "high risk of MetS" and "normal risk of MetS") based on an optimal cut-off of ePWV = 7.4 m/s from the ROC curve. As shown in Supplementary Table 1, Smoking (P < 0.001), CVD family history (P < 0.001), BMI (P < 0.001), SBP (P < 0.001), DBP (P < 0.001), MBP (P < 0.001), CAP (P < 0.001), LSM (P = 0.002), TG (P < 0.001), CHOL (P < 0.001), LDL-C (P < 0.001), FPG (P < 0.001) and HbA1c (P = 0.025) were significantly higher in the "high risk of MetS" group. Conversely, CD8+T counts (P < 0.001), HDL-C (P < 0.001), UA (P < 0.001) and eGFR (P < 0.001) were significantly higher in the "normal risk of MetS" group.

We compared the traditional ePWV threshold (10 m/s) with the new ePWV threshold (7.4 m/s) and revealed a substantial difference in their effectiveness in predicting MetS. The traditional ePWV threshold identified only 9.68% of MetS cases, while the new ePWV threshold successfully identified 76.79% of participants with MetS who had been overlooked by the traditional ePWV approach. Although the adoption of the 7.4 m/s cutoff led to a higher incidence of false positives, with 152 participants without MetS being misdiagnosed as MetS, it significantly reduced the rate of missed diagnoses, effectively identifying 79.03% of PLWH with coexisting MetS. This enhancement considerably heightened the sensitivity of ePWV as a predictive tool for MetS (Supplementary Table 2).

The Influence of HIV Infection and HAART on ePWV

We next investigated the influence of HIV infection and HAART exposure on ePWV level among PLWH. The $CD4^+$T cell counts (Figure 4A, P < 0.01) was significantly higher in high-ePWV group than in low-ePWV group, suggesting the influence of immune deficiency status on ePWV. However, there was no significance in other HIV-related parameters including $CD8^+$T cell counts, viral load, AIDS stage, HAART duration and HAART regimens (Figure 4B-F).

