

Evaluation of sex-based differences in below-the-knee plaque histology in patients who underwent amputation for chronic limb-threatening ischemia

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ABSTRACT

Objective: With the growing incidence of peripheral arterial disease (PAD) and the historic under-representation of female patients in cardiovascular trials, a comprehensive evaluation of sex-based variances in PAD presentation and treatment outcomes is needed. This study aims to evaluate sex-based differences in the vessel wall characteristics of patients who underwent amputation owing to critical limb-threatening ischemia to optimize personalized treatment planning and aid in the selection of endovascular devices for PAD patients.

Methods: A total of 35 lower limbs were collected from 34 patients with end-stage PAD undergoing major amputation. We selected, harvested, and cross-sectioned at 3- to 4-mm intervals 163 diseased below-the-knee arterial segments resulting in 1260 arterial rings. Histological analyses were conducted on each individual ring and later summarized by arterial segment.

Results: Male and female patients were remarkably similar across multiple plaque characteristics, including degree of stenosis, calcification severity and localization, and atherosclerotic patterns. A significant sex-based difference was noted in the presence of luminal thrombus, which was more prevalent in females (38.7% vs 25.0%; $P = .016$). Histopathological differences were noted between popliteal and tibial lesions, with popliteal segments demonstrating increased chronic total occlusion presence and atherosclerosis, whereas severe calcification occurred more often in tibial segments. A sex-based evaluation of the popliteal segments showed increased calcification (60.71% vs 28.0%; $P = .003$) and atherosclerosis (96.4% vs 73.0%; $P = .028$) in males compared with females.

Conclusions: Differences in the degree of calcification, incidence of atherosclerosis, and presence of luminal thrombus may pose important clinical implications for antiplatelet and anticoagulation regimen choice and guide treatment options. Further studies are warranted to evaluate the impact of these differences on outcomes of endovascular procedures. (JVS—Vascular Science 2025;6:100269.)

Keywords: Atherosclerosis; Calcification; Peripheral arterial disease; Critical limb ischemia; Medial calcification

Peripheral arterial disease (PAD) is recognized as a significant cause of cardiovascular-related morbidity and mortality.¹⁻³ The vascular disease affects >236 million individuals worldwide and accounts for approximately 51% of all major lower extremity amputations.² Increasingly severe stages of PAD such as chronic limb-threatening ischemia heighten rates of major amputation in patients by $\leq 40\%$ at 6 months, with a mortality rate of 20% to 25% after the first year of

presentation.⁴ Despite the widespread occurrence and severity of end-stage PAD, there is a significant lack of representation of female patients in large randomized controlled trials in the cardiovascular space.⁵ As such, sex-based variances in PAD manifestation and treatment remain critically understudied.^{6,7}

Owing to the traditional consideration of PAD as a male-dominant disease, data assessing differences in clinical symptoms, disease management, and treatment

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outcomes between male and female patients have been historically limited.^{8,9} However, recent studies indicate the prevalence of PAD in female patients to be equal if not greater than male patients in adult populations >40 years of age,^{8,10} prompting additional efforts to analyze sex disparities in PAD progression.

Risk factors for PAD, like most cardiovascular conditions, include presence of diabetes mellitus (DM), obesity, hypertension, and tobacco use. Although these indicators of vascular disease are common for both sexes, female patients are placed at a greater risk of complications compared with male patients, with conditions such as DM nearly doubling the likelihood of intermittent claudication in females.⁸ Female patients are also more likely to be diagnosed at a later age and present with more severe and atypical symptoms for PAD than males. Disparities are also observed in revascularization outcomes.^{7,8,11} Female patients are at a higher risk of graft failure, wound infections, limb loss, and mortality after surgical revascularization,⁸ but observational studies show conflicting reports regarding the technical success rate of endovascular procedures on female patients compared with males.^{8,12} The sex-related differences that are seen in PAD treatment outcomes may be attributed to variations within the vessel wall, such as calcification distribution, extent of atherosclerosis, and lesion morphology. Although existing studies have evaluated the vascular pathology of the lower extremities from cadaver and amputation models,^{13–15} there are limited reports analyzing sex-based variations in plaque morphology as seen in patients with end-stage disease.

