Utility of Ankle-brachial Index Score for Mortality Prediction in Hemodialysis Patients

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Abstract

Background: In our recent study involving non-hemodialysis patients, we created a novel ankle-brachial index (ABI) score, which was calculated by assigning one point each for low ABI and for high ABI difference (ABID). This score allowed us to take low ABI and high ABID into consideration simultaneously, whereby we found that ABI score could significantly predict overall and cardiovascular mortality in non-hemodialysis patients. However, no study has assessed the capacity of this ABI score to predict survival in patients under hemodialysis. Hence, the present study aimed to examine the ABI score's usefulness in predicting overall mortality in hemodialysis patients.

Methods: We included 207 routine hemodialysis patients. The ABI was measured using an ABI-form device. ABID was calculated as |right ABI-left ABI|. ABID ≥ 0.13 was defined as high ABID for the present study.

Results: The median follow-up to mortality was 122 months (25th–75th percentile: 58-157 months). One hundred and twenty-four mortality events were recorded during the follow-up period. Advanced age, presence of diabetes, high systolic blood pressure, high triglycerides, usage of calcium channel blockers, ABI < 0.9, ABID ≥ 0.13, high novel ABI score (hazard ratio: 1.582; 95% confidence interval: 1.193-2.096, P = 0.001) and decreased albumin were associated with increased overall mortality after multivariable analysis.

Conclusion: Our ABI score combining ABI < 0.9 and ABID ≥ 0.13 could significantly predict overall mortality even after adjusting for important clinical and laboratory parameters. This was the first study to confirm that this ABI score was a useful survival predictor in hemodialysis patients. Hence, it is worthwhile to calculate ABI score for better mortality prediction in hemodialysis patients.

Key words: ankle-brachial index, mortality, hemodialysis

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Introduction

Ankle-brachial index (ABI) is a useful tool to confirm the diagnosis and assess the severity of peripheral artery occlusion disease (PAOD).[1,2] Furthermore, ABI < 0.9 is well established as a helpful prognostic parameter in various populations, such as patients with chronic kidney disease under hemodialysis (HD),[3-6] patients with acute coronary syndrome[7,8] and older patients.[9] Because patients with HD frequently have heavily calcified and non-compressible vessels, and the prevalence of PAOD is very high in such patients, ABI measurement is almost a routine examination in HD patients.

Increased ABI difference (ABID), calculated as |right ABI-left ABI|, which may indicate unequal atherosclerosis of the limbs, has also been shown to be significantly correlated with increased major adverse cardiovascular events in patients under chronic HD[10] and with acute ischemic stroke.[11] In our recent study, enrolling non-HD patients, we created a novel ABI score, which was calculated by assigning one point for ABI < 0.9 and one point for ABID ≥ 0.17. This score enabled us to take low ABI and high ABID into consideration simultaneously, whereby we found, after multivariable analysis, that this ABI score could significantly predict overall and cardiovascular mortality.[12] However, no study to date has assessed the capacity of this ABI score to predict survival in patients under HD. Hence, the present study aimed to examine the usefulness of the ABI score in predicting overall mortality in HD patients.

Materials and Methods

Study population

The study was conducted in a regional hospital in southern Taiwan. All routine HD patients in this hospital were included except those who refused echocardiographic examination (n = 6) and those with atrial fibrillation (n = 4). Finally, 207 patients were included in this study.

Our study protocol was approved by the Institutional Review Board committee of Kaohsiung Medical University Hospital (KMUH-IRB). Informed consent was obtained from the patients and our study was conducted according to the principles expressed in the Declaration of Helsinki.

All patients received routine HD 3 times per week. Each HD session lasted for 3–4 hours using a dialyzer with a blood flow rate of 250 to 300 mL/min and dialysate flow of 500 mL/min.

Assessment of ABI

The ABI value was assessed using an ABI-form device (VP1000, Colin, Aichi, Japan), which automatically and simultaneously measured blood pressure in both arms and ankles by an oscillometric method.[13,14] ABI was calculated as the ratio of ankle blood pressure over the higher brachial systolic blood pressure. The ABI measurement was done once in each patient. After obtaining bilateral ABIs, the lower value was used for later analysis. In addition, ABID was calculated as |right ABI-left ABI|.

Collection of demographic and medical data

Demographic and medical data including age, sex, current smoking history and comorbidities were obtained from medical records or interviews with patients. The body mass index was calculated as the quotient of weight in kilograms divided by the square of height in meters. Laboratory data were measured from fasting blood samples using an autoanalyzer (Roche Diagnostics GmbH, D-68298 Mannheim COBAS Integra 400). The blood samples were obtained within 1 month of enrollment. Patients were considered to have diabetes if the fasting blood glucose exceeded 126 mg/dL or if hypoglycemic drugs were used to control blood glucose levels. Patients were considered to have hypertension if their systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or if anti-hypertensive agents were used to control blood pressure.

