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Name Sujin Lee Date 3/19/19

Evaluation of Peripheral Calcium Score as a Measure of Peripheral Arterial Disease Burden and Amputation Risk

By

Sujin Lee
Master of Science

Clinical Research

_____

Shipra Arya, MD
Advisor

_____

Mitch Klein, PhD
Committee Member

_____

Henry Blumberg, MD
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

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By

Sujin Lee
BA

Advisor: Shipra Arya, MD MSc

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2019

Abstract

Evaluation of Peripheral Calcium Score as a Measure of Peripheral Arterial Disease Burden and Amputation Risk

By Sujin Lee

Peripheral arterial disease (PAD) is a global atherosclerotic pandemic characterized by chronic occlusive arterial disease of the lower extremities. The ankle-brachial pressure index (ABI) and toe-brachial pressure index (TBI) are non-invasive tools used to diagnose PAD by measuring blood pressures at the ankle or toe compared to the arm at a pressure where no flow is detected by ultrasound. The ABI and TBI are flawed because they do not adequately represent arterial flow in calcified vessels. The purpose of this research is to evaluate whether a comprehensive peripheral calcium scoring (PCS) system would complement ABI and TBI to achieve a superior prognostic measure of PAD. We conducted a retrospective cohort of 50 patients, who reported to vascular surgery clinics from 2004 to 2014, to compare their distributions of ABI, TBI, and PCS, and to assess how well these prognostic indicators predicted the dichotomous outcome of an amputation of a lower limb. The particular interest was to evaluate how well PCS improved the prediction of amputation after controlling for ABI and TBI levels. We measured the calcium burden in peripheral vessels by applying the coronary calcium scoring module to non-contrast CT scans of the infra-renal aorta and lower extremity runoff. We built a predictive model using a dichotomized PCS variable as a predictor at an a priori cutoff value of 1000. Using multivariate logistic regression, the odds ratio for the association between tibial PCS and amputation was estimated at 6.61 (3.77-11.59, $p<0.001$, controlling for ABI and TBI, suggesting that PCS can be a useful prognostic indicator for PAD patients beyond ABI and TBI. We also built models using ABI, TBI, and continuous PCS separately and in combination to predict amputation. The best fitting model included ABI, TBI, and tibial PCS (AUC=0.87, $p<0.001$). This study underscores the importance of tibial PCS as an individual prognostic tool, as well as a significant supplemental tool, to improve the prognostication of patients with PAD.

Evaluation of Peripheral Calcium Score as a Measure of Peripheral Arterial Disease Burden and Amputation

Sujin Lee BA, Kanika Kalra MD, Benjamin Redpath BS, Adam Bernheim MD, Brent Little MD, Luke Brewster MD, Leslee Shaw PhD, Shipra Arya MD SM

From the Division of Vascular Surgery and Endovascular Therapy, Department of Surgery, Emory University School of Medicine, Atlanta GA; Surgical Service Line, Atlanta VA Medical Center, Decatur GA; Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta GA; Division of Vascular Surgery, Department of Surgery, Stanford University School of Medicine, Palo Alto, CA; Palo Alto VA Medical Center, Palo Alto, CA; Surgical Services, Palo Alto VA Medical Center, Palo Alto, CA.

Author conflict of interest: none.

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INTRODUCTION

Peripheral arterial disease (PAD) is a global atherosclerotic pandemic affecting 200 million people in the world and 8-12 million people in the US.[1] It is defined as chronic occlusive arterial disease of the lower extremities characterized by atherosclerotic and calcific processes. The most common presentation of PAD is claudication, which is lower extremity (LE) pain with walking due to decreased muscular perfusion.[2] Patients with PAD tend to be older with comorbid diabetes, hypertension, hyperlipidemia, and history of smoking. If left untreated, PAD can progress to rest pain, non-healing ulcers, lower limb amputations, and death.[3] Amputations pose high morbidity on functional status with detrimental effects.[4] Therefore, a major clinical goal for PAD patients is limb preservation.

The diagnostic gold standards of PAD are the ankle-brachial pressure index (ABI) and toe-brachial pressure index (TBI). These are ratios of blood pressures measured non-invasively at the ankle or toe compared to the arm at a pressure where no flow is detected by ultrasound. ABI and TBI can be categorized based on the clinical severity of PAD. However, the diagnosis and prognosis of PAD are complicated by vascular calcification, which is a biologic phenomenon attributed to aging vessels and metabolic disorders, including diabetes mellitus (DM) and chronic kidney disease (CKD).[5-7] In this study, we aimed to provide further evidence that a comprehensive peripheral calcium scoring system used to quantify vascular calcification in the peripheral vasculature would complement ABI and TBI in achieving a prognostic measure of PAD and a generalizable measurement of its severity.

BACKGROUND

In an increasingly aging world population, peripheral arterial disease (PAD) has been recognized as a global burden with high morbidity and mortality. Patients with leg symptoms are at three-fold increased risk of mortality and major cardiovascular events, such as heart attack and stroke, compared with those without PAD.[1,8] In addition to increased cardiovascular morbidity and death, patients with symptomatic PAD, which is defined as ABI < 0.9, have impaired lower extremity functioning and quality of life.[8] Having an accurate identification of PAD is essential to improving the prediction of cardiovascular risk and prevention of major cardiovascular and cerebrovascular events.

Due to the limitations of assessing lower extremity pain attributed to PAD, ankle brachial pressure index (ABI) has historically been used as an objective clinical measure of PAD. Although the specificity of ABI has been reported to be approximately 97%, the sensitivity is lower at 80%, in part due to the presence of stiff arteries with underlying medial calcification that falsely elevates the ABI. [9-11] The toe –brachial pressure index (TBI) is thought to be useful when obtained in conjunction with ABI in patients with non-compressible disease who have falsely elevated ABI because toe vessels are theoretically spared from medial arterial calcification, which can cause false pressure elevation.[12-14] However, TBI has a significant margin of error and is unreliable in identifying patients with PAD and comorbidities. In addition, studies have shown that TBI has limited prognostic utility, undergoing no significant change to reflect PAD progression when compared to ABI and other measures of distal perfusion, including posterior tibial peak forward velocity.[15,16] A new adjunctive measure for PAD identification is needed to better account for stiff vessels in the lower extremities attributed to medial artery calcification.

