BMJ Open

Relationship between percentage of mean arterial pressure at the ankle and mortality in participants with normal ankle-brachial index: an observational study

Yu-Hsuan Li,[1] Shih-Yi Lin,[1,2,3] Wayne Huey-Herng Sheu,[1,3,4] I-Te Lee[1,3,4]

For numbered affiliations see end of article.

Correspondence to
Dr I-Te Lee;
itlee@vghtc.gov.tw

ABSTRACT

Objectives: Peripheral arterial disease (PAD) is associated with all-cause mortality. Ankle-brachial index (ABI) is the most widely used tool for detecting PAD, but can yield false-negative results in patients with non-compressible vessels. Pulse volume recording may be an alternative tool for assessing PAD in such patients. However, the association between pulse volume recording and all-cause mortality has seldom been reported. We hypothesised that the percentage of mean arterial pressure (%MAP) and upstroke time (UT), which are indexes of the arterial wave obtained on pulse volume recording, can predict mortality.

Design: We conducted this as a retrospective cohort study.

Setting: Data were collected from the Taichung Veterans General Hospital.

Participants: We included 314 participants with complete data on ABI and pulse volume recording performed between June 2007 and November 2011.

Primary outcome measure: Mortality data served as the follow-up outcome. Mortality data were obtained from the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Executive Yuan, Taiwan.

Results: Participants with ABI ≤0.9 showed a highest mortality rate (p<0.001 in the log-rank test), but the mortality rate was not significantly different between participants with 0.9<ABI≤1.1 and those with 1.1<ABI≤1.3 (p=0.553). Among the participants with 0.9<ABI≤1.3, the high %MAP (>45%) group showed a higher risk of all-cause mortality than the low %MAP (≤45%) group (HR=5.389, p=0.004) after adjustment for ABI, pulse wave velocity, UT, age, sex, blood pressure, serum cholesterol, and history of cardiovascular disease and diabetes.

Conclusions: We thus demonstrated that a high %MAP based on pulse volume recording in participants with 0.9<ABI≤1.3 could predict all-cause mortality during 20.3 months of follow-up.

Strengths and limitations of this study

- Assessment of percentage of mean arterial pressure (%MAP) on ankle arterial wave recording and total mortality.
- Mortality data obtained from a National Health Insurance registry with a nationwide coverage rate of over 99% in Taiwan.
- A small sample size with a median follow-up period of 20.3 months.
- A cut-off %MAP value of 45% showing a high specificity, but low sensitivity, for predicting mortality.

INTRODUCTION

Peripheral artery disease (PAD) of the lower extremities is associated with increased mortality in the general population.[1] The ankle-brachial index (ABI) is helpful in screening for PAD of the lower extremities.[2] An ABI ≤0.9 is thought to indicate PAD.[3][4] However, a U-shaped curve rather than a linear association was observed between mortality and the ABI value.[5][6] An ABI value >1.3, which suggests a non-compressible vessel, has been reported to be associated with higher mortality rates compared with values of 0.9<ABI≤1.3.[7][8]

Furthermore, within a normal ABI range, an ABI value between 0.9 and 1.1 was reported to be associated with higher mortality than an ABI≥1.1.[1] In the Strong Heart Study, the nadir of mortality risk was observed in participants with 1.1≤ABI< 1.4.[5] However, a large cohort study found that there was no significant difference in mortality among participants with 0.9<ABI< 1.0, 1.0≤ABI< 1.1 and ABI ≥1.1.[9] Therefore, using only the ABI value to predict mortality

may not be reliable for participants with an ABI value within the normal range.

Brachial-ankle pulse wave velocity (baPWV) is a well-known measure for arterial stiffness.[10] High baPWV is associated with all-cause and cardiovascular mortality in participants with normal ABI.[11] Arterial stiffness is a process of ageing and, in a Chinese study, it was reported that the association between baPWV and mortality became non-significant after adjusting for age.[12] Pulse volume recording is another accurate modality for detecting arterial occlusion in the lower extremities.[13–15] However, the relationship between the pattern of the pulse volume waveform and mortality has not been well assessed. Therefore, the aim of the present study was to determine whether the percentage of mean arterial pressure (%MAP) and upstroke time (UT), which are indexes of pulse volume recording measured at ankle, predict mortality in participants with normal ABI.

MATERIALS AND METHODS
Participants
This retrospective cohort study was conducted at the Division of Endocrinology and Metabolism in Taichung Veterans General Hospital. We reviewed the medical records of adults who had undergone ABI assessment because they were suspected of having a high risk of PAD on the basis of their clinical manifestations, which included intermittent claudication, pulseless, pallor, paralysis or paraesthesia in the lower extremities. Participants with complete information on both ABI and pulse volume recording were enrolled from June 2007 to November 2011. Systolic blood pressure in the brachial arteries was measured bilaterally, and the higher of the two values was used for the ABI measurements. However, in participants undergoing haemodialysis, only one brachial artery was assessed because of the arterio-venous fistula on the other side. To avoid variability in ABI measurements, participants with end-stage renal disease were excluded. We used the last recorded measurement with complete data in the case of patients who underwent multiple assessments. Demographic characteristics and laboratory data were also collected. In addition to the clinical signs of lower limb ischaemia, the enrolled participants had the following risk factors for PAD, according to the 2005 American College of Cardiology/American Heart Association guidelines[16]: age >70 years, 156 patients; diabetes with age between 50 and 70 years, 124 patients; and neither of these two criteria, 34 patients. Mortality data were collected up to December 2011 and served as the follow-up outcome. Mortality data were obtained from the Collaboration Center of Health Information Application (CCHIA), Ministry of Health and Welfare, Executive Yuan, Taiwan.