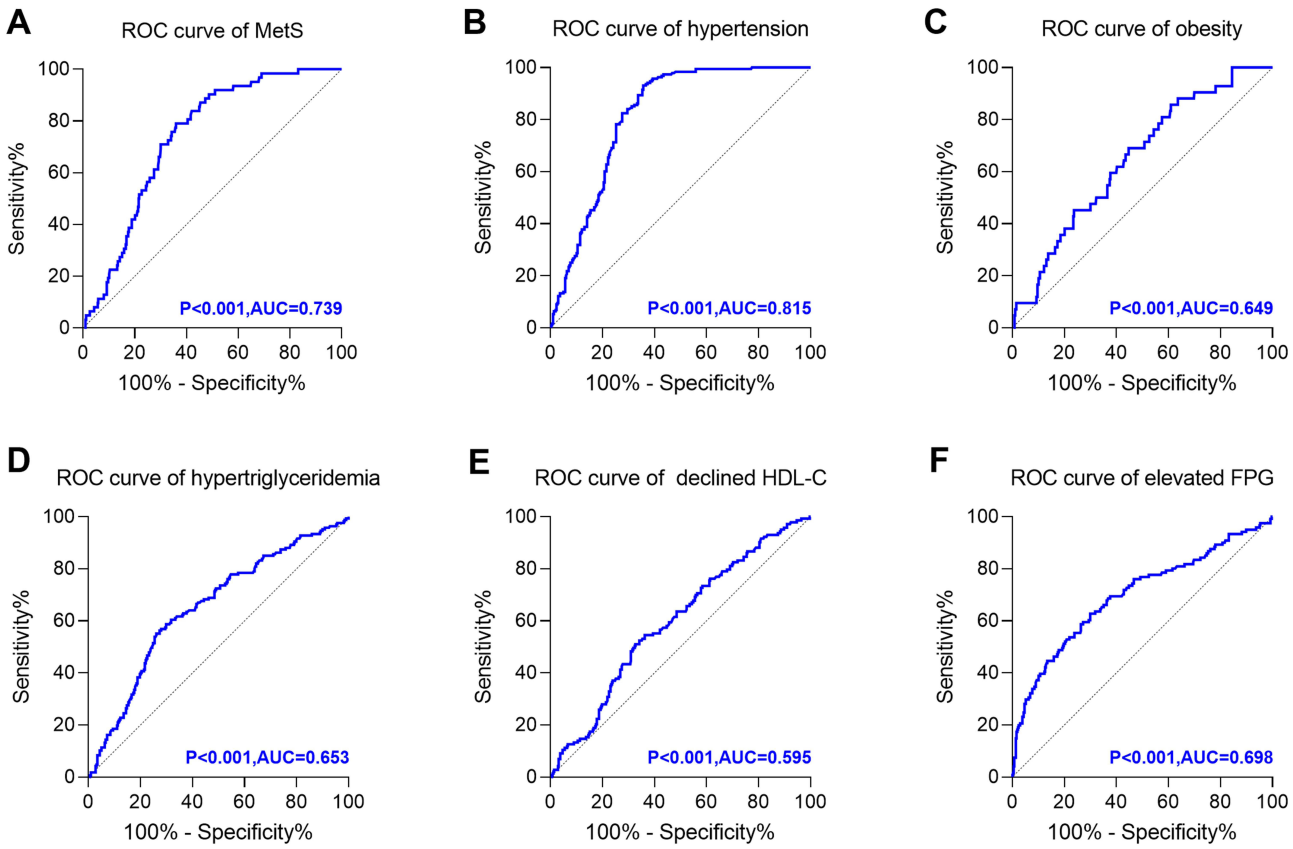

Figure 3 The diagnostic ability of ePWV in metabolic disorders. The ROC curve of ePWV level relating to MetS (**A**), hypertension (**B**), obesity (**C**), hypertriglyceridemia (**D**), declined HDL-C level (**E**) and elevated FPG level (**F**).
Abbreviations: AUC, area under the curve; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

We then performed the same analysis in the Non-MetS and MetS groups and found that only CD8+T counts ($P < 0.01$) and HAART regimens ($P < 0.05$) were significantly different between the two groups (Supplementary Figure 3).

Independent Factors for MetS Among PLWH

To evaluate risk factors associated with MetS among PLWH, we conducted both univariate and multivariate analyses. The results demonstrated that CAP (OR = 1.028, $P < 0.001$), LSM (OR = 1.444, $P = 0.004$), eGFR (OR = 0.969, $P = 0.022$), CD8+T cell counts level (OR = 1.001, $P = 0.038$) and CVD family history (OR = 2.212, $P = 0.042$) were independent risk factors associated with MetS among PLWH (Figure 5).

Discussion

Consistent evidence has demonstrated a robust correlation between PWV and MetS, as well as its components including FPG, hypertension, and waist circumference.[29,30] It has been documented by Kangas et al that PWV was 16–17% higher in participants with MetS compared to the healthy population.[31] Similarly, a large-scale multi-center study confirmed a substantial impact of MetS on PWV.[32] Yokoyama et al have discovered that as the number of MetS components increases, PWV exhibited a significant rise in individuals with diabetes.[33] Our current study evaluated the association between ePWV and MetS in PLWH. First, we realized that there were significant differences between the two groups divided by ePWV in terms of MetS related components. Furthermore, the results indicated a strong significance of ePWV in six groups categorized by the number of MetS components. Our linear analysis further unveiled a notable linear correlation between ePWV and these MetS components. In addition, the introduction of ROC curve analysis to assess ePWV's predictive accuracy for MetS, the grouping analysis again with new ePWV cutoff values, reinforced the association between ePWV and MetS, thus validating the original hypothesis.