Arterial calcification can occur in nearly all vascular beds. Coronary calcification has been comprehensively studied due to its association with cardiovascular events and the availability of CT-based imaging modalities. The coronary artery calcium score is routinely used to assess the presence and extent of atherosclerosis in patients at risk for coronary heart disease.[17] The measurement of coronary artery calcium has been essential to improving risk stratification and determining the intensity of treatment.[18] Furthermore, calcification in different locations, including carotid artery, breast artery, thoracic aorta, abdominal aorta, and renal artery, has been investigated in a limited number of studies, which have demonstrated associations between calcification and mortality that vary in different vascular beds.[19,20] The sum of knowledge supports that vascular calcification is a subcomponent of atheroma and effectively identifies at-risk patients. Therefore, vascular calcification must be further examined in different locations to provide unique information for risk of mortality from the underlying disease process.[21] Additional benefit is that calcification in a vascular bed is easily measured and is repeatable in terms of the density and volume of calcified plaque.

Like coronary artery disease, peripheral artery disease is a cardiac risk equivalent that can be assessed with CT imaging. Vascular calcification in PAD has been attributed to aging vessels, where the process is accelerated in metabolic disorders, including diabetes mellitus and chronic kidney disease.[22] Studies in small cohorts have demonstrated the association between lower extremity calcium score and the severity of PAD. For instance, when lower extremity arterial calcifications were analyzed on multi-detector computed tomography (MDCT) in patients with diabetes and end-stage renal disease, lower extremity calcium scores were higher in patients with PAD and correlated with severity of PAD.[23,24] Emerging literature has also demonstrated this relationship between lower extremity calcium score and its ability to predict outcome in patients

with symptomatic PAD and other cardiovascular risk factors.[21] The development of a peripheral calcium scoring system would complement ABIs and TBIs in achieving an accurate diagnosis of PAD and measurement of its severity. A proper assessment of the severity of PAD would provide vital information to prescribe an appropriate treatment modality, including medical and surgical management for PAD.[25,26]

Currently, there is no such standardized system for measuring calcification in the peripheral vasculature. To date, no studies have compared the prognostic value of peripheral calcium score (PCS) with that of the ABI and TBI in a general population with PAD. To improve the prognostic characterization of PAD patients using non-invasive tools, we assessed peripheral calcium score (PCS) on CT scans to obtain an anatomic measurement of calcium burden in the peripheral vasculature.

In this study, we measured the calcium burden in peripheral vessels by applying the coronary calcium scoring module to non-contrast CT scans of the infra-renal aorta and lower extremity runoff. After determining the relationship among ABI, TBI, and PCS, we compared the ability of ABI, TBI, and PCS to predict the primary outcome of amputation as individual and additive measures. We also designated an a priori cutoff value for PCS to determine whether higher values of PCS better predict amputation rate while controlling for ABI and TBI. This study underscores the movement towards a more consistent evaluation of PAD and an efficient integration of clinical definitions into practice guidelines.

METHODS

A retrospective cohort of 50 PAD patients was undertaken to compare the distributions of ABI, TBI, and PCS, and to assess how well these prognostic indicators predicted amputation of a lower limb.

Aim 1. Define 4 levels of PAD severity using ABI and compare the distribution of PCS within ABI categories among patients referred to vascular surgery clinics

Aim 2. Define 3 levels of PAD severity using TBI and compare the distribution of PCS within TBI categories among patients referred to vascular surgery clinics

Aim 3. Evaluate PCS as a predictor of amputation of a lower limb, accounting for ABI and TBI values among patients referred to vascular surgery clinics.

Hypothesis: Supplementing ABI and TBI with PCS will improve the prediction of having a lower limb amputation rather than using ABI and TBI alone.

Study population and data sources. In a retrospective cohort study, we used the Emory University Corporate Data Warehouse to identify patients who reported to vascular surgery clinics and/or received vascular noninvasive lab measurements, between January 1, 2004 and March 1, 2014 (Figure 2). We found 50 patients (100 lower limbs) with non-contrast CT scans of the infra-renal aorta and lower extremity and noninvasive measurements of ABI available for analysis. Inclusion criteria included availability of ABIs and CTs prior to any vascular procedures (grafts, stents, below-knee amputation, and above-knee amputation) with ABI obtained within 3 months of the CT. Exclusion criteria included patients with muscular dystrophies, familial hypercholesterolemia, hypercalcemia disorders, and abdominal aortic aneurysm greater than 5.5cm in diameter.

Study variables. Retrospective chart review was conducted to obtain patient variables, such as age, race, smoking status, history of hypertension, hyperlipidemia, type II diabetes, and chronic kidney disease. The primary outcome variable was below-knee or above-knee amputation, which was chosen as the primary leg-specific endpoint due to its detrimental effects on mobility, functional performance, and quality of life. The predictor of interest was total and segmental PCS, which was computed from pre-operative CT images as detailed below. The primary control variables were ABI and TBI measurements, which were obtained from the patients' charts. Patients were also categorized into 4 ABI groups and 3 TBI groups based on PAD severity (Table 1). Other demographic control variables included age, gender, race, and insurance status. Comorbidities including hypertension, hyperlipidemia, type II diabetes, and chronic kidney disease were not included in the regression models because they are part of the causal pathway that contribute to PAD progression.

Peripheral artery calcium scoring. Peripheral calcium scoring was performed using standardized calcium scoring software by two independent investigators who were blinded to the ABI values and baseline patient characteristics. The anonymized images of the patients were loaded into TeraRecon software, 3D reconstruction of the vessels was performed, and the calcium score was measured through the entire 3D reconstruction using a density-based contrast difference segmentation method. The calcium scores (CS) of the lower extremity were composed of 3 segments: the aorto-iliac (AI) segment, the femoro-popliteal (FP) segment, and the tibial segment (Figure 3). The AI segment included the infrarenal aorta, common iliac, and external iliac arteries. The FP segment included the common femoral, superficial femoral, and popliteal arteries. The tibial segment included the anterior tibial, posterior tibial, and peroneal arteries. A global and regional calcium score index was also developed. On cross-sectional images through the lower

extremities, total calcium score of plaques with density >130 HU and area >1mm^2 from infrarenal abdominal aorta to the foot was identified and scored. The PCS for each segment of interest was determined and expressed as an Agatston score according to the method described by Agatston et al.[27] Plaque density (in HU) and plaque volume measurements were recorded as both have been shown to contribute to risk assessment.[28]