Methods
ABI measurement and pulse volume recording were simultaneously performed using a validated automatic device (VP1000; Colin Co Ltd, Komaki, Japan). Each participant was examined in the supine position after having rested for at least 5 min, with electrocardiographic electrodes on both wrists, and cuffs on both arms and the both ankles.[3] The cuffs were connected to a plethysmographic sensor, which detected volume changes, and an oscillometric pressure sensor, which measured blood pressure. The baPWV value was calculated using the following formula: path distance of brachial–ankle/pulse transmission time of brachial–ankle. In addition, %MAP and UT were assessed based on the ankle pulse volume waveforms. UT is the time from the beginning of the wave to the peak amplitude of the wave. %MAP indicates the height, which represents the area of the arterial wave divided by the peak amplitude. The reproducibility of ABI, baPWV and pulse volume recording was examined in a group of 20 participants. Highly linear correlations of ABI (r=0.90, p<0.001), baPWV (r=0.97, p<0.001), %MAP (r=0.90, p<0.001) and UT (r=0.82, p<0.001) were noted between the results of the first and second measurement by the same operator. Highly linear correlations of ABI (r=0.95, p<0.001), baPWV (r=0.97, p<0.001), %MAP (r=0.81, p<0.001) and UT (r=0.95, p<0.001) were also noted between the results of measurements by different operators. Based on the Bland-Altman plots,[17] the intraobserver variability shown by 95% CIs was –0.01±0.08 for the bias of ABI, 1.3±143.2 for baPWV, 0.5±3.1 for %MAP and 3.3±25.7 for UT; and the interobserver variability, shown by 95% CIs, was –0.01±0.05 for ABI, 21±100 for baPWV, 0.6±3.2 for %MAP and 1.9 to 14.0 for UT. The lower value of the ABI between the lower limbs, and the higher values of baPWV, %MAP and UT between the lower limbs were recorded for the analyses.

Statistical analyses
The χ^2 test was used to examine differences in categorical variables across study groups. All continuous data were presented as the mean±SD. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR (mL/min/1.73 m^2)=186×[serum creatinine (mg/dL)]$^{-1.154}$×[age (year)]$^{-0.203}$(×0.742, if female), based on the Modification of Diet in Renal Disease (MDRD) equation.[18] After excluding participants with end-stage renal disease, we found that very few patients had ABI values >1.3, and therefore, these patients were not included in the analyses in the present study. Analysis of variance was used to detect differences in continuous variables across three groups. Independent-sample t tests were used to detect differences between two groups. The relationship of baPWV with %MAP and UT was determined using Pearson correlation.

The Kaplan-Meier product limit method was used to estimate the unadjusted survival curves for the three ABI groups. The log-rank test was applied to compare survival distributions among patients with different ABI values. Receiver operating characteristic (ROC) curve analysis

was applied to determine the optimal cut-off point of % MAP to predict mortality. Cox proportional hazards analysis was applied to assess all-cause mortality in the high and low %MAP groups in the participants with ABI >0.9. HRs and 95% CIs were reported. In the Cox analysis model, UT was categorised based on the median value; baPWV was categorised using a cut-off of 1600 cm/s[19]; hypercholesterolaemia was defined as low-density lipoprotein cholesterol ≥2.59 mmol/L (100 mg/dL); hypertension was defined as the use of antihypertensive medications or blood pressure ≥140/90 mm Hg; and diabetes mellitus was defined based on the American Diabetes Association criteria.[20] A value of p<0.05 was considered statistically significant. All analyses were performed using SPSS V.22.0 software (International Business Machines Co, New York, USA).

RESULTS

A total of 314 participants were included in the analyses. The participants were divided into three groups based on their baseline ABI values, which included 76 participants in the ABI ≤0.9 group, 139 in the 0.9<ABI≤1.1 group and 99 in the 1.1<ABI≤1.3 group (figure 1). There were no significant differences in age and gender among the three ABI groups (p>0.05 for both parameters). Systolic blood pressure was significantly higher in the participants in the ABI ≤0.9 group (p=0.034). Both %MAP and UT were higher in the ABI ≤0.9 group, and the difference reached statistical significance compared with the 0.9<ABI≤1.1 group and the 1.1<ABI≤1.3 group in post hoc analyses (p<0.001 for both parameters). Neither %MAP nor UT was significantly different between the 0.9<ABI≤1.1 and the 1.1<ABI≤1.3 groups (p=0.428 for %MAP, p=0.189 for UT) in post hoc analyses (table 1).

