

Brachial-Ankle Pulse Wave Velocity is Associated With the Risk of Osteoporosis: A Cross-Sectional Evidence From A Chinese Community-Based Cohort

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Research article

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Abstract

Background: Association of arterial stiffness and osteoporosis has been investigated in Chinese population. However, the relationship between arterial stiffness and osteoporosis by measuring brachial-ankle pulse wave velocity (baPWV) and the Osteoporosis Self-assessment Tool for Asia (OSTA) index is not established. The object of this study was to evaluate possible associations between baPWV and the risk of osteoporosis and bone fracture among a population of Chinese. Whether baPWV can be used as a predictor of osteoporosis on OSTA was further assessed.

Methods: This study was cross-sectional in design. Of 3,984 adults aged 40 years and older in the Yunyan district of Guiyang (Guizhou, China) who underwent both OSTA and baPWV measurements within one month, 1,407 were deemed eligible for inclusion (women: 1,088, men: 319).

Results: The mean baPWV was $1,475 \pm 302$ cm/s (range, 766-3,459 cm/s). baPWV in 110 individuals with high risk of osteoporosis (OSTA index < -4) was higher than that of individuals with non-high risk ($1,733 \pm 461$ cm/s versus $1,447 \pm 304$ cm/s, $P < 0.001$). OSTA index was negatively correlated with baPWV ($\rho = -0.296$, $P < 0.001$) after adjusting for age, sex, body mass index, waist circumference, diastolic blood pressure and creatinine clearance rate. baPWV was an independent predictor for the presence of high risk of osteoporosis ($\beta = -0.001$, $P < 0.001$) and the optimal baPWV cut-off value for predicting the presence of high risk of osteoporosis and fracture was 1,693 cm/s. The AUC was 0.722 (95% confidence interval [CI], 0.667-0.777; $P < 0.001$).

Conclusions: We conclude that arterial stiffness measured by baPWV is well correlated with the severity of osteoporosis evaluated by OSTA. baPWV index may be a valuable tool for identifying individuals with risk of developing osteoporosis.

Background

Osteoporosis is a systemic skeletal condition of low bone mass resulting in micro-architectural deterioration of bone tissue, leaving the bones brittle and prone to fractures(1). According to the latest nationwide, multicenter survey in China, a total of 60 million individuals (10.9 million men and 49.3 million women) are estimated to have osteoporosis(2). Based on years of life lost, research revealed that stroke and ischemic heart disease are the leading causes of death and disability at the national level in China(3).

As an independent risk factor, arterial stiffness contributes to cardiovascular morbidity and mortality (4).

Epidemiological studies consistently show correlations between osteoporosis and cardiovascular disease, they are both common chronic diseases that increased markedly with advancing age. They share some common risk factors and clinical characteristics(5). Lower bone mineral density (BMD) is reported in a meta-analysis involving 46,182 participants from 10 studies, to be associated with significantly increased risk of all-cause and cardiovascular mortality (6), meanwhile, coronary artery

calcification, plays a substantial role in aortic stiffness and increases risk for adverse cardiovascular events, increases with the progression of in the bone loss and bone quality decreasing (7).

According to the World Health Organization criteria, the gold-standard method to assess and diagnose osteoporosis is based on dual-energy X-ray absorptiometry(8). However, this tool also has certain limitations (e.g., high costs and large size of the equipment, exposure to ionizing radiation) that limit its widespread application for population screenings. On the other hand, some elderly and high-risk individuals often do not undergo regular screening and comprehensive examinations, probably due to health or financial reasons (9). This has resulted in an urgent need to develop rapid, non-invasive, low-cost, and simpler pre-screening tools for early detection, diagnosis of osteoporosis. Among several currently used tools(10–12), the Osteoporosis Self-Assessment Tool for Asians (OSTA) score developed by WHO has been shown to be the simplest and high effective tool to identify women at risk for osteoporosis(13). A significant correlation in a positive direction was found between the OSTA index and BMD (T-score) measured by dual energy X-ray absorptiometry(14, 15).

