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Usefulness of Upstroke Time per Cardiac Cycle for Cardiovascular and All-Cause Mortality Prediction in Patients with Normal Ankle-Brachial Index

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Aim: Abnormal ankle-brachial index (ABI) is regarded as peripheral artery disease and can be used to predict cardiovascular (CV) outcomes. However, the usefulness of ABI for the prediction of CV outcome in patients with normal ABI is limited. Upstroke time per cardiac cycle (UTCC) is recently reported to be associated with mortality in patients with acute myocardial infarction and the elderly. Therefore, we aimed to evaluate UTCC, left ventricular ejection fraction (LVEF), brachial-ankle pulse wave velocity (baPWV), and ABI for the prediction of mortality in patients with normal ABI.

Methods: Patients arranged for echocardiographic examinations were enrolled, and 1076 patients with normal ABI were included. ABI, baPWV, and UTCC were measured by an ABI-form device.

Results: The median follow-up to mortality was 95 months. There were 88 CV and 244 all-cause deaths. After multivariate analysis, UTCC was associated with increased CV and all-cause mortality ($P \leq 0.004$). Age, diabetes, heart failure, left ventricular hypertrophy, baPWV, and LVEF were also independent predictors of CV and all-cause mortality, but ABI was not. Furthermore, UTCC had a better additive predictive value than ABI, baPWV, and LVEF for CV mortality ($P \leq 0.012$). It also had a better additive predictive value than ABI and LVEF for all-cause mortality ($P \leq 0.013$).

Conclusions: UTCC is an independent predictor for CV and all-cause mortality in patients with normal ABI. It also has a better additive predictive value of CV and all-cause mortality than ABI and LVEF. Therefore, UTCC is a simple, novel, and useful parameter for identifying high-risk patients with normal ABI.

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Key words: Ankle-brachial index, All-cause mortality, Cardiovascular, Mortality, Left ventricular ejection fraction, Upstroke time per cardiac cycle

Introduction

Ankle-brachial index (ABI) is a useful diagnostic tool for peripheral arterial disease (PAD)[1, 2]. ABI of both <0.9 and >1.4 is considered abnormal ABI and was reported to be associated with poor cardiovascular (CV) outcome[3-10]. ABI within 0.9 and 1 is regarded as borderline ABI[3]. Conversely, ABI within 1 and 1.4 is regarded as normal ABI and has better long-term CV outcome than abnormal ABI[3, 11-13]. However, there are only a few studies about the prediction of long-term CV and all-cause mortality in patients with normal ABI, and the usefulness of ABI for the prediction of mortality in this patient group is limited.

Upstroke time (UT) calculated from the initial of the systolic rise to the peak of the pulse wave in the lower limb was shown to be an excellent indicator of peripheral artery disease (PAD)[14-16]. Recently, UT per

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cardiac cycle (UTCC) was reported to be a diagnostic tool of PAD and a predictor of mortality in patients with acute myocardial infarction and older population[17, 18]. Therefore, our study aimed to evaluate the usefulness of UTCC for the prediction of CV and all-cause mortality in patients with normal ABI. Additionally, we compared UTCC with other important parameters such as left ventricular ejection fraction (LVEF), brachial-ankle pulse wave velocity (baPWV), and ABI to see whether UTCC had a better predictive value of CV and all-cause mortality.

Methods

Study Population and Design

Study population was enrolled from the patients arranged for echocardiographic examinations at Kaohsiung Municipal Siaogang Hospital from 2010 to 2012. Our inclusion criterion was patient with normal ABI ($1 < ABI < 1.4$). Patients with significant atrial fibrillation and diseases of mitral and aortic valves were excluded. Finally, 1076 patients were included in our study. This study was approved by the institutional review board committee of the Kaohsiung Medical University Hospital (KMUH-IRB). We acquired informed consent from the patients and conducted our study according to the declaration of Helsinki.