Figure 2 shows the association of baPWV with %MAP and UT. The baPWV value was significantly and positively correlated with %MAP in the 1.1<ABI≤1.3 group (r=0.331, p<0.001; figure 2A) and the 0.9<ABI≤1.1 group (r=0.343, p<0.001; figure 2B), but was not significantly correlated with %MAP in the ABI ≤0.9 group
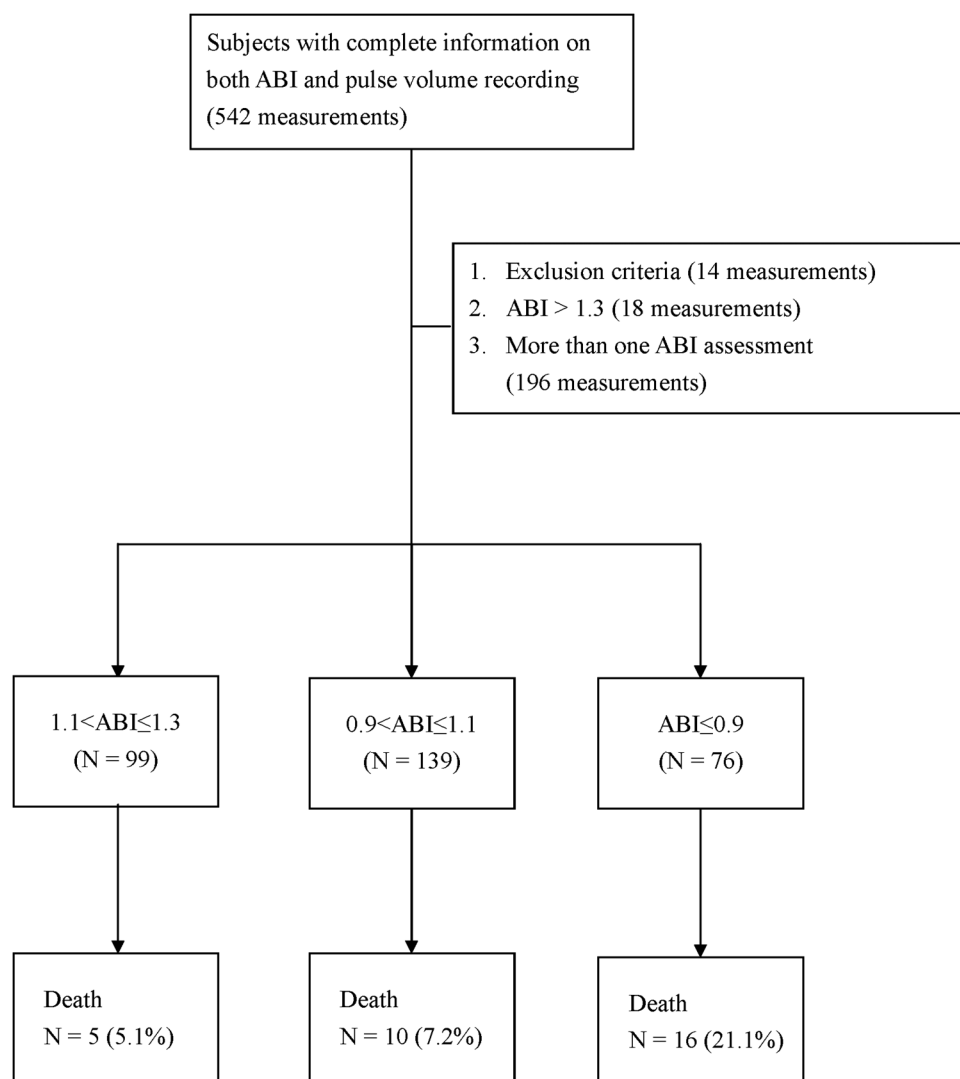

Figure 1 Flow diagram of the enrolment of the study participants. ABI, ankle-brachial index.

Table 1 Baseline characteristics of participants in different ABI groups

	1.1<ABI≤1.3 (N=99)	0.9<ABI≤1.1 (N=139)	ABI≤0.9 (N=76)	p Value
Age (years)	70±12	69±11	68±11	0.319
Male, n (%)	44 (44.4%)	58 (41.7%)	33 (43.4%)	0.913
Body weight (kg)	66.8±13.7	67.5±14.3	65.0±10.8	0.538
Systolic BP (mm Hg)	141±17	139±21	147±27*	0.034
Diastolic BP (mm Hg)	78±12	76±11	77±13	0.300
Fasting glucose (mmol/L)	11±10	10±6	9±6	0.411
eGFR (mL/min/1.73 m^2)	59±27	58±29	57±24	0.840
Total cholesterol (mmol/L)	4.3±0.9	4.2±1.0	4.5±1.2	0.240
HDL cholesterol (mmol/L)	1.3±0.4	1.2±0.4	1.2±0.4	0.487
Triglyceride (mmol/L)	1.5±0.7	1.8±1.4	1.8±1.4	0.345
ABI	1.2±0.0	1.0±0.1†	0.7±0.1*,†	<0.001
baPWV (cm/s)	1979±429	1887±433	2010±683	0.169
%MAP	39.7%±4.0%	40.4%±4.3%	48.4%±5.8%*,†	<0.001
UT (ms)	151±25	160±33	214±50*,†	<0.001
Diabetes mellitus, n (%)	78 (78.8)	107 (77.0)	59 (77.6)	0.947
CAD, n (%)	16 (16.2)	23 (16.5)	21 (27.6)	0.095

*Significantly different from the 0.9<ABI≤1.1 group.
†Significantly different from the 1.1<ABI≤1.3 group.
%MAP, percentage of mean arterial pressure; ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; PWV, pulse wave velocity; UT, upstroke time.

