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Original article

Development and validation of optimal cut-off value in inter-arm systolic blood pressure difference for prediction of cardiovascular events

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ABSTRACT

Background: An inter-arm systolic blood pressure difference (IAD) is associated with cardiovascular disease. The aim of this study was to develop and validate the optimal cut-off value of IAD as a predictor of major adverse cardiac events in patients with arteriosclerosis risk factors.
Methods: From 2009 to 2014, 1076 patients who had at least one cardiovascular risk factor were included in the analysis. We defined 700 randomly selected patients as a development cohort to confirm that IAD was the predictor of cardiovascular events and to determine optimal cut-off value of IAD. Next, we validated outcomes in the remaining 376 patients as a validation cohort. The blood pressure (BP) of both arms measurements were done simultaneously using the ankle-brachial blood pressure index (ABI) form of automatic device. The primary endpoint was the cardiovascular event and secondary endpoint was the all-cause mortality.
Results: During a median period of 2.8 years, 143 patients reached the primary endpoint in the development cohort. In the multivariate Cox proportional hazards analysis, IAD was the strong predictor of cardiovascular events (hazard ratio: 1.03, 95% confidence interval: 1.01–1.05, $p = 0.005$). The receiver operating characteristic curve revealed that 5 mmHg was the optimal cut-off point of IAD to predict cardiovascular events ($p < 0.001$). In the validation cohort, the presence of a large IAD (IAD ≥5 mmHg) was significantly associated with the primary endpoint ($p = 0.021$).
Conclusions: IAD is significantly associated with future cardiovascular events in patients with arteriosclerosis risk factors. The optimal cut-off value of IAD is 5 mmHg.

Introduction

Cardiovascular disease is a major health problem, accounting for 30% of all deaths in Asian countries [1]. This disease is a health problem that demands a clinical approach to prevention, early detection, and monitoring of the progression of the disease. Arteriosclerosis is a major contributor to the development of cardiovascular disease and is a major cause of mortality and morbidity [2,3]. Measurement of blood pressure (BP) is the most frequently and simplest method to assess the activity of arteriosclerosis [4]. In the clinical setting, cases with a difference of BP were found occasionally [5,6]. Meta-analyses reported that a difference in systolic BP of 10 mmHg or more between both arms was associated with development of cardiovascular events [7–9]. However, the cut-off value of 10 mmHg or 15 mmHg seems to be an equivocal index because of limited evidence [10]. The optimal cut-off value of inter-arm systolic blood pressure

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difference (IAD) is needed and should be tested to predict cardiac events. The aim of this study was to develop and validate the optimal cut-off value of IAD as a predictor of major adverse cardiovascular events in patients with arteriosclerosis risk factors.

Methods

Study design and data collection

This was a single center prospective observational study. A total of 1160 patients consulted Tokushima Prefectural Miyoshi Hospital, from April 2009 to December 2014, who received a medical service under health insurance. We included patients with at least one or more arteriosclerotic risk factors. Risk factors were diabetes mellitus, hypertension, dyslipidemia, smoking history, history of coronary artery disease, history of cerebrovascular disease, or history of peripheral arterial disease [11]. The exclusion criteria were inability to measure BP in both arms (e.g. deficiency or shunt), death within 1 month, or inability to keep track of or participate in follow-up. After the exclusions, 1076 patients were included for the analysis. There were no missing data during follow-up. This was a development and validation study. An independent data set was used to develop the model. Because of the necessity of large number of development cohort, we defined 700 randomly selected patients using a statistical software (SPSS for Windows version 22.0; SPSS Inc., Chicago, IL, USA) as a development cohort to confirm that IAD was the predictor of cardiovascular events and to determine optimal cut-off value of IAD. Next, we validated outcomes in the remaining 376 patients as a validation cohort [12,13]. The Institutional Review Board of the Tokushima University Hospital approved the study protocol.