Assessment of UTCC, baPWV, and ABI by ABI-form Device

We measured UTCC and ABI by ABI-form device (VP1000, Japan), which measures blood pressures of four limbs via oscillometric method[19, 20], and it can also obtain the data of ABI, baPWV, and UT at the same time. UT was shown by the device as the pulse foot-to-peak transit time. UTCC was calculated as the UT divided by cardiac cycle* 100%[17, 21]. After we acquired the UTCC of the bilateral foot, the higher one was selected as our data. For measuring baPWV, pulse waves that were acquired from the brachial and tibial arteries were recorded simultaneously, and the transmission time, which was defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to body height. The value of baPWV was automatically calculated as the transmission distance divided by the transmission time. ABI was calculated by the ratio of the lower ankle over the higher brachial systolic blood pressure. We performed measurement of the ABI-form device in each subject within the same day of echocardiographic examination.

Echocardiographic Examination

All echocardiographic examinations were conducted by a single experienced cardiologist. The cardiologist was blinded to the clinical data. The LVEF was measured by the Simpson method.

Definition of CV and All-Cause Mortality

We followed our patients till December 2018 and acquired survival information and causes of death from the official death certificate and final confirmation by the Ministry of Health and Welfare. The causes of death were classified by the International Classification of Diseases 10th Revision. Causes of CV mortality were defined as deaths due to cerebral vascular disease, ischemic heart disease, myocardial infarction, heart failure, valvular heart disease, and atherosclerotic vascular disease.

Collection of Demographic and Medical data

Demographic and medical data including age, gender, smoking history, and comorbid conditions were obtained from interviews or medical records of patients. The body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters. Heart failure was defined as left ventricular systolic dysfunction with a left ventricular ejection fraction of ≦40% or having a known history of heart failure. Hypertension was defined as systolic blood pressure of ≧140 mmHg or diastolic blood pressure of ≧90 mmHg, or anti-hypertensive drugs were prescribed. Diabetes was defined as a fasting blood glucose level of >126 mg/dL, or hypoglycemic agents were used to controlling blood glucose levels. Dyslipidemia was defined as total cholesterol of ≧200 mg/dL or low-density lipoprotein of ≧130 mg/dL. Additionally, medications of patients including aspirin, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics during the study period were obtained from medical records.

Statistical Analysis

SPSS 22.0 was used to conduct statistical analyses. Our data were shown as a percentage or mean ± standard deviation. Categorical variables were compared using the chi-square test. Continuous variables were compared using an independent sample *t*-test. We selected significant variables in our univariate analysis into multivariate analysis. We adjusted significant variables and time to mortality using Cox regression analysis. We also calculated the improvement of global chi-square to evaluate the additive value of ABI, baPWV, LVEF, and UTCC over a basic model for long-term CV and all-cause

Table 1. Comparison of clinical characteristics between patients with and without mortality

Baseline Characteristics	Mortality (-)	Mortality (+)	*P* value
Number	832	244	
Age (yr)	58 ± 12	68 ± 13	< 0.001
Male gender (%)	54.0%	63.0%	0.015
Smoking (%)	15.7%	11.8%	0.230
Diabetes (%)	21.4%	42.2%	< 0.001
Hypertension (%)	68.1%	70.1%	0.584
Dyslipidemia (%)	60.1%	54.0%	0.141
Coronary artery disease (%)	16.2%	20.2%	0.175
Heart failure (%)	3.1%	19.4%	< 0.001
LVH (%)	53.0%	74.8%	< 0.001
Body mass index (kg/m^2)	26.3 ± 3.7	25.8 ± 4.3	0.076
ABI	1.14 ± 0.06	1.14 ± 0.07	0.481
baPWV (cm/s)	1666 ± 345	1995 ± 517	< 0.001
LVEF (%)	65.6 ± 10.9	57.6 ± 16.2	< 0.001
UTCC (%)	16.1 ± 2.8	17.9 ± 3.6	< 0.001
Medication			
Aspirin (%)	31.8%	30.8%	0.853
β-blockers (%)	41.0%	44.9%	0.301
CCBs (%)	35.5%	35.0%	0.939
ACEIs (%)	9.0%	11.9%	0.177
ARBs (%)	43.9%	43.6%	0.942
Diuretics (%)	23.6%	33.1%	0.004