The patients included in this experimental cohort are patients who ultimately had to receive major lower limb amputation owing to critical limb-threatening ischemia, despite various conservative therapies and revascularization efforts. This study aims to characterize and evaluate differences in the arterial composition of these patients through histopathological analysis of peripheral artery lesions from amputated limbs. A comparative analysis is performed between the vessel wall characteristics as seen in male and female patients to improve understanding of sex-based variances in PAD plaque morphology to better inform therapeutic decision-making.

METHODS

Study population. We performed a retrospective analysis on samples collected from patients diagnosed with end-stage PAD who were enrolled prospectively in an ongoing magnetic resonance imaging (MRI) study at Houston Methodist Hospital (Houston, TX) approved by the Institutional Review Board under protocol number PRO00027258. All patients provided written, informed consent. The cohort included patients who had undergone major lower extremity amputation owing to chronic limb-threatening ischemia between 2021 and

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective analysis of prospectively collected data
- **Key Findings:** Histological analysis of vessel wall characteristics, performed on 1260 arterial rings obtained from 34 male and female patients undergoing major lower extremity amputation owing to critical limb-threatening ischemia, yielded remarkably similar results between both sexes at the end stage of disease. Luminal thrombus occurrence was noted to be significantly greater in female patients compared with males (38.7% vs 25.0%; $P = .016$).
- **Take Home Message:** Presentation of peripheral arterial disease, as seen from plaque morphology, seems to converge between male and female patients with end-stage disease, indicating a final common pathway. However, the significant prevalence of luminal thrombus in female patients may correlate with heightened platelet reactivity and coagulation. This factor may contribute to the sex-based disparities observed in the overall presentation and treatment outcomes of peripheral arterial disease.

2023; a total of 35 legs were obtained and studied from 34 patients. Only adult patients aged >40 years who were classified as presenting end-stage PAD (Rutherford categories 4–6) were included. The following factors were recorded for all patients: age, sex, date of surgery, amputation laterality, body mass index, presence of cardiovascular risk factors, prior ipsilateral and contralateral procedures, and harvested artery type. Patient age was taken at the date of surgery. All data were collected using the electronic medical record system, and patients were grouped by their biological sex assigned at birth. Risk factors included DM, tobacco use, hypertension, dyslipidemia, renal failure (Kidney Disease Outcomes Quality Initiative stage), deep vein thrombosis, malignancy, coronary artery disease, chronic obstructive pulmonary disease, arrhythmia/atrial fibrillation, transient ischemic attack or stroke, and autoimmune disease. Prior procedures were categorized as ipsilateral intervention, where treatment was performed on the harvested artery, and prior contralateral amputation. Incidence of device testing, including shockwave lithotripsy and balloon angioplasty, was recorded.

Sampling and histopathological analysis. After each major amputation, diseased arterial segments (including the distal below-knee portion of the popliteal artery [P3] and tibial vessels) were harvested, fixed in 10% neutral buffered formal, and decalcified as needed. Each segment was subsequently sectioned at 3- to 4-mm intervals. The resulting rings were submitted for standard tissue processing and embed in paraffin. Histological

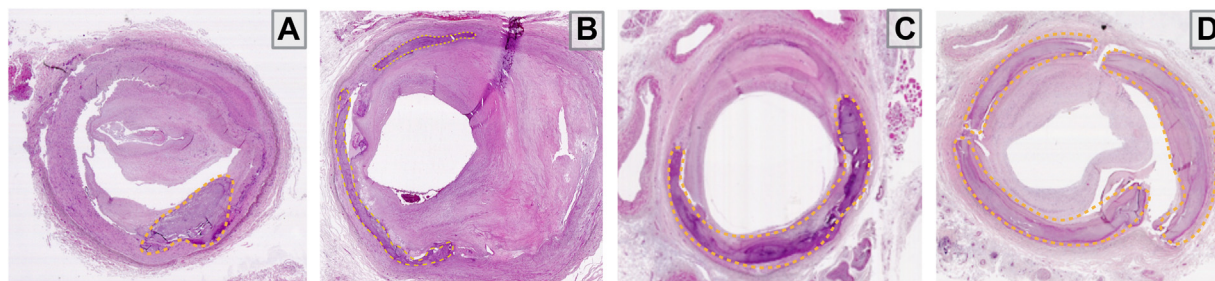


Fig 1. Histological examples of extent of calcification. (A) Stage I calcification appears in the lower right quadrant of lesion. (B) Stage II calcification spans two quadrants, at roughly 50% of the lesion. (C) Stage III calcification shown covers roughly 65% of lesion circumference. (D) calcification is apparent throughout the entire circumferential arc of the lesion, representing stage IV. The yellow dashed line represents calcification in each sample.

sections were cut at 5 μ m thickness, mounted on charged slides, and stained with hematoxylin-eosin and Movat's pentachrome. Any arterial segments with notable histological artifact or incomplete rings were excluded from the study. The remaining segments were submitted for histological evaluation by an expert cardiovascular pathologist for various lesion characteristics. After analysis, the histopathological scorings for each ring were grouped for their respective arterial segment.

