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# Ankle pulse volume recording associated with mortality in subjects with normal ankle-brachial index - an observational study

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**Running title:** Ankle pulse volume recording predicts mortality

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**Abstract**

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

**DESIGN:** We conducted this study as a retrospective cohort study.

**SETTING:** Data were collected from the Taichung Veterans General Hospital.

**PARTICIPANTS:** We included 314 subjects with complete ABI data and pulse volume recording from June 2007 to 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:** Subjects with ABI $\leq 0.9$ showed a significantly high mortality rate than those with ABI $> 0.9$ ($P < 0.001$ in the log-rank test), but the mortality rate was not significantly different between subjects with $0.9 < \text{ABI} \leq 1.1$ and those with $1.1 < \text{ABI} \leq 1.3$ ($P = 0.553$).

Among the subjects 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 adjusting 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 subjects with 0.9 < ABI ≤ 1.3 could predict all-cause mortality in a three-year of follow-up.

**Strengths and limitations of this study**

- Assessments for percentage of mean arterial pressure (%MAP) in ankle arterial wave 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 in the study with a median follow-up period of 20.3 months
- A cut-off value of 45% for %MAP showing a high specificity, but low sensitivity, for 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 be a positive finding for 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 subjects with 1.1 ≤ ABI < 1.4.[5] However, a large cohort study found that there was no significant difference in mortality among subjects with the 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 subjects with an ABI 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 subjects with normal ABI.[11] Arterial stiffness is a process of aging, and it was reported that the association between baPWV and mortality became non-significant after adjusting for age in a

Chinese study.[12] Pulse volume recording has been reported to be another accurate modality for detecting PAD in the lower extremities.[13-15] However, the relationship between pulse volume recording and mortality has not been well assessed. Therefore, the aim of the present study was to investigate whether pulse volume recording, quantified as the percentage of mean arterial pressure (%MAP) and the upstroke time (UT), in ankle arterial wave can predict mortality in subjects with a normal ABI range.

## MATERIAL AND METHODS

### Subjects

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 assessments of both ABI and pulse volume recording from June 2007 to November 2011. Subjects with ABI > 1.3 or end-stage renal disease were excluded. Demographic characteristics and laboratory data were collected. 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. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan before data collection.

## Methods

ABI and pulse volume recording were measured simultaneously using a validated automatic device (VP1000, Colin Cooperation, Hayashi, Komaki City, Japan). Each participant was examined in the supine position after resting for at least 5 min with electrocardiogram electrodes placed on both wrists, and cuffs placed on the brachia and the ankles bilaterally.[3] The cuffs were connected to both a plethysmographic sensor that detected volume change and an oscillometric pressure sensor that measured blood pressure. baPWV was calculated using the formula: path distance of brachial – ankle / pulse tramission 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 subjects. 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 ($r = 0.82$, $P < 0.001$) between the results of the first and second measurement were noted. Based on the Bland-Altman plots,[16] the 95% confidence intervals were -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 between repeated measurements. 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 analyses.

**Statistical analyses**

Chi-Square test was used to examine differences in categorical variables across study groups. All continuous data were presented as the mean ± standard deviation. The estimated glomerular filtration rate (eGFR) was calculated with 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.[17] ANOVA was used to detect differences in continuous variables across three groups. Independent-sample t-tests were used to detect differences between the two groups.

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 the equality of survival distributions for the different levels of ABI. The receiver operating characteristic (ROC) analysis curve was applied to determine the optimal cut-off point of %MAP for mortality. Cox proportional hazards analysis was applied to assess the association between two groups divided by the MAP cut-off point in the subjects with ABI >0.9. Hazard ratios and 95% confidence intervals (CI) were reported. In the Cox analysis model, UT was categorized based on the median; baPWV was categorized based on 1600 cm/sec;[18] hypercholesterolemia was defined as LDL cholesterol ≥ 2.59 mmol/L (100 mg/dL); hypertension was defined as use of anti-hypertensive medications or blood pressure ≥ 140/90

mmHg; and diabetes mellitus was defined based on the American Diabetes Association criteria.[19] A value of $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 22.0 software (International Business Machines Corp, New York, USA).

## RESULTS

A total of 314 subjects were included in the analyses. The subjects were divided into three groups based on their baseline ABI values, which included 99 subjects in the ABI ≤0.9 group, 139 in the $0.9 < ABI \leq 1.1$ group, and 76 in the $1.1 < ABI \leq 1.3$ group. There were no significant differences in age and gender among the three ABI groups (both P values > 0.05). Systolic blood pressure was significantly higher in the subjects 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 to the $0.9 < ABI \leq 1.1$ group and the $1.1 < ABI \leq 1.3$ group in post-hoc analyses (both P values < 0.001). Neither %MAP nor UT was significantly different between the $0.9 < ABI \leq 1.1$ and the $1.1 < ABI \leq 1.3$ groups ($P = 0.428$ for %MAP, $P = 0.189$ for UT) in post-hoc analyses (table 1).

During the three-year follow-up (median of 20.3 months, inter-quartile range between 9.4 and 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 1), 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 subjects with ABI >0.9, the other variables associated with mortality in these subjects should be assessed. There were 238 subjects 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 cm/sec vs. 1909 ± 427 cm/sec, 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 subjects that died compared with that of the survivors during the follow-up period. However, there was no significant difference in ABI or UT between the subjects that died and survived during the follow-up period (table 2). Using receiver operating characteristic 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 2).

Therefore, we divided the subjects with ABI > 0.9 into two groups: the %MAP > 45% group and the %MAP ≤ 45% group. In the Cox proportional hazards regression models, subjects in the %MAP > 45% group showed higher risks of all-cause mortality than those in the %MAP ≤ 45% group (hazard ratio= 5.389; 95%CI between 1.708 and 17.01; P = 0.004), after adjusting for age, gender, CAD, diabetes, hypertension, hypercholesterolemia, 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 subjects with an ABI value in the normal range. To the best of our knowledge, this study is the first to apply %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 subjects without PAD, pulse volume recording looks similar to a normal arterial wave.[2] However, in subjects with PAD, the waveform is flattened and has a delayed upstroke. A high-calculated %MAP as a result of a flattened arterial wave implies the presence of PAD.[20] Since PAD is associated with increased mortality in the general population,[1] a high %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".[21] However, PAD may exist in subjects with normal ABI. In a study by Nakashima et al.,[15] 63% of subjects with ABI >0.9 had significant degrees of stenosis as detected by intravenous or

intra-arterial subtraction angiography. A previous study also revealed that 0.9 < ABI < 1.0 in diabetic patients was associated with a significantly higher risk of mortality compared with 1.0 ≤ ABI < 1.4.[22] 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 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 show a false negative result for PAD in these patients with non-compressible vessels. 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 a certain pressure thereby occluding venous circulation, the volume change detected by a transducer is purely from the 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 non-compressible arterial vessels.[23] Our study population was composed of elderly subjects with a high prevalence of diabetes. Therefore, pulse volume recordings might have been more reliable for the assessment of PAD in this study. In our study, high %MAP was also an independent predictor for total mortality after adjusting for ABI value in the ABI > 0.9 group.