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; CCB, calcium channel blocker; LVEF, left ventricular ejection fraction; UTCC, upstroke time per cardiac cycle

mortality prediction. Kaplan–Meier survival curve was calculated from baseline to time of mortality events. A *P* value of <0.05 was considered statistically significant.

Results

Among the 1076 subjects, the median follow-up to mortality was 95 months (25th–75th percentile: 87–101 months). The mean age in our study was 60.4 ± 13.2 years. There were 88 CV and 244 all-cause deaths.

Table 1 shows the clinical characteristics of patients with and without mortality. Patients with mortality had older age, male gender, higher percentage of diabetes, heart failure, left ventricular hypertrophy, higher baPWV (1995 ± 517 versus 1666 ± 345, $P<0.001$), lower LVEF (57.6 ± 16.2 versus 65.6 ± 10.9, $P<0.001$), higher UTCC (17.9 ± 3.6 versus 16.1 ± 2.8, $P<0.001$), and higher percentage of diuretic use compared with patients without mortality. There was no significant difference between the percentage of smoking, hypertension, dyslipidemia, body mass index, and medication use (aspirin/beta blocker/calcium channel blocker use/angiotensin converting enzyme inhibitor/angiotensin II receptor blocker).

Table 2 displays the predictors of CV mortality using Cox regression analysis. Age, diabetes, dyslipidemia, coronary artery disease, heart failure, left ventricular hypertrophy, baPWV, LVEF, and UTCC are significant predictors of CV mortality in the univariate analysis. After multivariate analysis, age, diabetes, heart failure, left ventricular hypertrophy, baPWV, LVEF (hazard ratio [HR] = 0.950; 95% confidence interval [CI]: 0.926–0.976; $P<0.001$), and UTCC (HR = 1.134; 95% CI: 1.041–1.236; $P=0.004$) were significantly associated with CV mortality.

Because chronic kidney disease is also strongly associated with PAD, we further added the variable of estimated Glomerular filtration rate into multivariate analysis for CV mortality. Results showed that age, heart failure, left ventricular hypertrophy, LVEF (HR = 0.953; 95% CI: 0.929–0.977; $P<0.001$), and UTCC (HR = 1.139; 95% CI: 1.039–1.248; $P=0.005$) were significantly associated with CV mortality, but estimated Glomerular filtration was not ($P=0.482$).

Table 3 displays the predictors of all-cause mortality using Cox regression analysis. Age, diabetes,

