Original Article

The Association between Ankle-Brachial Index and Cardiovascular or All-Cause Mortality in Metabolic Syndrome of Elderly Chinese

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The ankle-brachial index (ABI) is a non-invasive, reliable measurement of lower-extremity ischemia. A low ABI is associated with increased risk of coronary heart disease, stroke and death. However, the relationship between ABI and all-cause mortality or cardiovascular disease (CVD) mortality in patients with metabolic syndrome (MetS) has not been well studied. Accordingly, we here investigated the association between ABI and all-cause and CVD mortality in an elderly Chinese population with MetS. A total of 2,274 MetS patients diagnosed under the criteria proposed by the International Diabetes Federation were divided into two groups based on repeated ABI measurement over a period of 13.6 months: ABI≤0.9 (n=525) and ABI 0.91–1.4 (n=1,749). Each of the baseline characteristics of age, systolic blood pressure, diabetes mellitus morbidity, and smoking history were significantly different between the two groups (p<0.05 or p<0.01). All-cause mortality and CVD mortality decreased gradually as the ABI increased from 0.4 to 1.4. In Cox regression analysis, the relative ratio of all-cause mortality to CVD mortality also showed a tendency to decrease with increasing ABI. In elderly patients with MetS, ABI is one of the most important indexes for determining the possible prognosis and predicting all-cause and CVD mortality. People with relatively older age, higher systolic blood pressure, diabetes mellitus morbidity and smoking history may be at risk of lower ABI (≤0.9) and higher all-cause and CVD mortality. Our results suggest the urgent need for repeated ABI measurement in clinical practice, both during individual visits and also over time, before diagnosing peripheral artery disease and making a therapeutic decision, especially in certain high-risk populations such as patients with MetS. (*Hypertens Res* 2007; 30: 613–619)

***Key Words*: ankle-brachial index, cardiovascular disease mortality, all-cause mortality, metabolic syndrome**

Introduction

The ratio of the ankle to the brachial systolic blood pressure (SBP), the ankle-brachial index (ABI), is an indicator of atherosclerotic vascular disease in the lower extremities and has been publicly considered as a single, non-invasive measurement of sub-clinical atherosclerosis (*1*). In a series of large-scale multicenter studies, the ABI has also been shown to be associated with cardiovascular disease (CVD) risk factors, including smoking (*2*–*4*), diabetes (*2*), total cholesterol (*2*, *3*), hypertension (*2*, *3*), and low weight (*4*). Previous studies have found that those with lower extremity arterial disease are 1.5 to 2 times more likely to experience a clinical CVD event (*5*). More interestingly, the ABI has a graded inverse association with mortality (*6*, *7*).

Moreover, many prospective studies have also shown that a low ABI (<0.9) can predict CVD and all-cause mortality in

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Table 1. Baseline Characteristics of the Study Population

Baseline characteristics	ABI (n=2,274)		p value
	≤0.90 (n=528)	0.91–1.40 (n=1,746)	
Age (years)	71.4±10.3	65.4±11.2	0.000
Men (n (%))	50.8	54.8	0.107
BMI (kg/m^2)	25.6±3.6	24.7±3.6	0.626
High BP (n (%))	82.6	72.6	0.000
SBP (mmHg)	144±25	139±22	0.000
DBP (mmHg)	81.3±13	81.0±13	0.677
Dislipidemia (n (%))	47.8	45.0	0.296
TC (mmol/L)	4.65±1.15	4.64±1.15	0.807
TG (mmol/L)	1.76±1.25	1.73±1.09	0.650
LDL-C (mmol/L)	2.75±0.91	2.79±1.78	0.623
HDL-C (mmol/L)	1.15±0.36	1.18±0.41	0.181
Serum creatinine (μmol/L)	107.59±12.28	101.74±9.10	0.068
Diabetes (n (%))	42.2	31.7	0.000
Glu (mmol/L)	6.25±2.51	6.23±2.64	0.859
Smokers (n (%))	43.0	37.6	0.025
All-cause mortality (%)	11.4	5.2	0.000
CVD mortality (%)	5.7	2.0	0.000

ABI, ankle-brachial index; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Glu, glucose; CVD, cardiovascular disease.

general populations and in patients with existing vascular risks, such as hypertension or type 2 diabetes mellitus, particularly in elderly men (*8*). The above-mentioned diseases have also been selected as the criteria for diagnosing metabolic syndrome (MetS), a newly described syndrome.