Mitsutake R, et al.[24] reported that UT was significantly associated with coronary artery

calcification score based on computed tomography findings. In our study, a prolonged UT was shown in the mortality group compared with that in the survival group, but this difference did not reach statistical significance. In accordance with our results, Nakashima et al. reported that UT was not significantly different in subjects with arterial occlusion based on angiography compared with the control group.[15]

High baPWV, a pathophysiological indicator of arterial stiffness, is a predictor for all-cause mortality.[12 25 26] A variety of optimal cutoff values have been reported for abnormal baPWV. A baPWV greater than 1400 cm/sec was reported to be associated with an increased risk for cardiovascular disease based on Framingham score or in diabetic population.[27,28] A baPWV greater than 1600 cm/sec was associated with cerebral infarction in a cross-sectional study.[18] In the study by Takashima et al.,[29] the subjects with baPWV greater than 1700cm/sec showed a significant increase in total mortality risk. Munakata M[11] suggested baPWV of 1800 cm/s as a cutoff value for clinical high risk. A recent meta-analysis demonstrated an increase in 100 cm/sec of baPWV was associated with a 6% increase in total mortality.[30] However, caution is needed in the clinical application of baPWV, because baPWV could not predict mortality well in subjects with symptomatic PAD or ABI < 0.9.[11 31 32] In the present study, high %MAP provided better mortality prediction than baPWV in the Cox regression model. Thus, patients with high %MAP may have PAD even though their ABI is within the normal range. In addition, the association between baPWV and mortality might

be attenuated after adjusting for age.[12]

There were several limitations in our study. First, the study was conducted with a small sample size and a limited follow-up duration; therefore, we did not further analyze the causes of mortality. Second, we did not assess the effect of %MAP in subjects with ABI ≤0.9 due to the small sample size in this group. Third, although the cut-off value of 45% for %MAP had a good level of specificity for mortality, the sensitivity was still relatively low. Future studies with larger sample sizes are needed to confirm these findings.

In conclusion, that high %MAP in pulse volume recordings of the lower limbs was a good predictor of total mortality in subjects with $0.9 < ABI \leq 1.3$ in this three-year observational study.

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**Conflict of Interests**

The authors declare that there was no conflict of interest with respect to the research, authorship, and/or publication of this article.

**Author contributions:**

YL and IL contributed to the study design. YL, SL, WHS and IL participated in the data collection. YL and IL participated in the analysis and interpretation of the data. YL drafted the manuscript. IL had full access to the data in the study. IL is the guarantor. All the authors performed a critical revision of the manuscript for important intellectual content.

**Data Sharing Statement:**

No additional unpublished data from the study

## FIGURE LEGENDS

**Figure 1.** Survival probability according to ABI groups

**Figure 2.** Receiver operating characteristic (ROC) analysis curve cut-off level of the mean arterial pressure (%MAP) for all-cause mortality

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**Table 1. Baseline characteristics of subjects in different ABI groups**

| | 1.1<ABI≤1.3 (N = 99) | 0.9<ABI≤1.1 (N = 139) | ABI≤0.9 (N = 76) | P |
|---|---|---|---|---|
| Age (year) | 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 (mmHg) | 141 ± 17 | 139 ± 21 | 147 ± 27[b] | 0.034 |
| Diastolic BP (mmHg) | 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[a] | 0.7 ± 0.1[ab] | <0.001 |
| PWV (cm/sec) | 1979 ± 429 | 1887 ± 433 | 2010 ± 683 | 0.169 |
| %MAP | 39.7% ± 4.0% | 40.4% ± 4.3% | 48.4% ± 5.8%[ab] | <0.001 |
| UT (ms) | 151 ± 25 | 160 ± 33 | 214 ± 50[ab] | <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 |

| | | | | |
|---|---|---|---|---|
| Antiplatelet, n (%) | 23 (23.2%) | 31 (22.3%) | 20 (26.3%) | 0.799 |
| Antihypertensive agents, n (%) | | | | |
| ACE inhibitor or ARB, n (%) | 48 (48.5%) | 63 (45.3%) | 32 (42.1%) | 0.701 |
| α-Blocker, n (%) | 9 (9.1%) | 13 (9.4%) | 7 (9.2%) | 0.998 |
| β-Blocker, n (%) | 12 (12.1%) | 19 (13.7%) | 13 (17.1%) | 0.634 |
| Calcium channel blocker, n (%) | 34 (34.3%) | 35 (25.2%) | 19 (25.0%) | 0.239 |
| Diuretics, n (%) | 11 (11.1%) | 26 (18.7%) | 13 (17.1%) | 0.273 |
| Antidiabetic drugs | | | | |
| Insulin therapy, n (%) | 30 (30.3%) | 33 (23.7%) | 29 (38.2%) | 0.082 |
| Insulin secretagogues, n (%) | 28 (28.3%) | 50 (36.0%) | 17 (22.4%) | 0.102 |
| Metformin, n (%) | 31 (31.3%) | 50 (36.0%) | 15 (19.7%)[b] | 0.046 |
| Thiazolidinediones, n (%) | 9 (9.1%) | 7 (5.0%) | 5 (6.6%) | 0.466 |
| α-Glucosidase inhibitor, n (%) | 6 (6.1%) | 3 (2.2%) | 9 (11.8%)[b] | 0.014 |
| Mortality, n (%) | 5 (5.1%) | 10 (7.2%) | 16 (21.1%)[ab] | <0.001 |

[a]Significantly different from the 1.1 < ABI ≤ 1.3 group

[b]Significantly different from the 0.9 < ABI ≤ 1.1 group

ABI = Ankle-brachial index, ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor antagonists, BP = blood pressure, CAD = coronary artery disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, PWV= pulse wave velocity, UT =

upstroke time, %MAP = percentage of mean arterial pressure.