Classification of lesions. A primary outcome of this study was the presence of calcification (yes/no) in male and female patients; as such, calcification features were recorded for all rings. Each lesion was characterized by presence of calcification (yes/no) and its circumferential degree (I, 0%-25%; II, 25%-50%; III, 50%-75%; IV, 75%-100%), as seen in Fig 1. Calcified plaque geometry was determined as concentric or eccentric depending on circumferential degree (stages I-III, eccentric; stage IV, concentric). Calcification within each ring was further classified by locality as being predominantly intimal, predominantly medial, or mixed (Fig 2). Lesions presenting intimal calcification along >60% of the circumferential arc were classified as predominantly intimal. Arterial rings displaying medial calcification across >60% of the ring circumference were classified as predominantly medial. In cases where both intimal and medial calcification are present in similar distributions (\leq 60% of the circumference of respective layers), the lesions were categorized as mixed calcification. Calcification patterns were also analyzed, including punctate, fragment, sheet, nodular, or bone formation.

Histological analysis of each segment also focused on assessing the degree of vessel stenosis, severity of calcification, and atherosclerotic features. The degree of stenosis for each ring was measured based on a modified scoring system defined by Barth et al.¹⁶ and classified by percentage into four groups (I, 0%-20%; II, 20%-40%; III, 40%-70%; IV, 70%-100%). Chronic total occlusion (CTO) and the presence of luminal thrombus were also noted. Thrombi were further categorized as acute,

organizing, or chronic. Restenosis was identified by myofibroblast proliferation in a myxoid matrix in cases of prior endovascular or surgical intervention.^{17,18}

Each ring was further analyzed for atherosclerosis and categorized as either atherosclerotic or nonatherosclerotic. Nonatherosclerotic lesions were identified as rings presenting with either adaptive intimal thickening or normal intima. The atherosclerotic features were identified based on the modified American Heart Association classification for coronary atherosclerotic lesions¹⁵ and included pathological intimal thickening, fibrous plaque, fibroatheroma, fibrocalcific plaque, or thin cap fibroatheroma. Adaptive intimal thickening is typically a response to hemodynamic stress on the vessel and is not indicative of atherosclerosis progression.¹⁹ Pathological intimal thickening is indicative of early stage atherosclerosis and is defined by the presence of lipid content and smooth muscle cells in the intima, along with varying presence of macrophages.²⁰ Fibrous plaque was identified by presence of collagen and muscle cells and absence of lipid content, while fibrocalcific plaque included the presence of collagen and calcification within the intima. A thick fibrous cap (>65 μ m) over a large pool of lipids with necrotic core and presence of macrophages is characteristic of fibroatheroma, and thin cap fibroatheroma was identified by a thin fibrous cap (<65 μ m) over the same content.^{21,22}

Statistical analysis. To assess the binary outcome of calcification presence between male and female patients, a logistic regression model was applied and controlled for all potential confounders, including demographics and comorbid conditions. Odds ratios and 95% confidence intervals were reported. All statistical analyses were performed using R version 4.3.3, with statistical significance set at a two-tailed *P* value of <.05.

Results for all categorical variables are reported as total number (n) and percentages (%), and continuous variables are expressed as mean \pm standard deviation. Categorical datasets were analyzed using Pearson's χ^2 and Fischer's exact tests. The Student *t* test was applied to

