Impact of peripheral artery disease on outcome in ischemic stroke patients with aortic atheroma

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Impact of peripheral artery disease on outcome in ischemic stroke patients with aortic atheroma

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ABSTRACT

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Aortic atheroma (AA) is a known risk factor of occurrence and recurrence of acute ischemic stroke. Ankle-brachial index (ABI) and brachial-ankle pulse wave velocity (baPWV) are two non-invasive markers of peripheral artery atherosclerosis and are both known to be correlated with increased cardiovascular risks and poor functional outcome after cerebral infarction. In this study, we investigated whether markers of peripheral artery atherosclerosis together with AA can better predict long-term outcomes in ischemic stroke patients. We reviewed 2452 ischemic stroke patients who have undergone both transesophageal echocardiography and baPWV, ABI measurements. Patients were regularly interviewed after discharge for their functional status depicted by the modified Rankin Scale, and the occurrence of major adverse cardiac event (MACE), defined as the occurrence of acute coronary syndrome, hospitalization due to heart failure, hemorrhagic stroke, recurrence of ischemic stroke, and all-cause death. Patients were divided into four groups by the combinations of AA and baPWV or AA and ABI. We used chi-square analysis and Kaplan-Meier survival analysis in analyzing the intergroup differences of functional outcome and MACE occurrence. Multivariate logistic regression analysis and Cox regression were performed to adjust for confounders. Chi-square analysis showed that patients with AA (+), ABI<0.9 and patients with AA (+), baPWV>20.33 m/s were more apt to have poor functional

outcome compared with patients with AA (-), ABI≥0.9 ($p<0.001$) and AA (-), baPWV≤20.33 m/s ($p<0.001$), respectively. Kaplan-Meier survival analysis revealed that patients with AA ($p<0.001$), ABI<0.9 ($p<0.001$), and baPWV>20.33 m/s ($p<0.001$) were more apt to MACE occurrence than their counterparts, respectively. When comparing among the four groups categorized by the combination of aortic atherosclerosis and peripheral artery atherosclerosis, patients with both AA and low ABI ($p<0.001$) or high baPWV ($p<0.001$) had a significantly higher risk of MACE occurrence than those without atherosclerosis in either artery. Multivariate analysis showed that the group with both AA and peripheral atherosclerosis were at significantly higher risk of MACE compared with the group without atherosclerosis in both the aorta and peripheral arteries (AA (+), ABI<0.9 vs. AA (-), ABI≥0.9: HR 1.71, 95% confidence interval [CI] 1.20-2.45; AA (+), baPWV>20.33 m/s vs. AA (-), baPWV≤20.33 m/s: HR 1.42, 95% CI 1.04-1.95). In this study, we showed that the patients who have both AA and peripheral atherosclerosis is associated with poorer functional outcomes and higher cardiovascular risk. Our findings suggest that systemic evaluation of atherosclerosis on the aorta and peripheral artery might be helpful for better predicting long-term outcome in acute ischemic stroke patients.

Key words : Ankle-brachial index, pulse wave velocity, aortic atheroma, acute ischemic stroke, functional outcome, major cardiovascular event

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I. INTRODUCTION

Arterial stiffness is an indicator that reflects the degree of arterial damage and systemic atherosclerosis. It is correlated with cardiovascular risks.[1] Brachio-ankle pulse wave velocity (baPWV), being one of the simplest ways of measuring arterial stiffness,[2] tends to be higher in patients with cardiovascular risk factors such as hypertension, diabetes mellitus,[3,4] and end stage renal disease.[5] As arterial stiffness reflects systemic atherosclerosis, more recent studies have discovered its correlations with cerebrovascular disorders as well. Prior research has found that baPWV is higher in acute cerebral infarction patients compared to control.[3,6] Other investigators found that higher PWV led to poorer functional outcomes after discharge in ischemic stroke patients.[7,8]

Likewise, ankle-brachial index (ABI), another noninvasive marker of peripheral artery atherosclerosis used to identify the presence of peripheral artery disease. It is a predictor of occurrence of ischemic stroke in general

population.[9] Previous studies have shown that low ABI is related with increased cardiovascular risk and poor functional outcome in stroke patients.[10,11]

Aortic atheroma (AA), another known risk factor for coronary artery disease,[12] is also considered as a risk for occurrence and recurrence of acute ischemic stroke.[13] AA is known to be associated with both large cerebral artery atherosclerosis[14-16] and small vessel disease in the brain.[17] Presence and nature of AA may also be associated with functional outcomes in ischemic stroke patients. One study stated that thicker aortic arch atheroma is associated with poor functional outcome in ischemic stroke patients.[18] However, to the best of our knowledge, the combined effect of AA with peripheral artery disease on post-stroke outcomes has not been thoroughly investigated.

We aim to analyze the association between indicators of peripheral atherosclerosis and the long-term outcomes of ischemic stroke patients including the occurrence of major adverse cardiac events (MACE). We also investigated whether patients with AA combined with high arterial stiffness or low ABI have poorer functional outcome and higher cardiovascular risk after stroke.

II. MATERIALS AND METHODS

1. Patients and evaluation

Subjects of this study were selected from acute ischemic stroke patients registered to the Yonsei stroke Registry who have admitted to Severance hospital from January 2012 to December 2018. All patients underwent extensive evaluation to determine stroke etiology including brain magnetic resonance imaging (MRI) and angiography (MRA), transthoracic and transesophageal echocardiography (TEE), baPWV measurement, and ECG monitoring. Stroke subtypes were classified during weekly conferences under the consensus of stroke neurologists according to TOAST classification.[19] We excluded TIA patients with no definite lesion on brain image studies. For this

study, we included the patients who have undergone both TEE and ABI, baPWV measurements.

2. Measurement of baPWV and ABI

baPWV was measured in a supine position using an automated device (VP-1000 or VP-1000 Plus; Colin Co. Ltd, Komaki, Japan) that has been verified in prior studies.[20,21] The device measures bilateral brachial and posterior tibial arterial pulse waveforms using oscillometric methods. PWV was calculated as transmission distance divided by transmission time. Detailed methods of PWV measurements are described elsewhere.[22] The higher value of the right or left baPWV was used in the analyses.

ABI was defined as the ratio of systolic blood pressure in the ankle (posterior tibial or dorsalis pedis artery) and the higher value between the two brachial arteries on either side. The lower value of the two ABI measurements was used in the analyses.

3. Measurement of aortic atheroma

AA was examined via TEE in available patients. TEE was performed during admission period in order to investigate the cause of ischemic stroke. Patients with unstable vital signs, altered mental status, intubated patients and patients without proper consents were not underwent TEE. Patients received local pharyngeal anesthesia with 10% topical lidocaine before undergoing TEE. A commercial TEE machine equipped with a 5 MHz transducer was used to evaluate aortic atherosclerosis. After examining for intracardiac mass which can act as potential cardioembolic source, the transducer was placed to examine for the presence of atheroma between the angles between 0 and 90 degrees in all segments of the aorta including the ascending, descending aorta, and the aortic arch. TEE images were acquired through transgastric, midesophageal and basal views. Thickness of AA was measured on a still image as a sum of aortic intima

and media. When multiple atheromas were found in the same area of the aorta, maximal thickness in each segment was used in the analysis. AA was classified as complex and simple aortic plaques according to their location and thickness.

4. Risk factors and clinical variables

During admission, all patients were thoroughly reviewed for past medical history and vascular risk factors including age, sex, smoking history, medical history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, peripheral artery disease, and previous ischemic stroke. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) score on admission and before discharge, respectively.

5. Follow-up and outcome measures

The primary outcomes of this study were functional state at 3 months after stroke onset, depicted by modified Rankin Scale (mRS) and occurrence of major adverse cardiac event (MACE). MACE was defined as acute coronary syndrome, hospitalization due to heart failure, stroke and all-cause mortality after stroke onset. We regularly kept track of functional state and occurrence of post-stroke MACE after discharge through direct interview by a clinician on regular outpatients clinic visit or a telephone interview by a research nurse. Follow up was conducted at first 3 month and every year. Patients with a 3-month mRS greater than 2 were classified as having a poor functional outcome. Patients who have not experienced MACE until December 31, 2019 were censored. Patients whose follow-up was lost were censored at the last follow-up date.