Brachial-ankle pulse wave velocity (ba-PWV), recording time taken by the pressure wave to travel over a specific distance, is the most common measure of arterial stiffness in Asian populations and an independent predictor of cardiovascular risk(16–18). The relation between arterial stiffness and osteoporosis by measuring ba-PWV and the OSTA index has been established and results of studies investigating relations between osteoporosis and the risk factors to date are inconsistent in Chinese populations(19, 20). The aim of this study was 1) to investigate the relation between baPWV measurement and the OSTA index and 2) to evaluate baPWV as a predictor of risk of osteoporosis in a large Chinese Community-based Cohort.

Methods

Study population

The present study was part of the baseline survey for the Risk Evaluation of Cancers in Chinese Diabetic Individuals: a longitudinal (REACTION) study, which was conducted among 259,657 adults aged 40 years and older in 25 communities across mainland China from 2011 to 2012(21-24). The study protocol was approved by the ethics committees at Guizhou Medical University Affiliated Hospital and informed consent had been obtained from each participant signed a form before the study. A total of 3,984 adults aged 40 to 80 years old who lived five years or longer in the Yunyan district of Guiyang (Guizhou, China) were selected by cluster random sampling. Major exclusion Criteria were shown in Figure 1 and 1,407 individuals were deemed eligible for inclusion (women: 1,088, men: 319).

Study method

(1) questionnaire survey: information collected includes demographic and other background information (sex, age, occupation, home address, contact number, family history, marital and childbirth history, etc.),

past medical history (history of diabetes, hypertension, dyslipidemia, cardiovascular disease history, etc. and treatment of related diseases).

(2) Physical examination: height, body weight, waist circumference (WC), blood pressure (BP) were measured. BP was measured three times in the supine position and the average was taken as the measurement value. The body mass index ($BMI = \text{weight}/\text{height}^2$) was calculated.

(3) Sample collection and measurement: venous blood samples were obtained in the morning and an overnight fasting. Fasting plasma glucose (FPG) concentration and [postprandial glucose](#) (PPG) levels was measured using the glucose oxidase technique with a Roche Hitachi P800 autoanalyzer (Roche Diagnostics GmbH, Mannheim). Lipid panel test including total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglyceride (TG) were measured using an autoanalyzer (ARCHITECT Ci16200). We used creatinine clearance rate (Ccr) as an indicator of kidney function.

(4) baPWV measurement

After a 10 minutes rest in the supine position, baPWV was automatically measured using the Omron device (BP-203RPEIII VP-1000 device; Omron Health Care, Kyoto, Japan). The validity and reliability of this device has been previously reported(25). Cuffs with sensors were wrapped on both upper arms and ankles. The transmission times and distances between the cuffs of arms and legs were recorded, and the device was able to compute baPWV automatically as the ratio of the travel distance divided by the time difference between the pulse waves. We used the mean value of the right and left baPWVs in our analysis(26).

(5) OSTA index calculation

OSTA index was calculated using the formula of $(\text{weight in kilograms} - \text{age in years}) \times 0.2$, established by Koh et al. (2001) (13). In our study, dichotomous cutoff was used according to its developer's recommendations as the following: < -4 for high risk.

Statistical Analyses

Continuous variables were expressed as means $\pm$ standard deviation (SD). For assessment of the differences in a variable between 2 groups, the t test was applied. Spearman's rank correlation analyses and partial correlation analyses were conducted to study the associations between baPWV and OSTA, anthropometric indices and serum biochemical parameters. Multivariable logistic regression analysis was performed to assess whether baPWV was independently associated with osteoporosis and, using variables showing significant relationships with OSTA in Spearman's rank correlation analysis. To explore the best cutoff value of baPWV for predicting high risk of osteoporosis and fracture ($OSTA \leq -4$), receiver-operating characteristic (ROC) curve analysis was used. The predictive accuracy was presently with the area under the curve (AUC). The statistical analysis was performed using SPSS 19.0 software (SPSS, Inc, Chicago, IL, USA).

Results

Baseline characteristics

The baseline anthropometric parameters and biochemical indices from 1,407 individuals are shown in Table 1. Males (age: 62.33 ± 7.99 years) were significantly older than females (age: 58.14 ± 7.52 years). Females had higher HDL, TC and Ccr ($P < 0.05$). BMI, SBP, DBP and PPG were higher in men than in women ($P < 0.05$). For total individuals, the mean baPWV was $1,475 \pm 302$ cm/s (range, 766-3,459 cm/s) and there was no significant difference between males and females in baPWV. Risk of osteoporosis measured by OSTA index is significantly higher in female (0.34 ± 2.53 in male versus -0.73 ± 2.30 in female).

