Title

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Journal

Kidney Medicine, 2(1)

ISSN

2590-0595

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Publication Date

2020

DOI

10.1016/j.xkme.2019.11.001

Peer reviewed

Association of Ankle-Brachial and Toe-Brachial Indexes With Mortality in Patients With CKD

Thejas P. Kamath, Ritika Prasad, Matthew A. Allison, Michael C. Criqui, Joachim H. Ix, Dena E. Rifkin, and Pranav S. Garimella

Rationale & Objective: A low ankle-brachial index (ABI) is used to diagnose peripheral artery disease (PAD) but may be normal or elevated in patients with medial arterial calcification and stiff vessels, as is common in chronic kidney disease (CKD). The toe-brachial index (TBI) has been recommended because it is not influenced by medial arterial calcification, but alone the TBI does not capture risk associated with medial arterial calcification. We hypothesized that the difference between ABI and TBI (ABI − TBI) would capture both PAD and medial arterial calcification and thus better identify mortality risk from PAD, particularly in those with CKD.

Study Design: Prospective cohort study.

Setting & Participants: 471 patients with clinical suspicion for PAD referred for vascular testing.

Exposures: ABI, TBI, and ABI − TBI.

Outcome: All-cause mortality.

Analytical Approach: Cox proportional hazards models evaluating the association of ABI − TBI with mortality over 7 years.

Results: Mean age was 68 years, 89% were men, 35% had diabetes, 64% had CKD, and mean estimated glomerular filtration rate was 55 mL/min/1.73 m^2. Median ABI was 0.96 (interquartile range [IQR], 0.73-1.08), median TBI was 0.62 (IQR, 0.46-0.81), and median ABI − TBI was 0.23 (IQR, 0.14-0.39). Higher ABI − TBI values were associated with increased risk in mortality only among participants with ABI values ≥ 0.9 ($P = 0.03$). Among participants with CKD and ABI values ≥ 0.9, participants with ABI − TBI values higher than the median had greater (HR, 1.79; 95% CI, 1.18-2.72) risk for mortality ($P = 0.005$). This was attenuated after age adjustment (HR, 1.41; 95% CI, 0.91-2.20) but did not change after further adjustment for confounders.

Limitations: Mainly male cohort derived from a vascular laboratory; lack of limb outcomes and data for albuminuria.

Conclusions: A high ABI − TBI value may be associated with higher risk for mortality in persons with CKD and a normal ABI. Age affects this association, and further studies evaluating ABI − TBI in larger populations are required.

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Kidney Med. 2(1):68-75. Published online January 8, 2020.

doi: 10.1016/j.xkme.2019.11.001

Ankle-brachial index (ABI) is the most common noninvasive test to assess significant obstructive lower-extremity peripheral arterial disease (PAD).[1] Although an ABI value < 0.9 is sensitive to diagnose PAD, the presence of either poorly compressible or noncompressible ankle arteries can elevate ankle blood pressures obtained using a blood pressure cuff, leading to high ABI values.[2] Medial artery calcification is nonobstructive calcification of the tunica media that occurs commonly in arteries of older adults and those with diabetes and chronic kidney disease (CKD), leading to elevated ABI values.[3-6] An ABI elevation due to medial artery calcification limits its diagnostic value.[4] By weakening the diagnostic sensitivity of the ABI, medial artery calcification may lead clinicians to underestimate the long-term risk for cardiovascular disease (CVD), mortality, and amputations.[7]

The toe-brachial index (TBI) is the ratio of systolic blood pressure at the great toe to that measured at the brachial artery and is an alternative measure to the ABI to evaluate for PAD.[8] Because arteries in the toe are less likely to be affected by medial artery calcification,[9] TBI may be more specific to diagnose PAD and identify persons at risk for major adverse cardiovascular events.[10] Currently, however, the Inter-Society Consensus for the Management of Peripheral Arterial Disease, American Heart Association/American College of Cardiology, and European Society of Cardiology/European Society for Vascular Surgery guidelines recommend measuring TBI to diagnose suspected PAD only when ABI is >1.4.[11-13]

This approach of using TBI in select cases with very high ABI values does not address the problem that PAD and medial artery calcification may coexist and result in values within the normal ABI range (ie, 0.9-1.4).[10] In these patients, a normal ABI may be falsely reassuring and reflect relatively stiff vasculature at the ankle while there is concomitant significant obstructive disease resulting in lower pressures in the ankle arteries. These individuals may have a relatively wide difference between ABI and TBI, indicating both stiffness at the ankle and atherosclerotic disease within the vessels. The clinical significance of this kind of discrepancy between ABI and TBI has not been evaluated systematically.