(r=0.172, p=0.137; figure 2C). The baPWV value was not significantly correlated with UT in any group.

During the follow-up (median 20.3 months; IQR 9.4–27.4 months), 31 deaths occurred. The ABI ≤0.9 group showed the lowest cumulative probabilities of survival (p<0.001 in the log-rank test; figure 3), and the difference was significant compared with the 0.9<ABI≤1.1 group (p=0.002) and the 1.1<ABI≤1.3 group (p=0.001). However, there was no significant difference in cumulative probabilities of survival between the 0.9<ABI≤1.1 and 1.1<ABI≤1.3 groups (p=0.553) in post hoc analyses.

Since the baseline ABI value could not predict mortality in these participants with ABI >0.9, the other variables associated with mortality in these participants should be assessed. There were 238 participants with ABI >0.9 in this study and 15 deaths occurred in this group. The baPWV was significantly higher in the non-survivors than in the survivors (2171±460 vs 1909±427 cm/s, p=0.023). Significantly higher %MAP (42.2±4.9% vs 40.0±4.1%, p=0.044) was also detected at baseline among the participants who died compared with that of the survivors during the follow-up period. However, there was no significant difference in ABI or UT between the participants who died and survived during the follow-up period (table 2). Using ROC curve analysis, a cut-off value of 45% in %MAP provided better prediction for mortality, with a sensitivity of 33% and a specificity of 91% (figure 4).

Therefore, we divided the participants with ABI >0.9 into two groups: the %MAP >45% group and the %MAP ≤45% group. In the Cox proportional hazards regression models, participants in the %MAP >45% group showed higher risks of all-cause mortality than those in the %MAP ≤45% group (HR=5.389; 95% CI 1.708 to 17.01; p=0.004), after adjusting for age, gender, coronary artery disease (CAD), diabetes, hypertension, hypercholesterolaemia, baseline ABI, baPWV and UT (table 3).

DISCUSSION

The main finding of the present study was that a higher %MAP in pulse volume recording was associated with a higher mortality risk in participants with an ABI value in the normal range. To the best of our knowledge, this study is the first to apply ankle %MAP to predict mortality.

Pulse volume recording is a waveform composed of an upstroke with a sharp peak, and a downstroke containing a dicrotic notch. In participants without PAD, pulse volume recording looks similar to a normal arterial wave.[2] However, in participants with arterial occlusion, the waveform is flattened and has a delayed upstroke. A high %MAP as a result of a flattened arterial wave implies the pattern of arterial occlusion.[21–23] Since peripheral arterial occlusion is associated with increased mortality in the general population,[1] a high ankle %MAP may play a role in predicting mortality.