Statistical Analysis. Using SAS statistical software, we obtained baseline characteristics of patients based on their ABI category and obtained the mean TBI in each ABI category (Table 2). For aim 1, we performed Spearman's rank order correlation between ABI and normalized PCS to assess their relationship as continuous measures. Then, we obtained distribution of PCS within categories of ABI. We also performed analysis of covariance (ANCOVA) adjusting for age, gender, and insurance status. For aim 2, we performed Spearman's rank order correlation between TBI and normalized PCS to assess their relationship as continuous measures. We then obtained distribution of PCS within categories of TBI. We also performed ANCOVA adjusting for age, gender, and insurance status. For aim3, we performed logistic regression to compare 3 models that included ABI, ABI +TBI, and ABI +TBI +PCS with amputation as the outcome. We obtained an odds ratio by dichotomizing PCS above a threshold and by controlling for ABI and TBI. We used the following model for the logistic regression:

$$logit\ P(amputation) = ß_0 + B_1PCS + B_2ABI1 + B_3ABI2 + B_4ABI4 + B_5TBI1 + B_6TBI2 + B_7age + B_8gender + B_9race1 + B_{10}race2 + B_{11}insurance.$$

ABI1, ABI2, and ABI4 were indicator variables representing four levels of ABI with the third level as the reference level. TBI1 and TBI2 were indicator variables representing three levels of TBI with the third level as the reference. Race1 and race2 represented three racial groups: black, white, and Hispanic.

For missing TBI values, we performed multiple imputation to replace missing data with 10 different imputed values based on the normalized dataset.[29] We averaged the 10 imputed values and accounted for their standard errors by fitting a model that included age, gender, race, insurance status as predictors of TBI. We also calculated the coefficient of concordance to obtain the distribution of calcium score obtained by 2 readers who scored 5 of the same legs and to assess the reliability of the PCS measure.

RESULTS

Baseline characteristics. We obtained baseline characteristics according to ABI categories (Table 2). Patients with normal ABI were more likely to be younger, less likely to have Type 2 diabetes and chronic kidney disease. They were also less likely to have critical limb ischemia and less likely to undergo amputation compared to patients in abnormal ABI categories. Patients with ABI >1.3 were more likely to be older with comorbid diabetes and chronic kidney disease. They were more likely to have critical limb ischemia and a higher amputation rate compared to patients in other ABI categories. We also obtained a high coefficient of concordance between the two readers of PCS (Intra class correlation 99%).

Relationship between PCS and ABI. On spearman's rank order correlation, normalized PCS was not correlated with ABI (r_s= -0.156, p=0.121). The relationship between the four levels of ABI and PCS was non-linear as the PCS levels were moderately high in the first (<0.5) and second (0.5-0.9) category of ABI, lowest in the third category (0.9-1.3), and highest in the fourth (>1.3). We found significantly lower PCS in the total, AI, FP, and tibial segments in the normal ABI group (third category) compared to the abnormal ABI groups (first, second, and fourth categories) using ANCOVA (Figure 5). When compared to patients with normal ABI (0.9-1.3), patients with ABI <0.5 had significantly higher AI PCS and higher total and FP PCS that trended towards significance (p=0.06). Patients with ABI between 0.5 and 0.9 had significantly higher total, AI, FP, and tibial PCS. Those with ABI>1.3 had significantly higher total and tibial PCS compared to patients with normal ABI. We found no significant difference in percent PCS when comparing the normal ABI group to other ABI categories. However, we found significant differences in percent FP and percent tibial PCS when comparing patients with ABI>1.3 to other ABI categories.

Relationship between PCS and TBI. Normalized PCS had a weak negative correlation with TBI (r_s= -0.261, p=0.017) and ABI had a moderately positive correlation with TBI (r_s= 0.544, p=<0.001) (Table 3). In the abnormal TBI group, we found significantly higher PCS in the AI segment when compared to the normal TBI group (Figure 6). When compared to patients with normal TBI, those with TBI<0.4 had significantly higher total, AI, and tibial PCS. Patients with TBI between 0.4 and 0.7 had significantly higher FP and tibial PCS compared to those with normal TBI. Furthermore, patients in abnormal TBI categories had significantly higher percent AI and percent tibial PCS compared to those in the normal TBI group. Based on this data, we included tibial PCS as the best measure of calcium burden in the peripheral vasculature when performing logistic regression analyses.

Amputation as primary outcome. To compare the ability of ABI, TBI, and tibial PCS to predict the risk of amputation, we used logistic regression to build predictive models using dichotomized and continuous PCS variables as predictors. To dichotomize the PCS variable, we used a cutoff value of 1000, which was chosen a priori to avoid data fishing. 1000 Agatston score was 75th percentile of the tibial PCS values. The odds ratio was estimated at 6.61 (95% CI: 3.77-11.59, p<0.001) for the association between tibial PCS and amputation, controlling for ABI and TBI, which suggests that PCS is a strong predictor for amputation holding ABI and TBI levels constant. We also estimated an odds ratio of 3.81 (95% CI: 2.04-7.12) comparing the amputation rate of African Americans and Caucasians (Table 4).

For continuous PCS variables, we obtained the area under the ROC curve (AUC) for each individual measure and performed an ROC contrast test between ABI, TBI, and tibial PCS (Figure 7). Tibial PCS (AUC=0.80, p=0.001) and ABI (AUC=0.76, p<0.001) had significantly larger AUC than TBI (AUC=0.67), although there was no significant difference in AUC between

tibial PCS and ABI ($p=0.35$). The area under the ROC curve for models that included 1) only ABI, 2) ABI and TBI, and 3) ABI, TBI, and tibial PCS were compared (Figure 8). The model containing all three indices had significantly larger AUC (0.87, $p<0.001$) compared to the other two models: ABI (AUC=0.76) and ABI+TBI (AUC=0.81).