A single inclusive measure that captures both atherosclerotic PAD and medial artery calcification would be helpful but does not yet exist in clinical practice. We hypothesized that calculating the difference of ABI and TBI (ABI − TBI) may improve identification of persons at risk for all-cause mortality. We initially developed the concept

of the ABI − TBI in a small study of 37 dialysis patients because persons undergoing dialysis often have significant atherosclerosis and vascular calcification. The study demonstrated that low TBI was associated with increased mortality risk. [14] The ABI − TBI had similar directional association but failed to achieve statistical significance, likely due to the small study sample. In the current study, we aimed to evaluate ABI − TBI in a larger cohort of patients with a lesser degree of decreased kidney function.

We hypothesized that higher ABI − TBI value would be more strongly associated with all-cause mortality than lower ABI − TBI, especially in persons with ABI values > 0.9. We further hypothesized that this relationship would be modified by the presence of CKD (a priori *P* for interaction < 0.2), given that persons with CKD are at particular risk for developing both low and high ABI values. [15]

METHODS

Population

We studied patients originally enrolled in a cohort designed to assess changes in noninvasive measures of PAD. The patient population has been described in depth in prior work and the cohort design is depicted in Figure 1A. [7,16,17] In brief, 510 participants were recruited in 1990 to 1994 from 2,265 potentially eligible patients who had previously had at least 1 noninvasive lower-extremity arterial test between 1980 and 1990 at the San Diego Veterans Administration Medical Center or the University of California, San Diego Medical Center vascular laboratory. [7,16,17] The goal was to create a cohort of patients with suspected PAD and systematically assess them in follow-up. These participants had noninvasive lower-extremity vascular tests done in the research setting between 1990 and 1994. Participants were then followed up through December 31, 2001 (median follow up, ~7 years) to ascertain outcomes. The study ended in 2001, and further follow-up data were not collected.

Of the 510 participants in the cohort, we excluded those who were missing ABI, TBI, creatinine, demographic data (ethnicity, age, and sex), mortality data, or several CVD risk factors (body mass index, diabetic status, hypertension, and smoking history). Thus, our final analysis sample comprised 471 participants who had complete data for demographics, ABI, TBI, mortality, and CVD risk factors (Fig 1A). All participants completed written informed consent forms. These forms, original study protocol, and analysis of these data for this project were approved by the University of California, San Diego Investigational Review Board (Project #171059X).

Exposure

ABI and TBI were obtained after blood pressure measurement on ankles, first toe, and arms using the sphygmomanometric technique. [16] The signals were detected by photoplethysmography at the first toe and third finger. [17] All patients underwent TBI measurements irrespective of findings of the ABI, imaging, or waveform information as per institution protocol. Given the correlation between subclavian stenosis and PAD, [18] ABI and TBI were calculated using the higher brachial systolic blood pressures. The 95% confidence interval (CI) for reproducibility of ABI is 0.10 to 0.15. Variability in TBI has been reported to be similar to that for the ABI. [19–23] The entire protocol for obtaining ABI and TBI have been described in prior studies. [16,17] We did not exclude participants with very low or high baseline ABI values (ie, ABI < 0.6 or >1.4). ABI − TBI was calculated as the difference between the ABI and TBI, thus generating 2 ABI − TBI values per patient (right and left). We used the higher of the ABI − TBI values