According to the 2011 American College of Cardiology Foundation and American Heart Association Task Force guidelines for the management of patients with PAD, PAD has been defined as an ABI ≤0.9.[2] This threshold value has been reported to have high levels of sensitivity and specificity compared with angiography, which is the current 'gold standard' for detecting PAD.[24] However, PAD may exist in participants with normal ABI. In a study by Nakashima et al,[15] 63% of participants with ABI >0.9 had significant degrees of stenosis as detected by intravenous or intra-arterial subtraction angiography.
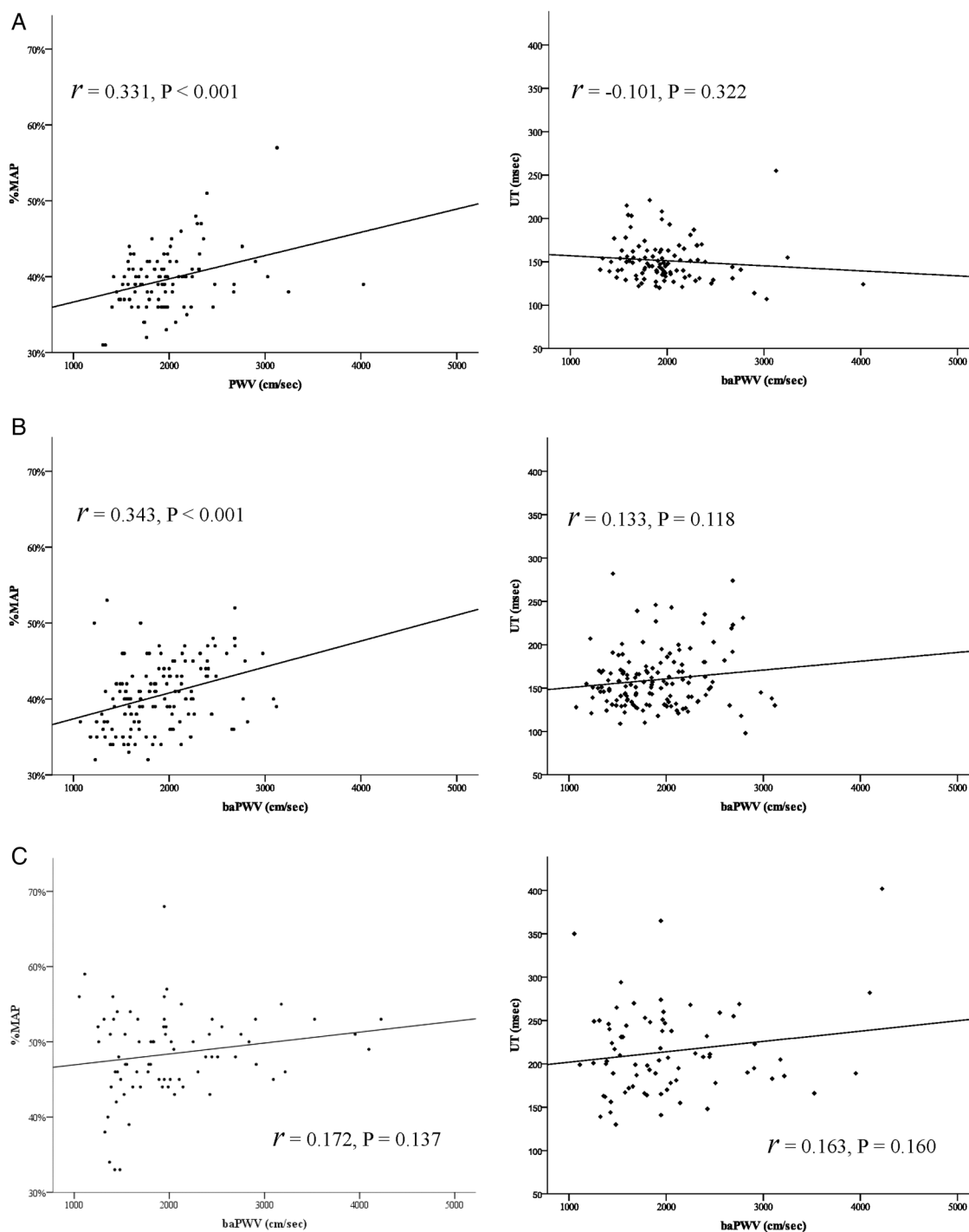
Figure 2 Relationship of brachial-ankle pulse wave velocity (baPWV) with percentage of mean arterial pressure (%MAP) and upstroke time (UT) in participants with 1.1<ankle-brachial index (ABI)≤1.3 (A), 0.9<ABI≤1.1 (B) and ABI ≤0.9 (C).

A previous study also revealed that 0.9<ABI<1.0 in patients with diabetes was associated with a significantly higher risk of mortality compared with 1.0≤ABI<1.4.[25] Current guidelines recommend that 0.9<ABI<1.0 should represent borderline ABI because of the higher risk of mortality in this group of patients.[4] This increase in mortality could be partially explained by the fact that ABI is less sensitive in calcified vessels. The ABI value can be falsely elevated in the vessels with a non-compressible

nature.[4] Patients with diabetes, renal insufficiency and advanced age are at high risk of such calcified non-compressible vessels.[14] ABI measurement might yield a false-negative result for PAD in these patients with non-compressible vessels.[26] It should, however, be noted that an elevated ABI is also associated with a high risk of arterial occlusion.[27] High mortality rates have been observed in participants with high ABI values.[7] In the present study, however, there were too few participants
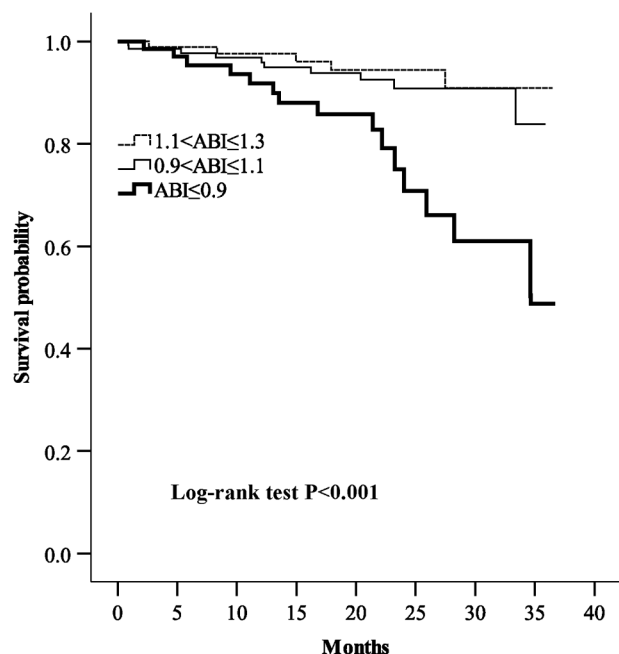
Figure 3 Survival probability in different ankle-brachial index (ABI) groups.

with ABI >1.3 to be included for the analyses in the present study.