Association of OSTA with baPWV and biochemical parameters

Spearman's rank correlation analysis presented a significant negative correlation between OSTA index and baPWV ($\rho = -0.290$, $P < 0.001$) (Table 2). Further, we calculated the partial correlation between OSTA index and baPWV, adjusting for age, sex, BMI, WC, DBP and Ccr. The correlation in a negative direction between OSTA index and baPWV was not significantly affected by other demographic or biochemical variables ($\rho = -0.294$, $P < 0.001$). Further subgroup analysis by sex showed significant negative association between OSTA index and baPWV in both male and female population, association persisted after adjusting for age, BMI, WC, DBP and Ccr ($\rho = -0.263$, $P < 0.001$; $\rho = -0.305$, $P < 0.001$, respectively).

baPWV as a predictor of high risk of Osteoporosis

Stepwise multiple regression analysis was further applied for access the independent relationships between OSTA and baPWV. As shown in Table 3, multivariate stepwise regression analysis revealed that among those factors that showed associations with OSTA in correlation analysis, baPWV was an independent factors responsible for the changes in OSTA ($\beta = -0.001$, $P < 0.001$). Further subgroup analysis showed baPWV was an independent factor responsible for the changes in OSTA in both male and female population (Table 4).

Overall, 110 individuals with high risk of osteoporosis (OSTA index < -4) was identified, baPWV measurement of these individuals was higher than that of individuals with non-high risk ($1,733 \pm 461$ cm/s versus $1,447 \pm 304$ cm/s, $P < 0.001$). In the ROC curve analysis, the optimal cutoff point of baPWV value for predicting the presence of high risk of osteoporosis and fracture was 1,693 cm/s with sensitivity of 51.8% and specificity of 83.6 %. The AUC was 0.722 (95% confidence interval [CI], 0.667-0.777; $P < 0.001$). In male population, the AUC was 0.716 (95% confidence interval [CI]: 0.545-0.886, $P = 0.005$), slightly lower than the AUC in female population (AUC 0.726, 95% confidence interval [CI]: 0.669-0.783, $P < 0.001$) (Figure 2).

Discussion

The present study, conducted in a large Chinese Community-based Cohort, showed that baPWV, a promising yet relatively simple test, has significant negative correlation with the degree of risk for osteoporosis as quantified by OSTA. The association between baPWV and osteoporosis risk was independent of age, sex and traditional risk factors, which was concluded using the multivariable analysis. For predicting high risk of osteoporosis and fracture, we showed a baPWV cut-off value of 1,693 cm/s had the best predictive power resulted in AUCs of about 0.722.

Correlations between arterial stiffness and BMD have been frequently reported in both retrospective and cross-sectional studies. A cross-sectional study involving around four thousand Chinese men and women aged 65–92 reported that ankle brachial index (ABI) as a measurement for peripheral arteriosclerosis was positively correlated with hip BMDs(27). Further, prospective studies have also reported findings in evaluating whether low BMD predicts cardiovascular events. In China, a prospective osteoporosis study followed 1,724 postmenopausal women for 5 years, they found the presence of aortic calcifications assessed using semiquantitative radiography at baseline was associated with a higher rate of vertebral fractures (12.2% vs. 4.5% in women with and without aortic calcifications, ($P = 0.01$))(28). This study was pooled in a further meta-analysis on the relationship of aortic calcifications to the risk of fracture, which demonstrated that aortic calcifications was significantly and independently associated with a higher fracture risk, recruiting 14,632 participants in total(27). For peripheral arterial disease (PAD), in a prospective study of 1,332 individuals, peripheral arterial disease (PAD) measured by ABI was not associated with the occurrence of fractures(29). However, another study involved measurements of ABI and of BMD in 5,781 men aged 65 years or older found inconsistent result with previous mentioned study, which reported that individuals with PAD had higher rates of bone loss and increased risk of non-spine fractures(30).

The possible pathophysiological mechanism linking high baPWV and osteoporosis could be oxidative stress, an imbalance between exposure to toxic reactive oxygen species (ROS) and antioxidant systems, considering that it is associated with both arterial stiffness and osteoporosis(31, 32). Hormonal changes associated with menopause and ageing affect both arterial stiffness and bone resorption and reconstruction, it could be another mechanism behind the predictive value of baPWV for osteoporosis risk(33). Diverse studies revealed significant correlations between the severity of arterial stiffness/osteoporosis and inflammatory markers, it could also be another common pathway for the pathogenesis of arterial stiffness and osteoporosis(34).