Statistical analysis

We used SPSS 22.0 software (SPSS, Chicago, IL, USA) to perform statistical analysis. Data were presented as mean ± standard deviation, percentage, or median (25th–75th percentile) for the follow-up period. Multiple comparisons among patients with different ABI scores were made by one-way analysis of variance followed by a post-hoc test adjusted with Fisher's least significant difference test. Categorical variables were compared between groups by Chi-squared analysis. We selected the significant variables from the univariable analysis to include in the multivariable analysis. Time to the overall mortality event and covariates of risk factors were modeled using the Cox proportional hazards model. Kaplan-Meier survival plot was calculated from baseline to time of mortality event. All tests were 2-sided and the level of significance was established as P < 0.05.

Results

Among the 207 subjects, the mean age was 59 ± 13 years. The prevalence of ABI < 0.9 and ABID ≥ 0.13 was 13% (n = 27) and 13% (n = 27), respectively. There were 167, 26, and 14 patients with ABI score 0, 1, and 2, respectively. Table 1 compares the baseline characteristics according to ABI scores. There were significant

Table 1. Comparison of baseline characteristics according to ABI score

Characteristics	ABI score = 0 (n = 167)	ABI score = 1 (n = 26)	ABI score = 2 (n = 14)	P	All patients (n = 207)
Age (years)	57 ± 13	66 ± 12*	68 ± 9*	<0.001	59 ± 13
Male gender	47%	35%	36%	0.407	44%
Diabetes mellitus	32%	69%*	57%*	0.001	39%
Hypertension	70%	73%	86%	0.423	71%
Current smoking	10%	4%	0%	0.313	8%
SBP (mmHg)	143 ± 23	155 ± 32*	148 ± 24	0.068	145 ± 25
DBP (mmHg)	80 ± 15	80 ± 19	73 ± 16	0.261	80 ± 15
Body mass index (kg/m^2)	23.8 ± 3.6	24.0 ± 3.8	23.9 ± 3.6	0.807	23.9 ± 3.6
Heart rate (min^{-1})	80 ± 13	80 ± 12	79 ± 15	0.980	80 ± 13
Albumin (g/dL)	3.85 ± 0.28	3.78 ± 0.22	3.68 ± 0.34*	0.064	3.83 ± 0.28
Hemoglobin (g/dL)	9.9 ± 1.1	9.7 ± 0.8	10.9 ± 1.4*	0.003	9.9 ± 1.1
Triglyceride (mg/dL)	170 ± 136	173 ± 93	194 ± 126	0.811	172 ± 130
Total cholesterol (mg/dL)	186 ± 42	178 ± 32	186 ± 52	0.792	185 ± 42
Medications					
ACEI and/or ARB use	21%	12%	14%	0.505	19%
β-blocker use	18%	22%	14%	0.883	19%
CCB use	37%	36%	29%	0.837	36%
ABI data					
ABI < 0.9	0%	50%*	100%*#	<0.001	13%
ABID ≥ 0.13	0%	50%*	100%*#	<0.001	13%

ABI: ankle-brachial index; ABID: ankle-brachial index difference between legs; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; DBP: diastolic blood pressure; SBP: systolic blood pressure. ABI score was calculated by assigning 1 point for ABI < 0.9 and 1 point for ABID ≥ 0.13. *P <0.05 compared with ABI score = 0; #P < 0.05 compared with ABI score = 1.

differences in age, prevalence of diabetes mellitus, hemoglobin and prevalence of ABI < 0.9 and ABID ≥ 0.13.

Mortality data of the study subjects were collected up to December 2019. Mortality information was acquired from the Collaboration Center of Health Information Application (CCHIA), Ministry of Health and Welfare, Executive Yuan, Taiwan. The median follow-up to mortality was 122 months (25th–75th percentile: 58-157 months). One hundred and twenty-four mortality events were recognized during the follow-up period.

To find the appropriate cut-off value of ABID as a predictor of overall mortality, we created several models using different cut-off values of ABID. Using the Chi-squared value to select the model with the best performance, we found ABID ≥ 0.13 had the best performance in predicting overall mortality.

Table 2 shows the predictors of overall mortality using the Cox proportional hazards model in the univariable analysis of our 207 study patients. Increased age, presence of diabetes, high systolic blood pressure, high triglycerides, usage of calcium channel blockers, ABI < 0.9, ABID ≥ 0.13, high ABI score and decreased albumin were all associated with increased overall mortality.