DISCUSSION/CONCLUSIONS

In the current study, we demonstrate the utility of calculating PCS from non-contrast CT scans of patients with PAD to better evaluate the severity of calcification in peripheral vessels and measure the progression of disease. We determined that ABI and TBI have a positive correlation, which we anticipated from the increasing severity of disease as the measures increase from 0 to 1. We also found that TBI and total PCS have a negative correlation, meaning that increased severity of PAD, which is represented by lower TBI values, is characterized by higher PCS values.

The extent of calcification reflected by total, AI, FP, and tibial PCS was significantly higher in abnormal ABI categories, whereas tibial and percent tibial PCS were significantly higher in abnormal TBI categories. Guzman et al. echoed the clinical significance of tibial PCS by demonstrating that tibial artery calcification was a better marker of PAD severity and amputation risk compared to traditional risk factors and abnormal ABI.[30] Other studies have also suggested an association between distal calcification and amputation, especially in patients with diabetes and chronic kidney disease.[31-33] We did not control for these comorbidities because they are known causes of medial artery calcification and part of the causal pathway for PAD progression. Furthermore, tibial artery disease alone has been shown to lead to amputation.[34]

An important goal for treating PAD patients is to prevent the need for major lower limb amputation. We performed a logistic regression with amputation of a lower limb as the outcome of interest. Our hypothesis was that a patient's PCS level improves the prediction of an amputation after accounting for the commonly used diagnostic indices of ABI and TBI. To obtain an odds ratio, we dichotomized tibial PCS above 1000 versus below 1000 Agatston score. This was an a priori cutoff that represented approximately the 75th percentile of PCS in our data.

We selected our cutoff point a priori to avoid the issue of multiple comparisons. That is, we did not want to select our cutoff based on trial and error with the goal of finding the strongest effect (i.e., data fishing). Using logistic regression, we found that tibial PCS increased the odds of amputation by a factor of 6.61 while controlling for ABI and TBI. This was a significant finding that highlighted the utility of tibial PCS as a prognostic indicator beyond the information provided by ABI and TBI regarding amputation.

When comparing the models that combined ABI, TBI, and PCS, we found that the area under the curve (AUC) increased progressively as TBI was added to ABI and as tibial PCS was added to both ABI and TBI. Therefore, the AUC of the predictive model for amputation was maximized by combining ABI, TBI, and tibial PCS as diagnostic measures. We provide evidence that tibial PCS is a valid measure of PAD severity, and we contribute to existing data that PCS may be used as a prognostic tool to stratify patients based on amputation rate.

To date, no studies have compared PCS with ABI and TBI in characterizing amputation rate. Recent investigations have compared differing calcium scoring systems, including the lower limb arterial calcification (LLAC) scores and Bollinger scores, which characterize the severity of stenoses visualized on angiography, have been used to differentiate between above knee and below knee disease.[32,35] They demonstrate the association between PCS classification systems and increased cardiovascular mortality and morbidity.[32] However, expanding the investigation to compare PCS with the ubiquitous diagnostic measures of ABI and TBI is essential to improving risk stratification of PAD patients. There is an unmet need for further investigations to better characterize PAD progression and to translate prognostic classification into clinical practice.

The benefits of PCS align with those of the coronary artery calcium score, which include a greater area under the ROC curve than other risk factor-based prognostic paradigms.[36]

Compared to ABI and TBI, PCS accounts for the location of the plaque within different anatomic segments of the peripheral vasculature, which allows for the prediction of potentially disastrous outcomes involving proximal plaques that are more prone to rupture and more likely to undergo thrombotic occlusion.[23,30,32] In our study, we also account for the distribution of calcification by calculating the percentage of calcium in the tibial arteries compared to the total calcium present from the infra-renal aorta to the foot. This method underscores the idea that vessel-specific calcium scoring standardized to the individual's vasculature may be more informative than calcium scoring based solely on absolute total values.

Follow-up measurements are vital in tracking disease progression that may be masked by peripheral neuropathy in patients with diabetes and chronic kidney disease,.[6,7,37,38] These patients are also shown to have a higher baseline risk of ulceration, infection, critical limb ischemia, and amputation.[31,33,39,40] Due to the inability of the ABI and TBI to fully capture the progression of vessel calcification, current PAD screening recommendations for patients with diabetes and chronic kidney disease may be inadequate.[15,41] Therefore, PCS may help characterize PAD in patients with subclinical disease and aid in early intervention to decrease amputation risk.

We also highlight the feasibility of obtaining PCS using non-contrast CT scans of the lower extremity vessels.[42,43] Our readers obtained a very high coefficient of concordance by using a simple, semi-automated approach and applying the coronary calcium scoring module to peripheral vessels. The low interrater variability indicates that PCS can be accurately and reliably determined on non-contrast CT. In addition, the technique applied to the scans is standardized on the imaging software and does not require any additional reconstruction. PCS assessment can be done by obtaining the scan prior to contrast injection, which helps directly visualize and evaluate the peripheral vasculature. Therefore, PCS may be easily applicable in daily clinical practice.

A key limitation of our study was a small sample size, with each limb counting as a unit of analysis. The small sample size limited our ability to conduct sub-analyses of the groups categorized by PAD severity. Having a larger number of patients in the non-compressible ABI group could reveal important information in high-risk PAD patients. In addition, the data from this study was collected retrospectively, which limits the deduction of causal associations between vascular calcification and PAD outcomes. Larger trials are needed to clarify the role of PCS in accurately capturing the extent of disease progression in PAD patients.

To the best of our knowledge**,** this study is the first of its kind to determine the relationship among ABI, TBI, and PCS and demonstrate the significance of tibial PCS in predicting amputation with an estimated OR of 6.61 while controlling for ABI and TBI. We also achieve a reliable measurement of PAD severity through a simple and generalizable scoring method. We believe that this is an essential step in developing and validating a peripheral calcium scoring system. Overall, our study demonstrates the utility of a comprehensive PCS system to diagnose and evaluate PAD severity, particularly in high-risk subpopulations where non-invasive studies may be unreliable.