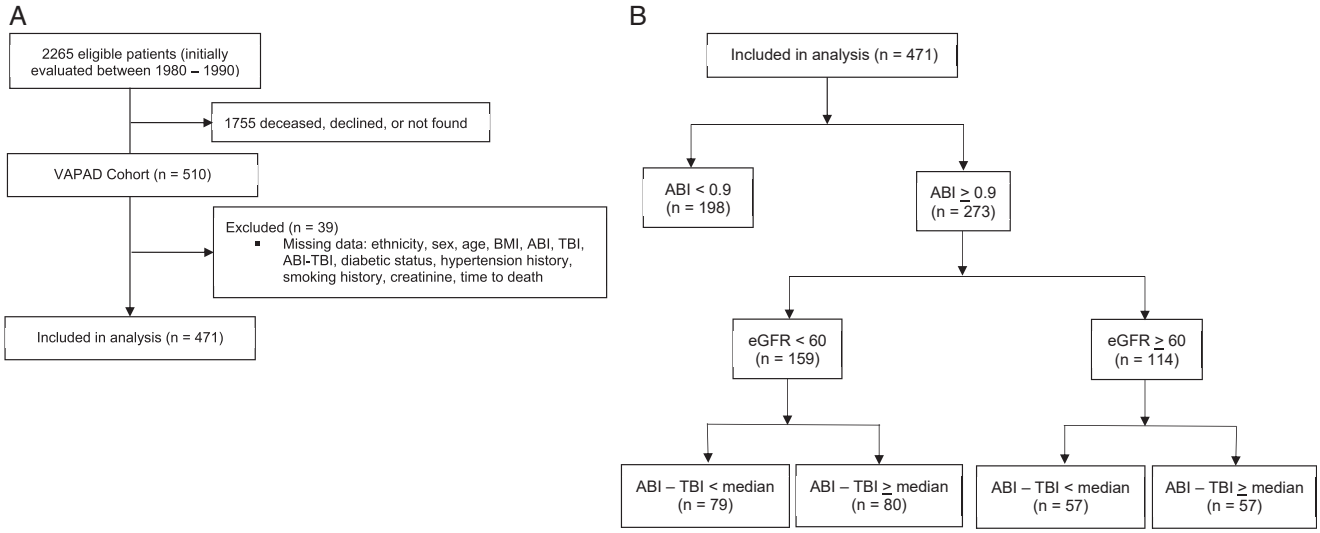

Figure 1. (A) Population selection algorithm. (B) Flowchart of the selection of the study groups. Abbreviations: ABI − TBI, ankle brachial index − toe brachial index; BMI, body mass index; eGFR, estimated glomerular filtration rate; VAPAD, Veterans Administration Peripheral Arterial Disease.

Table 1. Baseline Patient Characteristics

	ABI < 0.9			ABI ≥ 0.9		
	ABI − TBI < 0.18[a] (99 [21%])	ABI − TBI ≥ 0.18[a] (99 [21%])	*P*	ABI − TBI < 0.31[a] (136 [29%])	ABI − TBI ≥ 0.31[a] (137 [29%])	*P*
Age, y	68 ± 7	71 ± 7	0.005	65 ± 9	69 ± 10	<0.001
Women	8 (8%)	11 (11%)	0.5	16 (12%)	17 (12%)	0.9
African American	3 (3%)	6 (6%)	NA	8 (6%)	1 (1%)	NA
Diabetes	43 (43%)	42 (42%)	0.9	33 (24%)	48 (35%)	0.05
Hypertension	88 (89%)	85 (86%)	0.5	102 (75%)	108 (79%)	0.5
CKD	73 (73%)	70 (70%)	0.6	71 (52%)	88 (64%)	0.04
Smoking			0.004			0.04
Current smoker	38 (38%)	30 (30%)		45 (33%)	31 (23%)	
Former smoker	57 (58%)	50 (51%)		77 (57%)	78 (57%)	
Never smoked	4 (4%)	19 (19%)		15 (11%)	28 (20%)	
Cholesterol, mg/dL						
Total	216 ± 46	211 ± 42	0.4	206 ± 38	204 ± 38	0.7
HDL	44 ± 12	46 ± 13	0.2	47 ± 15	47 ± 13	1.0
BMI, kg/m^2	27 ± 4	27 ± 4	0.5	27 ± 5	27 ± 5	0.7
eGFR, mL/min/1.73 m^2	52 ± 16	52 ± 15	0.7	58 ± 15	54 ± 13	0.02
TBI	0.53 ± 0.17	0.42 ± 0.12	<0.001	0.90 ± 0.15	0.60 ± 0.17	<0.001
ABI	0.63 ± 0.14	0.71 ± 0.12	<0.001	1.05 ± 0.09	1.15 ± 0.21	<0.001

Note: Patients with negative ABI − TBI values are not included in this table. Categorical data are expressed as number (percent), and continuous data, as mean ± standard deviation.
Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CKD, chronic kidney disease (eGFR < 60 mL/min/1.73 m^2); eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NA, not available; TBI, toe-brachial index.
[a]Represents the median ABI − TBI value for this ABI category.