Table 2. Predictors of total mortality using Cox proportional hazards model in all study patients

Parameter	Univariate		Multivariate (forward)	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.070 (1.053-1.087)	< 0.001	1.064 (1.046-1.082)	< 0.001
Male gender	0.872 (0.611-1.244)	0.450		
Diabetes mellitus	2.356 (1.651-3.361)	< 0.001	1.609 (1.115-2.323)	0.011
Hypertension	1.353 (0.905-2.023)	0.141		
Current smoking	1.144 (0.631-1.075)	0.658		
SBP (mmHg)	1.010 (1.003-1.018)	0.007		
DBP (mmHg)	0.993 (0.981-1.005)	0.253		
Body mass index (kg/m^2)	1.005 (0.956-1.057)	0.852		
Heart rate (min^{-1})	0.997 (0.984-1.011)	0.699		
Albumin (g/dL)	0.326 (0.189-0.562)	< 0.001		
Hemoglobin (g/dL)	1.068 (0.915-1.247)	0.404		
Triglyceride (mg/dL)	1.002 (1.000-1.003)	0.013	1.001 (1.000-1.003)	0.043
Total cholesterol (mg/dL)	1.001 (0.997-1.005)	0.691		
Antihypertensive medications				
ACEI and/or ARB use	1.203 (0.775-1.866)	0.410		
β-blocker use	1.102 (0.637-1.909)	0.728		
CCB use	1.437 (1.004-2.056)	0.047		
ABI data				
ABI < 0.9	3.533 (2.253-5.539)	< 0.001		
ABID ≥ 0.13	2.421 (1.532-3.827)	< 0.001		
ABI score	2.146 (1.644-2.802)	< 0.001	1.582 (1.193-2.096)	0.001

HR: hazard ratio; CI: confidence interval; other abbreviations as in Table 1. Covariates in the multivariable model included the significant variables from the univariable analysis, consisting of age, diabetes mellitus, SBP, albumin, triglyceride and use of CCBs.

Figure 1 shows the Kaplan-Meier curves for overall mortality-free survival in study patients, subdivided according to ABI score (Log-rank P < 0.001).

Discussion

This study aimed to evaluate our ABI score (concurrent consideration of ABI < 0.9 and ABID ≥ 0.13) in survival prediction in patients under HD. We found that the ABI score combining ABI < 0.9 and ABID ≥ 0.13 could significantly predict overall mortality, even after adjusting for important clinical and laboratory parameters. This was the first study to confirm that our novel ABI score (combined consideration of low ABI and high ABID) was a useful survival predictor in HD patients.

ABI < 0.9 has long been a practical parameter for diagnosis of PAOD[15,16] with the potential to predict long-term overall and cardiovascular mortality in different patient groups, including patients with coronary artery disease,[17] diabetes,[18] chronic kidney disease[3] or HD.[19] Additionally, Lin et al. showed that an ABID ≥ 0.15 is an independent risk factor for overall mortality in HD patients, although cardiovascular mortality might be affected through the impact of peripheral vascular disease.[10] Recently, Han et al. enrolled 2901 acute stroke patients to examine the capacity of ABID for short- and long-term outcome prediction. They found that ABID is related to poor short-term functional outcomes, long-term occurrence