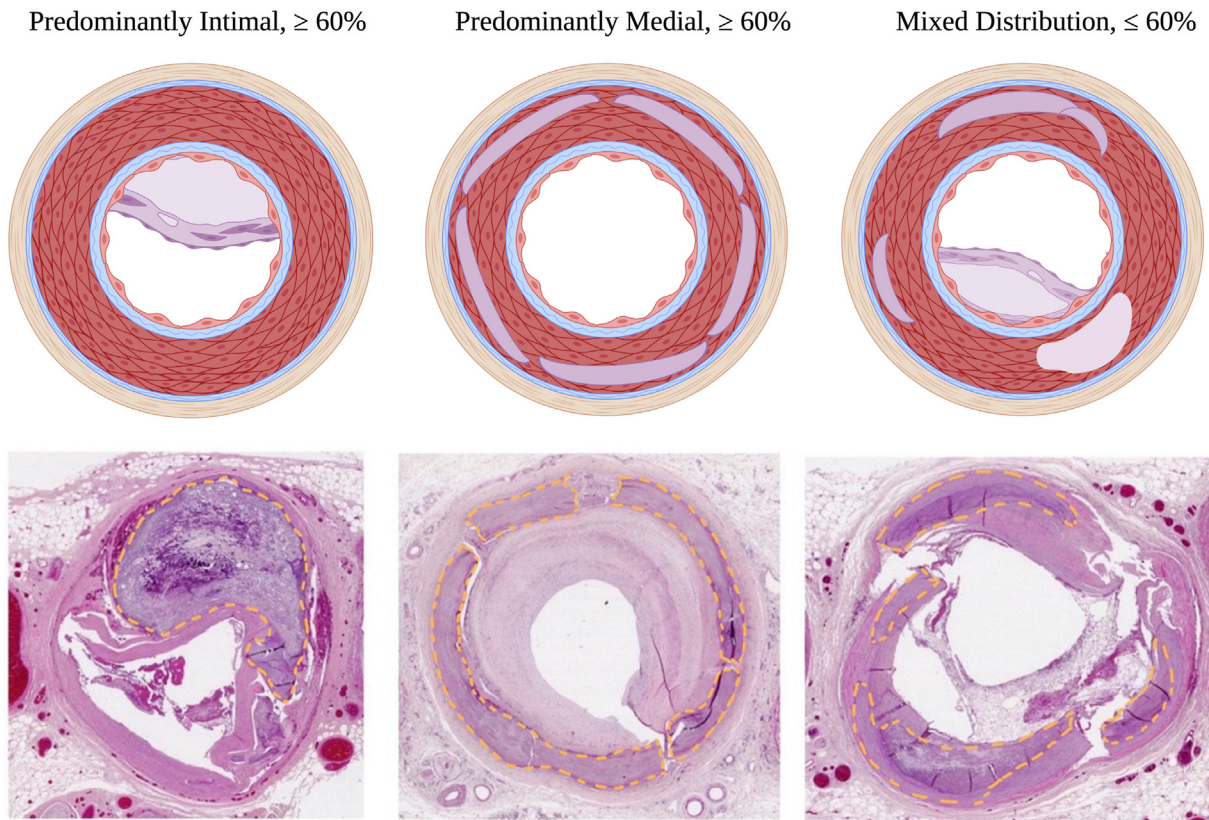


Fig 2. Histological samples of lesions demonstrating predominantly intimal, predominantly medial, and mixed distribution calcification patterns. Predominantly intimal and medial calcification categorizations include lesions with $>60\%$ of the of presenting calcification in the intima and media, respectively. Mixed distribution calcification is noted when lesions demonstrate $\leq 60\%$ of both intimal and medial calcification. The yellow dashed line represents calcification in each sample.

determine significant differences between normally distributed continuous variables, and the Mann-Whitney U test was used for variables with nonparametric distribution. Statistical significance for the study was defined as a P value of $<.05$. Minitab Statistical Software version 21.1.0 was used for these statistical analyses.

RESULTS

The 34 patients included in this study (mean age, 71 ± 8.2 years; 16 female patients) yielded 163 arterial segments (male, 96; female, 67) at approximately 3 to 4 mm in length. A total of 1260 rings were individually assessed (male, 765; female, 495) and the results were summarized for each arterial segment. Percent stenosis, CTO presence, and luminal thrombus occurrence were evaluated by the maximum grade noted in the segment, while calcification quadrants were evaluated by mean.

Of the below-the-knee arteries included in this study, popliteal, anterior tibial, and posterior tibial arteries were the most occurrent in addition a smaller group of arteries including peroneal, tibioperoneal, foot, plantar arch, and dorsal pedal. The study demographics are shown in [Table I](#).

No significant sex-based differences were noted in the general demographics of the cohort. Male and female patients were observed to be similar in age, reflecting a deviation from the existing literature conclusions of increased age in female patients with chronic limb-threatening ischemia.²³ The multivariable model assessing calcification presence yielded no significant differences between males and females (odds ratio, 0.12; 95% confidence interval, 0.00-10.23; $P = .35$). A comprehensive description of the multivariable analysis is shown in [Table II](#).