Increased arterial stiffness is associated with risk variables of MetS in middle-age adults (*9*). However, little is know regarding the influence of ABI on MetS and the further association between this relationship and all-cause or CVD mortality, particularly in elderly Chinese. Therefore, we conducted a community-based study to determine the distribution of ABI in Chinese elderly, both in order to provide baseline data for a prospective study, and to determine the possible clinical significance of ABI levels to the choice of anti-atherosclerosis therapy. It is hoped that these findings will help to improve the longevity of patients with peripheral artery diseases.

Methods

Study Population

This investigation employs the data from a large-scale epidemiological study in P.R. China with cross-sectional and longitudinal parts. The present study cohort comprises 2,274 members (mean age, 68.4±10.5 years; range, 54–81 years) selected from among the inpatients of several hospitals in two communities in P.R. China: Shanghai and Beijing. The local ethics committee approved the study and all participants gave their written informed consent. All patients were non-invasively screened for manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis. Participants were required to be community-living, Han Chinese over 35 years of age, and to have no blood relationships with any of the other patients. All patients were admitted to the hospital because of hypertension, hyperlipidemia, diabetes, stroke, acute coronary syndrome, renal disease. Patients with any of the following were eliminated: multiple organs dysfunction, pregnancy or current lactation, mental disorder, serious diabetes or hypertension and their complications (*e.g.*, ketoacidosis or hypertensive crisis), secondary hypertension, or type 1 diabetes.

Definitions

MetS was diagnosed according to the latest criteria proposed by the International Diabetes Federation (IDF, 2005) on the basis of visceral obesity (waist circumference >102 cm in men and >88 cm in women). MetS was diagnosed when two or more of the following metabolic abnormalities were present: SBP ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg, hypertriglyceridemia (serum triglycerides [TG]≥1.7 mmol/L), low high-density lipoprotein cholesterol ([HDL-C] ≤0.9 mmol/L in men and ≤1.1 mmol/L in women) and high fasting glucose ([FSG] ≥5.6 mmol/L). Diagnosis of essential hypertension and diabetes mellitus were based on WHO/ISH guidelines (1999) and ADA criteria (1997), respectively (*10*).

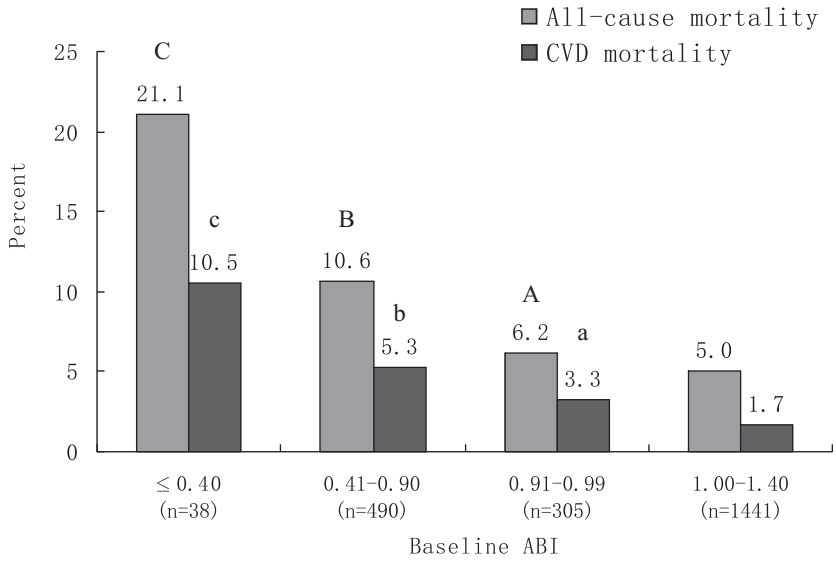

Fig. 1. *Percentages of CVD mortality and all-cause mortality in the different ABI groups. a–c: $p < 0.05$ vs. ABI 1.00–1.40; A–C: $p < 0.05$ vs. ABI 1.00–1.40.*

However, because the original cut-off for abdominal obesity in the NCEP definition has previously been shown to be inappropriate for Asian populations (*11*, *12*), and the number of subjects in P.R. China who met these criteria was extremely low, the cut-off limit of waist circumference was adjusted to the criteria of ≥94 cm in men and ≥80 cm in women, which were based on the risk of obesity-related disorders in a large-scale study of Beijing citizens. These criteria were also considered as the standard of MetS classification in Chinese patients specifically.

During this examination, participants were classified in accordance with the presence or absence of six preexisting CVDs: acute myocardial infarction (AMI), angina, chronic heart failure, stroke, transient ischemic attack, and intermittent claudication. Participants with any of these six conditions were classified as having prevalent CVD.