6. Statistical analysis

Patients were divided into four groups according to the combination baPWV

cutoff value and the presence of AA or the combination of ABI cutoff value and the presence of AA, respectively. Statistical analyses were performed using SPSS for Windows (version 25, SPSS, Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations or medians (interquartile ranges [IQR]). Categorical variables were described as numbers (%). A receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value of baPWV with the highest Youden index. Medcalc software (version 19.6, MedCalc Software Ltd, Ostend, Belgium) was used to analyze receiver operating characteristics (ROC) curve. Student's t-test and Mann-Whitney test was used to compare the means of continuous variables between groups. Chi-square test was used to analyze the intergroup differences in the ratio of patients with poor functional outcome. We analyzed the intergroup differences in the ratio of occurrence of MACE using Kaplan-Meier survival analysis. On multivariate analysis, logistic regression was used to identify the risk factors of poor functional outcome. Cox regression analysis was used to identify the risk factors of MACE. All p-values were 2-tailed, and the results of the analyses were considered significant when $p < 0.05$.

III. RESULTS

1. Patient enrollment

A total of 4969 patients with acute ischemic stroke were registered to Yonsei Stroke Registry during the study period. Exclusion criteria were no TEE assessment (n=1917); tissue-based TIA (n=160); no information on 3-month mRS (n=113); and no baPWV measurement (n=327). After excluding 600 patients according to these exclusion criteria, a total of 2452 patients were finally included in the study.

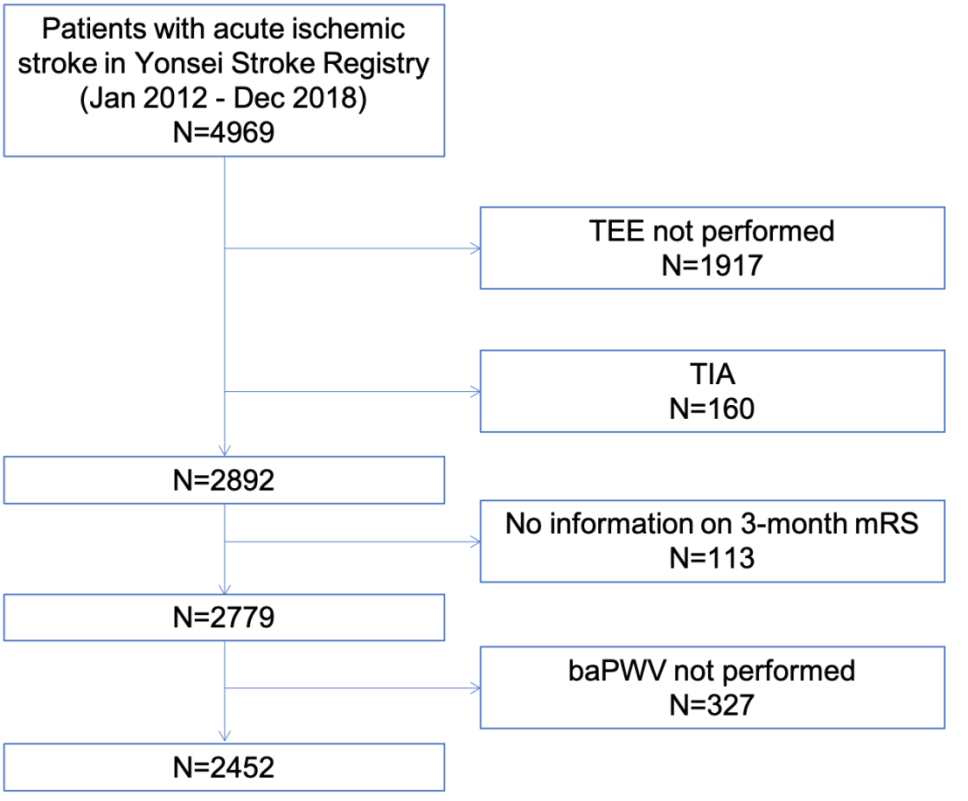


Fig. 1. Flow chart of inclusion and exclusion criteria of the study. baPWV stands for brachial-ankle pulse wave velocity; and TIA, transient ischemic attack.

2. Baseline characteristics

Table 1 shows the demographic characteristics of the patients enrolled in the study. The mean age of the studied patients was 64.53±13.51, where 1504 (61.3%) were male patients. The median value of baPWV was 19.28 (IQR 16.02-22.93), and the median value of ABI was 1.10 (IQR 1.02-1.16). Poor functional outcome at 3-months was observed in 574 (23.4%) patients. They showed significantly higher baPWV (21.37 [IQR 17.90-25.33] vs. 18.62 [15.67-22.33], $p<0.001$] and lower ABI (1.09 [1.01-1.15] vs. 1.10 [1.03-1.16], $p=0.003$) than those with good functional outcome. The 1678 (68.4%) patients with AA had lower ABI (1.09 [1.01-1.16] vs. 1.11 [1.05-1.16], $p<0.001$) and higher baPWV (20.14 [17.13-23.85] vs. 16.78 [14.23-20.67], $p<0.001$) than the 774 patients without AA.

Table 1. Demographics and risk factors of the study population

Variables	**Study Patients (n=2452)**
Male sex, N (%)	1504 (61.3)
Age, y	64.53±13.51
NIHSS at admission	2 (1-5)
Stroke subtype	
Large artery atherosclerosis	395 (16.1)
Lacunar infarction	197 (8.0)
Cardioembolism	735 (29.9)
Undetermined	1039 (42.3)
Other determined causes	86 (3.5)
Risk factors	
Hypertension	1794 (73.1)
Diabetes mellitus	762 (31.0)
Dyslipidemia	462 (18.8)
Atrial fibrillation	450 (18.3)
Congestive heart failure	62 (2.5)
Peripheral artery disease	13 (0.5)
Coronary artery disease	782 (31.9)
Previous stroke history	393 (16.0)
Current smoker	559 (22.8)
Aortic atheroma	1678 (68.4)
ABI	1.10 (1.02-1.16)
Pulse wave velocity, m/s	19.28 (16.02-22.93)

3. Analysis on functional outcome

The optimal cutoff value of maximal baPWV was >20.33 m/s according to the ROC curve analysis. Univariate analysis showed that older age, female sex, history of hypertension, diabetes mellitus, atrial fibrillation, current non-smoker, higher NIHSS score at admission, greater baPWV, lower ABI and the presence of AA were significantly associated with poor functional outcome at 3 months.

In the multivariate logistic regression analysis, after including age, sex and variables that showed significance (P<0.05) on the univariate analysis (hypertension, diabetes mellitus, atrial fibrillation, current smoking and initial NIHSS on admission) as covariates, only baPWV remained an independent predictor of poor functional outcome. Patients with baPWV greater than the cutoff value more frequently had poor functional outcome (adjusted odds ratio [OR], 2.14; 95% CI, 1.69-2.71) than their counterparts, while ABI and AA lost significance in predicting poor functional outcome in the multivariate analysis (Table 2).

Table 2. Univariate and multivariate logistic regression analysis of atherosclerosis markers on poor functional outcome

	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
AA (+)	1.53 (1.23-1.89)	<0.001	1.09 (0.85-1.41)	0.495
ABI<0.9	1.70 (1.23-2.34)	0.001	1.15 (0.79-1.67)	0.465
baPWV>20.33 m/s	2.37 (1.96-2.87)	<0.001	2.14 (1.69-2.71)	<0.001

* Adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking status and NIHSS on admission

The patients were divided into 4 groups by the cutoff value of ABI and the presence of AA or the cutoff value of baPWV and the presence of AA, respectively. Chi-square analysis between the four groups categorized by the cutoff value of ABI and the presence of AA showed that patients with AA (+), ABI≥0.9 (n=1515) and patients with AA (+), ABI<0.9 (n=163) were significantly associated with having a poor functional outcome than those with AA (-), ABI≥0.9 (n=750). On the other hand, patients with AA (-), ABI<0.9 (n=24) did not show statistically significant difference compared to patients with AA (-), ABI≥0.9. When including the combination of AA and ABI in the multivariate analysis, having AA together with low ABI was no longer a significant risk factor of poor functional outcome (Table 3).

Table 3. Combination analysis of AA and ABI using univariate and multivariate logistic regression analysis on poor functional outcome

	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Patient group				
AA (-), ABI≥0.9	Ref.	Ref.	Ref.	Ref.
AA (-), ABI<0.9	1.17 (0.43-3.18)	0.464**	0.92 (0.29-2.88)	0.882
AA (+), ABI≥0.9	1.45 (1.17-1.81)	0.001	1.08 (0.83-1.40)	0.582
AA (+), ABI<0.9	2.39 (1.65-3.46)	<0.001	1.26 (0.81-1.97)	0.309

* Adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking status and NIHSS on admission.