Table 2. Predictors of cardiovascular mortality using Cox regression analysis

Parameter	Univariate (CV mortality)		Multivariate (CV mortality)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (yr)	1.078 (1.052-1.104)	<0.001	1.063 (1.031-1.095)	<0.001
Male gender	1.153 (0.683-1.944)	0.594		
Hypertension (Yes or No)	1.020 (0.580-1.792)	0.946		
Diabetes (Yes or No)	2.823 (1.691-4.711)	<0.001	1.880 (1.023-3.457)	0.042
Dyslipidemia (Yes or No)	0.503 (0.282-0.896)	0.020	-	0.222
Coronary artery disease (Yes or No)	2.140 (1.218-3.761)	0.008	-	0.265
Heart failure (Yes or No)	7.760 (4.308-13.978)	<0.001	2.495 (1.066-5.836)	0.035
LVH (Yes or No)	4.159 (2.043-8.467)	<0.001	2.346 (1.084-5.077)	0.030
Smoking (ever vs no)	0.645 (0.277-1.501)	0.309		
Body mass index (per kg/m^2)	0.955 (0.890-1.025)	0.202		
ABI (per 1SD)	0.033 (0.001-1.661)	0.088		
baPWV (per 10 cm/s)	1.014 (1.008-1.019)	<0.001	1.008 (1.001-1.015)	0.018
LVEF (%)	0.951 (0.935-0.968)	<0.001	0.950 (0.926-0.976)	<0.001
UTCC (%)	1.234 (1.147-1.328)	<0.001	1.134 (1.041-1.236)	0.004
Medications				
Aspirin use	1.246 (0.731-2.124)	0.419		
Beta blocker use	1.177 (0.704-1.968)	0.535		
Calcium channel blocker use	1.092 (0.650-1.836)	0.739		
ACEI use	1.242 (0.534-2.891)	0.614		
ARB use	1.520 (0.907-2.548)	0.112		
Diuretic use	1.219 (0.700-2.122)	0.484		

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; SD: standard deviation; other abbreviations as in Table 1.

Table 3. Predictors of all-cause mortality using Cox regression analysis

Parameter	Univariate (all-cause mortality)		Multivariate (all-cause mortality)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (yr)	1.079 (1.063-1.094)	<0.001	1.065 (1.046-1.086)	<0.001
Male gender	1.279 (0.932-1.754)	0.127		
Hypertension (Yes or No)	1.046 (0.743-1.471)	0.797		
Diabetes (Yes or No)	2.331 (1.709-3.181)	<0.001	1.840 (1.277-2.650)	0.001
Dyslipidemia (Yes or No)	0.609 (0.431-0.861)	0.005	-	0.068
Coronary artery disease (Yes or No)	1.288 (0.875-1.896)	0.200		
Heart failure (Yes or No)	4.639 (3.084-6.978)	<0.001	1.820 (1.006-3.293)	0.048
LVH (Yes or No)	2.119 (1.489-3.015)	<0.001	1.498 (1.001-2.243)	0.049
Smoking (ever vs no)	0.798 (0.500-1.275)	0.346		
Body mass index (per kg/m^2)	0.951 (0.911-0.993)	0.022	-	0.972
ABI (Per 1SD)	0.439 (0.043-4.475)	0.487		
baPWV (Per 10cm/s)	1.015 (1.02-1.018)	<0.001	1.009 (1.005-1.013)	<0.001
LVEF (%)	0.964 (0.953-0.975)	<0.001	0.965 (0.950-0.981)	<0.001
UTCC (%)	1.197 (1.144-1.252)	<0.001	1.084 (1.028-1.143)	0.003
Medications				
Aspirin use	0.970 (0.694-1.357)	0.860		
Beta blocker use	1.107 (0.811-1.512)	0.521		
Calcium channel blocker use	0.935 (0.680-1.287)	0.681		
ACEI use	0.883 (0.490-1.590)	0.678		
ARB use	0.937 (0.688-1.277)	0.680		
Diuretic use	1.380 (0.996-1.914)	0.053		

CI: confidence interval; HR: hazard ratio; SD: standard deviation; other abbreviations as in Table 1.