ABI was calculated as the ratio of the ankle SBP to the brachial SBP on the homolateral side. ABI was diagnosed according to the latest criteria (USA, 2005): 1.00–1.40 in both legs was considered normal; 0.91–0.99 was defined as borderline for development into peripheral artery disease (PAD); rest ABI between 0.41–0.90 in at least one leg was defined as decreased and was considered an independent predictor of PAD with one site of stenosis in at least one leg; and ABI of ≤0.40 strongly indicated more than one site of stenosis in at least one leg (*13–15*).

Study Design and Methods

This is a retrospective study. At the time of enrollment (November 2004), all patients passed a standardized protocol, including a health questionnaire on current medication use, past medical history, familial vascular history and atherosclerotic risk factors. Height, body weight, body mass index (BMI), waist circumference and blood pressure were measured. Fasting blood was sampled to determine lipid levels (TG, total cholesterol [TC], HDL-C and low-density lipoprotein cholesterol [LDL-C]) and serum glucose. The same methods were used for the laboratory test measurements at all institutes.

The resting ABI was measured with the subject in a supine position with a 5 MHz continuous wave Doppler Probe (CBA1304), and the inflatable cuff of the sphygmomanometer was 10 cm in width and 40 cm in length (Sanofi-Aventis Corp., Ltd., Beijing, P.R. China). The value of the highest SBP measured at the ankle was divided by the highest SBP measured in both arms. The ratio (ABI) was calculated for both legs.

After a follow-up period of 13.6 months ending in April 2006, almost all participants were investigated about the CVD mortality and all-cause mortality respectively by contacting with themselves or their relatives.

Identification of Deaths Due to All-Cause or CVD Mortality

Deaths were identified through the records of the eight participating university hospitals or by contact with participants and their families. The cause of death was further investigated using medical records and informant interviews. All materials were reviewed independently by physicians participating in the ABI cohort study to confirm the cause of death.

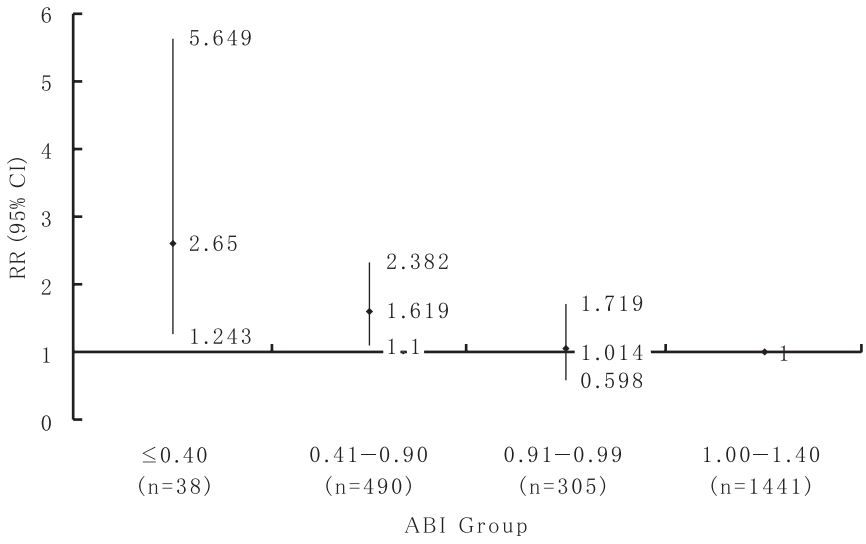

Fig. 2. *Relative risk (RR) of all-cause mortality (95% CI) (adjusted for age, gender, history of hypertension, diabetes mellitus and smoking).*

Statistical Analysis

Differences between patients with and without ABI abnormality were tested with χ^2 (categorical variables), unpaired *t*-test (continuous normal distributed variables) or Mann-Whitney *U* test (continuous skewed variables). Intergroup comparisons were made using analysis of variance (ANOVA). The results were adjusted for age, gender, smoking, and history of hypertension and diabetes to investigate the influence of ABI on CVD and all-cause mortality with Cox regression analysis.

All statistical analyses were performed using the SAS software package, version 6.0 (SAS Institute, Cary, USA) and the Statistical Package for Social Sciences, version 11.5 (SPSS, Chicago, USA).