** P value was derived from Fisher's exact test result

Likewise, chi-square analysis between the four groups categorized by the cutoff value of baPWV and the presence of AA showed that patients with AA (-), baPWV>20.33 m/s (n=210), patients with AA (+), baPWV≤20.33 m/s (n=860), and patients with AA (+), baPWV>20.33 m/s (n=818) were significantly associated with having a poor functional outcome compared to the patients with AA (-), baPWV≤20.33 m/s (n=564). When including the combination of AA and ABI in the multivariate analysis, patients with high baPWV were more prone to have poor functional outcome regardless of the presence of AA, compared to patients with no AA and low baPWV (Table 4).

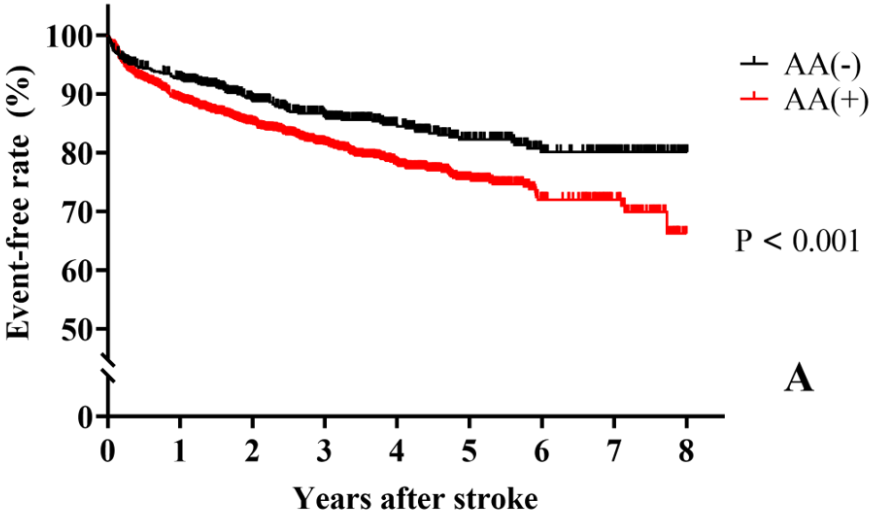
Table 4. Combination analysis of AA and baPWV using univariate and multivariate logistic regression analysis on poor functional outcome

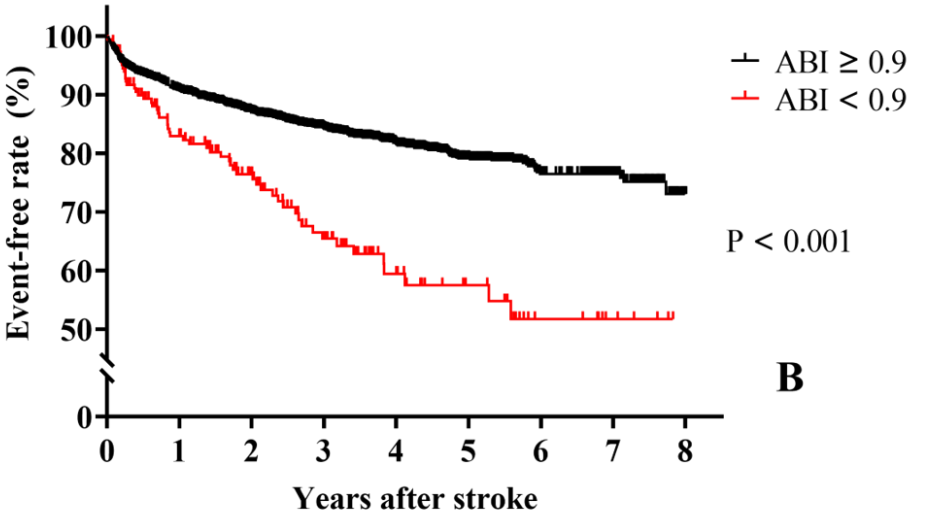
	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Patient group				
AA (-), low PWV	Ref.	Ref.	Ref.	Ref.
AA (-), high PWV	2.50 (1.71-3.65)	<0.001	2.55 (1.64-3.95)	<0.001
AA (+), low PWV	1.41 (1.04-1.92)	0.042	1.19 (0.84-1.68)	0.322
AA (+),high PWV	2.97 (2.25-3.92)	<0.001	2.40 (1.67-3.46)	<0.001

* Adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, current smoking status and NIHSS on admission

4. Analysis on MACE

The mean follow-up period was 3.10±2.14 years. There were 432 (17.6%) MACE occurred during follow-up. Figure 2 shows the Kaplan-Meier curves for MACE according to AA, ABI<0.9, and baPWV>20.33 m/s, respectively. These curves showed that patients with AA (+), ABI<0.9, and baPWV>20.33 m/s had higher risk of MACE occurrence than their counterparts.





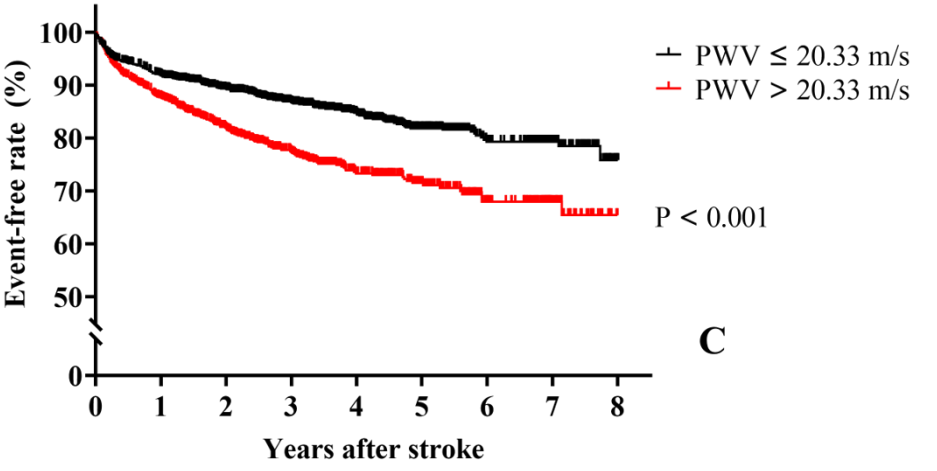


Fig. 2. Kaplan-Meier curves of MACE occurrence depending on each markers of atherosclerosis. Patients with AA were at high risk of MACE occurrence than those without AA (A). Likewise, patients with lower ABI (B) and higher baPWV (C) had higher risk of MACE occurrence than their counterparts.

Univariate Cox regression analysis showed that the incidence of MACE was significantly higher in patients with AA (relative hazards ratio [HR], 1.47; 95% confidence interval [CI], 1.18-1.82), ABI<0.9 (relative HR, 2.21; 95% CI, 1.67-2.93), and baPWV>20.33 m/s (relative HR, 1.71; 95% CI, 1.42-2.07), compared to their counterparts, respectively (Table 5, Fig. 2). To determine the factors that can be inserted as covariates on the multivariate analysis, we performed multivariate Cox regression analysis without AA, baPWV and ABI, which showed that age, sex, history of diabetes mellitus, congestive heart failure, stroke and the NIHSS on admission were significant factors associated with MACE occurrence. These factors were included as covariates on the multivariate analysis. When preforming multivariate Cox regression analysis adjusting for covariates, baPWV>20.33 m/s and ABI<0.9 remained as significant risk factors of MACE occurrence.

Table 5. Univariate and multivariate Cox regression analysis of atherosclerosis markers on MACE occurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
AA (+)	1.47 (1.18-1.82)	0.001	1.06 (0.85-1.34)	0.598
ABI<0.9	2.21 (1.67-2.93)	<0.001	1.62 (1.21-2.16)	0.001
baPWV>20.33 m/s	1.71 (1.42-2.07)	<0.001	1.34 (1.09-1.65)	0.005

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

Comparison of MACE incidence among the four groups categorized by the combination of AA and ABI cutoff value showed that patients with AA (+), ABI<0.9 had higher risk for occurrence of MACE compared to those with AA and ABI<0.9 (relative HR, 2.96; 95% CI, 2.12-4.14) (Table 6, Fig. 3A). When including the combination of AA and ABI in the multivariate analysis, having AA together with ABI<0.9 remained as a significant risk factor.