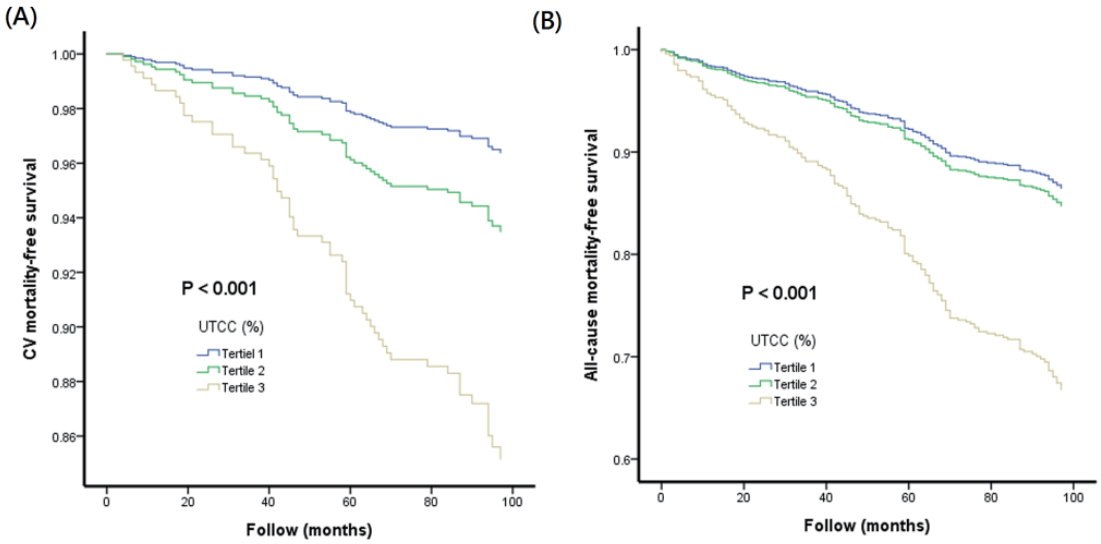

Fig. 1. Kaplan–Meier curves of UTCC divided into tertile for CV (Fig. 1A) and all-cause mortality-free survival (Fig. 1B)
Abbreviation: CV, cardiovascular; UTCC, upstroke time per cardiac cycle

dyslipidemia, heart failure, left ventricular hypertrophy, body mass index, baPWV, LVEF, and UTCC are significant predictors of all-cause mortality in the univariate analysis. After multivariate analysis, age, diabetes, heart failure, left ventricular hypertrophy, baPWV, LVEF (HR=0.965; 95% CI: 0.950–0.981; $P<0.001$), and UTCC (HR=1.084; 95% CI: 1.028–1.143; $P=0.003$) were significantly associated with all-cause mortality.

Fig. 1 shows the Kaplan–Meier curves of UTCC divided into tertile for CV **(Fig. 1A)** and all-cause mortality-free survival **(Fig. 1B)** (both $P<0.001$). Tertile 1 included UTCC of <15%. Tertile 2 included UTCC within 15% and 17.5%. Tertile 3 included UTCC of >17.5%.

Fig. 2 illustrates the Nested Cox model for CV **(Fig. 2A)** and all-cause mortality **(Fig. 2B)** prediction. The basic model in **Fig. 2A** included age, diabetes, dyslipidemia, coronary artery disease, heart failure, and left ventricular hypertrophy. After adding ABI, baPWV, LVEF, and UTCC into the basic model respectively, we found that basic model + baPWV, basic model + UTCC, and basic model + LVEF had better predictive values for CV mortality than the basic model alone ($P \leq 0.010$). Basic model + UTCC also had better a predictive value than basic model + ABI ($P<0.001$), basic model + baPWV ($P=0.005$), and basic model + LVEF ($P=0.012$). Additionally, basic model + LVEF + UTCC had better predictive values for CV mortality than basic model + LVEF ($P<0.001$). Basic model + LVEF + UTCC also had a better predictive value than basic model + LVEF + ABI for CV mortality ($P=0.002$). The basic model in **Fig. 2B** included age, diabetes, dyslipidemia, heart failure, left ventricular hypertrophy, and body mass index. After adding ABI, baPWV, LVEF, and UTCC into the basic model respectively, we found that basic model + baPWV, basic model + UTCC, and basic model + LVEF had better predictive values for all-cause mortality than the basic model alone ($P<0.001$). Basic model + UTCC also had a better predictive value than basic model + LVEF ($P=0.013$). Furthermore, basic model + LVEF + UTCC had a better predictive value for all-cause mortality than basic model + LVEF ($P<0.001$). Basic model + LVEF + UTCC also had a better predictive value than basic model + LVEF + ABI for all-cause mortality ($P<0.001$).