Because the majority of patients with PAD require some form of antiplatelet or anticoagulation therapy, sex-based differences between medication regimens were also assessed. Patients on one or two antiplatelet medications (aspirin, clopidogrel [Plavix], or ticagrelor) were categorized as mono and dual antiplatelet, respectively. Patients on both antiplatelet and anticoagulant medications (including apixaban, rivaroxaban [Xarelto], and warfarin) were classified as such. No significant differences were found between the antiplatelet and anticoagulant regimen of male and female patients, as shown in [Table III](#).

Table I. Patient characteristics

Characteristics	Male (n = 18)	Female (n = 16)	Total (n = 34)	P value
Age, years	71.4 ± 8.2	71.1 ± 10.9	71.2 ± 9.4	.923
BMI	25.9 (17.4-38.0)	24.7 (17.2-37.6)	25.4 (17.2-38.0)	.565
Renal failure (KDOQI stage 5)	8 (44.4)	6 (37.5)	13 (38.2)	.518
Diabetes	12 (66.7)	11 (68.8)	24 (70.6)	.901
Smoking	11 (61.1)	11 (68.8)	22 (64.7)	.653
Hypertension	18 (100)	16 (100)	34 (100)	1.0
Dyslipidemia	14 (77.8)	10 (62.5)	24 (70.6)	.3
Prior ipsilateral intervention	14 (77.8)	13 (81.3)	27 (79.4)	.809
Prior contralateral intervention	4 (22.2)	4 (25.0)	8 (23.5)	.925
Coronary artery disease	13 (72.2)	11 (68.8)	24 (70.6)	.831
DVT	5 (27.8)	9 (56.25)	14 (41.2)	.126
Malignancy	4 (22.2)	4 (25.0)	8 (23.5)	.855
COPD	4 (22.2)	7 (43.8)	11 (32.4)	.197
Arrhythmia/atrial fibrillation	8 (44.4)	11 (68.8)	19 (55.9)	.162
TIA	8 (44.4)	9 (56.25)	17 (50.0)	.507

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; KDOQI, Kidney Disease Outcomes Quality Initiative; TIA, transient ischemic attack.
Values are mean (range) or number (%).

Table II. Multivariable analysis for calcification presence (yes = 1 vs no = 0)

Variables	Odds Ratio (95% CI)	P value
Gender (female; male = ref)	0.12 [0-10.23]	.35
Age	1.09 [0.87-1.37]	.45
Diabetes (yes; no = ref)	2.11 [0.06-79.77]	.69
Smoking (yes; no = ref)	0.15 [0-10.37]	.38
Dyslipidemia (yes; no = ref)	1.47 [0.05-45.14]	.83
Prior ipsilateral intervention (yes; no = ref)	6.25 [0.2-195.35]	.3
Prior ipsilateral arterial intervention (yes; no = ref)	0.32 [0.01-11.53]	.53
Prior ipsilateral bypass (yes; no = ref)	0.33 [0.01-13.56]	.56
Prior contralateral amputation (yes; no = ref)	1.54 [0.03-73.84]	.83
Other peripheral atherosclerotic disease (yes; no = ref)	2.39 [0.08-67.57]	.61
DVT (yes; no = ref)	0.72 [0.02-32.44]	.86
COPD (yes; no = ref)	6.33 [0.14-285.02]	.34
TIA/stroke (yes; no = ref)	1.27 [0.08-21.58]	.87

CI, Confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; TIA, transient ischemic attack.

Table III. Antiplatelet and anticoagulant medication history

Medication type	Male (n = 18)	Female (n = 16)	Total (n = 34)	P value
Mono antiplatelet	2 (11.1)	1 (6.3)	3 (8.8)	>.99
Dual antiplatelet	4 (22.2)	8 (50.0)	12 (35.3)	>.99
Antiplatelet + anticoagulant	12 (66.7)	7 (43.8)	19 (55.9)	.5

Values are number (%).

Sex-based differences in general plaque characteristics

Vessel stenosis was observed in all arterial segments, with severe narrowing (stages III and IV) noted in female (62.7%)

and male (50.0%) patients. Differences in presence of CTOs, neointimal hyperplasia, and restenosis were not statistically significant between both groups (Fig 3).