Table 6. Combination analysis of AA and ABI using univariate and multivariate Cox regression analysis on MACE occurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), ABI≥0.9	Ref.	Ref.	Ref.	Ref.
AA (-), ABI<0.9	1.54 (0.63-3.76)	0.349	1.17 (0.48-2.89)	0.728
AA (+), ABI≥0.9	1.36 (1.09-1.71)	0.007	1.02 (0.80-1.29)	0.878
AA (+), ABI<0.9	2.96 (2.12-4.14)	<0.001	1.71 (1.20-2.45)	0.003

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

Similarly, comparison between the four groups categorized by a combination of AA and baPWV cutoff value showed that patients with AA and high baPWV had higher risk of MACE than those without AA and low baPWV (relative HR, 2.21; 95% CI, 1.66-2.92) (Table 7, Fig. 3B). When including the combination of AA and baPWV in the multivariate analysis, having AA together with baPWV>20.33 m/s remained significant.

Table 7. Combination analysis of AA and baPWV using univariate and multivariate Cox regression analysis on MACE occurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), low PWV	Ref.	Ref.	Ref.	Ref.
AA (-), high PWV	1.82 (1.24-2.67)	0.002	1.41 (0.95-2.10)	0.090
AA (+), low PWV	1.40 (1.05-1.87)	0.021	1.08 (0.80-1.46)	0.628
AA (+),high PWV	2.21 (1.68-2.92)	<0.001	1.42 (1.04-1.95)	0.029

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

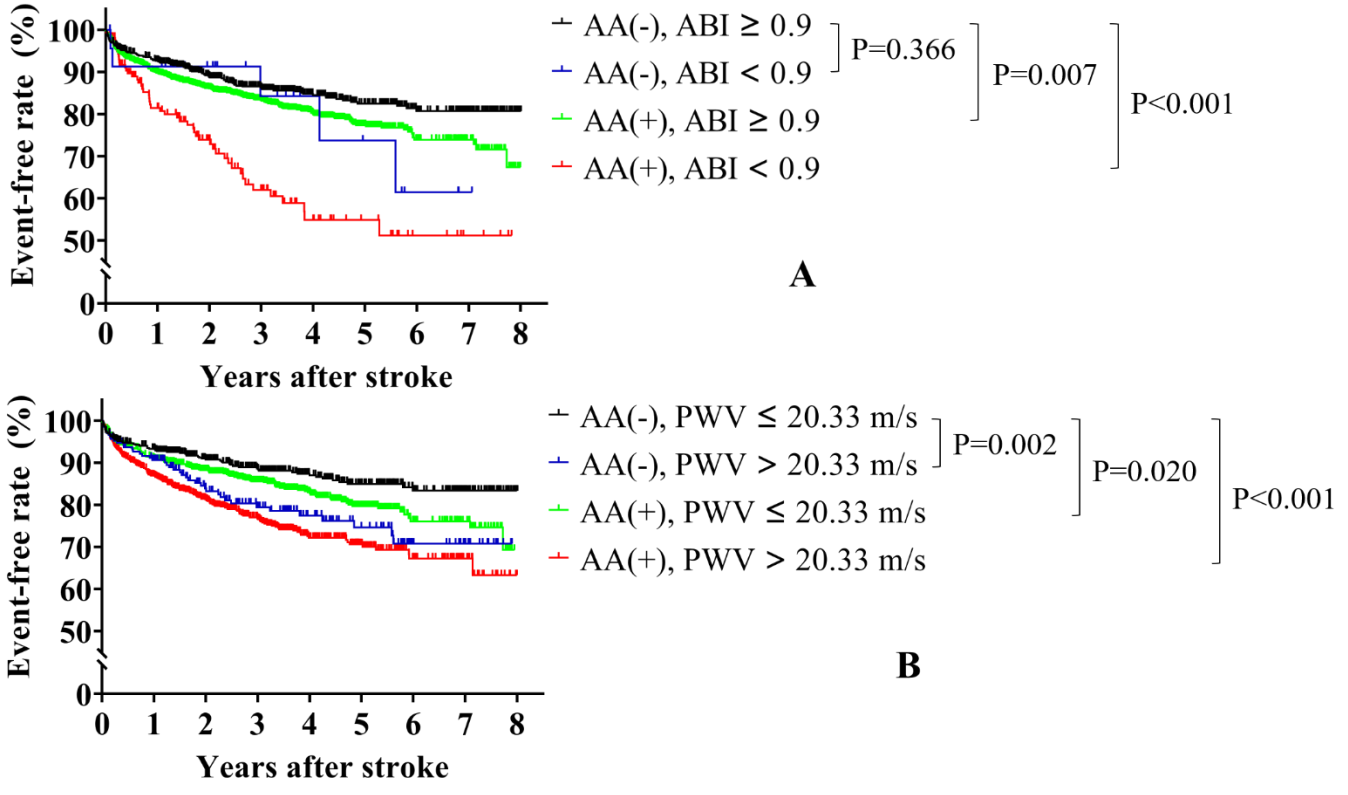


Fig. 3. Kaplan-Meier curves of MACE occurrence in patient groups categorized by combinations of AA, ABI (A) and AA, baPWV (B).

5. Analysis on ischemic stroke recurrence

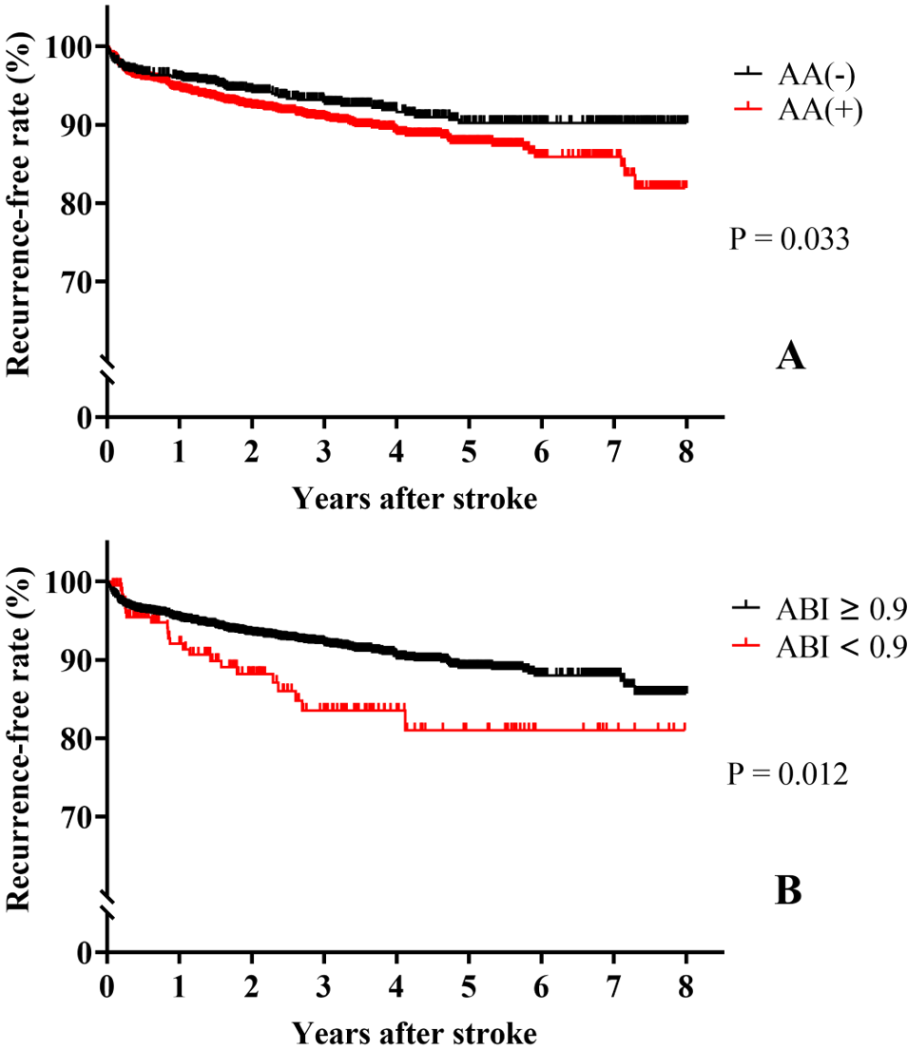
Additionally, we compared ischemic stroke recurrence and all-cause mortality between patients with and without AA and peripheral artery atherosclerosis to investigate how these factors applied as risk factors of MACE. This was done by performing Kaplan-Meier analysis and multivariate Cox regression analysis in the same manner as done in the analysis of MACE occurrence. Identical variables were inserted as covariates on multivariate analyses.