Discussion

Our study aimed to evaluate the usefulness of UTCC for the prediction of CV and all-cause mortality in patients with normal ABI, and we found several major findings in the present study. First, higher UTCC was significantly associated with increased CV and overall mortality. Second, age, diabetes, heart failure, left ventricular hypertrophy, baPWV, and LVEF were also significant predictors of CV and all-cause mortality in this patient group. Third, UTCC had a better additive predictive value than ABI, baPWV, and LVEF for CV mortality. It also had better additive predictive than ABI and LVEF for all-cause mortality.

Abnormal ABI is not only regarded as a diagnostic indicator of PAD but also associated with

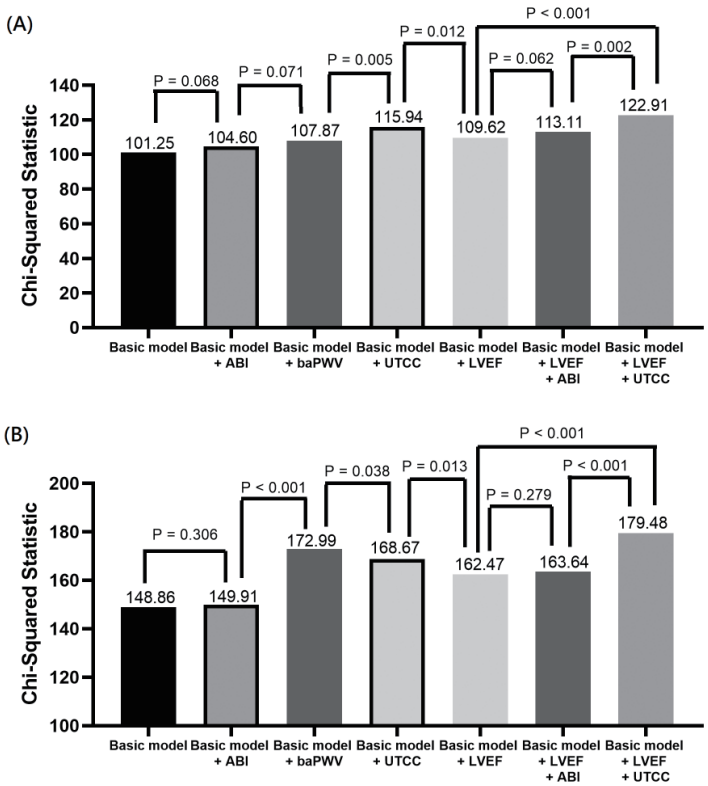

Fig. 2. The nested Cox model for CV (Fig. 2A) and all-cause mortality (Fig. 2B) prediction by calculating the improvement in global chi-square value

The basic model in Fig. 2A included age, diabetes, dyslipidemia, coronary artery disease, heart failure, and left ventricular hypertrophy. The basic model in Fig. 2B included age, diabetes, dyslipidemia, heart failure, left ventricular hypertrophy, and body mass index.
Abbreviation: ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; LVEF, left ventricular ejection fraction; UTCC, upstroke time per cardiac cycle

higher CV and all-cause mortality[3-10]. Compared with patients with abnormal ABI, those with normal ABI had better CV outcomes and lower morbidity and mortality[11-13]. Although ABI is a useful predictor of future CV outcome in several populations such as the general population, patients with diabetes, hypertension, chronic kidney disease, dialysis, stroke, and so on[6-13], the usefulness of ABI for the prediction of long-term CV and all-cause mortality in patients with normal ABI is limited.