Results

Baseline Characteristics

The baseline characteristics of the study population are listed in Table 1. Five hundred and twenty-eight patients (23.2%) showed an abnormal ABI (≤0.90), and 1,746 patients (76.8%) had borderline or normal ABI (0.91–1.40). There was no significant difference in BMI between these two groups ($p>0.05$), mainly because all the participants met the diagnostic criteria for MetS and most of them were overweight. Similarly, there were no significant differences in fasting blood glucose (6.252±2.508 mmol/L and 6.228±2.642 mmol/L for the abnormal ABI group and the borderline/normal ABI group, respectively) or dyslipid morbidity, since most of the patients we examined were undergoing glucose and/or serum lipid down-regulation therapies. However, the mean age (71.36±10.25 in the abnormal ABI group and 65.35±11.18 in the normal ABI group) and percentage of smokers (43.0% and 37.6%) were significantly different between the two ABI groups. Blood pressure, especially SBP (143.65±25.162 mmHg and 138.86±21.987 mmHg), and diabetes morbidity (42.2%, 31.7%) also were significantly different between the two groups ($p<0.01$) (Table 1).

Outcomes of Interest

As shown in Table 1, the rates of both all-cause mortality (dystrophy, tumor, *etc*.) and CVD mortality (AMI, stroke, heart failure, and hemopericardium) were significantly different between the group with an ABI ≤0.90 (11.4% and 5.7%) and the group with an ABI of 0.91–1.40 (5.2% and 2.0%), respectively. The numbers of deaths due to all-cause mortality in these two groups were 60 and 91, while the number of CVD mortalities were 30 and 35, respectively (AMI, heart failure, stroke, and hemopericardium were the causes of death in 12, 7, 7, and 4 members of the group with ABI ≤0.90 and in 10, 9, 10, and 6 members of the group with an ABI of 0.91–1.40).

As shown in Fig. 1, there was a correlation between the ABI and the percentages of both all-cause mortality and CVD mortality. That is, all-cause mortality and CVD mortality both decreased gradually when ABI changed from below 0.40 to over 0.90 (from 21.1 to 5.0 and from 10.5 to 1.7, respectively). As to all-cause mortality and CVD mortality, the results adjusted age, gender, history of hypertension, diabetes and smoking and found almost the same trend as in Fig. 1 (Figs. 2, 3). The mortality rate gradually decreased from serious PAD (ABI≤0.40) to a relatively normal ABI (1.00–1.40).

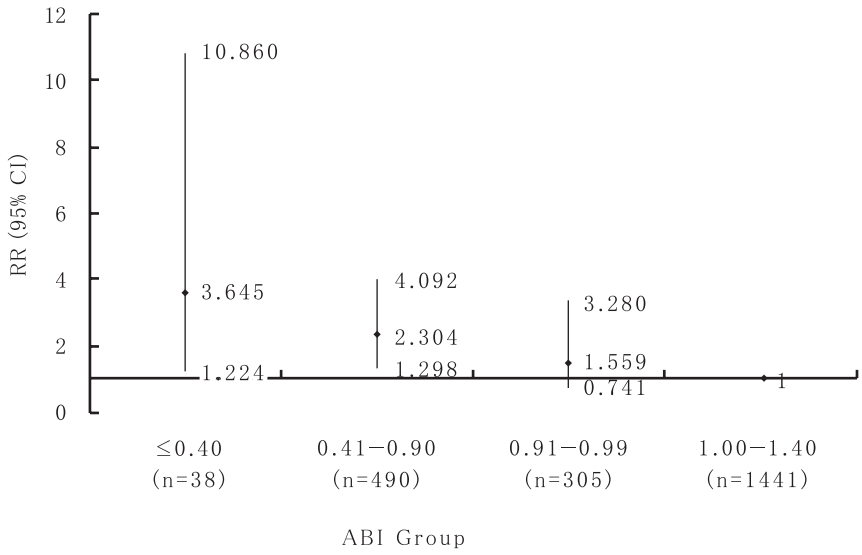

Fig. 3. *Relative risk (RR) of CVD mortality (95% CI) (adjusted for age, gender, history of hypertension, diabetes mellitus and smoking).*

Discussion

Peripheral artery disease commonly results from progressive narrowing of the arteries in the lower extremities due to atherosclerosis. It can be determined with high precision using the ABI, a simple, non-invasive measurement (*16*). The results of the National Health and Nutrition Examination Survey (NHANES, 1999–2000) demonstrated that there is a high prevalence of both traditional and non-traditional cardiovascular risk factors among persons with PAD. More than 95% of individuals with PAD have at least one traditional cardiovascular risk factor, and the majorities have multiple factors. These findings highlight the importance of aggressive prognosis and related CVD or all-cause mortality in persons with PAD or abnormal ABI and in those with subnormal or normal ABI (*17*). Wild *et al*. (*18*) performed a survey of 1,467 men and women aged 35–74, and found that 25% of the study population had MetS. During the follow-up period, 226 of the 1,467 participants died from CVD and 462 from nonfatal cardiovascular events. This study indicated that low ABI is more prevalent among people with MetS than among those without it. The MetS is a major public health challenge worldwide. It is not benign; it is associated with a substantially elevated risk of type 2 diabetes (5-fold) and of CVD (2- to 3-fold), and its increasing prevalence could possibly reverse the gains made through the recent decline in CVD mortality.