Pulse volume recordings are a feasible alternative tool for diagnosing PAD with calcified vessels.[4] By injecting a standard volume of air into pneumatic cuffs to obtain a certain pressure to occlude the venous circulation, we can ensure that the volume changes detected by the transducer are solely attributable to arterial circulation. The transducer translates the volume change into a pulsatile pressure waveform.[2] The main value of pulse volume recording may be that it is not affected by the presence of non-compressible arteries.[28] Our study population was composed of elderly participants with a high prevalence of diabetes. Therefore, pulse volume recordings might have been more reliable for the assessment of PAD in this study. We found that high %MAP was an independent predictor for total mortality after adjusting for ABI value in participants with ABI >0.9.

Mitsutake *et al*[29] reported that UT was significantly associated with coronary artery calcification score based on CT findings. In our study, a more prolonged UT was shown in the non-survivor group as compared with that in the survivor group, but the difference did not reach

Table 2	Characteristics of participants with normal ABI		
	Non-survivors (N=15)	**Survivors (N=223)**	**p Value**
Age (years)	70±9	69±12	0.933
Male, n (%)	6 (40.0)	96 (43.0)	0.999
Body weight (kg)	64.7±13.5	67.4±14.1	0.576
Systolic BP (mm Hg)	134±22	140±19	0.300
Diastolic BP (mm Hg)	73±9	77±12	0.193
Fasting glucose (mmol/L)	12.7±11.1	9.9±7.2	0.160
eGFR (mL/min/1.73 m^2)	56±22	59±28	0.749
Total cholesterol (mmol/L)	4.4±1.0	4.3±0.9	0.674
HDL cholesterol (mmol/L)	1.2±0.3	1.3±0.4	0.421
Triglyceride (mmol/L)	1.9±0.9	1.6±1.2	0.369
ABI	1.1±0.1	1.1±0.1	0.688
baPWV (cm/s)	2171±460	1909±427	0.023
%MAP	42.2%±4.9	40.0%±4.1	0.044
UT (ms)	166±41	155±29	0.167
Diabetes mellitus, n (%)	12 (80.0)	173 (77.6)	0.999
CAD, n (%)	2 (13.3)	37 (16.6)	0.999
Antiplatelet, n (%)	2 (13.3)	52 (23.3)	0.565
Antihypertensive agents			
ACE inhibitor or ARB, n (%)	8 (53.3)	103 (46.2)	0.787
α-Blocker, n (%)	4 (26.7)	18 (8.1)	0.052
β-Blocker, n (%)	2 (13.3)	29 (13.0)	0.999
Calcium channel blocker, n (%)	2 (13.3)	67 (30.0)	0.277
Diuretics, n (%)	4 (26.7)	33 (14.8)	0.390
Antidiabetic drugs			
Insulin therapy, n (%)	4 (26.7)	59 (26.5)	0.999
Insulin secretagogues, n (%)	3 (20.0)	75 (33.6)	0.421
Metformin, n (%)	3 (20.0)	78 (35.0)	0.366
Thiazolidinediones, n (%)	0 (0.0)	16 (7.2)	0.588
α-Glucosidase inhibitor, n (%)	0 (0.0)	9 (4.0)	0.925

%MAP, percentage of mean arterial pressure; ABI, ankle-brachial index; ARB, angiotensin II receptor antagonists; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; UT, upstroke time.

Figure 4 Receiver operating characteristic (ROC) curve analysis to determine the area under the curve (AUC) and the cut-off level of mean arterial pressure (%MAP) for predicting all-cause mortality.

ROC curve
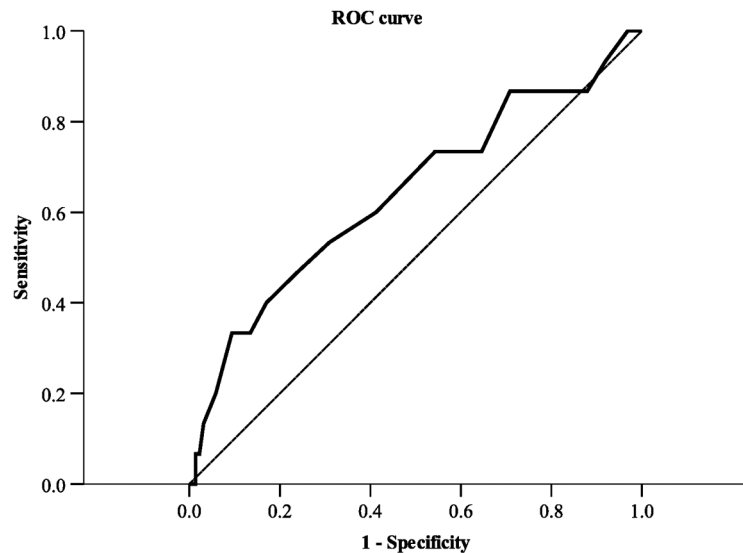
The optimal cut-off values for percentage of mean arterial pressure (%MAP) for mortality

AUC	95% CI of AUC	P	Cut-off value	Sensitivity	Specificity
0.64	(0.61, 0.81)	<0.001	45%	0.33	0.91

statistical significance. In accordance with our results, Nakashima *et al*[15] reported that UT was not significantly different between participants with arterial occlusion detected using angiography, and the control group. CAD history and age were not independent predictors of total mortality in the Cox regression analyses in our study. The possible cause of this result is that only 16.4% participants with normal ABI had a history of CAD. Consistent with this finding, a previous ABI study reported that CAD contributed a similar HR of 1.11 to the total mortality in Olmsted county patients followed up for a mean of 5.8 years.[30] Furthermore, it has been

reported that baPWV might be influenced by age, and this attenuates the association between age and total mortality.[12 31] A similar result was reported in dialysis patients followed up for 43 months, in whom age contributed a relatively low HR to mortality after adjustment for PWV.[32]