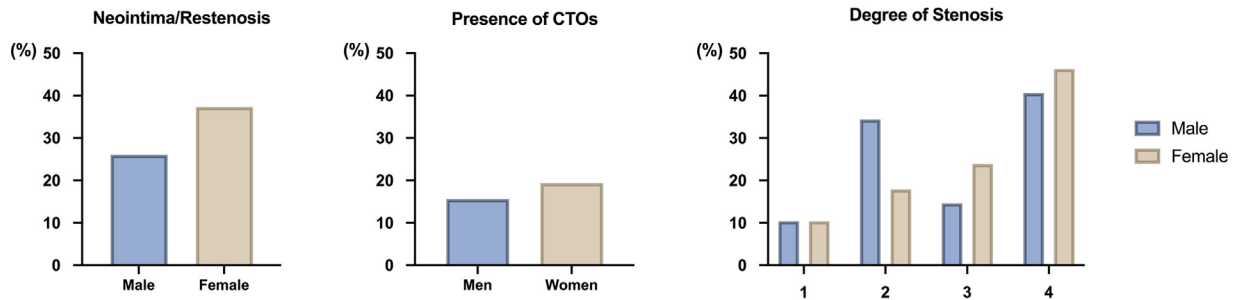


Fig 3. Presence of neointimal hyperplasia/restenotic tissue, chronic total occlusions (CTOs), and degree of stenosis in arterial segments obtained from male and female patients with end-stage peripheral arterial disease (PAD). Neointima/restenosis and presence of CTOs are comparable between male and female patients. Both groups demonstrate increasingly severe stenosis, with >50% of lesions in stages 3 and 4.

Luminal thrombus was present in 38.7% of arterial segments from female patients (9/16 patients), significantly greater than the 25.0% of segments observed from males (8/18 patients) ($P = .016$). Acute, organizing, and chronic thrombi were observed. Acute thrombus was more occurrent in males (3/18 patients [6.3%]) than females (0/0 patients [0.0%]; $P = .016$), whereas chronic thrombus was greater in female patients (7/16 patients [26.9%]) than males (5/18 patients [10.4%]; $P = .016$). Organizing thrombus was comparable between both male and female patients at 8.3% (6/18 patients) and 11.9% (4/16 patients), respectively (Fig 4).

Localization of calcium and calcification severity were comparable between male and female patients (Fig 5). Analysis of calcification patterns, which included punctate, fragment, sheet, nodular, and bone calcium, did not yield statistically significant results between both sexes (Fig 6, Supplementary Table I).

Atherosclerotic features were present and similar in both groups, observed in 57.3% of arterial segments obtained from male patients and 52.2% of segments from female patients. Males were significantly more likely to present with fibrocalcific lesions (male = 46.9%, female = 31.3%; $P = .023$), as shown in Fig 7.

Pathological disparities between popliteal and tibial arterial segments

Of the 163 arterial segments included in this study, 152 tibial and popliteal arterial segments were further analyzed for variations in the vessel wall based on location (tibial, 99; popliteal, 53). Presence of CTO was significantly greater in popliteal segments than tibial (30.2% vs 11.1%; $P = .003$). Popliteal segments also displayed higher prevalence of atherosclerosis than below-the-knee arteries (popliteal, 86.8%; tibial, 45.5%; $P < .001$). Calcification manifestation within the vessels was noted with increased severity in tibial vessels (62.6%) relative to popliteal (28.3%; $P < .001$). A majority of tibial arteries presented medial calcification, while popliteal arteries were predominantly intimal. No significant differences were observed in luminal thrombus occurrence between

popliteal and tibial arteries (Fig 8, Supplementary Table II).

Sex-based variations within popliteal and tibial.

Within the tibial arterial segments (male, 62 segments; female, 37 segments), there were no significant differences in CTO presence, atherosclerosis, or calcification distribution between male and female patients. However, notable sex-based differences were observed in the popliteal arteries (male, 28; female, 25). Arterial segments obtained from male patients were significantly more likely to present with severe calcification in stages III and IV (60.7%) compared with female patients (28.0%; $P = .003$). The presence of atherosclerosis was also more prevalent in male patients than female patients (96.4% vs 73.0%; $P = .028$), as shown in Fig 9.