While patients with AA (relative HR, 1.39; 95% CI, 1.03-1.88), ABI<0.9 (relative HR, 1.73; 95% CI, 1.12-2.67), and baPWV>20.33 m/s (relative HR, 1.73; 95% CI, 1.32-2.26) more frequently had ischemic stroke recurrence on univariate analysis (Fig. 4), only baPWV>20.33 m/s remained significant after adjusting for covariates (Table 8).

Table 8. Univariate and multivariate Cox regression analysis of atherosclerosis markers on ischemic stroke recurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
AA (+)	1.39 (1.03-1.88)	0.033	1.13 (0.82-1.57)	0.446
ABI<0.9	1.73 (1.12-2.67)	0.013	1.38 (0.89-2.16)	0.153
baPWV>20.33 m/s	1.73 (1.32-2.26)	<0.001	1.54 (1.15-2.07)	0.004

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission



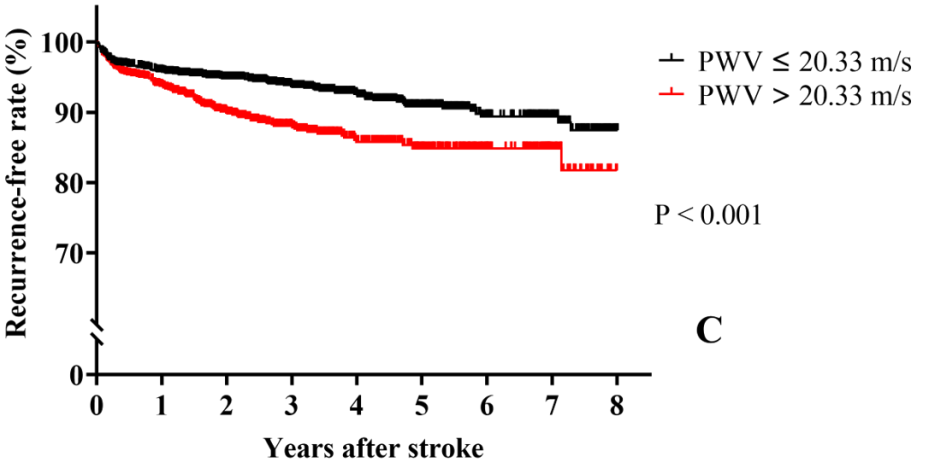


Fig. 4. Kaplan-Meier curves of ischemic stroke recurrence depending on each markers of atherosclerosis. Patients with AA were at high risk of ischemic stroke recurrence than those without AA (A). Likewise, patients with lower ABI (B) and higher baPWV (C) had higher risk of ischemic stroke recurrence than their counterparts.

Comparison between the four groups categorized by the combination of AA and peripheral artery atherosclerosis showed that ischemic stroke recurrence was higher in patients with AA and ABI<0.9 compared to those with no atheroma and ABI≥0.9 (relative HR, 2.33; 95% CI, 1.42-3.82) (Table 9, Fig. 5A). Adjusting for covariates showed that having AA and baPWV>20.33 m/s remained as a significant risk factor of ischemic stroke recurrence.

Table 9. Combination analysis of AA and ABI using univariate and multivariate Cox regression analysis on ischemic stroke recurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), ABI≥0.9	Ref.	Ref.	Ref.	Ref.
AA (-), ABI<0.9	0.59 (0.08-4.22)	0.595	0.47 (0.07-3.41)	0.455
AA (+), ABI≥0.9	1.29 (0.94-1.76)	0.112	1.07 (0.77-1.49)	0.677
AA (+), ABI<0.9	2.33 (1.42-3.82)	0.001	1.62 (0.96-2.75)	0.072

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

Similarly, patients with AA and baPWV>20.33 m/s had higher ischemic stroke recurrence compared to those with no AA and baPWV≤20.33 m/s (relative HR, 2.00; 95% CI, 1.38-2.91) (Table 10, Fig. 5B). On multivariate analysis adjusting for covariates, having AA and ABI<0.9 lost its significance.

Table 10. Combination analysis of AA and baPWV using univariate and multivariate Cox regression analysis on ischemic stroke recurrence

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), low PWV	Ref.	Ref.	Ref.	Ref.
AA (-), high PWV	1.36 (0.78-2.38)	0.280	1.20 (0.67-2.15)	0.534
AA (+), low PWV	1.13 (0.76-1.68)	0.558	0.97 (0.64-1.47)	0.881
AA (+),high PWV	2.00 (1.38-2.91)	<0.001	1.60 (1.04-2.46)	0.032

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

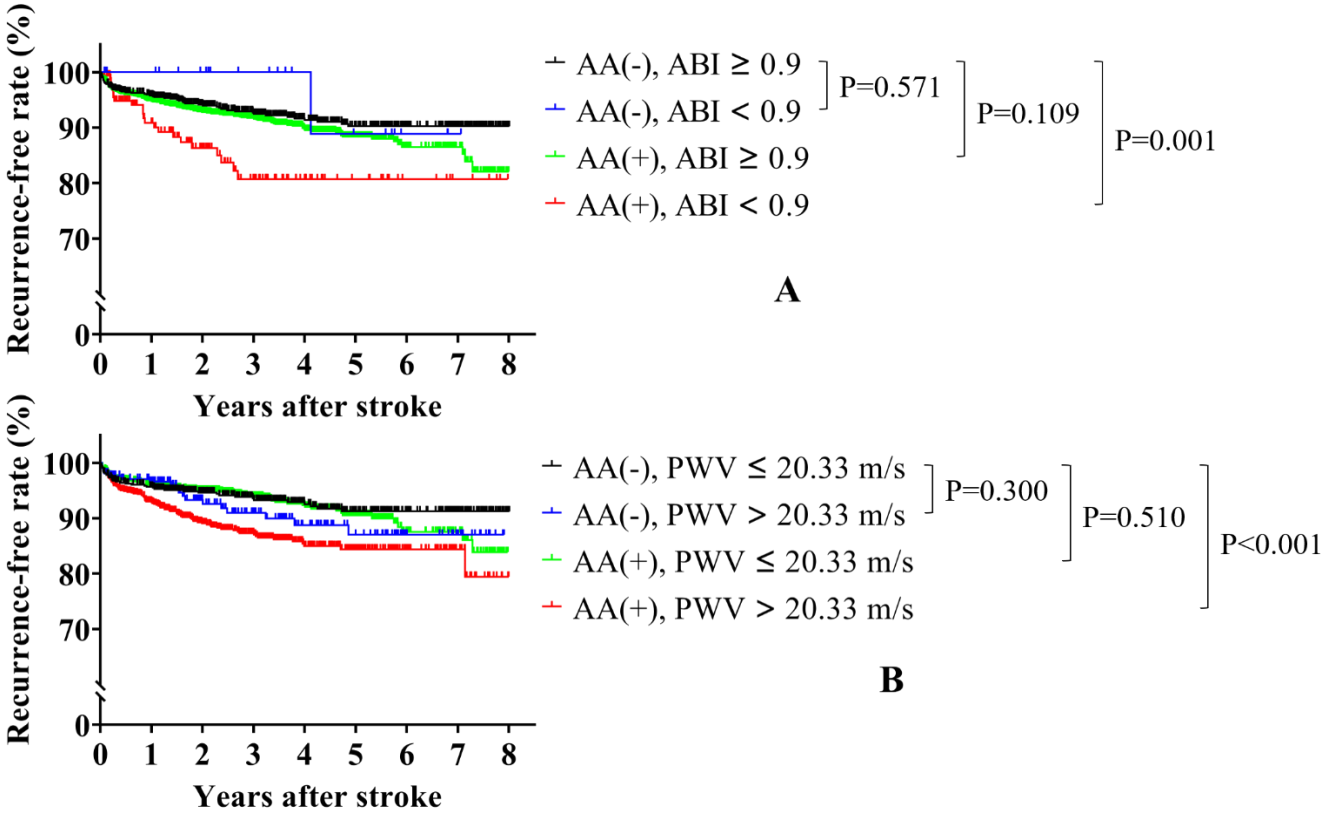


Fig. 5. Kaplan-Meier curves of ischecmic stroke recurrence in patient groups categorized by combinations of AA, ABI (A) and AA, baPWV (B).