(potentially indicative of both greater atherosclerosis and medial artery calcification) as the index ABI − TBI per patient, and the ABI and TBI measures used to generate this index ABI − TBI as the index ABI and TBI per patient.

Outcomes

All-cause mortality was ascertained by linking cohort data to the Social Security Death Index.[24]

Covariates

Demographics included age, sex, and race. Lifestyle and comorbid conditions included smoking status (current, former, or never smokers), diabetes (defined as fasting plasma glucose ≥ 126 mg/dL, use of insulin, or use of oral hypoglycemic medications), hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or use of antihypertensive medications), body mass index (calculated from values for weight [kg]/height [m^2]), dyslipidemia (categorized as use of lipid-lowering drugs or a ratio of total cholesterol to high-density lipoprotein cholesterol >5), coronary artery disease (defined as having prior myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty), and prior peripheral artery disease (defined as prior limb revascularization). Kidney function included estimated glomerular filtration rate (eGFR) calculated from serum creatinine level (Jaffé method) using the 4-variable CKD Epidemiology Collaboration equation.[25] We defined CKD as eGFR < 60 mL/min/1.73 m^2.

Statistical Analysis

We described the distribution of ABI − TBI using summary statistics (median and interquartile range [IQR]). After stratification by ABI categories (ABI < 0.9 and ≥0.9; Fig 1B),[1] we described baseline participant characteristics (demographics, kidney function, and CVD risk factors) across ABI − TBI categories (ABI − TBI < median, ABI-TBI ≥ median). Given that no prior studies have evaluated ABI − TBI, we chose the median as a point of reference to categorize into high versus low groups. We first used Cox proportional hazards models to evaluate the associations of ABI − TBI with all-cause mortality in individuals with ABI > 0.9, using the median ABI − TBI of these persons for stratification. After stratifying by CKD status in those with ABI > 0.9, we calculated risk estimates for a 0.1 increment in ABI − TBI.

We used a series of nested models. Model 1 was unadjusted, model 2 was adjusted for age, model 3 was adjusted for model 2 plus sex and ethnicity, model 4 was adjusted for model 3 plus eGFR, and a final model 5 was adjusted for demographics, CVD risk factors (diabetes, smoking status, coronary artery disease, and prior PAD), and laboratory variables listed in covariates above. The proportional hazards assumption for covariates of interest was valid for these models as tested using Schoenfeld residuals.

Additionally, we generated restricted cubic splines to evaluate the association between ABI − TBI and hazard for all-cause mortality. We tested for an interaction between

ABI − TBI and CKD status ([ABI − TBI] × CKD status) in an unadjusted model ($P < 0.2$) and when statistical significance was found, we presented results stratified by CKD status. We similarly tested for an interaction between ABI − TBI and diabetes status ([ABI − TBI] × diabetic status]. Hazard ratios (HRs) and their corresponding 95% CIs were reported. In sensitivity analysis, we further stratified the CKD subgroup by diabetic status to evaluate whether diabetic status differentially affected the association between ABI − TBI and mortality among persons with CKD.

All analyses were completed using R, version 3.4.1 (R Foundation for Statistical Computing).[26] $P < 0.05$ was considered statistically significant for all analyses, excluding interaction terms. $P < 0.2$ was considered statistically significant for interaction terms.

RESULTS

Among the 471 participants, mean age was 68 years, 89% were men, 35% had diabetes, 64% had CKD, and mean eGFR was 55 mL/min/1.73 m^2. Median ABI was 0.96 (IQR, 0.73-1.08), median TBI was 0.62 (IQR, 0.46-0.81), and median ABI − TBI was 0.23 (IQR, 0.14-0.39).

Table 1 shows baseline demographic data and clinical characteristics of participants stratified initially by ABI and then by ABI − TBI categories (the respective median ABI − TBI). Among individuals with ABI < 0.9 (median ABI = 0.69, median TBI = 0.48), those with ABI − TBI values higher than the median were significantly older and more likely to be never smokers. Among individuals with ABI ≥ 0.9 (median ABI = 1.07, median TBI = 0.76), those with ABI − TBI values greater than the median were significantly older, more likely to be diabetic, less likely to be current smokers, and had significantly lower eGFRs.