**Table 2. Characteristics of subjects with normal ABI**

| | Mortality (N = 15) | Survival (N = 223) | P |
|---|---|---|---|
| Age (year) | 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 (mmHg) | 134 ± 22 | 140 ± 19 | 0.300 |
| Diastolic BP (mmHg) | 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 |
| PWV (cm/sec) | 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 |

ABI = Ankle-brachial index, ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor antagonists, BP = blood pressure, CAD = coronary artery disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, UT = upstroke time, %MAP = percentage of mean arterial pressure

**Table 3. Cox regression analysis for total mortality in subjects with normal ABI values.**

| | Hazard ratio | 95% CI | P |
|---|---|---|---|
| Age (year) | 1.006 | (0.964, 1.049) | 0.799 |
| Male | 1.134 | (0.384, 3.352) | 0.820 |
| CAD | 1.088 | (0.228, 5.203) | 0.916 |
| Diabetes mellitus | 1.296 | (0.303, 5.552) | 0.727 |
| Hypertension | 0.797 | (0.229, 2.770) | 0.721 |
| Hypercholesterolemia | 0.688 | (0.228, 2.075) | 0.506 |
| High %MAP (>45%) | 5.389 | (1.708, 17.01) | 0.004 |
| UT (>150msec) | 0.862 | (0.271, 2.738) | 0.801 |
| ABI (<1.1) | 1.154 | (0.364, 3.659) | 0.807 |
| PWV (>1600 cm/sec) | 2.123 | (0.453, 9.954) | 0.339 |

ABI = Ankle-brachial index, BP = blood pressure, CAD = coronary artery disease, UT = upstroke time, %MAP = percentage of mean arterial pressure.

*Median of UT was 150 msec

**Figure 1**

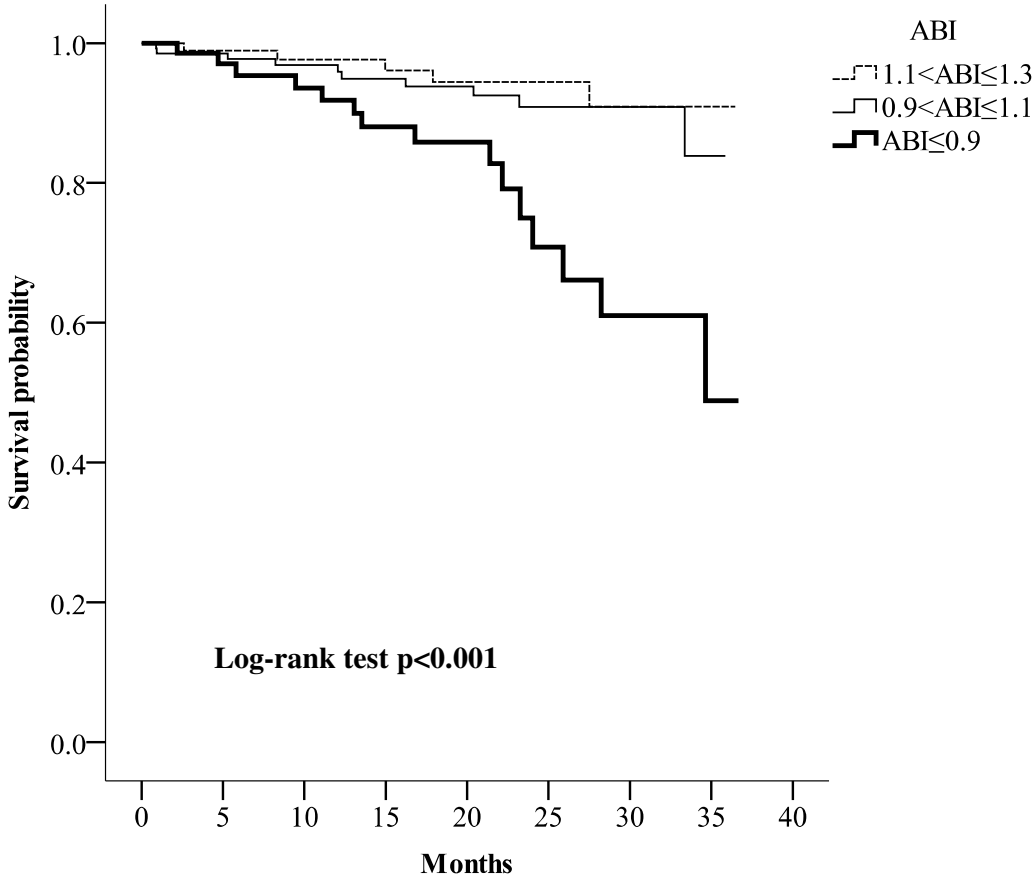
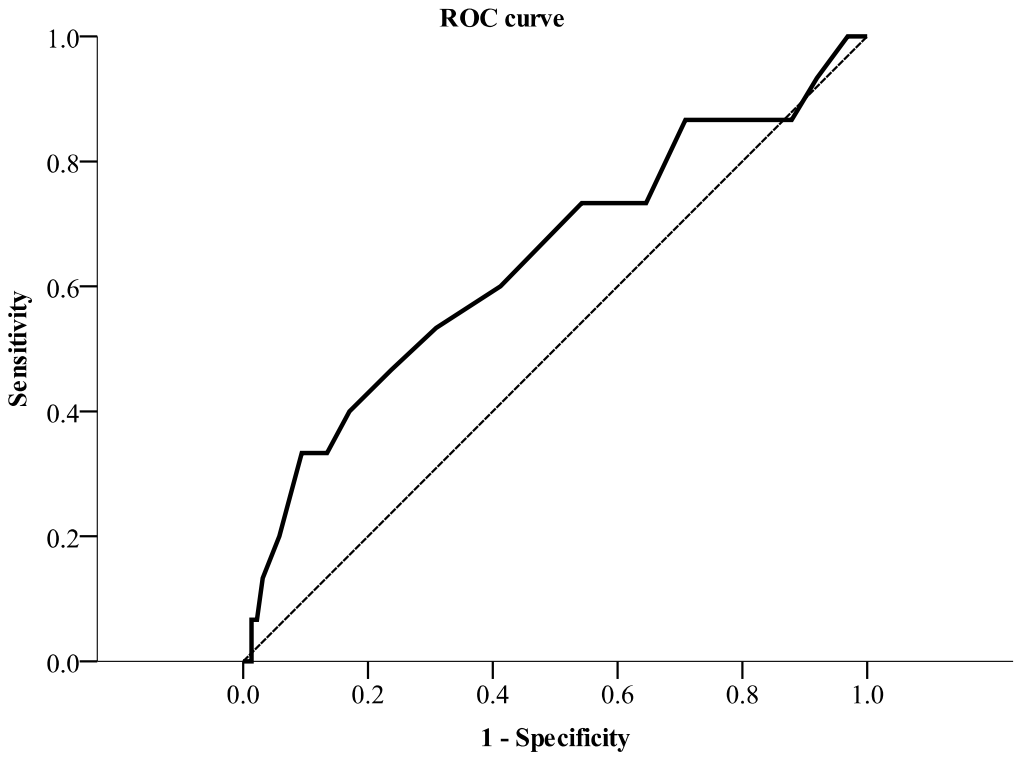