It is important to obtain a simple and effective way to predict osteoporosis and cardiovascular disease risk, considering the huge aging population of People's Republic of China. As far as we know, the first study to report the relationship between OSTA and baPWV in Chinese population was published in 2019, involving 129 elderly individuals and suggests the OSTA index was negatively correlated with baPWV in linear regression analysis and baPWV as a valuable predictive factor for potential osteoporotic risk(35). Our findings have proven the association in a large Chinese Community-based Cohort involving 1,407 individuals, the AUC was 0.722 in ROC curve analysis for evaluating baPWV as a predictor of high risk of osteoporosis and fracture ($OSTA \leq -4$), close to the AUC (0.742) reported in the above mentioned

study(35). However, we reported a low sensitivity value of 51.8% for the optimal cutoff point of baPWV value in predicting the presence of high risk of osteoporosis and fracture. This is probably due to the age heterogeneity in our study, since we recruited all the adults aged 40 years and older.

Low BMI having been frequently shown to increase risk of fracture, possibly due to its association with bone loss, less soft tissue, and muscle weakness(36). In our study, we found BMI, WC are positively associated with OSTA. However, there were studies reporting high BMI increases the risk of osteoporotic and hip fractures risk(37). In a meta-analysis involving 398,610 women, it is interesting to find that the association between BMI and fracture risk is complex, differs across skeletal sites. Since there is no consistent conclusion from these analyses, a healthy and normal BMI might be suggested to help minimize the risk of fracture risk. Only few observational studies have investigated the association between serum lipid level and bone fractures in Chinese population, and the conclusions between studies are also controversial. In our study, we found a negative association between HDL and OSTA. In a cross-sectional study involving around 5,000 healthy volunteers, the authors reported that the subjects with a BMI lower than 18.5 had a higher incidence of osteoporosis than BMI ≥ 18.5 in both sexes(38). Another cross-sectional study including 1,791 participants (62.1% postmenopausal women and 213 fractures), reported a significant positive association between HDL-C level and risk of osteoporotic fracture in total participants (OR 1.37, P = 0.023). These findings are consistent with what have been reported in our study. However, a recent study applied two-sample Mendelian randomization (MR) methods to explore the causal association between blood lipid levels and fracture. They reported that HDL may have an indirect influence on fracture mediated by BMD(39). According to what we have discussed above, the relationship between lipid levels in blood and the risk of fracture is currently controversial and the causal association remains elusive, further research is required.

The study described here included 1,407 participants aged 40 years and older. This relatively large sample size and subgroup analysis strengthens the thoroughness of our findings. According to what we have found, we proposed that baPWV had moderate discrimination ability for high risk of osteoporosis. However, several limitations of our study should be thoroughly discussed. First, as a cross-sectional study, no causal inference can be concluded. Further well-designed longitudinal studies are needed to validate the relationship identified in this study. Second, OSTA was the only measurement representing osteoporosis and fracture risk in this study. Future studies should search a link between other markers of osteoporosis and arterial stiffness, such as Mandibular cortical width, a marker of osteoporosis detected by dental panoramic radiographs(40). Third, information such as physical activity and alcohol consumption were not collected. These behavioral factors might have to affect fracture risk profoundly.

Conclusion

In summary, we have found the independent predictive value of baPWV for osteoporosis risk in a large Chinese Community-based Cohort. Furthermore, the inverse association of the OSTA index and baPWV was statistically significant. baPWV may be a simple and useful indicator of osteoporosis and fracture risk.

List Of Abbreviations

brachial-ankle pulse wave velocity, baPWV

Osteoporosis Self-assessment Tool for Asia, OSTA

bone mineral density, BMD

receiver-operating characteristic, ROC

area under the curve, AUC

standard deviation, SD

peripheral arterial disease, PAD

reactive oxygen species, ROS

body mass index, BMI

waist circumferences, WC

systolic blood pressure, SBP

diastolic blood pressure, DBP

fasting plasma glucose, FPG

postprandial glucose, PPG

high-density lipoprotein cholesterol, HDL

low-density lipoprotein cholesterol, LDL

total cholesterol, TC

triglyceride, TG

creatinine clearance, Ccr

Declarations

Ethics approval and consent to participate

The present study was part of the baseline survey for the Risk Evaluation of Cancers in Chinese Diabetic Individuals: a longitudinal (REACTION) study. The study protocol was approved by the ethics committees

at Guizhou Medical University Affiliated Hospital and informed consent had been obtained from each participant signed a form before the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conceptualization: KT and LXS. Data collection and Data curation: QZ, NCP, YH. Methodology: SJX , MZ , RW. Writing - original draft: KT. Writing - review & editing and Supervision: LXS. Funding acquisition: LXS.