Figure 2 shows Kaplan-Meier survival curves of the ABI − TBI groups and risk for all-cause mortality, stratified by ABI. In unadjusted analysis, among participants with ABI ≥ 0.9, higher ABI − TBI values were associated with increased risk in all-cause mortality (Fig 2B; $P = 0.03$). A significant difference in all-cause mortality risk between ABI − TBI categories was not observed in patients with ABI < 0.9 (Fig 2A; $P = 0.2$). When examined as a continuous variable in unadjusted restricted cubic spline analysis, there was a linear relationship between ABI − TBI values > 0.35 and all-cause mortality.

Among individuals with ABI < 0.9, each 0.1 increment in ABI − TBI was not associated with all-cause mortality. In participants with ABI ≥ 0.9, each 0.1 increment in ABI − TBI was associated with a 10% increase in all-cause mortality in an unadjusted model (HR, 1.10; 95% CI, 1.04-1.16). This result was no longer significant when models were adjusted for multiple confounders (HR, 1.05; 95% CI, 0.98-1.11). In individuals with ABI ≥ 0.9, having an ABI − TBI greater than the median value was associated with 44% increased risk in all-cause mortality in an unadjusted Cox model (HR, 1.44; 95% CI, 1.04-2.01) but not after adjustment for the confounders listed (HR, 1.11; 95% CI, 0.78-1.59; Table 2).

We found a statistically significant interaction between ABI − TBI value and CKD status in an unadjusted model among individuals with ABIs ≥ 0.9 (P-interaction = 0.19). However, we did not find a statistically significant interaction between ABI − TBI value and diabetic status (P-interaction = 0.9). Figure 3 depicts Kaplan-Meier survival curves for the association between ABI − TBI and all-cause mortality among individuals with ABI ≥ 0.9, stratified by CKD status. In unadjusted analysis among those with CKD and in patients with ABI ≥ 0.9, those with ABI − TBI higher than the median had higher risk for all-cause mortality (Fig 3A; $P = 0.005$). Specifically, this was associated with 79% increased risk in all-cause mortality in an unadjusted Cox model (HR, 1.79; 95% CI, 1.18-2.72; Table 3). HRs were attenuated when models were adjusted for age (HR, 1.41; 95% CI, 0.91-2.20); minimal further attenuation was seen

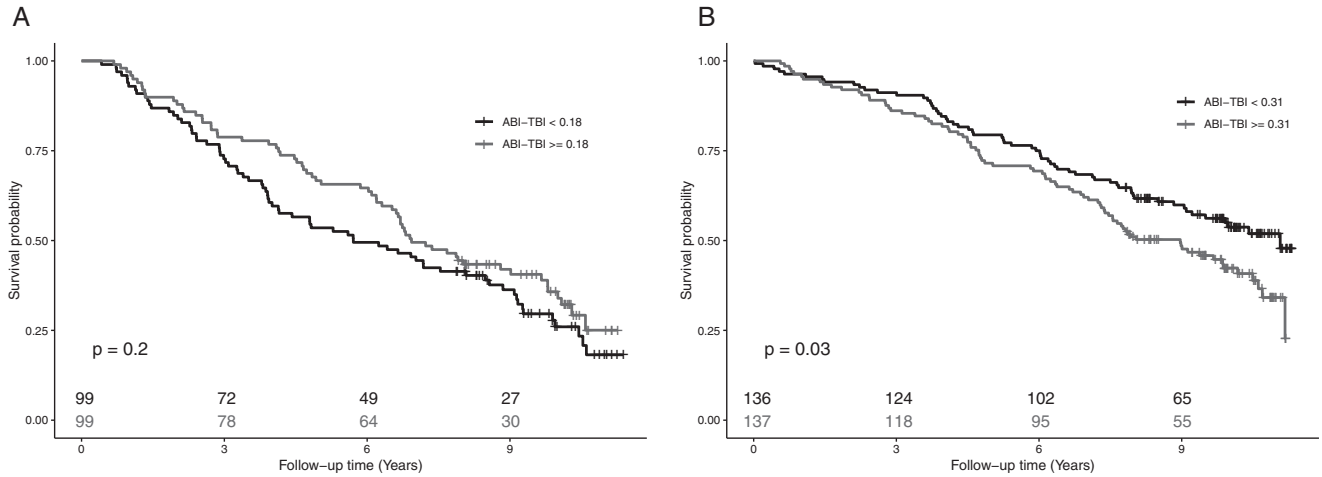

Figure 2. Kaplan-Meier curves of ankle brachial index − toe brachial index (ABI – TBI) categories and risk for all-cause mortality in individuals with (A) ABI < 0.9 compared with (B) ABI ≥ 0.9. Crosses on curves indicate censoring events.