**Figure 2**




The optimal cut-off values 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 |

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 13 |
| Study size | 10 | Explain how the study size was arrived at | NA |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Figure 1 and Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Figure 2 and Table 2 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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



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

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**Running title:** Ankle pulse volume recording predicts mortality

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**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 hypothesized 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 study as a retrospective cohort study.

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

**Participants:** We included 314 subjects 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:** Subjects with ABI $\leq 0.9$ showed a highest mortality rate ($P < 0.001$ in the log-rank test), but the mortality rate was not significantly different between subjects with $0.9 < ABI \leq 1.1$ and those with $1.1 < ABI \leq 1.3$ ($P = 0.553$). Among the subjects with $0.9 < ABI \leq 1.3$, 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 subjects 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 subjects with 1.1 ≤ ABI < 1.4.[5] However, a large cohort study found that there was no significant difference in mortality among subjects with the 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 subjects with an ABI 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 subjects with normal ABI.[11] Arterial stiffness is a process of aging, and it was reported that the association between baPWV and mortality became non-significant after adjusting for age in a Chinese study.[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 subjects with normal ABI.

## MATERIALS AND METHODS

### Subjects

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 paresthesia in the lower extremities. Subjects 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 subjects undergoing hemodialysis, only one brachial artery was assessed because of the arteriovenous fistula on the other side. To avoid variability in ABI measurements, subjects with end-stage renal disease were excluded. We used the last recorded measurement with complete data in the case of patients who underwent multiple aseessments. Demographic characteristics and

laboratory data were also collected. In addition to the clinical signs of lower-limb ischemia, the enrolled subjects 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. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan, before data collection.

**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 subjects. 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 intra-observer variability shown by 95% confidence intervals (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 inter-observer 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**

Chi-Square test was used to examine differences in categorical variables across study groups. All continuous data were presented as the mean ± standard deviation. 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 subjects 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 subjects with ABI >0.9. Hazard ratios and 95%CIs were reported. In the Cox analysis model, UT was categorized based on the median value; baPWV was categorized using a cut-off of 1600 cm/sec;[19] hypercholesterolemia was defined as LDL cholesterol ≥ 2.59 mmol/L (100 mg/dL); hypertension was defined as the use of anti-hypertensive medications or blood pressure ≥ 140/90 mmHg; 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 version 22.0 software (International Business Machines Co., New York, USA).

## RESULTS

A total of 314 subjects were included in the analyses. The subjects were divided into three groups based on their baseline ABI values, which included 76 subjects 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 subjects 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 to 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 ($r$ = 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; inter-quartile range, 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 subjects with ABI >0.9, the other variables associated with mortality in these subjects should be assessed. There were 238 subjects 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 cm/sec vs. 1909 ± 427 cm/sec, 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 subjects that died compared with that of the survivors during the follow-up period. However, there was no significant difference in ABI or UT between the subjects that 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 subjects with ABI > 0.9 into two groups: the %MAP > 45% group and the %MAP ≤ 45% group. In the Cox proportional hazards regression models, subjects in the %MAP > 45% group showed higher risks of all-cause mortality than those in

the %MAP ≤ 45% group (hazard ratio= 5.389; 95%CI between 1.708 and 17.01; P = 0.004), after adjusting for age, gender, coronary artery disease (CAD), diabetes, hypertension, hypercholesterolemia, 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 subjects 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 subjects without PAD, pulse volume recording looks similar to a normal arterial wave.[2] However, in subjects 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 subjects with normal ABI. In a study by Nakashima et al.,[15] 63% of subjects with ABI >0.9 had significant degrees of stenosis as detected by intravenous or intra-arterial subtraction angiography. A previous study also revealed that 0.9 < ABI < 1.0 in diabetic patients 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 subjects with high ABI values.[7] In the present study, however, there were too few subjects 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 subjects 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 subjects with ABI > 0.9.

Mitsutake, et al.[29] reported that UT was significantly associated with coronary artery calcification score based on computed tomography findings. In our study, a prolonged UT was shown in the non-survivor group as compared with that in the survivor group, but the difference did not reach statistical significance. In accordance with our results, Nakashima et al. reported that UT was not significantly different between subjects with arterial occlusion detected using angiography and the control group.[15] 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% subjects with normal ABI had a history of CAD. Consistent with this finding, a previous ABI study reported that CAD contributed a similar hazard ratio 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 hazard ratio 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 cutoff values have been reported for abnormal baPWV. A baPWV greater than 1400 cm/sec was reported to be associated with an increased risk for cardiovascular disease based on Framingham score or in diabetic population.[35 36] A baPWV greater than 1600 cm/sec was associated with cerebral infarction in a cross-sectional study.[19] In the Takashima study, the subjects with baPWV greater than 1700cm/sec showed a significant increase in total mortality risk.[37] Munakata[11] suggested baPWV of 1800 cm/s as a cutoff value for a high cardiovascular risk. A recent meta-analysis demonstrated that an increase of 100 cm/sec 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 subjects with symptomatic PAD or ABI < 0.9.[11 39 40] Interestingly, we also found that %MAP was significantly correlated with baPWV in subjects with normal ABI, but the correlation was not significant in the subjects 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 present study. Thus, patients with high %MAP may have both characteristic 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 subjects 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 subjects with normal ABI.[41] Furthermore, the use of TBI < 0.6 as a cutoff to diagnose PAD revealed a high prevalence of PAD and a high-mortality rate among subjects 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 analyze the causes of mortality. Second, we did not assess the effect of %MAP in subjects 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 subjects with 0.9 < ABI ≤ 1.3 in this observational study.