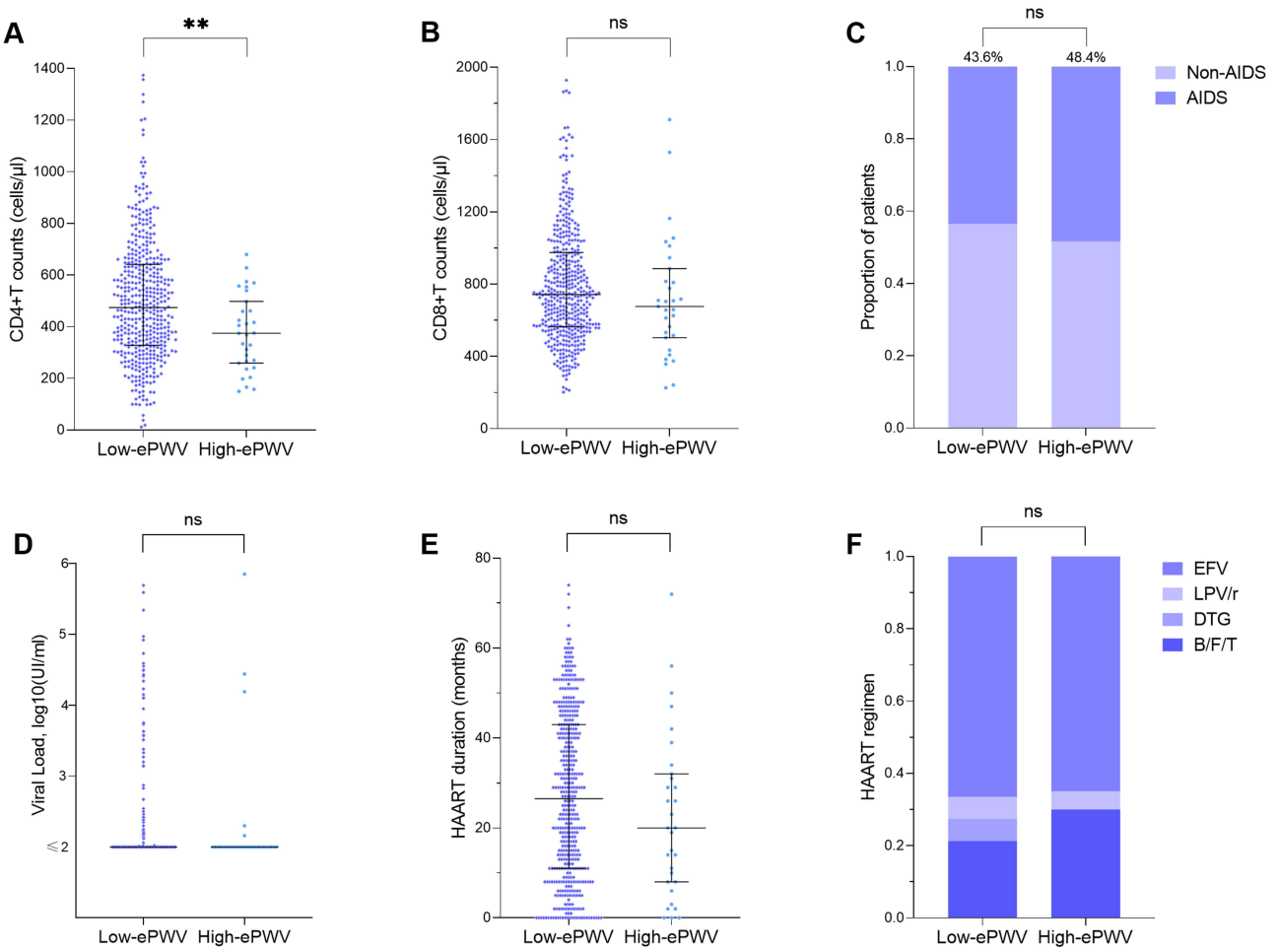

Figure 4 The influence of HIV infection and HAART between low-ePWV group and high-ePWV group among PLWH. (**A**) CD4+T counts level in PLWH between low-ePWV group and high-ePWV group (474.50 [329.00, 640.50] versus 375.00 [262.50, 480.00]; P < 0.01). (**B**) CD8+T counts level in PLWH between low-ePWV group and high-ePWV group (742.50 [564.00, 973.50] versus 676.00 [509.00, 850.00]; P > 0.05). (**C**) The proportion of PLWH in AIDS stage between low-ePWV group and high-ePWV group (198 (43.61%) versus 15 (48.39%); P > 0.05). (**D**) HIV viral load level in PLWH between low-ePWV group and high-ePWV group (2.00 [2.00, 2.00] versus 2.00 [2.00, 2.00]; P > 0.05). (**E**) HAART duration in PLWH between low-ePWV group and high-ePWV group (26.50 [11.00, 43.00] versus 20.00 [8.00, 31.50]; P > 0.05). (**F**) The proportion of PLWH with different HAART regimens between low-ePWV group and high-ePWV group (P > 0.05).

Notes: ns indicates P value > 0.05; ** indicates P value < 0.01.

Abbreviations: ePWV, estimated pulse wave velocity; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; EFV, Efavirenz group; LPV/r, lopinavir/ritonavir group; DTG, dolutegravir group; B/F/T, Bictegravir group.

In recent years, PWV has emerged as a widely adopted indicator for predicting disease risk across diverse populations, including the general populace, individuals with a history of stroke, and those afflicted by CVD.[34] Notably, cfPWV and baPWV have gained recognition as the gold standard methods for the non-invasive assessment of AS, crucial for predicting CVD risk.[35] However, it is imperative to acknowledge that these methodologies demand specialized expertise and access to costly instrumentation. In contrast, ePWV stands as a convenient and cost-effective alternative. ePWV integrates age and blood pressure parameters, offering an accessible means to evaluate AS when compared to the complexities and expenses associated with cf-PWV.[36] Blood pressure and age represent readily accessible parameters that can be measured conveniently within community hospitals or even at home. This accessibility renders them particularly well-suited for risk assessment and healthcare management among individuals living with HIV. Hence, ePWV emerges as a promising novel biomarker for evaluating the mortality risk in PLWH with MetS. Its suitability for widespread screening and self-monitoring within these demographics underscores its potential significance in healthcare management. It's worth noting that ePWV did not emerge as an independent risk factor for MetS. This observation may be attributed to the relatively younger mean age of the cohort and the stronger age-dependent effect of ePWV. However, this does not diminish the utility of ePWV in predicting MetS. Besides, our study proposes the new ePWV threshold of 7.4m/