REFERENCES

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res.* 2015;116(9):1509-1526.
2. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med.* 2002;347(24):1941-1951.
3. Muluk SC, Muluk VS, Kelley ME, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. *J Vasc Surg.* 2001;33(2):251-257; discussion 257-258.
4. Vogel TR, Petroski GF, Kruse RL. Impact of amputation level and comorbidities on functional status of nursing home residents after lower extremity amputation. *J Vasc Surg.* 2014;59(5):1323-1330 e1321.
5. Ho CY, Shanahan CM. Medial Arterial Calcification: An Overlooked Player in Peripheral Arterial Disease. *Arterioscler Thromb Vasc Biol.* 2016;36(8):1475-1482.
6. Chen NX, Moe SM. Pathophysiology of Vascular Calcification. *Curr Osteoporos Rep.* 2015;13(6):372-380.
7. Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. *Circulation.* 2008;117(22):2938-2948.
8. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation.* 2004;110(6):738-743.
9. Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. *Eur J Vasc Endovasc Surg.* 2011;41(1):110-116.
10. Stein R, Hriljac I, Halperin JL, Gustavson SM, Teodorescu V, Olin JW. Limitation of the resting ankle-brachial index in symptomatic patients with peripheral arterial disease. *Vasc Med.* 2006;11(1):29-33.
11. Feringa HH, Karagiannis SE, Schouten O, et al. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2007;34(2):206-213.
12. Hoyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. *J Vasc Surg.* 2013;58(1):231-238.
13. Hyun S, Forbang NI, Allison MA, Denenberg JO, Criqui MH, Ix JH. Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. *J Vasc Surg.* 2014;60(2):390-395.
14. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(12):e726-e779.
15. Bird CE, Criqui MH, Fronek A, Denenberg JO, Klauber MR, Langer RD. Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. *Vasc Med.* 1999;4(1):15-21.
16. Alvaro-Afonso FJ, Garcia-Morales E, Molines-Barroso RJ, Garcia-Alvarez Y, Sanz-Corbalan I, Lazaro-Martinez JL. Interobserver reliability of the ankle-brachial index, toe-brachial index and distal pulse palpation in patients with diabetes. *Diab Vasc Dis Res.* 2018;15(4):344-347.

17. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med.* 2004;164(12):1285-1292.
18. Sharma RK, Sharma RK, Voelker DJ, et al. Cardiac risk stratification: role of the coronary calcium score. *Vasc Health Risk Manag.* 2010;6:603-611.
19. van Gils MJ, Bodde MC, Cremers LG, Dippel DW, van der Lugt A. Determinants of calcification growth in atherosclerotic carotid arteries; a serial multi-detector CT angiography study. *Atherosclerosis.* 2013;227(1):95-99.
20. Rifkin DE, Ix JH, Wassel CL, Criqui MH, Allison MA. Renal artery calcification and mortality among clinically asymptomatic adults. *J Am Coll Cardiol.* 2012;60(12):1079-1085.
21. Huang CL, Wu IH, Wu YW, et al. Association of lower extremity arterial calcification with amputation and mortality in patients with symptomatic peripheral artery disease. *PLoS One.* 2014;9(2):e90201.
22. Karwowski W, Naumnik B, Szczepanski M, Mysliwiec M. The mechanism of vascular calcification - a systematic review. *Med Sci Monit.* 2012;18(1):RA1-11.
23. Ohtake T, Oka M, Ikee R, et al. Impact of lower limbs' arterial calcification on the prevalence and severity of PAD in patients on hemodialysis. *J Vasc Surg.* 2011;53(3):676-683.
24. Singh DK, Winocour P, Summerhayes B, et al. Prevalence and progression of peripheral vascular calcification in type 2 diabetes subjects with preserved kidney function. *Diabetes Res Clin Pract.* 2012;97(1):158-165.
25. Adams HP, Jr., del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation.* 2007;115(20):e478-534.
26. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007;45 Suppl S:S5-67.
27. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15(4):827-832.
28. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA.* 2014;311(3):271-278.
29. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
30. Guzman RJ, Brinkley DM, Schumacher PM, Donahue RM, Beavers H, Qin X. Tibial artery calcification as a marker of amputation risk in patients with peripheral arterial disease. *J Am Coll Cardiol.* 2008;51(20):1967-1974.
31. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA.* 2002;287(19):2570-2581.
32. Chowdhury MM, Makris GC, Tarkin JM, et al. Lower limb arterial calcification (LLAC) scores in patients with symptomatic peripheral arterial disease are associated with increased cardiac mortality and morbidity. *PLoS One.* 2017;12(9):e0182952.

33. Dolan NC, Liu K, Criqui MH, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care.* 2002;25(1):113-120.
34. Wolfle KD, Bruijnen H, Reeps C, et al. Tibioperoneal arterial lesions and critical foot ischaemia: successful management by the use of short vein grafts and percutaneous transluminal angioplasty. *Vasa.* 2000;29(3):207-214.
35. Stoner MC, Calligaro KD, Chaer RA, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J Vasc Surg.* 2016;64(1):e1-e21.
36. Hecht HS. Coronary artery calcium scanning: past, present, and future. *JACC Cardiovasc Imaging.* 2015;8(5):579-596.
37. American Diabetes A. Peripheral arterial disease in people with diabetes. *Diabetes Care.* 2003;26(12):3333-3341.
38. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296-1305.
39. Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: the killer of patients with chronic kidney disease. *J Am Soc Nephrol.* 2009;20(7):1453-1464.
40. O'Hare AM. Management of peripheral arterial disease in chronic kidney disease. *Cardiol Clin.* 2005;23(3):225-236.
41. Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronek A. Risk factors for progression of peripheral arterial disease in large and small vessels. *Circulation.* 2006;113(22):2623-2629.
42. Blaha MJ, Mortensen MB, Kianoush S, Tota-Maharaj R, Cainzos-Achirica M. Coronary Artery Calcium Scoring: Is It Time for a Change in Methodology? *JACC Cardiovasc Imaging.* 2017;10(8):923-937.
43. Pavitt CW, Harron K, Lindsay AC, et al. Technical feasibility and validation of a coronary artery calcium scoring system using CT coronary angiography images. *Eur Radiol.* 2016;26(5):1493-1502.