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Conflict of interest

The authors declare no conflict of interest.

Role of the funding source

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Tables

Table 1 General characteristics of male and female patients

	Male	Female	T-value	P-value
N	319	1,088		
Age (year)	62.33 ± 7.99	58.14 ± 7.52	8.347	<0.001
BMI (kg/m ²)	23.04 ± 2.74	22.54 ± 2.89	2.789	0.005
WC (cm)	85.14 ± 7.72	84.16 ± 8.57	1.832	0.067
SBP (mmHg)	118.89 ± 11.23	113.77 ± 12.37	6.648	<0.001
DBP (mmHg)	76.22 ± 7.66	73.00 ± 7.99	6.401	<0.001
FPG (mmol/L)	5.28 ± 0.47	5.26 ± 0.40	0.513	0.608
PPG (mmol/L)	7.02 ± 1.62	6.79 ± 1.52	2.276	0.023
HDL (mmol/L)	1.44 ± 0.28	1.49 ± 0.28	2.440	0.015
LDL (mmol/L)	2.73 ± 0.57	2.78 ± 0.52	1.450	0.147
TC (mmol/L)	4.72 ± 0.62	4.82 ± 0.58	2.472	0.014
TG (mmol/L)	1.14 ± 0.30	1.11 ± 0.31	1.508	0.132
Ccr (ml/min)	89.23 ± 8.77	92.68 ± 11.13	5.789	<0.001
BaPWV (cm/s)	1461.43 ± 391.11	1471.55 ± 307.43	0.425	0.671
OSTA	0.34 ± 2.53	-0.73 ± 2.30	6.813	<0.001

BMI, body mass index; WC, waist circumferences; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, [postprandial glucose](#); HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Ccr, creatinine clearance; baPWV, brachial-ankle pulse wave velocity; OSTA: Osteoporosis Self-assessment Tool for Asia.

Table 2 Correlations of OSTA index with baPWV and various clinical and biochemical parameters

OSTA index		
	ρ	P-value
baPWV	-0.290	<0.001
Age	-0.543	<0.001
Sex	-0.174	<0.001
BMI	0.459	<0.001
WC	0.380	<0.001
FPG	0.000	0.993
PPG	-0.036	0.172
SBP	0.000	0.996
DBP	0.182	<0.001
Ccr	0.239	<0.001
HDL	-0.042	0.113
LDL	0.009	0.724
TC	-0.022	0.402
TG	0.024	0.370

BMI, body mass index; WC, waist circumstancs; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, [postprandial glucose](#); HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Ccr, creatinine clearance; baPWV, brachial-ankle pulse wave velocity; OSTA: Osteoporosis Self-assessment Tool for Asia.

Table 3 Multivariate stepwise regression analysis showing the factors independently associated with OSTA

Characteristics	β	SE	Standardized β	P
BMI	0.279	0.021	0.334	<0.001
Age	-0.182	0.005	-0.594	<0.001
Sex	-1.642	0.093	-0.287	<0.001
WC	0.042	0.007	0.146	<0.001
baPWV	-0.001	0.000	-0.185	<0.001

BMI, body mass index; WC, waist circumstanes; Ccr, creatinine clearance; baPWV, brachial-ankle pulse wave velocity; OSTA: Osteoporosis Self-assessment Tool for Asia.