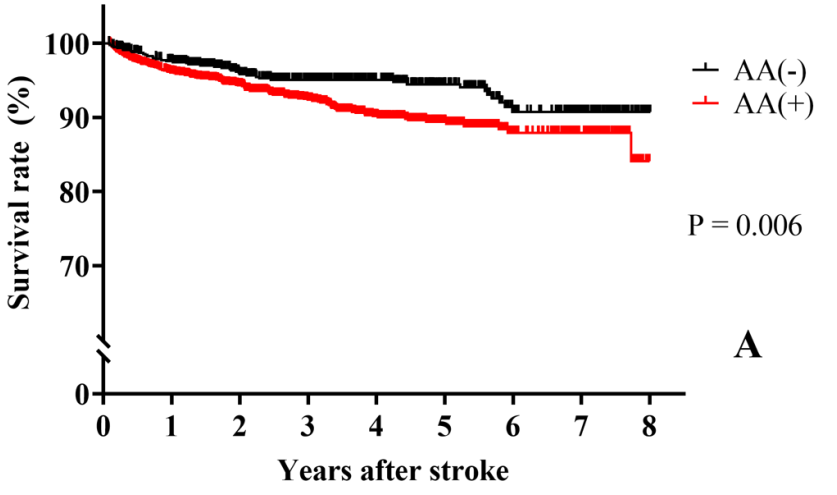
6. Analysis on all-cause mortality

Repeating the same process on all-cause mortality showed that patients with AA (relative HR, 1.62; 95% CI, 1.15-2.30), ABI<0.9 (relative HR, 2.94; 95% CI, 1.97-4.39), and baPWV>20.33 m/s (relative HR, 2.19; 95% CI, 1.62-2.95) had lower survival on univariate analysis (Table 11, Fig. 6), where only ABI<0.9 remained as a significant risk factor after adjusting for covariates.

Table 11. Univariate and multivariate Cox regression analysis of atherosclerosis markers on survival

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
AA (+)	1.62 (1.15-2.30)	0.006	0.91 (0.63-1.32)	0.627
ABI<0.9	2.94 (1.97-4.39)	<0.001	1.85 (1.23-2.78)	0.003
baPWV>20.33 m/s	2.19 (1.62-2.95)	<0.001	1.37 (0.99-1.88)	0.058

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission



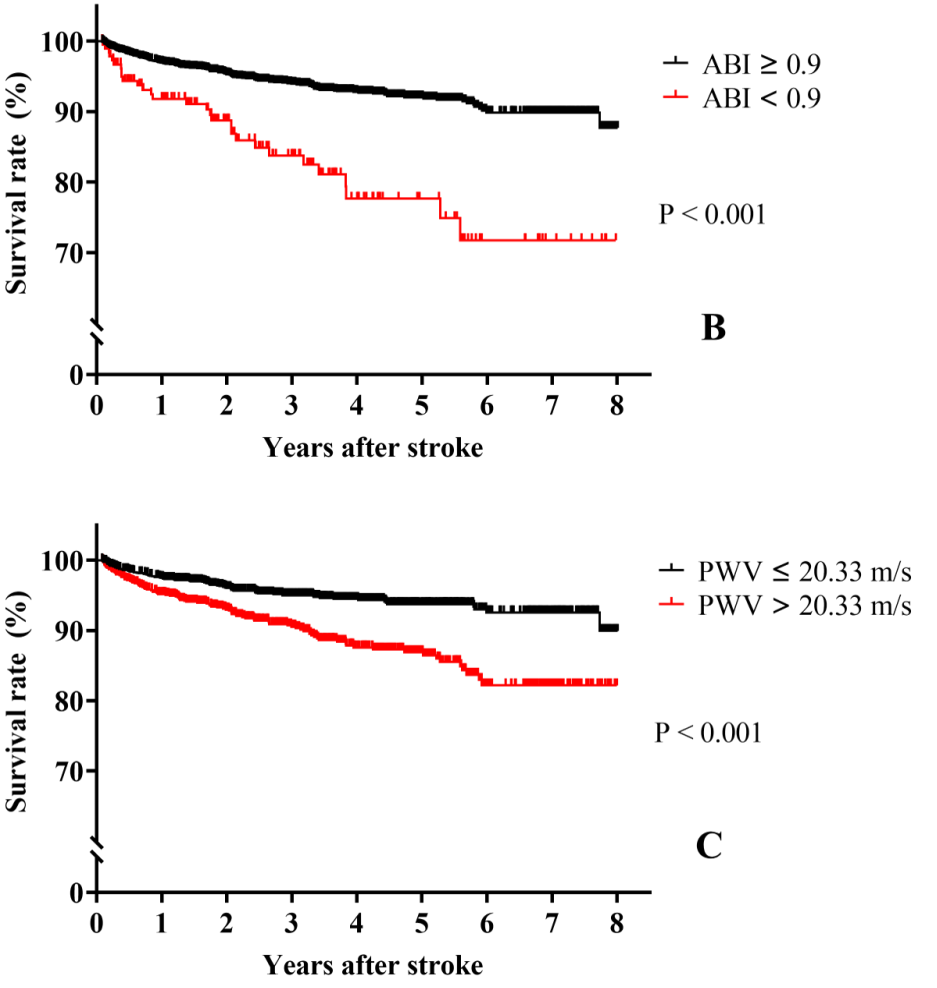


Fig. 6. Kaplan-Meier curves of survival depending on each markers of atherosclerosis. Patients with AA were at high risk of all-cause mortality than those without AA (A). Likewise, patients with lower ABI (B) and higher baPWV (C) had higher risk of death than their counterparts.

Comparison between the four groups categorized by the combinations of AA and ABI showed that patients with AA and ABI<0.9 had lower survival than patients with no AA and ABI≥0.9 (relative HR, 4.11; 95% CI, 2.50-6.76) (Table 12, Fig. 7A). Multivariate analysis showed that these results were not significant after adjusting for covariates, although patients with AA (+), ABI<0.9 had a tendency for poorer survival compared with patients with AA (-), ABI≥0.9 (relative HR, 1.63; 95% CI, 0.96-2.77).

Table 12. Combination analysis of AA and ABI using univariate and multivariate Cox regression analysis on survival

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), ABI≥0.9	Ref.	Ref.	Ref.	Ref.
AA (-), ABI<0.9	2.59 (0.80-8.40)	0.112	1.95 (0.60-6.35)	0.270
AA (+), ABI≥0.9	1.49 (1.03-2.14)	0.035	0.88 (0.60-1.29)	0.501
AA (+), ABI<0.9	4.11 (2.50-6.76)	<0.001	1.63 (0.96-2.77)	0.068

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

Likewise, patients with AA and baPWV>20.33 m/s had lower survival than those with no AA and baPWV ≤20.33 m/s (relative HR, 3.23; 95% CI, 2.00-5.23) (Table 13, Fig. 7B). None of these results were significant after adjusting for covariates in the multivariate analysis.

Table 13. Combination analysis of AA and baPWV using univariate and multivariate Cox regression analysis on survival

	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Patient group				
AA (-), low PWV	Ref.	Ref.	Ref.	Ref.
AA (-), high PWV	2.93 (1.60-5.37)	<0.001	1.74 (0.93-3.25)	0.085
AA (+), low PWV	1.76 (1.06-2.92)	0.029	1.05 (0.62-1.77)	0.851
AA (+), high PWV	3.23 (2.00-5.23)	<0.001	1.34 (0.79-2.28)	0.276

* Adjusted for age, sex, history of diabetes mellitus, congestive heart failure, previous stroke and NIHSS on admission