TABLES/FIGURES

Table 1. Categories of ankle-brachial index (ABI) and toe-brachial index (TBI) by severity of peripheral artery disease (PAD)

PAD severity	Severe	Moderate	Normal	Non-compressible
ABI	<0.5	0.5-0.9	0.9-1.3	>1.3
TBI	<0.4	0.4-0.7	>0.7	

Table 2. Baseline Cohort Characteristics Stratified by ABI Category

	Categories of ABI by PAD Severity				
	ABI<0.5	**0.5<ABI<0.9**	**0.9<ABI<1.3**	**ABI>1.3**	Cohort
	N=19	N=37	N=36	N=8	N=100
Age, y	64.6±11	69.1±11	59.0±13	67.0±11	64.5±12
Male, sex, n (%)	12 (63)	18 (49)	17 (47)	7 (88)	54 (54)
Insured, n (%)	15 (79)	34 (92)	33 (92)	8 (100)	90 (90)
Ethnicity, n (%)					
Caucasian	12 (63)	24 (65)	29 (81)	3 (38)	68 (68)
African American	7 (37)	13 (35)	7 (19)	5 (63)	32 (32)
Clinical characteristics					
Diabetes Mellitus, n (%)	7 (37)	17 (46)	12 (33)	8 (100)	44 (44)
Chronic Kidney Disease, n (%)	3 (16)	8 (22)	2 (6)	5 (63)	18 (18)
Hypertension, n (%)	15 (79)	36 (97)	29 (81)	8 (100)	88 (88)
Hyperlipidemia, n (%)	10 (53)	32 (86)	20 (56)	2 (25)	64 (64)
Ever smoking, n (%)	13 (68)	26 (70)	26 (72)	5 (63)	70 (70)
Mean TBI, y	0.31±0.19	0.62±0.16	0.76±0.20	0.24±0.23	0.52±0.28
Critical limb ischemia, n (%)	4 (14)	2 (7)	2 (5)	3(38)	11 (11)
Scores					
Aorto-iliac Agatston	5167 (1825-10765)	5639 (2696-10170)	2022 (97-7818)	6802 (1268-13885)	4543 (1461-9678)
Femoral-popliteal Agatston	362 (56-7981)	3371 (1033-5949)	191 (3-1970)	455 (33-6949)	1058 (55-4213)
Tibial Agatston	84 (24-1862)	433 (18-1783)	100 (0-513)	1621 (83-16639)	170 (11-932)
Total Agatston	5496 (1965-22763)	11269 (4108-16973)	2437 (366-11910)	13177 (2920-31343)	6677 (1901-14061)
Aorto-iliac percent calcium	82 (52-94)	61 (44-79)	73 (54-92)	45 (34-96)	66 (45-91)
Femoral-popliteal percent calcium	14 (3-38)	33 (19-41)	11 (4-28)	3 (2-14)	20 (4-37)
Tibial percent calcium	4 (0.6-8)	5 (0.3-14)	4 (0-12)	38 (0.6-54)	4 (0.3-14)
Event					
Amputation (%)	3 (16)	4 (11)	2 (6)	4 (50)	13 (13)

Table 3. Spearman's rank order correlation coefficients comparing the distribution of ABI, TBI, and normalized PCS

Comparisons of diagnostic measures	ABI v TBI	ABI v normalized PCS	TBI v normalized PCS
Coefficient	0.544	-0.156	-0.261
P-value	<0.001	0.121	0.017
n	83	100	83

Table 4. Odds ratio estimates for predictors of logistic regression model with amputation as outcome

Variable	Comparisons	Odds Ratio	95% CI
Gender	Female vs Male	0.28	0.13-0.63
Race	African American vs Caucasian	3.81	2.04-7.12
	Hispanic vs Caucasian	0.95	0.38-2.37
Insurance status	Not insured vs Insured	1.20	0.49-2.91
ABI	0-0.5 vs 0.9-1.3	0.64	0.29-1.4
	0.5-0.9 vs 0.9-1.3	0.41	0.17-1.0
	>1.3 vs 0.9-1.3	1.06	0.39-2.87
TBI	0-0.5 vs >0.7	2.03	0.72-5.76
	0.5-0.7 vs >0.7	0.52	0.20-1.36
Tibial PCS	>1000 vs 0-1000	6.61	3.77-11.6

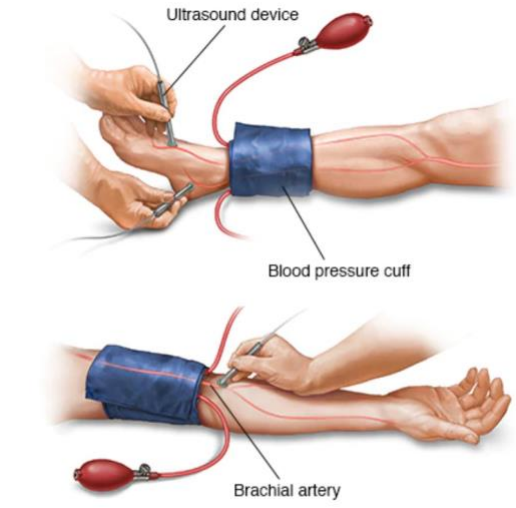
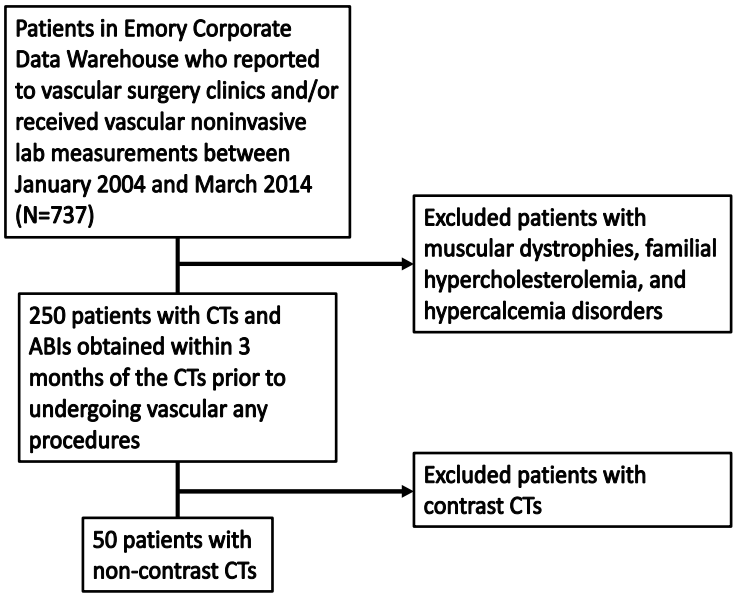
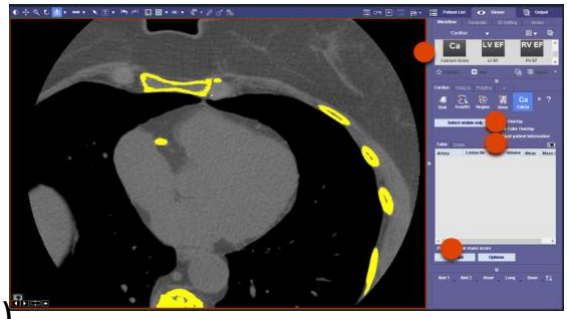


Figure 1. Measurement of ankle-brachial index (ABI) by calculating the ratio of the ankle pressure and the arm pressure at which no flow is detected by ultrasound.