**Acknowledgments**

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**Conflicts of Interest**

The authors declare that there isno conflict of interest with respect to the research, authorship, and/or publication of this article.

**Data sharing**

No additional unpublished data available from the study.

**Author contributions**

YL and IL contributed to the study design. YL, SL, WHS and IL participated in the data collection. YL and IL participated in the analysis and interpretation of the data. YL drafted the manuscript. IL had full access to the data in the study. IL is the guarantor. All the authors performed a critical revision of the manuscript for important intellectual content.

## FIGURE LEGENDS

**Figure 1.** Flow diagram of the enrollment of the study subjects.

**Figure 2.** Relationship of brachial-ankle pulse wave velocity (baPWV) with percentage of mean arterial pressure (%MAP) and upstroke time (UT) in subjects with 1.1<ABI≤1.3 (A), 0.9<ABI≤1.1 (B) and ABI≤0.9 (C)

**Figure 3.** Survival probability in different ABI groups

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

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**Table 1. Baseline characteristics of subjects in different ABI groups**

| | 1.1<ABI≤1.3 (N = 99) | 0.9<ABI≤1.1 (N = 139) | ABI≤0.9 (N = 76) | P |
|---|---|---|---|---|
| Age (year) | 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 (mmHg) | 141 ± 17 | 139 ± 21 | 147 ± 27[b] | 0.034 |
| Diastolic BP (mmHg) | 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[a] | 0.7 ± 0.1[ab] | <0.001 |
| baPWV (cm/sec) | 1979 ± 429 | 1887 ± 433 | 2010 ± 683 | 0.169 |
| %MAP | 39.7% ± 4.0% | 40.4% ± 4.3% | 48.4% ± 5.8%[ab] | <0.001 |
| UT (ms) | 151 ± 25 | 160 ± 33 | 214 ± 50[ab] | <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 |

| | | | |
|---|---|---|---|
| Mortality, n (%) | 5 (5.1%) | 10 (7.2%) | 16 (21.1%)[ab] <0.001 |

[a]Significantly different from the 1.1 < ABI ≤ 1.3 group

[b]Significantly different from the 0.9 < ABI ≤ 1.1 group

ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, 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, PWV= pulse wave velocity, UT = upstroke time, %MAP = percentage of mean arterial pressure.

**Table 2. Characteristics of subjects with normal ABI**

| | Non-survivors (N = 15) | Survivors (N = 223) | P |
|---|---|---|---|
| Age (year) | 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 (mmHg) | 134 ± 22 | 140 ± 19 | 0.300 |
| Diastolic BP (mmHg) | 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/sec) | 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 |

ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, 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, %MAP = percentage of mean arterial pressure

**Table 3. Cox regression analysis for total mortality in subjects with normal ABI values.**

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

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

*Median UT, 150 msec

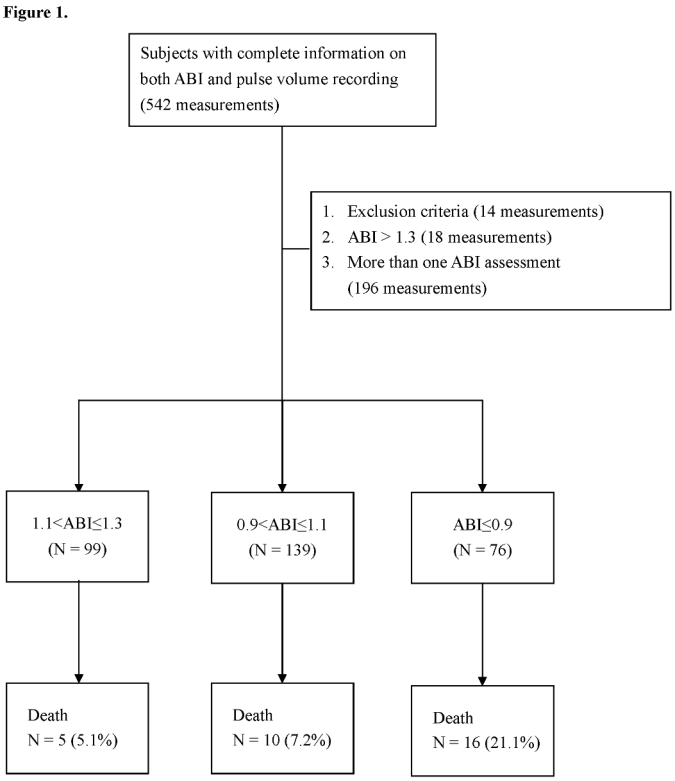


Figure 1
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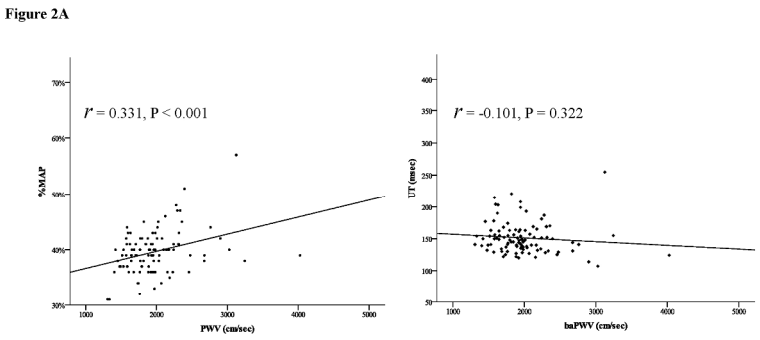


Figure 2A
279x215mm (300 x 300 DPI)

Figure 2B

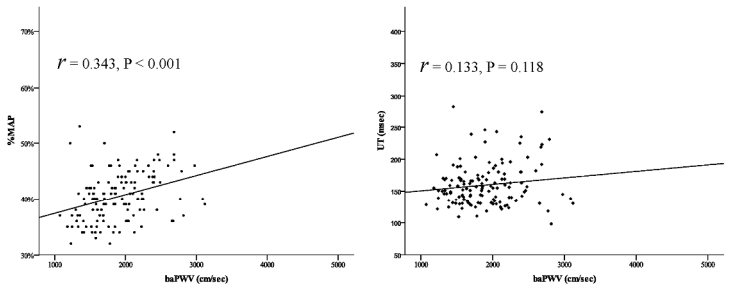


Figure 2B
279x215mm (300 x 300 DPI)