Our current study clarified the relationship between low ABI and mortality in patients with MetS. We chose a population of patients with MetS because the complications of MetS vary widely, and can include PAD, particularly in diabetic patients. A cross-sectional study performed by Walters *et al*. (*19*) found an 8.7% prevalence of PAD among patients with type 2 diabetes and a 23.5% prevalence of type 2 diabetes. It is not yet common practice to routinely screen for the disease for PAD in patients with diabetes, and the higher prevalence of insidious symptoms existed in the "borderline" cases with an ABI 0.80 to <0.90 (*20*). However, the standard of ABI classification was changed to 0.91–0.99 in the US in 2005. In the present study, when MetS patients, whose ABI was below the borderline of 0.91, two main CVD risk factors (age and smoking history), became strong characteristics in 2 groups. Our results fully support the findings of Choi *et al*. (*21*) that ABI was significantly associated with the features of cardiovascular risk factors and therefore exacerbated the formation of CVD or even death related to it. In the present study, we also found that in patients with the ABI≤0.90, the percentage of patients with diabetes and hypertension (high SBP) were higher than in the group with an ABI of 0.91–1.40. This result indicated that the contribution of the clustered components of MetS appeared to be additive, with the subjects having more CVD risk factors showing a substantially lower ABI than those with fewer risk factors in both sexes (*22*, *23*).

In different ABI groups, the same trend appeared when ABI was below 0.91 and an extremely high mortality percentage occurred when ABI was below 0.41 (group with ABI≤0.40). The reason why the lower ABI was related to higher CVD or all-cause mortality may be the presence of atherosclerosis that led to arterial stiffening. Farrar *et al*. (*24*) demonstrated in monkeys that an atherogenic diet increased ABI and aortic intimal area, while an atherosclerosis regression diet decreased both parameters. Arterial lesions then commenced as fatty streaks, progressed to raised lesions and were complicated by ulceration, calcification or even hemorrhage, which led to severe diseases such as stroke, PAD, thrombosis, *etc*. (*25*). In addition, the aortic wall undergoes

progressive accumulation of calcium in the elastin-rich layer of the media during aging, especially in diabetic patients, and results in medial arterial calcification. Therefore ABI, which indicated the degree of aortic calcification, is a predictor of subsequent cardiovascular morbidity and mortality (*26*). Recently, the Framingham Heart Study, a prospective study spanning more than 20 years, reported that the severity of aortic calcification was correlated with subsequent CVD and death (*27*).

Our study also had some potential limitations. First, we were unable to determine whether cardiovascular risk factors were casually related to the ABI values because this study was cross-sectional. Second, we might have underestimated the prevalence of low ABI owing to our reliance on volunteers. Third, ABI is an indirect maker of increased arterial stiffness or decreased arterial compliance and we could not determine the relative influence of arterial wall remodeling on the relationship between cardiovascular risk factors on arterial stiffness. Fourth, the response rate in our study was relatively low compared with that of similar surveys. Finally, we were not able to provide the prevalence of patients with a history of coronary artery disease and therefore could not include this information as a confounding factor in the Cox regression analysis (*28*, *29*).

In summary, we researched the association between low ABI and the clustering of MetS components in a population of elderly Chinese. Our findings indicated that low ABI ($\leq$0.90), especially ABI$\leq$0.40, may be a useful marker of CVD and predictor of CVD or all-cause mortality. The specificity of low ABI to predict future cardiovascular outcome is high, but its sensitivity is low. ABI should be taken into consideration as part of the vascular risk assessment among selected individuals. It is a surrogate end-point in epidemiological studies and may act as a tool for evaluating CVD risk in clinical practice.

Because PAD is an under-diagnosed and under-treated condition in P.R. China, ABI measurement should be a routine part of the clinical evaluation of high risk patients. Atherosclerotic risk factors such as diabetes, hypercholesterolemia and hypertension can and should be treated adequately, and smoking should be strongly discouraged.

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