Figure 2. Schema for Study Population



(a)



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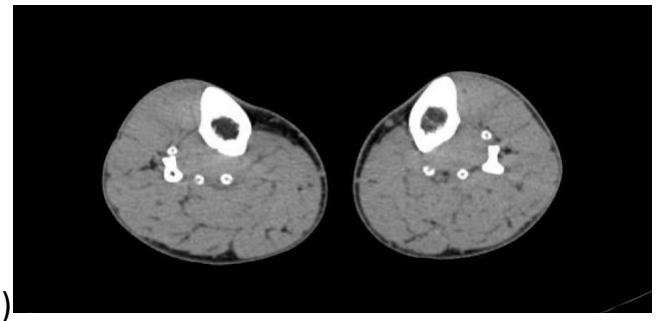


Figure 3. Coronary calcium scoring applied to peripheral vessels on TeraRecon. (a)TeraRecon calcium scoring. Plaques with density >130 Hounsfield units and area >1 mm^2 highlighted in yellow. (b) Axial view of calcified tibial vessels on non-contrast CT.

Figure 4. Vessel Segmentation from Infra-renal Aorta to the Feet

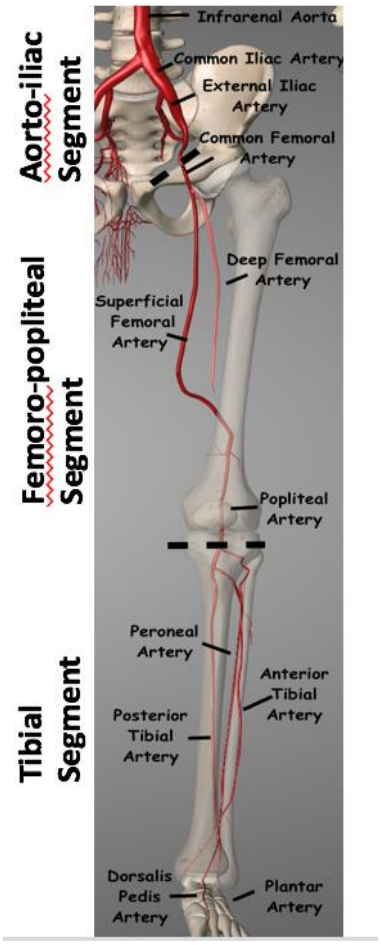
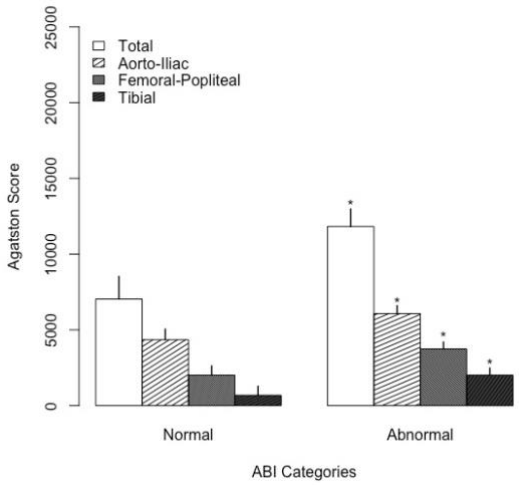


Figure 5. Comparing PCS and Percent PCS Between Categories of ABI

a.