Figure 2C

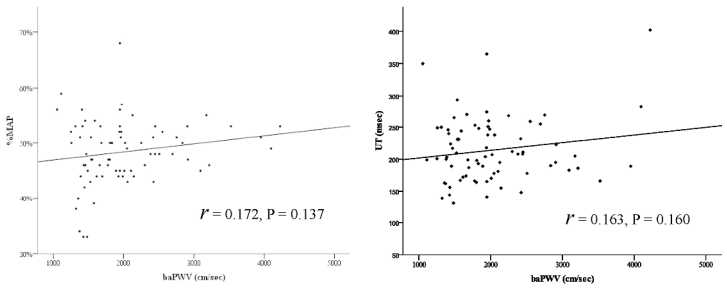


Figure 2C
279x215mm (300 x 300 DPI)

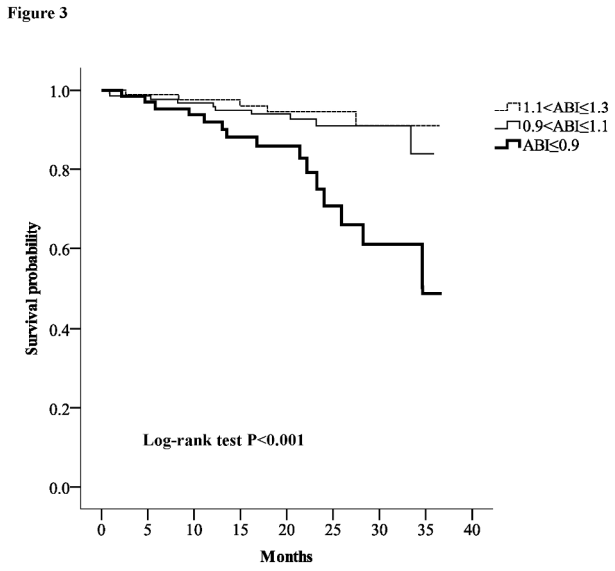


Figure 3
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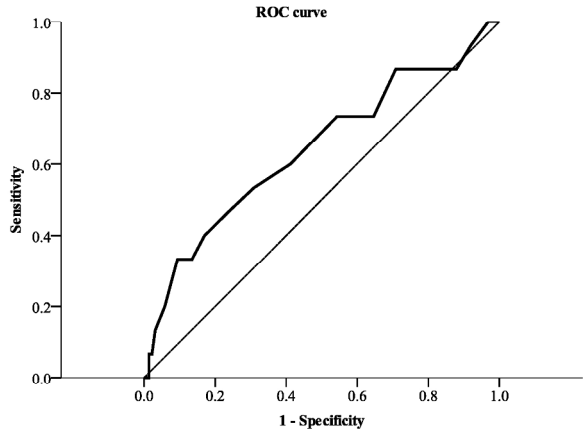
Figure 4




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 |

Figure 4
210x297mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 13 |
| Study size | 10 | Explain how the study size was arrived at | NA |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Figure 1 and Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Figure 2 and Table 2 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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



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| | |

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

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**Running title:** Ankle pulse volume recording predicts mortality

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**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 hypothesized 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 study as a retrospective cohort study.

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

**Participants:** We included 314 subjects 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:** Subjects with ABI $\leq 0.9$ showed a highest mortality rate ($P < 0.001$ in the log-rank test), but the mortality rate was not significantly different between subjects with $0.9 < ABI \leq 1.1$ and those with $1.1 < ABI \leq 1.3$ ($P = 0.553$). Among the subjects with $0.9 < ABI \leq 1.3$, 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 subjects 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 subjects with 1.1 ≤ ABI < 1.4.[5] However, a large cohort study found that there was no significant difference in mortality among subjects with the 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 subjects with an ABI 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 subjects with normal ABI.[11] Arterial stiffness is a process of aging, and it was reported that the association between baPWV and mortality became non-significant after adjusting for age in a Chinese study.[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 subjects with normal ABI.

## MATERIALS AND METHODS

### Subjects

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 paresthesia in the lower extremities. Subjects 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 subjects undergoing hemodialysis, only one brachial artery was assessed because of the arteriovenous fistula on the other side. To avoid variability in ABI measurements, subjects with end-stage renal disease were excluded. We used the last recorded measurement with complete data in the case of patients who underwent multiple aseessments. Demographic characteristics and

laboratory data were also collected. In addition to the clinical signs of lower-limb ischemia, the enrolled subjects 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. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan, before data collection.

**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 subjects. 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 intra-observer variability shown by 95% confidence intervals (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 inter-observer 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**

Chi-Square test was used to examine differences in categorical variables across study groups. All continuous data were presented as the mean ± standard deviation. 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 subjects 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 subjects with ABI >0.9. Hazard ratios and 95%CIs were reported. In the Cox analysis model, UT was categorized based on the median value; baPWV was categorized using a cut-off of 1600 cm/sec;[19] hypercholesterolemia was defined as LDL cholesterol ≥ 2.59 mmol/L (100 mg/dL); hypertension was defined as the use of anti-hypertensive medications or blood pressure ≥ 140/90 mmHg; 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 version 22.0 software (International Business Machines Co., New York, USA).

## RESULTS

A total of 314 subjects were included in the analyses. The subjects were divided into three groups based on their baseline ABI values, which included 76 subjects 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 subjects 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 to 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 ($r$ = 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; inter-quartile range, 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 subjects with ABI >0.9, the other variables associated with mortality in these subjects should be assessed. There were 238 subjects 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 cm/sec vs. 1909 ± 427 cm/sec, 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 subjects that died compared with that of the survivors during the follow-up period. However, there was no significant difference in ABI or UT between the subjects that 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 subjects with ABI > 0.9 into two groups: the %MAP > 45% group and the %MAP ≤ 45% group. In the Cox proportional hazards regression models, subjects in the %MAP > 45% group showed higher risks of all-cause mortality than those in

the %MAP ≤ 45% group (hazard ratio= 5.389; 95%CI between 1.708 and 17.01; P = 0.004), after adjusting for age, gender, coronary artery disease (CAD), diabetes, hypertension, hypercholesterolemia, 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 subjects 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 subjects without PAD, pulse volume recording looks similar to a normal arterial wave.[2] However, in subjects 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 subjects with normal ABI. In a study by Nakashima et al.,[15] 63% of subjects with ABI >0.9 had significant degrees of stenosis as detected by intravenous or intra-arterial subtraction angiography. A previous study also revealed that 0.9 < ABI < 1.0 in diabetic patients 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 subjects with high ABI values.[7] In the present study, however, there were too few subjects 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 subjects 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 subjects with ABI > 0.9.