An ABI-form device (VP 1000) could automatically measure blood pressures of four limbs via oscillometric method[19, 20]. It could also acquire the values of ABI and UT at the same time. According to the literature, UT plays an important role in the diagnosis of PAD, and it is also significantly correlated with ABI[17, 21]. In recent years, Yu S *et al.* reported that UTCC was significantly correlated with renal and vascular damage in the old Chinese population[21]. Sheng CS *et al.* showed that UTCC was equivalent to ABI for the diagnosis of PAD and can be used as a novel predictor for the prediction of mortality in the old Chinese population[17]. Chang LH *et al.* also demonstrated that UTCC was associated with CV outcomes and in patients with type 2 diabetes[22]. Furthermore, our previous study revealed that UTCC was an independent predictor of long-term CV and all-cause mortality in patients with acute myocardial infarction[18]. According to the abovementioned literature[17, 21], UT and UTCC were useful parameters for the diagnosis of PAD and could be used to evaluate the peripheral vascular function and future outcomes. Therefore, we tried to evaluate whether UTCC is also an independent predictor of long-term mortality in patients with normal ABI. Additionally, we compared the additive predictive values of UTCC, ABI, baPWV, and LVEF for CV and all-cause mortality. As we know, LVEF is regarded as an important parameter for CV outcome and mortality in the literature[23-25]. In our study, UTCC, baPWV, and LVEF are all significant and independent predictors of CV and all-cause mortality after multivariate analysis, but ABI was not. This finding might suggest that for patients with normal ABI, ABI

was not a good indicator of adverse CV events or mortality. Furthermore, we performed a nested Cox model for the prediction of CV and all-cause mortality. For CV mortality **(Fig. 2A)**, baPWV, UTCC, and LVEF all had additive predictive value to the basic model. Basic model + UTCC showed a better predictive value than basic model + ABI, basic model + baPWV, and basic model + LVEF ($P \leq 0.012$). For all-cause mortality **(Fig. 2B)**, baPWV, UTCC, and LVEF all had additive predictive value to the basic model. Additionally, basic model + UTCC had a better predictive value than basic model + ABI and basic model + LVEF ($P \leq 0.013$). Therefore, these findings might suggest that UTCC was a better parameter than ABI and LVEF in predicting long-term CV and all-cause mortality in patients with normal ABI.

Because UT and UTCC were both useful parameters for the diagnosis of PAD and predictors for CV outcomes[14-18], the improvement of UT or UTCC might have a good impact on future outcomes. PAD is one of the vascular bed diseases with extremely high morbidity and mortality. It also has a higher chance to have a coexistent disease in other vascular beds such as coronary artery disease and cerebrovascular disease. Arita Y *et al.* ever reported that after endovascular treatment for PAD, ABI, and UT had improved[26]. As we know, endovascular therapy for PAD could improve the symptom of claudication, limb function, walking performance, and wound healing and decrease the risk of amputation, which might improve the survival of patients with PAD. Therefore, the improvement of UT or UTCC by endovascular therapy might improve future CV outcomes. Other treatment strategies that can improve UT or UTCC might also have the chance to improve CV outcomes; however, we still need further studies to investigate the issue.

Study Limitations

First, our study did not evaluate the non-fatal outcomes for patients with normal ABI. Second, we did not withdraw the CV medications because of ethical issues. However, we had adjusted the CV medications in our multivariate analysis, and the influence of medications might be reduced after the adjustment. Third, statin use was not recorded initially in our study. In our hospital, the chart was not available if patients did not visit our hospital again for more than 10 years. Therefore, the data of statin were incomplete and could not be analyzed in this study.

Conclusions

Our study is the first to investigate the usefulness of UTCC for the prediction of long-term CV and all-cause mortality in patients with normal ABI. Our study revealed that UTCC is significantly associated with long-term CV and all-cause mortality in this patient group. Additionally, it has a better additive predictive value of CV and all-cause mortality than ABI and LVEF. Therefore, UTCC is a simple, novel, and useful parameter for identifying a high-risk patient with normal ABI.

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None.

Competing Interests

The authors have declared no competing interest exists.

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