Table 2. Association of ABI − TBI With All-Cause Mortality in Individuals With ABI ≥ 0.9

Group	No. of Events	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 4[d] HR (95% CI)	Model 5[e] HR (95% CI)
ABI − TBI < 0.31[f]	62	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
ABI − TBI ≥ 0.31[f]	81	1.44 (1.04-2.01)	1.14 (0.80-1.62)	1.15 (0.81-1.63)	1.17 (0.82-1.66)	1.11 (0.78-1.59)

Abbreviations: ABI − TBI, ankle brachial index − toe brachial index; CI, confidence interval; HR, hazard ratio.
[a]Unadjusted.
[b]Adjusted for age.
[c]Adjusted for age, sex, and ethnicity.
[d]Adjusted for age, sex, ethnicity, and estimated glomerular filtration rate.
[e]Adjusted for age, sex, ethnicity, diabetes, smoking (current, former, never), and estimated glomerular filtration rate.
[f]Represents the median ABI − TBI for this ABI category.

with adjustment for demographics (HR, 1.40; 95% CI, 0.90-2.19), eGFR (HR, 1.45; 95% CI, 0.92-2.27), and clinical characteristics (HR, 1.36; 95% CI, 0.85-2.19). There was no statistically significant difference in all-cause mortality risk between the ABI − TBI groups among participants without CKD and ABI ≥ 0.9 (Fig 3B; P = 0.3).

In sensitivity analysis, diabetes was significantly associated with all-cause mortality after age adjustment, but this was no longer statistically significant after further multivariable adjustment (Table S1).

DISCUSSION

Our study evaluated risk factors associated with ABI − TBI and the association between ABI − TBI and all-cause mortality in a cohort of patients with clinically suspected PAD who underwent systematic measurements of both ABI and TBI in a controlled setting. This cohort thus provided a unique opportunity to evaluate both ABI and TBI, unlike most clinically available cohorts that would have measured TBIs only in a select subset of individuals with high ABIs. We demonstrate that in individuals with ABI values ≥ 0.9, those with a higher ABI − TBI value were significantly older, were more likely to have diabetes, and have lower kidney function. In these patients, ABI − TBI values greater than the median were associated with greater risk for all-cause mortality in unadjusted analysis. Although overall findings and those in the CKD subset were attenuated by adjustment for age, the direction of the findings remained suggestive of greater risk with higher ABI − TBI value. Although this is not a definitive finding, we believe the ABI − TBI warrants further study, particularly in the CKD and diabetes populations.

Older age, diabetes, and CKD are all associated with increased risk for arterial stiffness.[3-6] Our study found that diabetic status and lower eGFRs were associated with greater ABI − TBI in those with ABIs ≥ 0.9. We conclude that in these individuals, the ABI − TBI value identifies risk factors that promote arterial stiffening, which may otherwise be more difficult to identify by relying solely on a high ABI (ABI ≥ 1.4). Although a parallel finding was lacking in those with low ABI values, it is possible that ABI − TBI is still important in cases in which even a lower ABI is artificially elevated and would not trigger clinical concern.

ABI − TBI may serve as a single inclusive measure that can capture both atherosclerosis and arterial stiffness. For instance, a high ABI − TBI in the setting of ABI ≥ 0.9 and TBI < 0.7 may indicate the presence of both atherosclerotic disease and arterial stiffness, while a low ABI − TBI value in