Mitsutake, et al.[29] reported that UT was significantly associated with coronary artery calcification score based on computed tomography findings. In our study, a prolonged UT was shown in the non-survivor group as compared with that in the survivor group, but the difference did not reach statistical significance. In accordance with our results, Nakashima et al. reported that UT was not significantly different between subjects with arterial occlusion detected using angiography and the control group.[15] 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% subjects with normal ABI had a history of CAD. Consistent with this finding, a previous ABI study reported that CAD contributed a similar hazard ratio 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 hazard ratio 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 cutoff values have been reported for abnormal baPWV. A baPWV greater than 1400 cm/sec was reported to be associated with an increased risk for cardiovascular disease based on Framingham score or in diabetic population.[35 36] A baPWV greater than 1600 cm/sec was associated with cerebral infarction in a cross-sectional study.[19] In the Takashima study, the subjects with baPWV greater than 1700cm/sec showed a significant increase in total mortality risk.[37] Munakata[11] suggested baPWV of 1800 cm/s as a cutoff value for a high cardiovascular risk. A recent meta-analysis demonstrated that an increase of 100 cm/sec 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 subjects with symptomatic PAD or ABI < 0.9.[11 39 40] Interestingly, we also found that %MAP was significantly correlated with baPWV in subjects with normal ABI, but the correlation was not significant in the subjects 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 present study. Thus, patients with high %MAP may have both characteristic 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 subjects 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 subjects with normal ABI.[41] Furthermore, the use of TBI < 0.6 as a cutoff to diagnose PAD revealed a high prevalence of PAD and a high-mortality rate among subjects 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 analyze the causes of mortality. Second, we did not assess the effect of %MAP in subjects 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 subjects with 0.9 < ABI ≤ 1.3 in this observational study.

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**Conflicts of Interest**

The authors declare that there isno conflict of interest with respect to the research, authorship, and/or publication of this article.

**Author contributions**

YL and IL contributed to the study design. YL, SL, WHS and IL participated in the data collection. YL and IL participated in the analysis and interpretation of the data. YL drafted the manuscript. IL had full access to the data in the study. IL is the guarantor. All the authors performed a critical revision of the manuscript for important intellectual content.

## Data sharing

No additional data available.

## FIGURE LEGENDS

**Figure 1.** Flow diagram of the enrollment of the study subjects.

**Figure 2.** Relationship of brachial-ankle pulse wave velocity (baPWV) with percentage of mean arterial pressure (%MAP) and upstroke time (UT) in subjects with 1.1<ABI≤1.3 (A), 0.9<ABI≤1.1 (B) and ABI≤0.9 (C)

**Figure 3.** Survival probability in different ABI groups

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

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**Table 1. Baseline characteristics of subjects in different ABI groups**

| | 1.1<ABI≤1.3 (N = 99) | 0.9<ABI≤1.1 (N = 139) | ABI≤0.9 (N = 76) | P |
|---|---|---|---|---|
| Age (year) | 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 (mmHg) | 141 ± 17 | 139 ± 21 | 147 ± 27[b] | 0.034 |
| Diastolic BP (mmHg) | 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[a] | 0.7 ± 0.1[ab] | <0.001 |
| baPWV (cm/sec) | 1979 ± 429 | 1887 ± 433 | 2010 ± 683 | 0.169 |
| %MAP | 39.7% ± 4.0% | 40.4% ± 4.3% | 48.4% ± 5.8%[ab] | <0.001 |
| UT (ms) | 151 ± 25 | 160 ± 33 | 214 ± 50[ab] | <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 |

[a]Significantly different from the 1.1 < ABI ≤ 1.3 group

[b]Significantly different from the 0.9 < ABI ≤ 1.1 group

ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, 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, PWV= pulse wave velocity, UT = upstroke time, %MAP = percentage of mean arterial pressure.

**Table 2. Characteristics of subjects with normal ABI**

| | Non-survivors (N = 15) | Survivors (N = 223) | P |
|---|---|---|---|
| Age (year) | 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 (mmHg) | 134 ± 22 | 140 ± 19 | 0.300 |
| Diastolic BP (mmHg) | 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/sec) | 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 |

ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, 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, %MAP = percentage of mean arterial pressure

**Table 3. Cox regression analysis for total mortality in subjects with normal ABI values.**

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

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

*Median UT, 150 msec

**Figure 1.**

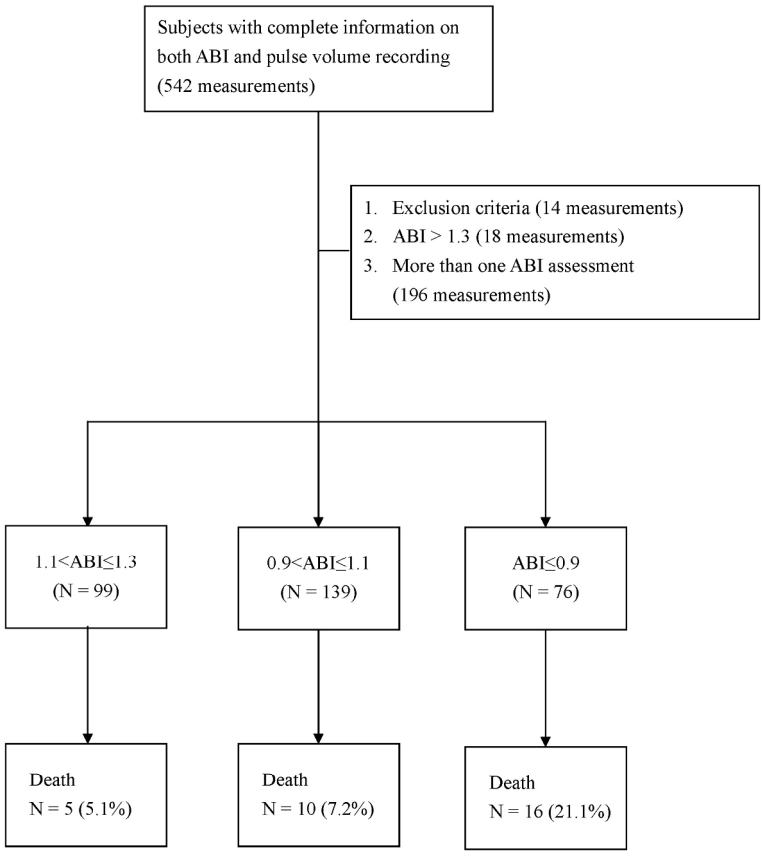



Figure 1
197x261mm (300 x 300 DPI)