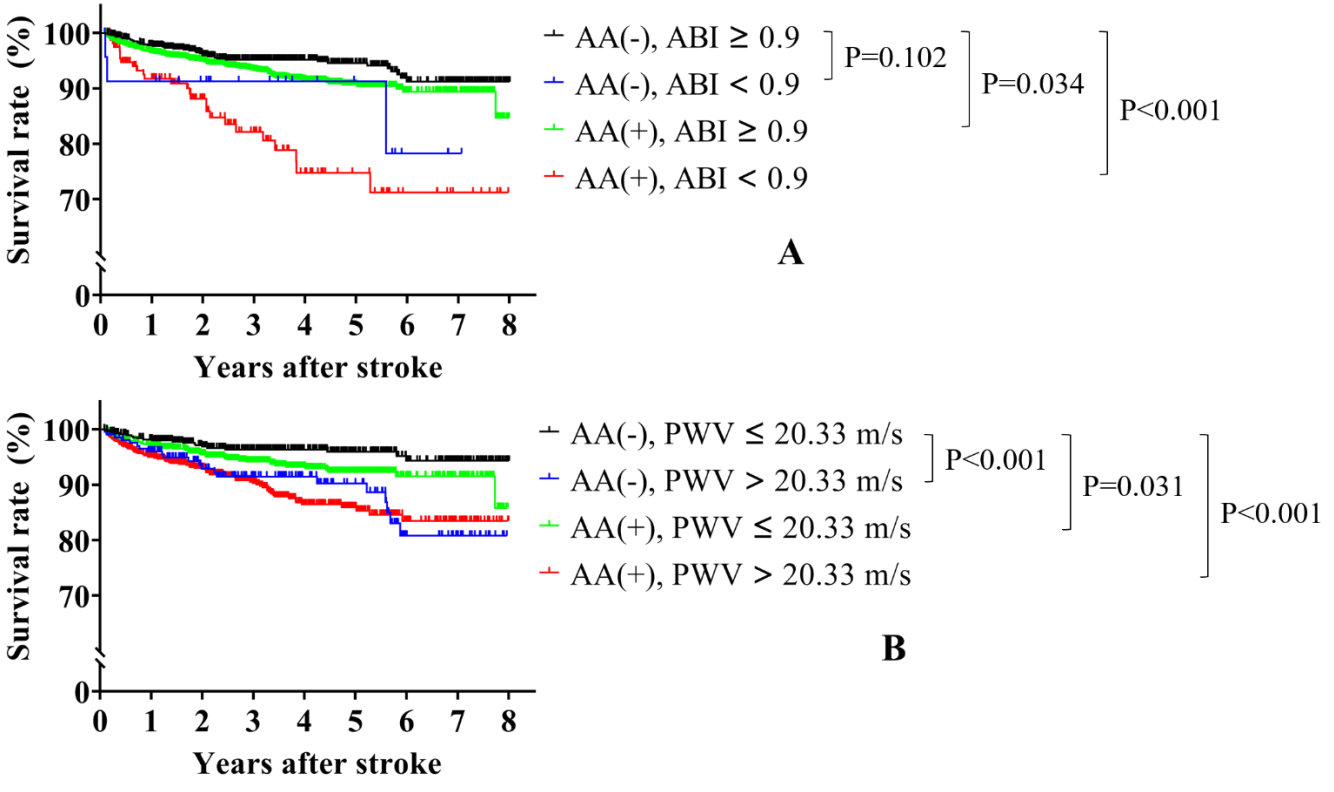


Fig. 7. Kaplan-Meier curves of survival in patient groups categorized by combinations of AA, ABI (A) and AA, baPWV (B).

IV. DISCUSSION

In this study, we investigated how AA and peripheral artery atherosclerosis affect the functional outcome and long-term cardiovascular risk in ischemic stroke patients. We found that patients with both AA and high baPWV are associated with poorer functional outcome. We also found that having both AA and peripheral artery atherosclerosis (i.e. ABI<0.9 or baPWV>20.33 m/s) was an independent risk factor of MACE. Having AA and high baPWV was associated with higher ischemic stroke recurrence, which may account for the higher occurrence of MACE.

Aortic atherosclerosis has been shown to be associated with cardiovascular and cerebrovascular risk. Atherosclerotic plaques >4 mm thick in the aortic arch were significant predictors of recurrent ischemic stroke (HR 3.8, 95% CI 1.8-7.8) and other vascular events (HR 3.5, 95% CI 2.1-5.9).[24] Gu et al. investigated the relationship between thoracic aortic atherosclerosis and coronary artery disease. They found that thoracic aortic plaques were associated with increasing severity of coronary artery disease regardless of stroke history.[25] Fujimoto et al. showed that AA that was ≥4.0 mm in thickness can predict the recurrence of ischemic stroke.[26] This association may be explained by findings of another study that showed the association between aortic atherosclerosis and hypercoagulability.[26] The Aortic Plaque and Risk of Ischemic Stroke (APRIS) study also found that coexistence of hypercoagulability and large aortic plaques is associated with greater risk of recurrent stroke and mortality.[27]

We found that the presence of AA was significantly associated with poor outcome and MACE occurrence in univariate analysis. However, unexpectedly our multivariate analysis on the relationship between AA and MACE occurrence did not show any significant correlation after adjusting for other confounding factors. It is not clear why the association between AA and MACE occurrence was not found in our study population. We assumed that there is an unrecognized factor among ischemic stroke patients with AA, which may be a

major confounder in vascular events or deaths.

We also found that patients who have atherosclerosis in both the aorta and peripheral artery disease were at higher risk of MACE occurrence compared to patients with neither AA nor peripheral artery disease. In Reduction of Atherothrombosis for Continued Health (REACH) Registry, polyvascular disease was defined as having atherothrombosis in 2 or 3 arterial beds (coronary, peripheral, cerebrovascular arteries). The risk of cardiovascular death, myocardial infarction or stroke was 25% within 4 years in patients with polyvascular disease. Hazard ratio of event occurrence in patients with polyvascular disease was 1.99 compared to those without.[28] We previously reported that patients with AA were associated with intracranial atherosclerosis.[15] Although the definition of polyvascular disease is different, one can assume that atherosclerosis in multiple vascular beds have increased risk of future vascular events or deaths.

The present study is novel in that we have additionally explored the combined effects of the presence of AA with peripheral artery disease (high baPWV or low ABI) on post stroke functional outcomes and risk of MACE. We categorized the patients into 4 groups by a combination of atherosclerosis in the aorta and peripheral arteries. Comparison among these 4 groups showed that patients with atherosclerosis on both the aorta and peripheral vessels had worst functional outcome and higher risk of MACE occurrence. Especially, on the multivariate Cox regression analysis comparing the MACE occurrence, the group with atherosclerosis in both the aorta and peripheral arteries was the only group among the 4 groups that was independently associated with higher risk of future MACE occurrence, compared with the group with no atherosclerosis in either the aorta and peripheral arteries.

One of the primary outcomes of this study was the functional outcome at 3 months. Our univariate analysis on the association between the presence of AA and poor functional outcomes yielded significant results but was no longer

significant after adjustments for covariates including vascular risk factors and the NIHSS on admission, inferring that the association of AA and poor post-stroke functional outcome may be attributed to other vascular risk factors and initial severity of stroke. There also have been a study on the association of AA with stroke prognosis. Abe et al. showed that in cerebral infarction patients of unknown origin, aortic arch plaques thicker than 4 mm was an independent predictor of poor functional outcome at 90 days after stroke onset[18].

However, there is a controversy on the association between AA and ischemic stroke outcomes. A previous study had stated that thicker aortic arch plaques with mobile component are associated with the number of multiple infarctions including multiple vascular territories.[29] Our previous study showed that patients who have AA $\geq$4mm frequently had multiple small cortical lesions or a single subcortical lesion.[30] In another study, we previously showed that ischemic stroke patients with AA without any other potential cardiac source of embolism had smaller lesion size with minor symptoms compared to those with potential cardiac source of embolism.[31] Also, in a study on ischemic stroke patients with AA, the investigators found that although the presence of AA was associated with higher NIHSS at presentation, it was not associated with poor outcome during follow-up.[32] Therefore, the lesion patterns, stroke severities and functional outcomes of patients with AA are different among studies.

Still, there have been studies that give insight on how AA can affect post-stroke prognosis. Previous studies stated that atherosclerotic plaques in the descending aorta may also act as a source of aortogenic embolism through retrograde flow.[33,34] Multiple brain lesions may be associated with poor functional outcome, although further studies should elucidate the association between multiple brain lesions and long-term outcomes. Also, these findings suggest that AA of any locations can act as an embolic source, which may increase not only the risk of stroke recurrence but also myocardial infarction and other cardiovascular events. Especially, when atheroma of the descending

aorta is coexistent with high arterial stiffness, the stiff aorta may facilitate the embolization of the aortic plaque by higher retrograde flow during the diastolic phase, resulting in a higher risk of cardiovascular event and stroke recurrence, accounting for our study results.