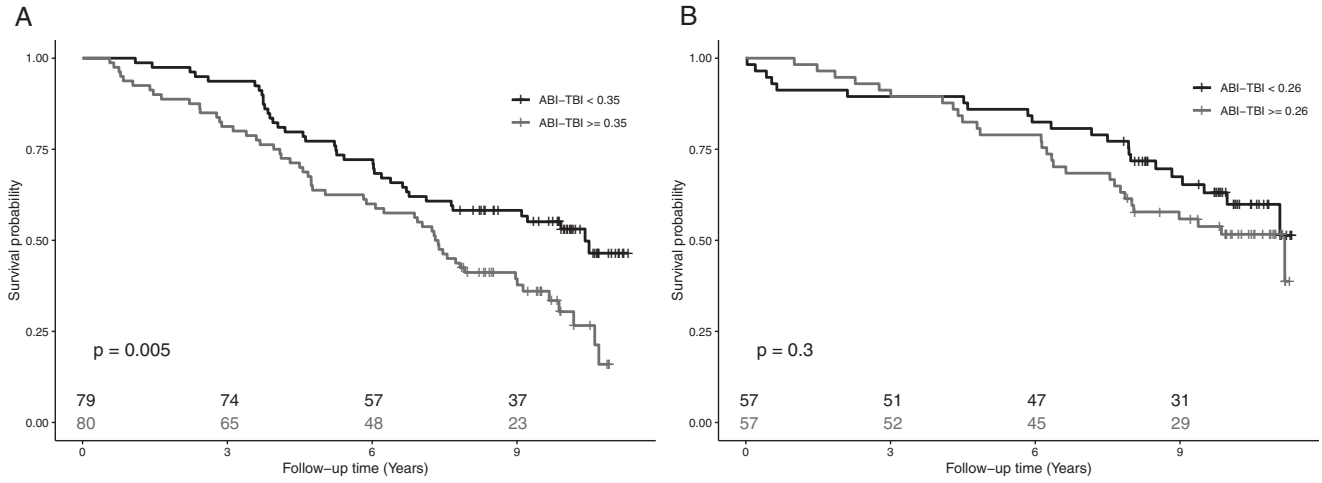

Figure 3. Kaplan-Meier curves of ankle brachial index − toe brachial index (ABI − TBI) categories and risk for all-cause mortality in individuals with (A) ABI ≥ 0.9 and CKD compared with (B) ABI ≥ 0.9 and without CKD. Crosses on curves indicate censoring events.

Table 3. Association of ABI − TBI With All-Cause Mortality in Individuals With ABI ≥ 0.9 Stratified by eGFR

Group[a]	No. of Events	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)	Model 3[d] HR (95% CI)	Model 4[e] HR (95% CI)	Model 5[f] HR (95% CI)
Continuous:						
eGFR ≥ 60 mL/min/1.73 m^2	50	1.05 (0.96-1.15)	1.04 (0.94-1.14)	1.03 (0.93-1.13)	1.03 (0.94-1.13)	1.03 (0.94-1.13)
eGFR < 60 mL/min/1.73 m^2	93	1.13 (1.05-1.22)	1.10 (1.02-1.20)	1.09 (1.01-1.19)	1.07 (1.00-1.16)	1.06 (0.97-1.15)
Noncontinuous:						
eGFR < 60 mL/min/ 1.73 m^2: ABI − TBI < 0.35[g]	38	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
eGFR < 60 mL/min/1.73 m^2: ABI − TBI ≥ 0.35[g]	55	1.79 (1.18-2.72)	1.41 (0.91-2.20)	1.40 (0.90-2.19)	1.45 (0.92-2.27)	1.36 (0.85-2.19)

Abbreviations: ABI − TBI, ankle brachial index − toe brachial index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]$P = 0.19$ for interaction by eGFR in individuals with ABI ≥ 0.9.
[b]Unadjusted.
[c]Adjusted for age.
[d]Adjusted for age, sex, and ethnicity.
[e]Adjusted for age, sex, ethnicity, and eGFR.
[f]Adjusted for age, sex, ethnicity, diabetes, smoking (current, former, never), coronary artery disease, prior peripheral artery disease, and eGFR.
[g]Represents the median ABI − TBI for this eGFR category.

the setting of ABI < 0.9 may indicate the likelihood of significant atherosclerotic disease without arterial stiffness. In this study, we demonstrate the association between high ABI − TBI value and increased risk for all-cause mortality in individuals with ABI values that would otherwise be considered normal.

If this is confirmed in other studies, there may be clinical utility in reporting ABI − TBI such that clinicians may more easily recognize the presence of arterial stiffness in patients with PAD because individual data points in a busy clinical practice may not stand out to the clinician. For example, ABI of 1.3 and TBI of 0.8 are putatively normal and will not individually get flagged in a vascular laboratory report. However, the difference may carry meaning that is missed when looking at the ABI and TBI separately, but may still be of clinical significance. In other disciplines, clinical calculations are given in laboratory or electronic medical record output when relevant, such as Framingham score from clinical variables or eGFR from demographic variables and serum creatinine level. If our findings are confirmed, ABI − TBI may be a relevant additional variable in the vascular laboratory report.