Table 4 Multivariate stepwise regression analysis showing the factors independently associated with OSTA in Female and male subgroup

Male population	Characteristics	β	SE	Standardized β	P
	Age	-0.170	0.013	-0.535	<0.001
	WC	0.130	0.013	0.396	<0.001
	baPWV	-0.001	0.000	-0.195	<0.001
	Ccr	-0.013	0.006	-0.086	0.042
Male population	Characteristics	β	SE	Standardized β	P
	Age	-0.187	0.005	-0.612	<0.001
	WC	0.035	0.007	0.130	<0.001
	baPWV	-0.001	0.000	-0.190	<0.001
	BMI	0.300	0.021	0.379	<0.001
	DBP	0.011	0.005	0.038	0.033

BMI, body mass index; WC, waist circumstanes; Ccr, creatinine clearance; baPWV, brachial-ankle pulse wave velocity; OSTA: Osteoporosis Self-assessment Tool for Asia.

Figures

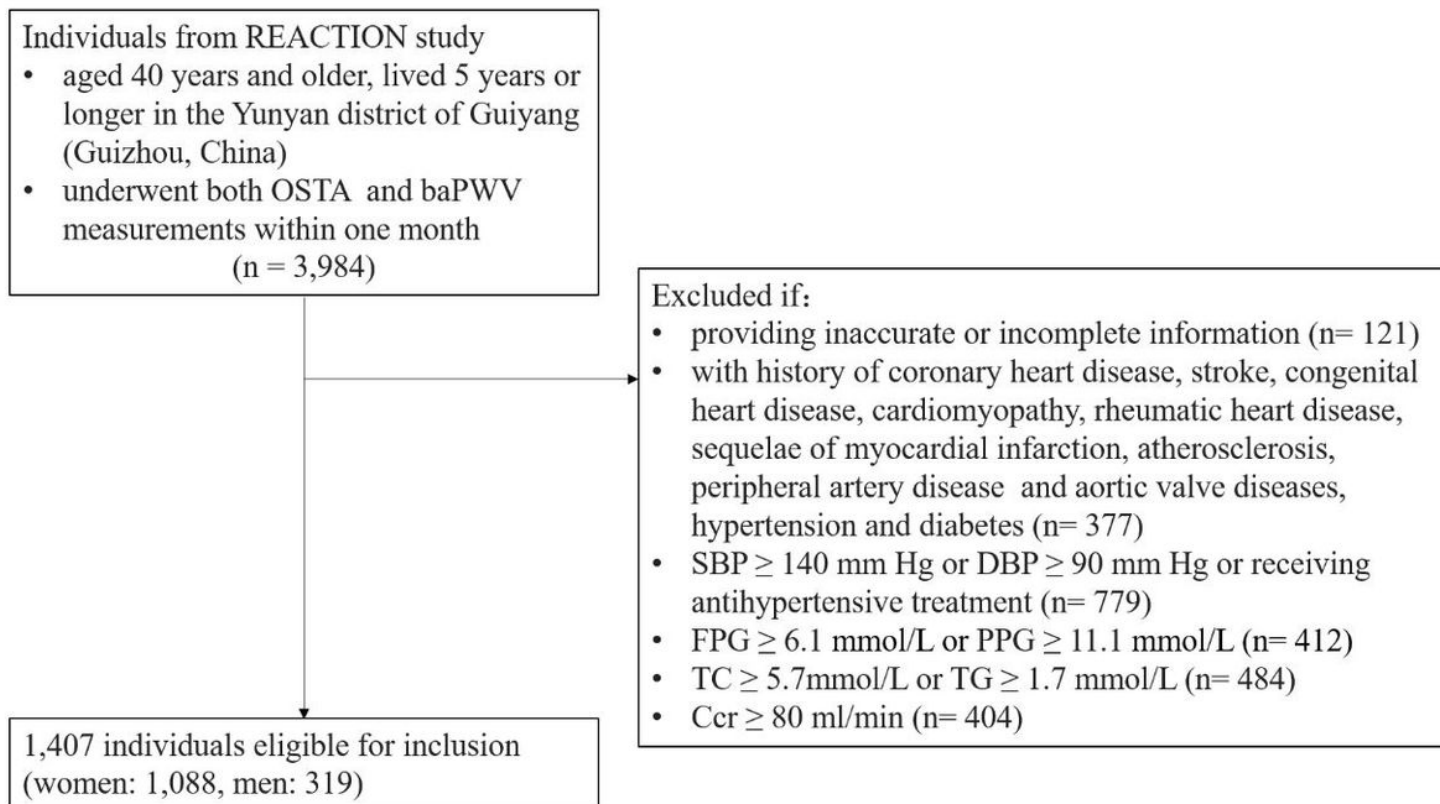


Figure 1

ROC curve of the association between baPWV and the high risk of osteoporosis and fracture (corresponding to OSTA < -4.0) in total sample and subgroups. The AUC was 0.722 for total sample, 0.716 for male subgroup and 0.726 for female subgroup.