High baPWV, a pathophysiological indicator of arterial stiffness, is a predictor of all-cause mortality.[12 33 34] A variety of optimal cut-off values have been reported for abnormal baPWV. A baPWV greater than 1400 cm/s was reported to be associated with an increased risk for cardiovascular disease based on Framingham score or in a diabetic population.[35 36] A baPWV greater than 1600 cm/s was associated with cerebral infarction in a cross-sectional study.[19] In the Takashima study, the participants with baPWV greater than 1700 cm/s showed a significant increase in total mortality risk.[37] Munakata[11] suggested baPWV of 1800 cm/s as a cut-off value for a high cardiovascular risk. A recent meta-analysis demonstrated that an increase of 100 cm/s in baPWV was associated with a 6% increase in total mortality.[38] However, caution is needed in the clinical application of baPWV, because baPWV could not predict mortality well in participants with symptomatic PAD or ABI <0.9.[11 39 40] Interestingly, we also found that %MAP was significantly correlated with baPWV in participants with normal ABI, but the correlation was not significant in the participants with low ABI. In addition, the association between baPWV and mortality might be attenuated after adjusting for age.[12] High %MAP provided better mortality prediction than baPWV in the Cox regression model in the

Table 3 Cox regression analysis for total mortality in participants with normal ABI values

	HR	95% CI	p Value
Age (years)	1.006	(0.964 to 1.049)	0.799
Male	1.134	(0.384 to 3.352)	0.820
CAD	1.088	(0.228 to 5.203)	0.916
Diabetes mellitus	1.296	(0.303 to 5.552)	0.727
Hypertension	0.797	(0.229 to 2.770)	0.721
Hypercholesterolaemia	0.688	(0.228 to 2.075)	0.506
High %MAP (>45%)	5.389	(1.708 to 17.01)	0.004
UT (>150 msec)*	0.862	(0.271 to 2.738)	0.801
ABI (<1.1)	1.154	(0.364 to 3.659)	0.807
baPWV (>1600 cm/sec)	2.123	(0.453 to 9.954)	0.339

*Median UT, 150 ms.
%MAP, percentage of mean arterial pressure; ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CAD, coronary artery disease; UT, upstroke time.

present study. Thus, patients with high %MAP may have both characteristics of arterial occlusion and arterial stiffness even though their ABI is within the normal range.

The toe-brachial index (TBI) is also an important assessment in participants with unreliable ABI results due to incompressible vessels.[4] However, data on toe pressure were not collected in the present study because this assessment is not routinely performed in our hospital. In our previous study, TBI was positively associated with eGFR in participants with normal ABI.[41] Furthermore, the use of TBI <0.6 as a cut-off to diagnose PAD revealed a high prevalence of PAD and a high-mortality rate among participants with high ABI.[7 27]

There are several limitations to our study. First, the study was conducted with a small sample size and a limited follow-up duration; therefore, we did not further analyse the causes of mortality. Second, we did not assess the effect of %MAP in participants with ABI ≤0.9, due to the small sample size in this group. Third, although smoking is a predictor of mortality, we did not assess the smoking status, as it was difficult to collect this information in a retrospective cohort study. Fourth, we did not assess the association between arterial occlusion on image studies and high %MAP in this study. Therefore, the mechanism underlying the link between high ankle %MAP and mortality is still unknown. In addition, although a %MAP cut-off value of 45% showed good specificity for predicting mortality, its sensitivity was relatively low. Future studies with larger sample sizes are needed to confirm these findings.

In conclusion, high %MAP on pulse volume recording of the lower limbs was a good predictor of total mortality in participants with 0.9<ABI≤1.3 in this observational study.

Author affiliations
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung City, Taiwan
[2]Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung City, Taiwan
[3]School of Medicine, National Yang-Ming University, Taipei City, Taiwan
[4]School of Medicine, Chung Shan Medical University, Taichung City, Taiwan

Data sharing statement No additional data are available.