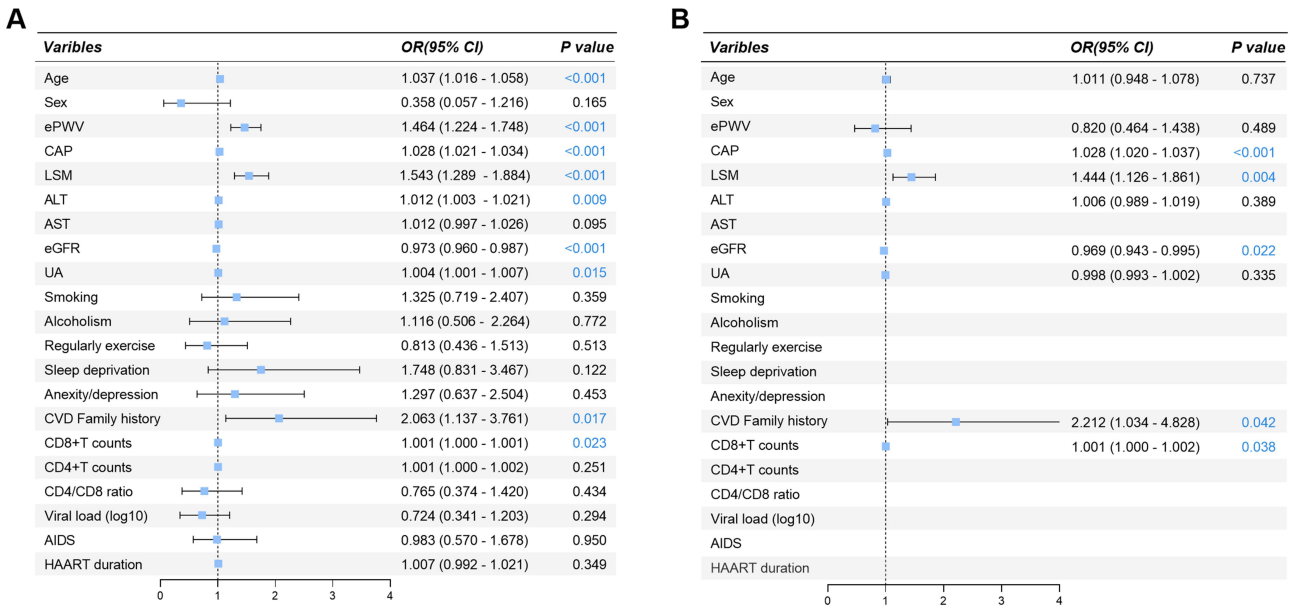

Figure 5 Factors associated with MetS among PLWH. (**A**) Forest plot of univariate analysis. (**B**) Forest plot of multivariate analysis.
Notes: blue text indicates P value < 0.05.
Abbreviations: ePWV, estimated pulse wave velocity; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; ALT, alanine aminotransferase; AST, aspartic aminotransferase; eGFR, estimated glomerular filtration rate; UA, uric acid; CVD, cardiovascular disease; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy.

s as an optimal cut-off point for predicting MetS, providing valuable guidance for health management and clinical intervention in PLWH.

We emphasized that our study revealed a noteworthy observation regarding the positive correlation between ePWV and eGFR, as elucidated through rigorous linear correlation analysis. Yan et al found that females with eGFR levels below 60 mL/min/1.73m² exhibit higher PWV, underlining a compelling inverse relationship between eGFR and PWV.[37] Ilyas et al have reported a similar inverse association between PWV and eGFR in individuals afflicted with coronary artery disease and devoid of known renal pathologies.[38] Moreover, researchers delved into AS and its intricate connection with renal function. Ford et al have meticulously investigated this association and have convincingly documented that, in subjects grappling with advanced chronic kidney disease, marked by eGFR levels ranging from 15 to 59 mL/min/1.73m^2,[39] AS emerges as an independent harbinger of renal function decline. Consequently, in consonance with these antecedent studies, our investigation augments the mounting evidence corpus, collectively substantiating the proposition that the deterioration of renal function indeed assumes a pivotal role in the pathogenesis of AS. Taken together, our findings have significant implications by highlighting ePWV's potential as a predictive marker of early renal impairment in PLWH, as it may facilitate early detection and timely intervention, ultimately improving the management and prognosis of PLWH by addressing AS and renal function.

HIV-specific mechanisms encompass immune dysfunction and heightened inflammatory responses, which in turn, may precipitate elevated thrombotic risk and perturbations in lipid profiles and cholesterol metabolism.[40] A study conducted in Poland in 2018 revealed that CD4 counts in PLWH were at their lowest (< 350 cells/mm³), which is considered an HIV-specific risk factor for MetS.[8] Moreover, in 2022, Ortíz et al in Guatemala identified the CD4 count as the sole HIV-related factor linked to MetS in PLWH.[41] Our results are consistent with previous research findings. We performed an analysis to test the influence of HIV infection and HAART regimen on ePWV in PLWH. The results confirmed a significant difference ($P < 0.01$) between ePWV and CD4+T cell counts, which reflected the effect of low-grade immune status of PLWH on ePWV.