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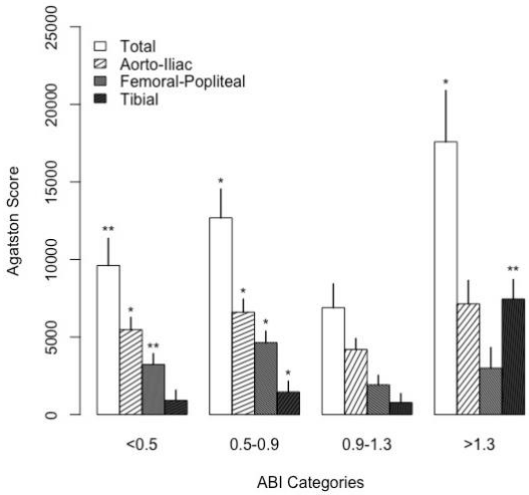
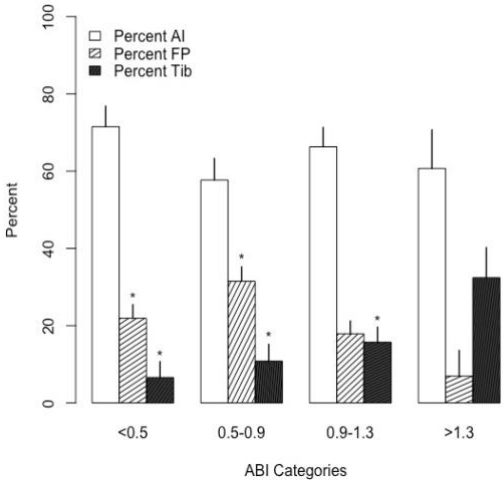
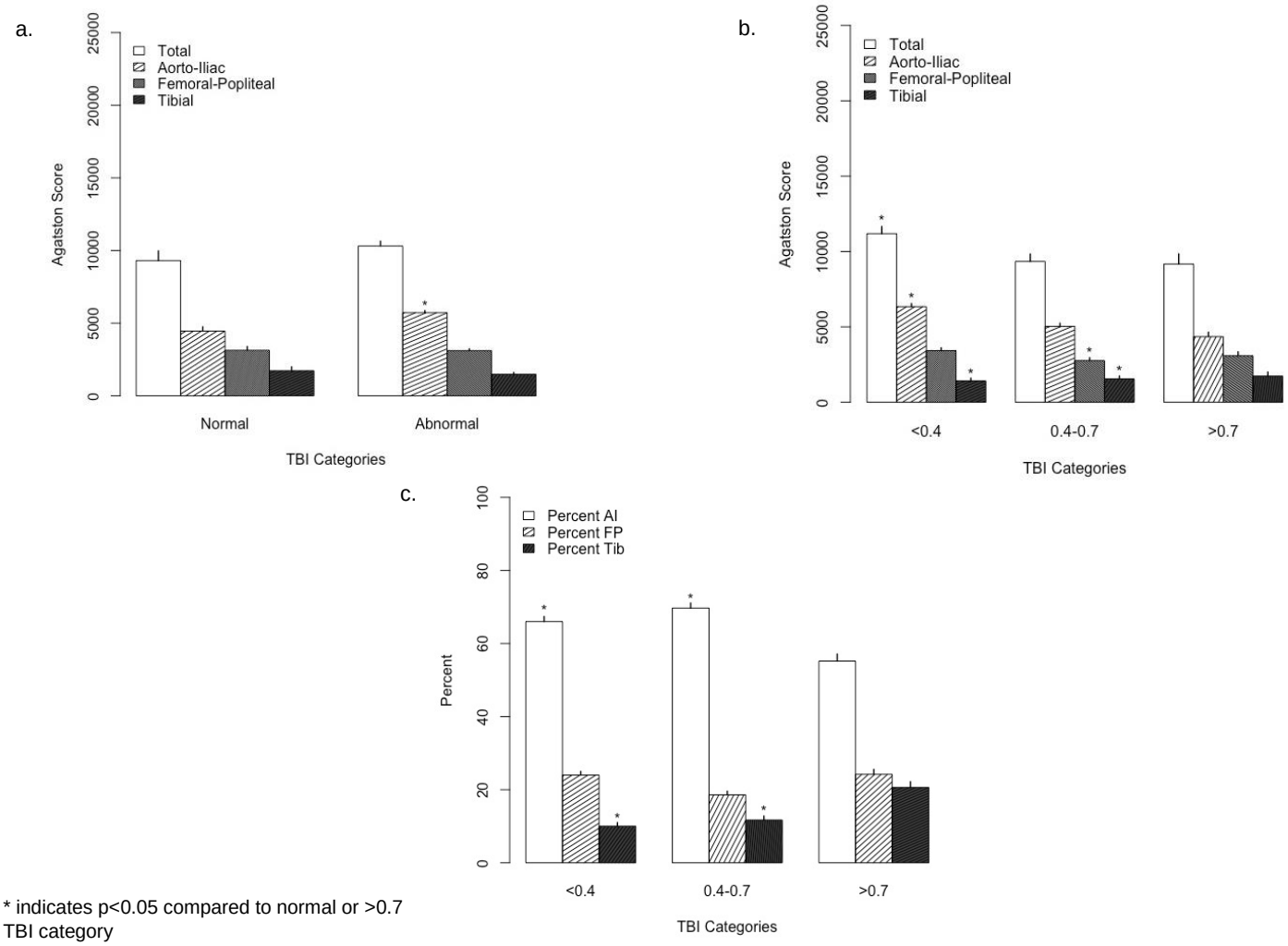


c.



* indicates p<0.05 compared to normal (a), 0.9-1 ABI category (b), or >1.3 ABI category (c)
** indicates p~0.06

Figure 6. Comparing PCS and Percent PCS Between Categories of TBI



* indicates p<0.05 compared to normal or >0.7 TBI category

Figure 7. Comparing ABI, TBI, and Tibial PCS in Individually Predicting Amputation Rate using ROC Plot

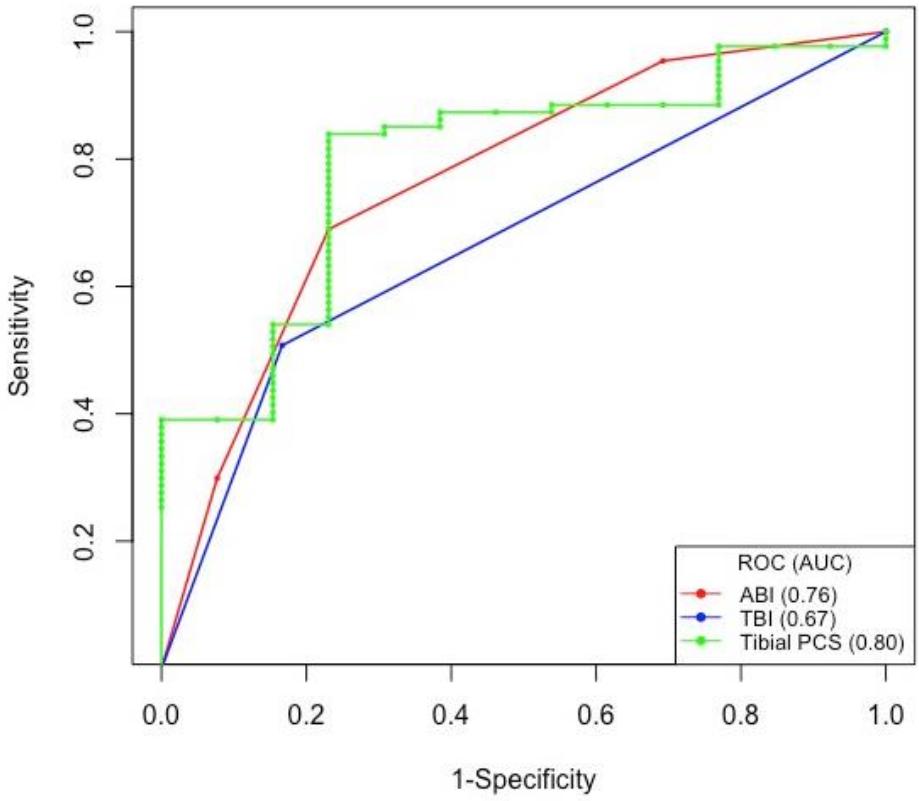


Figure 8. Comparing Additive Effects of ABI, TBI, and Tibial PCS in Predicting Amputation Rate using ROC Plot