REFERENCES

1. Diehm C, Lange S, Darius H, et al. Association of low ankle brachial index with high mortality in primary care. Eur Heart J 2006;27:1743–9.
2. Gerhard-Herman M, Gardin JM, Jaff M, et al. Guidelines for noninvasive vascular laboratory testing: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Vasc Med 2006;11:183–200.
3. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001;344:1608–21.
4. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2011;58:2020–45.
5. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004;109:733–9.
6. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197–208.
7. Suominen V, Uurto I, Saarinen J, et al. PAD as a risk factor for mortality among patients with elevated ABI—a clinical study. Eur J Vasc Endovasc Surg 2010;39:316–22.
8. Silvestro A, Diehm N, Savolainen H, et al. Falsely high ankle-brachial index predicts major amputation in critical limb ischemia. Vasc Med 2006;11:69–74.
9. Leng GC, Fowkes FG, Lee AJ, et al. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996;313:1440–4.
10. Munakata M, Sakuraba J, Tayama J, et al. Higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis in end-stage renal disease. Hypertens Res 2005;28:9–14.
11. Munakata M. Brachial-ankle pulse wave velocity in the measurement of arterial stiffness: recent evidence and clinical applications. Curr Hypertens Rev 2014;10:49–57.
12. Sheng CS, Li Y, Li LH, et al. Brachial-ankle pulse wave velocity as a predictor of mortality in elderly Chinese. Hypertension 2014;64:1124–30.
13. Darling RC, Raines JK, Brener BJ, et al. Quantitative segmental pulse volume recorder: a clinical tool. Surgery 1972;72:873–7.
14. Cao P, Eckstein HH, De Rango P, et al. Chapter II: diagnostic methods. Eur J Vasc Endovasc Surg 2011;42(Suppl 2):S13–32.
15. Nakashima R, Inoue Y, Sugano N, et al. Upstroke time and percentage of mean arterial pressure with ABI-form. J Jpn Coll Angiol 2005;45:7–10.
16. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to develop guidelines for the management of patients with peripheral arterial disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:1239–312.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
18. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.
19. Yokokawa H, Goto A, Watanabe K, et al. Evaluation of atherosclerosis-associated factors and pulse wave velocity for

predicting cerebral infarction: a hospital-based, case-control study in Japan. *Intern Med J* 2007;37:161–7.
20. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care* 2012;35(Suppl 1):S11–63.
21. Eslahpazir BA, Allemang MT, Lakin RO, *et al*. Pulse volume recording does not enhance segmental pressure readings for peripheral arterial disease stratification. *Ann Vasc Surg* 2014;28:18–27.
22. Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg* 1979;138:211–18.
23. Watanabe Y, Masaki H, Yunoki Y, *et al*. Ankle-brachial index, toe-brachial index, and pulse volume recording in healthy young adults. *Ann Vasc Dis* 2015;8:227–35.
24. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000;31:S1–S296.
25. Natsuaki C, Inoguchi T, Maeda Y, *et al*. Association of borderline ankle-brachial index with mortality and the incidence of peripheral artery disease in diabetic patients. *Atherosclerosis* 2014;234:360–5.
26. Potier L, Halbron M, Bouilloud F, *et al*. Ankle-to-brachial ratio index underestimates the prevalence of peripheral occlusive disease in diabetic patients at high risk for arterial disease. *Diabetes Care* 2009;32:e44.
27. Suominen V, Rantanen T, Venermo M, *et al*. Prevalence and risk factors of PAD among patients with elevated ABI. *Eur J Vasc Endovasc Surg* 2008;35:709–14.
28. Potier L, Roussel R, Labreuche J, *et al*. Interaction between diabetes and a high ankle-brachial index on mortality risk. *Eur J Prev Cardiol* 2015;22:615–21.
29. Mitsutake R, Miura S, Saku K. Association between coronary artery calcification score as assessed by multi-detector row computed tomography and upstroke time of pulse wave. *Intern Med* 2007;46:1833–6.
30. Arain FA, Ye Z, Bailey KR, *et al*. Survival in patients with poorly compressible leg arteries. *J Am Coll Cardiol* 2012;59:400–7.
31. Learoyd BM, Taylor MG. Alterations with age in the viscoelastic properties of human arterial walls. *Circ Res* 1966;18:278–92.
32. Adragão T, Pires A, Birne R, *et al*. A plain X-ray vascular calcification score is associated with arterial stiffness and mortality in dialysis patients. *Nephrol Dial Transplant* 2009;24:997–1002.
33. Miyano I, Nishinaga M, Takata J, *et al*. Association between brachial-ankle pulse wave velocity and 3-year mortality in community-dwelling older adults. *Hypertens Res* 2010;33:678–82.
34. Ninomiya T, Kojima I, Doi Y, *et al*. Brachial-ankle pulse wave velocity predicts the development of cardiovascular disease in a general Japanese population: the Hisayama Study. *J Hypertens* 2013;31:477–83; discussion 483.
35. Yamashina A, Tomiyama H, Arai T, *et al*. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003;26:615–22.
36. Maeda Y, Inoguchi T, Etoh E, *et al*. Brachial-ankle pulse wave velocity predicts all-cause mortality and cardiovascular events in patients with diabetes: the Kyushu Prevention Study of Atherosclerosis. *Diabetes Care* 2014;37:2383–90.
37. Turin TC, Kita Y, Rumana N, *et al*. Brachial-ankle pulse wave velocity predicts all-cause mortality in the general population: findings from the Takashima study, Japan. *Hypertens Res* 2010;33:922–5.
38. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, *et al*. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension* 2012;60:556–62.
39. Kals J, Lieberg J, Kampus P, *et al*. Prognostic impact of arterial stiffness in patients with symptomatic peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2014;48:308–15.
40. Kitahara T, Ono K, Tsuchida A, *et al*. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 2005;46:688–96.
41. Sheen YJ, Lin JL, Lee IT, *et al*. Low estimated glomerular filtration rate is a major determinant of low ankle-brachial index and toe-brachial index in type 2 diabetes. *Angiology* 2012;63:55–61.