Our research has significant advantages. On the one hand, this marks a groundbreaking use of ePWV as a novel non-invasive predictive marker in PLWH. Furthermore, our study introduces a new cutoff point for ePWV when predicting MetS of PLWH. This new threshold diverges from the conventional 10 m/s cutoff point typically utilized for

cardiovascular risk prediction, which underscores the importance of tailoring risk assessment to the unique and complex characteristics of PLWH.

Nonetheless, our study is not without limitations. On the one hand, our use of cross-sectional data restricts our capacity to establish causal relationships. Future studies should adopt a longitudinal prospective design to unravel the causal link between ePWV and MetS. On the other hand, it is important to recognize that our study was exclusively conducted within the Chinese population. Therefore, the generalizability of our findings to other population groups may be limited.

Conclusion

In conclusion, our study indicated the potential application of ePWV as a sensitive and specific non-invasive biomarker in the early diagnosis of MetS among PLWH. Early detection of MetS can trigger timely intervention to prevent the progression of related cardiovascular risk factors, which carries profound implications for enhancing the overall medical management of PLWH.

Abbreviation

AIDS, Acquired Immunodeficiency Syndrome; ALT, Alanine Aminotransferase; AS, Arterial Stiffness; AST, Aspartic Aminotransferase; baPWV, brachial-ankle Pulse Wave Velocity; BMI, Body Mass Index; CAP, Controlled Attenuation Parameter; cfPWV, carotid-femoral pulse wave velocity; CHOL, Total Cholesterol; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; eGFR, estimated Glomerular Filtration Rate; ePWV, Estimated Pulse Wave Velocity; FPG, Fasting Plasma Glucose; HAART, Highly Active Antiretroviral Therapy; HbA1c, Glycated Hemoglobin A1c; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; LSM, Liver Stiffness Measurement; MBP, Mean Blood Pressure; MetS, Metabolic Syndrome; PLWH, People Living With HIV; ROC, Receiver Operating Characteristic; SBP, Systolic Blood Pressure; TG, Triglyceride.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The study was approved by the Institutional Ethics Committee of Nanfang Hospital (study identifier, NFEC-2021-448) and the study protocol was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all individuals.

Acknowledgments

We express our gratitude to our colleagues in the Department of Infectious Diseases at Nanfang Hospital for their assistance and support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Key Research and Development Program of China (No.2022YFC2304800) and the National Natural Science Foundation of China (No.82203300).

Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Fang CT, Chang YY, Hsu HM, et al. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy. *QJM: Int J Med*. 2007;100(2):97–105. doi:10.1093/qjmed/hcl141
2. Deeken JF, Tjen-A-Looi A, Rudek MA, et al. The Rising Challenge of Non–AIDS-Defining Cancers in HIV-Infected Patients. *Clin Infect Dis*. 2012;55(9):1228–1235. doi:10.1093/cid/cis613
3. Shah ASV, Stelzle D, Lee KK, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV, Systematic Review and Meta-Analysis. *Circulation*. 2018;138(11):1100–1112. doi:10.1161/CIRCULATIONAHA.117.033369
4. Liu J, Hou Y, Sun L, et al. High population-attributable fractions of traditional risk factors for non-AIDS-defining diseases among people living with HIV in China, a cohort study. *Emerging Microbes Infect.* 2021;10(1):416–423. doi:10.1080/22221751.2021.1894904
5. Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, Bechara MD, Sloan KP, Sloan LA. Metabolic syndrome and cardiovascular diseases, Going beyond traditional risk factors. *Diabetes Metab Res Rev*. 2022;38(3):e3502. doi:10.1002/dmrr.3502
6. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. *Int J Obes Lond*. 2008;32(Suppl 2):S25–29. doi:10.1038/ijo.2008.32
7. Nix LM, Tien PC. Metabolic Syndrome, Diabetes, and Cardiovascular Risk in HIV. *Curr HIV/AIDS Rep*. 2014;11(3):271–278. doi:10.1007/s11904-014-0219-7
8. Rogalska-Płońska M, Grzeszczuk A, Rogalski P, Łucejko M, Flisiak R. Metabolic syndrome in HIV infected adults in Poland. *Kardiol Pol*. 2018;76(3):548–553. doi:10.5603/KP.a2017.0249
9. Wilkinson IB, Mäki-Petäjä KM, Mitchell GF. Uses of Arterial Stiffness in Clinical Practice. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1063–1067. doi:10.1161/ATVBAHA.120.313130
10. Gagliardino JJ, Salazar MR, Espeche WG, et al. Arterial Stiffness, Its Relation with Prediabetes and Metabolic Syndrome and Possible Pathogenesis. *J Clin Med*. 2021;10(15):3251. doi:10.3390/jcm10153251
11. Greve SV, Blicher MK, Kruger R, et al. Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity. *J Hypertens*. 2016;34(7):1279–1289. doi:10.1097/HJH.0000000000000935
12. Vishram-Nielsen JKK, Laurent S, Nilsson PM, et al. Does Estimated Pulse Wave Velocity Add Prognostic Information?, MORGAM Prospective Cohort Project. *Hypertension*. 2020;75(6):1420–1428. doi:10.1161/HYPERTENSIONAHA.119.14088
13. Chen H, Chen G, Zhang L, et al. Estimated pulse wave velocity can predict the incidence of new-onset atrial fibrillation, A 11-year prospective study in a Chinese population. *Front Cardiovasc Med*. 2022;9:912573. doi:10.3389/fcvm.2022.912573
14. Jae SY, Heffernan KS, Kim HJ, et al. Impact of estimated pulse wave velocity and socioeconomic status on the risk of stroke in men, a prospective cohort study. *J Hypertens*. 2022;40(6):1165–1169. doi:10.1097/HJH.0000000000003118
15. Bao W, Chen C, Chen C, et al. Association between estimated pulse wave velocity and risk of diabetes, A large sample size cohort study. *Nutr, Metab Cardiovasc Dis*. 2023;33(9):1716–1724. doi:10.1016/j.numecd.2023.05.032
16. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness, methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588–2605. doi:10.1093/eurheartj/ehl254
17. Semmler G, Wöran K, Scheiner B, et al. Novel reliability criteria for controlled attenuation parameter assessments for non-invasive evaluation of hepatic steatosis. *United Eur Gastroenterol J*. 2020;8(3):321–331. doi:10.1177/2050640619900820
18. Zhang Y, Li Y, Zheng X, Zhu L, Xu B. Association between alcohol consumption in midlife and cognitive function in old age, Findings from the China health and Nutrition Survey. *Nutr Metab Cardiovasc Dis*. 2021;31(11):3044–3053. doi:10.1016/j.numecd.2021.07.023
19. World Health Organization. *Global Recommendations on Physical Activity for Health*. World Health Organization; 2010.
20. Watson NF, Badr MS, et al. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the Recommended Amount of Sleep for a Healthy Adult, Methodology and Discussion. *Sleep*. 2015;38(8):1161–1183. doi:10.5665/sleep.4886
21. The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors, 'establishing normal and reference values. *Eur Heart J*. 2010;31(19):2338–2350. doi:10.1093/eurheartj/ehq165
22. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Med*. 2006;23(5):469–480. doi:10.1111/j.1464-5491.2006.01858.x
23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–163. doi:10.1016/S0140-6736(03)15268-3
24. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and Treatment of Hypertriglyceridemia, An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2012;97(9):2969–2989. doi:10.1210/jc.2011-3213
25. Singh V, Sharma R, Kumar A, Deedwania P. Low high-density lipoprotein cholesterol, current status and future strategies for management. *Vascular Health and Risk Management*. 2010;6:979–996. doi:10.2147/VHRM.S5685
26. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. *Trend Cardiovasc Med*. 2020;30(3):160–164. doi:10.1016/j.tcm.2019.05.003
27. Petersen JL, McGuire DK. Impaired glucose tolerance and impaired fasting glucose — a review of diagnosis, clinical implications and management. *Diabetes Vasc Dis Res*. 2005;2(1):9–15. doi:10.3132/dvdr.2005.007
28. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2012;35(Suppl 1):S64–S71. doi:10.2337/dc12-s064
29. Levisianou D, Melidonis A, Adamopoulou E, et al. Impact of the metabolic syndrome and its components combinations on arterial stiffness in Type 2 diabetic men. *Int Angiol*. 2009;28(6):490–495.
30. Moreira GC, Cipullo JP, Ciorlia LAS, Cesarino CB, Vilela-Martin JF. Prevalence of Metabolic Syndrome, Association with Risk Factors and Cardiovascular Complications in an Urban Population. *PLoS One*. 2014;9(9):e105056. doi:10.1371/journal.pone.0105056
31. Kangas P, Tikkakoski A, Kettunen J, et al. Changes in hemodynamics associated with metabolic syndrome are more pronounced in women than in men. *Sci Rep*. 2019;9(1):18377. doi:10.1038/s41598-019-54926-0
32. Topouchian J, Labat C, Gautier S, et al. Effects of metabolic syndrome on arterial function in different age groups, the Advanced Approach to Arterial Stiffness study. *J Hypertens*. 2018;36(4):824–833. doi:10.1097/HJH.0000000000001631