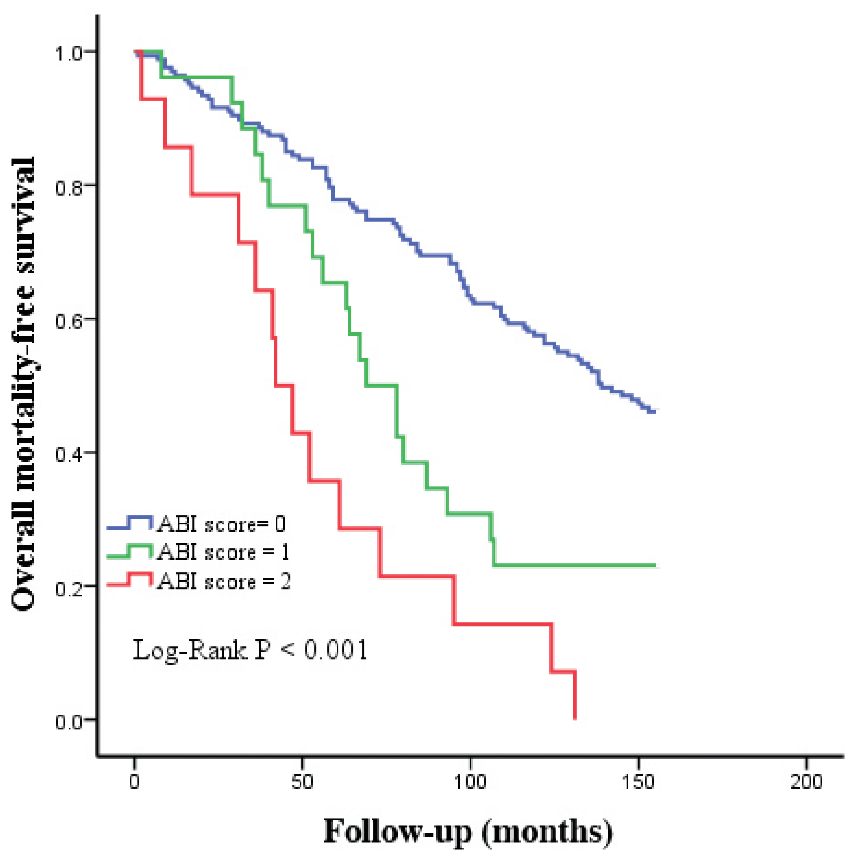

Figure 1. Kaplan-Meier analysis for total mortality-free survival in study patients, subdivided according to ankle brachial index (ABI) score.

of major adverse cardiovascular events and all-cause mortality.[11] Our previous study confirmed that our ABI score is a useful parameter for the prediction of overall and cardiovascular mortality in non-HD patients.[12] However, to date, there has been no study to assess whether concurrent consideration of low ABI and high ABID might be helpful in predicting survival in HD patients. In the present study, we employed a novel ABI score which assigned 1 point for ABI < 0.9 and 1 point for ABID ≥ 0.13, whereby we found that this ABI score was a useful parameter in the prediction of long-term overall mortality in HD patients. Among our 27 study subjects with ABID ≥ 0.13, there were 13 patients (48%) without ABI < 0.9. Because ABID ≥ 0.13 was a helpful parameter in survival prediction, the consideration of ABI < 0.9 alone might not be adequate for mortality prediction. Similarly, among the 27 patients with ABI < 0.9, there were 13 patients (48%) without ABID ≥ 0.13. Because ABI < 0.9 was a helpful parameter in survival prediction, the consideration of ABI ≥ 0.13 alone might not be adequate for mortality prediction. Hence, a novel ABI score which could simultaneously take into consideration ABI < 0.9 and ABID ≥ 0.13 should be able to provide a good survival prediction result. In fact, after adjusting for important clinical and laboratory parameters, the novel ABI score retained the capacity to predict long-term overall mortality in our HD patients.

Decreased ABI and increased ABID have been reported to be correlated with the presence of peripheral artery disease (PAD).[20,21] However, decreased ABI has been shown to be insufficiently sensitive to detect asymptomatic PAD reliably in the general population.[22] Therefore, in some patients, PAD might not be detected using ABI < 0.9. Increased ABID has been associated with the presence of PAD, hence ABID might be useful in the detection of PAD in patients with normal ABI.[11,12,23] It follows that a novel ABI score with concurrent consideration of ABI < 0.9 and ABID ≥ 0.13 could have the potential to identify more patients with PAD than ABI < 0.9 or ABID ≥ 0.13 alone. The higher ABI score of HD patients might suggest an increased prevalence of PAD and concomitant atherosclerosis, and thus potentially higher mortality.

Study limitations

There were several limitations to this study. Our study patients were enrolled from the HD room of one regional hospital in southern Taiwan, so the generality of included patients was limited. Lack of data on some baseline characteristics and comorbidities, such as primary kidney disease (causes of HD), smoking and history of PAOD and coronary artery disease, along with extremely diverse patient numbers among groups may have influenced our results. Because there was no established cutoff valve of ABID for the prediction of mortality, we used the Chi-squared value to determine the best cutoff value of ABID. Our optimal cutoff value of ABID for the prediction of mortality was 0.13. This value differed from that used in previous studies. Hence, a future large-scale study to confirm a reliable cutoff value of ABID for survival prediction is necessary. Furthermore, our present study only aimed to evaluate total mortality events, so cardiovascular mortality and non-fatal events were not studied. Finally, although ABI < 0.9 and ABID ≥ 0.13 have different contributions to mortality prediction, we arbitrarily assigned one point for ABI < 0.9 and one point for ABID ≥ 0.13 when calculating the novel ABI score. While this ABI score calculation method was simple, it might not be the most adequate.

Conclusions

Our present study demonstrated that our novel ABI score combining ABI < 0.9 and ABID ≥ 0.13 could significantly predict overall mortality in multivariable analysis, even after adjusting for important clinical and laboratory parameters. This was the first study to confirm that this ABI score (combined consideration of low ABI and high ABID) was a useful survival predictor in HD patients. Hence, it is worthwhile to calculate this novel ABI score for better mortality prediction in HD patients.

Disclosure

We have no financial interest with regard to the information contained in this manuscript.

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