Our work suggests that the clinical utility of ABI − TBI may be most apparent among patients with CKD, especially when ABI is not low. Presently, major guidelines recommend obtaining TBI to diagnose patients with suspected PAD only when ABI is >1.4 or the ABI is incompressible.[11-13] While investigating the association between ABI − TBI and all-cause mortality, we found that patients with CKD with putatively normal ABI measurements and ABI − TBI values greater than the group's median had comparatively higher risk for all-cause mortality. Our study's finding suggests that patients with CKD referred for vascular testing with ABI values > 0.9 may yet have underlying vascular disease, and that these individuals could benefit from receiving a concurrent TBI during their initial vascular assessment.

Our study has limitations that should be considered when interpreting the results. First, although ABI − TBI serves as a single inclusive measure that potentially captures information regarding both atherosclerosis and arterial stiffness, it cannot discriminate between these 2 distinct pathologic states. For instance, higher ABI − TBI value may be driven by the presence of medial artery calcification causing a high ABI or of atherosclerotic plaque causing a low TBI. In addition, TBI captures both micro- and macrovascular disease at the level below the ankle, and without waveform analysis, we cannot distinguish between these.[8,27] Second, urine albumin data were unavailable to compute albumin-creatinine ratios; thus, CKD status was determined only by eGFR. Third, the absence of lower-limb angiography does not allow for us to confirm the presence of PAD. Fourth, because major adverse limb events were not collected in the study, we were unable to generate data for amputation and amputation-free survival, which would be useful to assess limb-based risks. Fifth, the cohort is mostly male, reflecting heavy sampling from the Veterans Affairs Medical Center, and thus generalizability is limited. Furthermore, patients who underwent vascular laboratory testing were referred based on clinical suspicion of atherosclerotic PAD as opposed to being an asymptomatic screening cohort, introducing a degree of referral bias.

Our study also has many strengths. The study sample is relatively large with good follow-up data and robust ascertainment of mortality. Importantly, since all patients in the study underwent both ABI and TBI irrespective of baseline ABI or waveform information per institutional protocol, potential indication bias was significantly reduced and we were able to evaluate for the presence of a low TBI value in those with low and normal ABI values, not just high ABI as is currently recommended by PAD guidelines.[11-13] The significance of TBI in patients with normal ABI values with respect to diagnosis, major adverse limb events, and wound healing has been previously well described in individuals with critical limb ischemia.[28] Furthermore, ABI − TBI has been previously studied in patients with and without diabetes, with no association

found between larger ABI − TBI values and the presence of diabetes in individuals with critical limb ischemia.[29] However, to our knowledge, this is the first study attempting to capture both calcification and atherosclerotic disease using a single diagnostic parameter (ABI − TBI) with mortality as the primary outcome and adds to the literature the need to evaluate these tests more rigorously, specifically in patients with kidney disease.

In conclusion, ABI − TBI may serve as a useful construct that captures information regarding both vessel stiffness and atherosclerosis. Although it allows the possibility of quantifying the degree of both disease processes, additional studies are required to assess the prospect of distinguishing the contribution of each pathology to the magnitude of the ABI − TBI. Among individuals with ABI > 0.9, there is an association between higher ABI − TBI value and risk for all-cause mortality. Further studies in patients at risk for medial artery calcification, such as those with CKD who may require testing with TBI in addition to ABI, are needed to confirm our preliminary findings. Additional studies evaluating these risk factors in association with limb outcomes would be an important way to identify at-risk patients and potentially provide them with earlier treatment.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Association of ABI − TBI with all-cause mortality in individuals with ABI ≥ 0.9 and eGFR < 60 stratified by diabetic status

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Authors' Contributions: Research idea and study design: TPK, MAA, MCC, JHI, DER, PSG; data acquisition: TPK, JHI, MAA MCC; data analysis/interpretation: TPK, RP, JHI, DER, PSG; statistical analysis: TPK, DER, PSG; supervision or mentorship: JHI, DER, PSG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This study was supported by a short-term training grant to Mr Kamath from the UAB-UCSD O'Brien Center for Acute Kidney Injury Research. Dr Garimella was supported by a career development grant (K23 DK114556) from the National Institute of Diabetes and Digestive and Kidney Diseases. Dr Rifkin was supported by VA HSR&D Merit IIR 15-369. The funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received April 29, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form November 15, 2019.

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