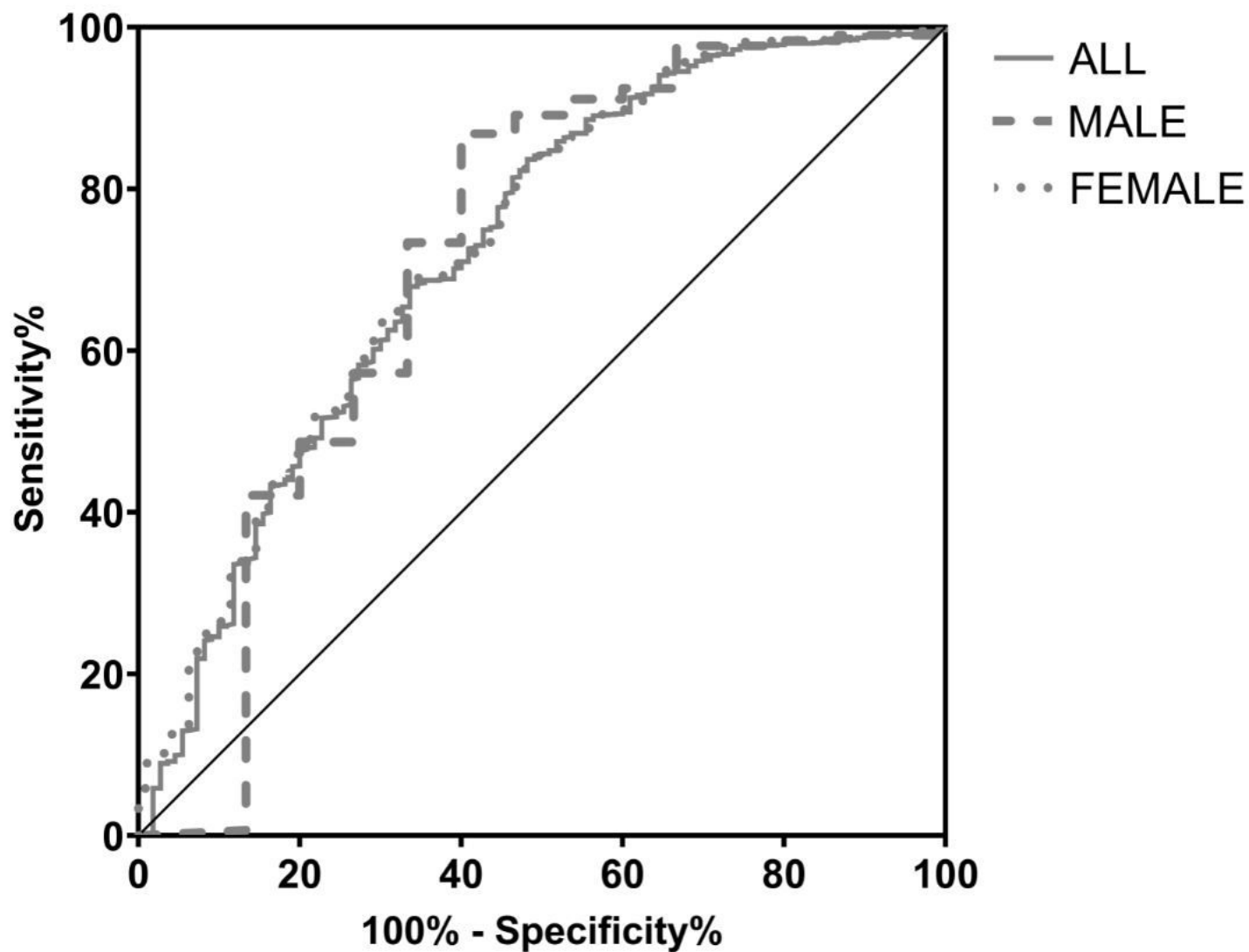


Figure 2

ROC, receiver-operating characteristic; baPWV, brachial-ankle pulse wave velocity; OSTA: Osteoporosis Self-assessment Tool for Asia; AUC, area under curve; CI, confidence interval.