Our study showed that baPWV>20.33 m/s was an independent risk factor of having a poor functional outcome at 3 months after stroke onset in the multivariate analysis. In addition, we found that baPWV>20.33 m/s was associated with future occurrence of MACE in ischemic stroke patients. BaPWV, as a marker of atherosclerosis of peripheral arteries, have been shown to be correlated with various vascular risk factors, coronary artery disease and ischemic stroke.[1,3,4,6,9] There have been studies elucidating how baPWV is related with post-stroke functional outcomes and cardiovascular risk. Lee et al. had shown that stroke patients with mRS≥3 had significantly higher baPWV values than those with mRS≤2.[7] A previous study conducted at our institute also showed that higher baPWV value is associated with high mRS.[8] As for long-term mortality, another study conducted by the same researchers showed that high baPWV was an independent predictor of vascular and all-cause death after stroke onset.[35]

There are several mechanisms that can explain the correlation between increased PWV and poor post-stroke outcomes. Patients with higher PWV have stiffer arteries, implying that underlying atherosclerosis in systemic and cerebral arteries in these patients is more severe. This can lead to increased post-stroke mortality and morbidity.[22,36] In addition, stiffened artery results in premature return of the reflected late-systolic waves, leading to higher pulse pressure.[37] This increase in pulse pressure had been shown to have bidirectional effect on the process of atherosclerosis.[38] It also results in arterial damage through stretch, necrosis, calcification, hypertrophy, fibrosis and remodeling of the vessel wall.[39,40] Increase in large arterial stiffness is also associated with structural alterations of small resistance arteries.[41] Increased arterial stiffness also leads to

end organ injury including the myocardium, coronary perfusion, kidney and brain.[40,42,43] The brain, being supplied by low resistance arteries, is especially susceptible to increased pulsatile pressure.[40] Patients with higher arterial stiffness also showed impaired microvascular reactivity to ischemia and lower ability to form collateral blood flow.[44-46] These factors may increase cerebral damage through ischemia during acute ischemic stroke and result in poorer functional outcomes and higher mortality.

Previous studies have shown that low ABI is also associated with higher rates of concomitant coronary and cerebrovascular disease, cardiovascular risk factors, thus an indicator of generalized atherosclerosis.[47] Meta-analysis including studies of the general population showed that low ABI acts as an independent risk factor of all-cause mortality, cardiovascular mortality and major coronary events, compared with the Framingham Risk Score.[48] In a study focusing on the population of ischemic stroke patients, low ABI was associated with increased 5-year cardiovascular risk and mortality, which may be related to the increased global burden of atherosclerosis in low ABI patients.[11] Although there are some differences in the study population and primary outcomes, these results are largely consistent with our study results where we showed that ABI < 0.9 is associated with MACE.

Matsushima et al. had described how patients with ABI < 0.9 had higher OR of having poor functional outcome in patients with non-cardioembolic stroke.[10] Although cross analysis conducted in our study showed similar results, ABI < 0.9 was no longer significantly correlated with having poor functional outcomes after adjusting for significant risk factors. This difference may be attributed to the inclusion of cardioembolic stroke patients as well as non-cardioembolic stroke patients in our study.

We found that the presence of AA with high baPWV was associated with higher ischemic stroke recurrence, whereas the presence of AA with low ABI had a tendency of higher ischemic stroke recurrence without significance. For

all-cause mortality, the presence of AA with peripheral artery atherosclerosis was not a significant factor for survival. These findings infer that higher MACE occurrence in patients with both AA and peripheral artery atherosclerosis may be attributed to higher ischemic stroke recurrence.

Our study has some limitations. First, this is an observational study conducted in a single institution, mostly composed of Asian race. However, we enrolled the consecutive patients who underwent TEE, baPWV, and ABI measurements, and analysis was performed in a relatively large number of participants. Second, we did not exclude patients with other determined etiologies or undertermined etiologies although those subtypes may have uncertain influences on outcome. Third, we included patients with cardioembolic stroke. Because patients with cardioembolic stroke usually show worst outcome among stroke subtypes, we wanted to seek the exact influence of AA and peripheral artery disease in determined etiologies. Half of cardioembolic stroke is atrial fibrillation. There is a concern regarding the accuracy of ABI or baPWV measurements in patients with CE. To address this concern, a study evaluated the reliability of ABI measurements during atrial fibrillation. The researcher compared ABI values measured during atrial fibrillation and sinus rhythm for the same patients. The study concluded that the ABI could be considered accurate for the diagnosis of peripheral artery disease during atrial fibrilation.[49] Lastly, we did not include patients who have not undergone baPWV measurements or TEE studies, which may have caused selection bias.

V. CONCLUSION

We investigated the influence of peripheral artery disease on short and long-term outcome in acute ischemic stroke patients with AA. We found that peripheral artery atherosclerosis is a risk factor of poorer functional outcome and cardiovascular events in patients with AA. Higher cardiovascular risk in these patients could be attributed to higher ischemic stroke recurrence.

Our results support the previous studies in the aspect of arterial stiffness and ABI being predictors of poor functional outcome and cardiovascular risk factors in stroke patients. In addition, we found that patients with both peripheral and aortic atherosclerosis had poorer functional outcome and were more prone to have adverse cardiovascular events in long-term observation of stroke patients. Therefore, performing ABI and baPWV measurements may be helpful in predicting post-stroke prognosis in ischemic stroke patients with AA.

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ABSTRACT(IN KOREAN)

급성 뇌경색 환자에서 대동맥 죽상경화와 말초혈관질환이 예후에 미치는 영향

<지도교수 남효석>

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정재욱

대동맥 죽상경화는 급성 허혈성 뇌졸중의 발생과 재발의 위험 요인으로 알려져 있다. 발목-상완지수(ABI)와 상완-발목 맥파 속도(baPWV)는 비침습적으로 측정할 수 있는 말초 동맥의 동맥경화 지표로, 뇌경색 후 심혈관 위험 증가 및 기능 결과 저조와 상관관계가 있는 것으로 알려져 있다. 본 연구에서는 말초 동맥의 동맥경화와 대동맥의 동맥경화를 동시에 고려함으로써 예후 예측을 더 정확히 할 수 있는지 분석하였다. 우리는 경식도 심초음파 검사와 baPWV, ABI 측정을 모두 시행한 허혈성 뇌졸중 환자 2452명을 분석하였다. 퇴원 후 정기적 면담을 통해 대상 환자들의 수정된 랭킨 척도(modified Rankin Scale)와 급성 관상동맥증후군의 발생, 심부전으로 인한 입원, 출혈성 뇌졸중, 허혈성 뇌졸중의 재발, 모든 원인에 의한 사망 여부를 추적하여 기능 장애의 정도와 주요 심혈관 사건(MACE)의 발생 여부를 확인하였다. 환자들은 대동맥 죽상경화와 baPWV, 또는 대동맥 죽상경화와 ABI의 조합에 따라 4개 군으로 나뉘었다. 기능 장애와 MACE 발생의 그룹 간 차이를 분석하기 위해 카이-제곱 분석과 Kaplan-Meier 생존 분석을 사용하였으며, 다변량 로지스틱 회귀 분석 및 Cox 회귀 분석을 수행하여 교란 요인을 조정했다. 교차 분석 결과 대동맥 죽상경화가 있고 ABI<0.9인 환자들과 대동맥 죽상경화가 있고 baPWV>20.33 m/s인 환자들은 각각 대동맥 죽상경화가 없으며

ABI≥0.9인 환자들과 대동맥 죽상경화가 없고 baPWV≤20.33 m/s인 환자들에 비해 기능 결과가 좋지 않은 경향을 보였다. Kaplan-Meier 생존 분석 결과, 대동맥 죽상경화, ABI<0.9, baPWV>20.33 m/s인 환자가 각각 그렇지 않은 환자보다 MACE 발생 가능성이 더 높은 것으로 나타났다. 대동맥 동맥경화와 말초동맥 동맥경화의 조합에 따라 분류된 4개 환자군 간의 비교에서, 대동맥, 말초동맥 모두에 동맥경화가 있는 환자들은 대동맥, 말초동맥 모두에 동맥경화증이 없는 환자에 비해 MACE 발생 위험이 유의하게 높았다. 다변량 분석 시 대동맥, 말초동맥 모두에 동맥경화증이 있는 환자들은 4개 군 중에서 대동맥과 말초동맥 모두에서 동맥경화증이 없는 집단과 비교하여 MACE 발생 위험이 유의하게 높은 유일한 집단이었다. 본 연구에서는 대동맥 죽상경화와 말초동맥경화증의 조합이 급성 허혈성 뇌졸중 환자들의 기능 장애 및 심혈관 위험과 상관관계가 있음을 보여 주었다. 따라서, 대동맥 죽상경화가 있는 허혈성 뇌졸중 환자에서 ABI와 baPWV 측정하는 것이 환자의 장기 결과를 예측하는 데 도움이 될 수 있다.

핵심되는 말 : 맥파 속도, 급성 허혈성 뇌졸중, 대동맥 죽상경화, 기능 장애, 주요 심혈관 사건

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