33. Sipilä K, Koivistoinen T, Moilanen L, et al. Metabolic syndrome and arterial stiffness, The Health 2000 Survey. *Metabolism*. 2007;56(3):320–326. doi:10.1016/j.metabol.2006.10.008
34. Ji C, Gao J, Huang Z, et al. Estimated pulse wave velocity and cardiovascular events in Chinese. *International Journal of Cardiology Hypertension*. 2020;7:100063. doi:10.1016/j.ijchy.2020.100063
35. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39 (33):3021–3104. doi:10.1093/eurheartj/ehy339
36. Li D, Cao F, Cheng W, Xu Y, Yang C. Predictive value of estimated pulse wave velocity for cardiovascular and all-cause mortality in individuals with obesity. *Diabetol Metab Syndr*. 2023;15(1):40. doi:10.1186/s13098-023-01011-2
37. Yun BH, Chon SJ, Cho SH, Choi YS, Lee BS, Seo SK. Decreased Renal Function Is a Risk Factor for Subclinical Coronary Atherosclerosis in Korean Postmenopausal Women. *J Menopausal Med*. 2016;22(3):167–173. doi:10.6118/jmm.2016.22.3.167
38. Ilyas B, Dhaun N, Markie D, et al. Renal function is associated with arterial stiffness and predicts outcome in patients with coronary artery disease. *QJM*. 2009;102(3):183–191. doi:10.1093/qjmed/hcn171
39. Ford ML, Tomlinson LA, Chapman TPE, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. *Hypertension*. 2010;55(5):1110–1115. doi:10.1161/HYPERTENSIONAHA.109.143024
40. Paula AA, Falcão MC, Pacheco AG. Metabolic syndrome in HIV-infected individuals, underlying mechanisms and epidemiological aspects. *AIDS Res Ther*. 2013;10(1):32. doi:10.1186/1742-6405-10-32
41. Ortíz DW, Marroquin HE, Larson L, et al. Metabolic syndrome in people with HIV from Guatemala, analysis of components and risk factors. *Int J STD AIDS*. 2022;33(11):987–994. doi:10.1177/09564624221119321