Blood pressure measurements

The BP measurements of both arms were done simultaneously using the ankle-brachial BP index (ABI) form of automatic device (Omron Healthcare, Kyoto, Japan) [14,15]. Measurements were taken in the sequence of right arm, left arm, right ankle, and left ankle and repeated twice in the supine position with appropriately sized cuffs. First measurement is performed to estimate BP roughly and synchronizes a phase at the pressurization of the cuffs, and second measurement is performed subsequently for the actual value. Therefore, this method has fewer random variations than a method using two sphygmomanometers. The IAD was defined as the absolute difference of systolic BP of both arms. The maximal difference between arms was used. The ABI and brachial-ankle pulse wave velocity (baPWV) were measured after a 15-min rest period in the supine position in an air-conditioned room using a vascular testing device [16]. The ABI was calculated separately for each leg, and the lower of the 2 ABI values was used for analysis and the higher of the 2baPWV values was used for the analysis [17].

Clinical outcomes

The endpoints were obtained by reviewing all medical records including the last hospitalization, nursing home records, and personal physical records. Based on past studies, the primary endpoint was cardiovascular event defined as new onset of acute myocardial infarction, angina, coronary restenosis, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, or peripheral arterial disease [18,19]. Each diagnosis was based on a coronary angiography, coronary computed tomography (CT), magnetic resonance imaging of the brain, head CT or contrast vascular CT. The second endpoint was all-cause mortality. The duration of follow-up began at the time of the initial tests and ended in March 2016.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA) [20]. Multiple logistic regression analysis for Cox proportional hazards models was used to predict a factor of cardiovascular events and all-cause mortality. Significant variables in univariate analysis ($p < 0.05$) were selected as the covariates for multivariate analysis for Cox proportional hazards models. A receiver operating characteristic curve (ROC) was constructed on the basis of the sensitivity and specificity of the predictions for cardiovascular events from the development cohort. We determined the optimal cut-off value using Youden index [21]. This optimal cut-off value was used to validate the prediction of cardiovascular events. We divided a validation cohort into two groups with the optimal cut-off value of IAD. An event-free curve was estimated using the Kaplan–Meier method. The log-rank test was used to compare the differences in event-free rates between two groups. The differences between groups were checked by Chi-square test for categorical variables or by independent t test for continuous variables. To assess the reproducibility of BP differences between arms, the second measurements of BP using ABI-form was done in 50 randomly selected patients. To evaluate the measurement accuracy about this cut-off value, we used Pearson's correlation test. A value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

One thousand and seventy six patients were enrolled in this study. The purposes of measurement were a screening examination for arteriosclerotic disease ($n = 770$, 71.6%) and to rule out peripheral arterial disease ($n = 306$, 28.4%). Patients in the development cohort ($n = 700$) had a mean age of 72 years, 48% were female. The comorbidities in this cohort were 69% of patients with hypertension, 30% of patients had diabetes mellitus, 20% were smokers, and 42% had dyslipidemia. Median IAD was 4 mmHg. In the BP examination, 506 patients (72%) had no difference, less than 5 mmHg. Eighty-one patients (11%) were lower in the right arm, and 113 patients (16%) were lower with the left arm. All patients in the development cohort were followed for an average of 2.8 ± 1.6 years. Patients in the validation cohort ($n = 376$) had a mean age of 73 years, 42% were female. All patients in the validation cohort were also followed for an average of 2.8 ± 1.6 years. We show patient characteristics that compared the development cohort with the validation cohort in Table 1. No significant differences were observed with regard to clinical background between the two groups.

Development cohort

In the development cohort, 143 (20%) patients reached the primary endpoint (cardiovascular events), and 78 (11%) patients reached the secondary endpoint (all-cause death). The causes of cardiovascular events were defined as new onset of acute myocardial infarction ($n = 4$, 3%), angina ($n = 33$, 23%), coronary restenosis ($n = 2$, 1%), cerebral infarction ($n = 27$, 19%), cerebral hemorrhage ($n = 6$, 4%), subarachnoid hemorrhage ($n = 4$, 3%), transient ischemic attack ($n = 6$, 4%) and peripheral arterial disease ($n = 40$, 28%).

In univariate analysis for Cox proportional hazards models, age, IAD, diabetes mellitus, hypertension, smoking, ABI, baPWV, hemoglobin, serum creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hemoglobin A1c, brain natriuretic peptide, diuretic, statin, and anti-platelet were