Figure 2A

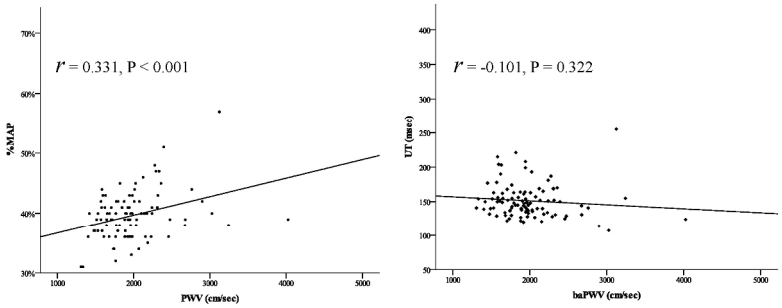



Figure 2A
259x136mm (300 x 300 DPI)

Figure 2B

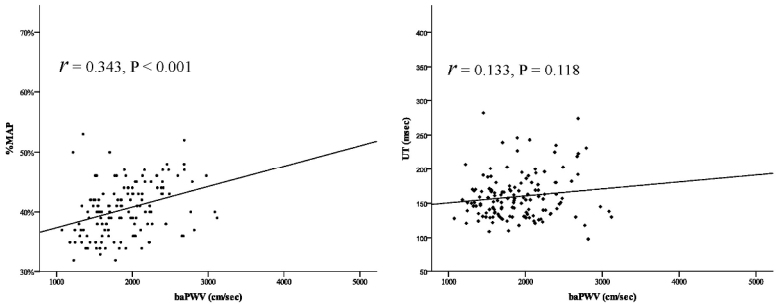



Figure 2B
260x149mm (300 x 300 DPI)

Figure 2C

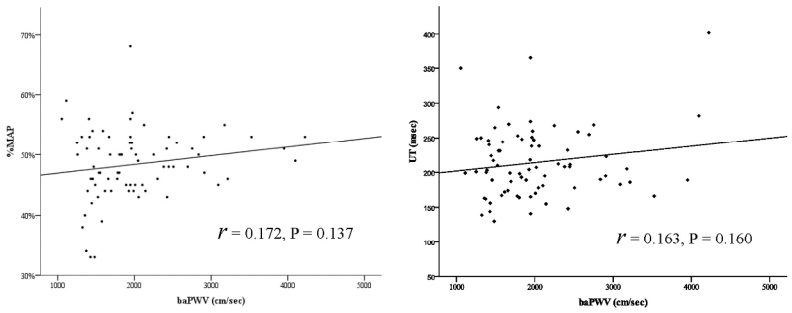



Figure 2C
256x152mm (300 x 300 DPI)

Figure 3

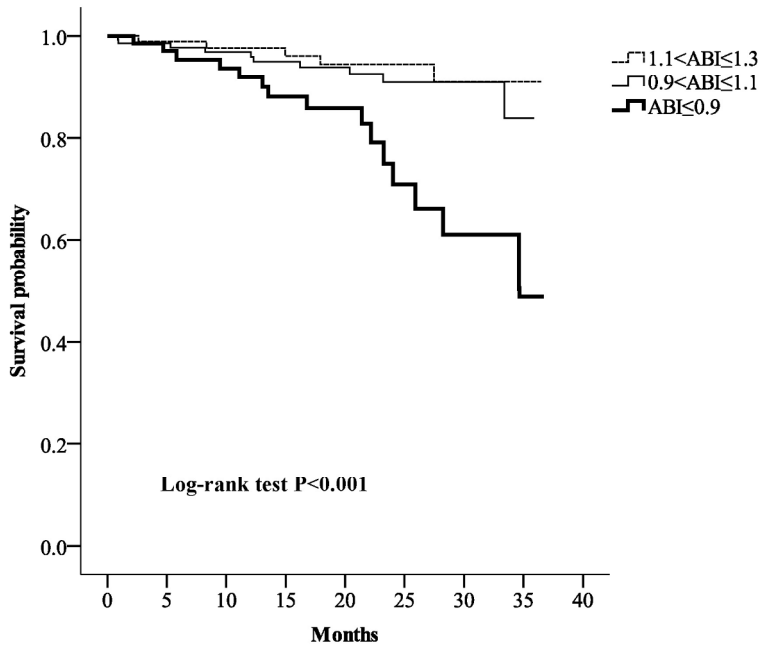
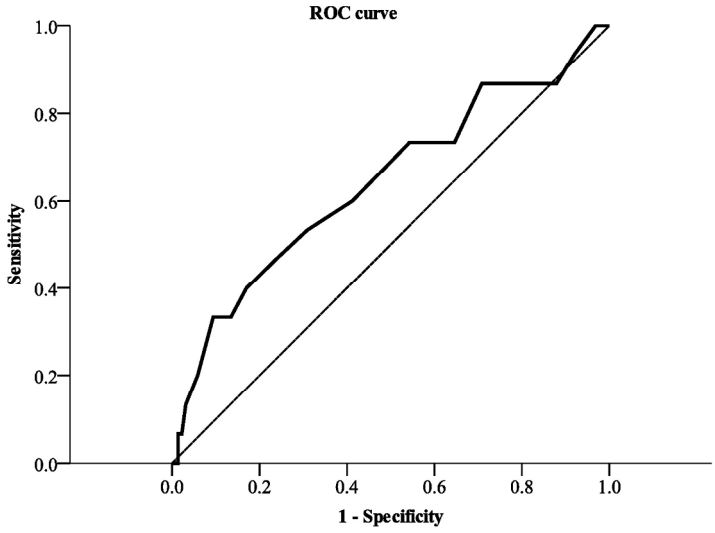



Figure 3
193x193mm (300 x 300 DPI)

**Figure 4**




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 |

Figure 4
190x241mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 13 |
| Study size | 10 | Explain how the study size was arrived at | NA |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Figure 1 and Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Figure 2 and Table 2 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.