DISCUSSION

Our study reports an in-depth analysis of sex-based variances in lesion composition of below-the-knee arteries in patients undergoing major amputation and diagnosed with end-stage PAD. We looked at a number of different plaque measures and found remarkable similarity in the vessel walls of male and female patients. Severe degree of vessel stenosis in stages III and IV was observed widely, reflective of the extent of disease progression within the study cohort. At this stage, the lack of significant sex-based differences at the vessel wall level indicates converging PAD presentation and a potential final common pathway for both male and female patients. Supporting literature indicates that postmenopausal female patients see a decrease in the protective effects of estrogen,²⁴ causing increased prevalence and severity of PAD symptoms that is on par with male patients of similar age.⁸

The notable sex-based difference found in vessel wall composition was the presence of luminal thrombus. Females were observed to display a significantly greater presence of luminal thrombus as compared with male patients (38.7% vs 25.0%; $P = .016$). The existing literature regarding sex-based differences in plaque formation indicates that female patients have greater platelet

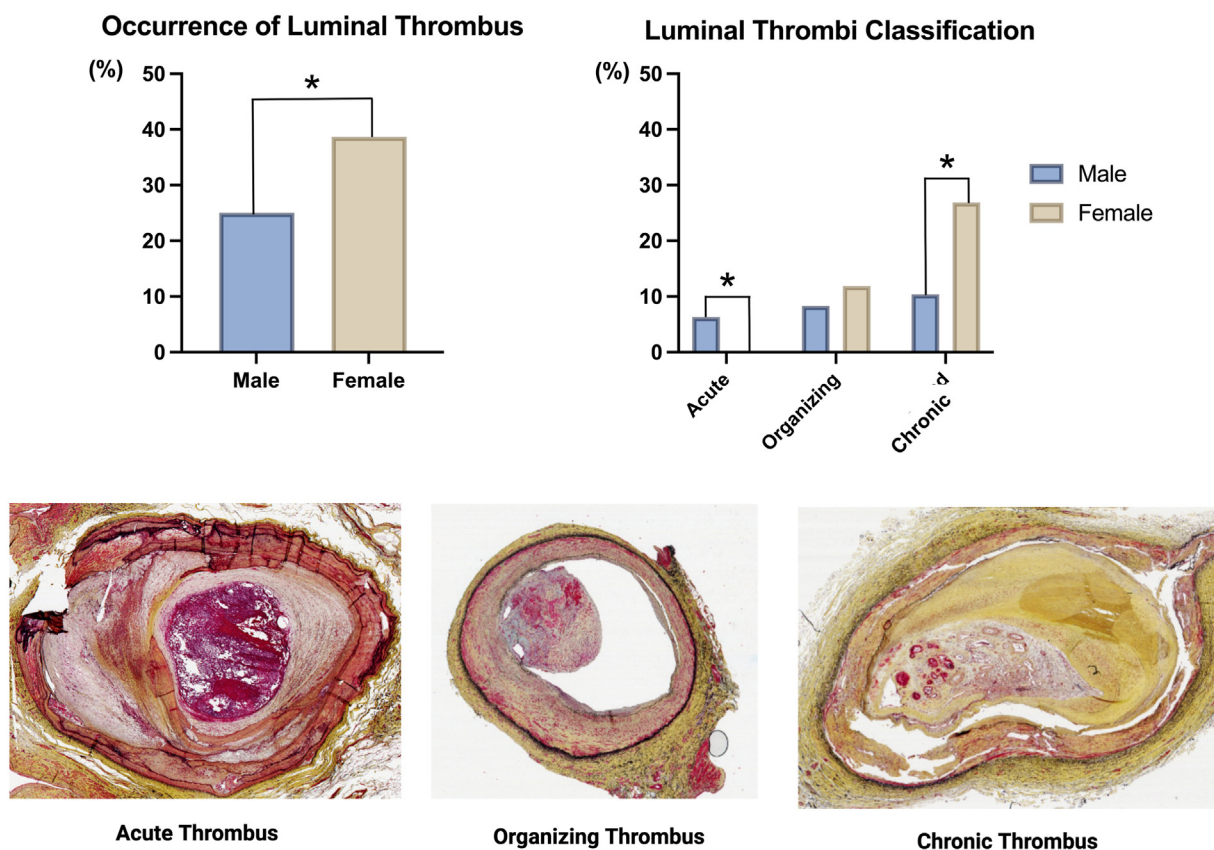


Fig 4. Luminal thrombus occurrence in male and female patients. Female patients display significantly greater occurrence of luminal thrombus than males. Histological cross-sections depict examples of acute thrombi (more prevalent in male patients), organizing thrombi, and chronic luminal thrombi (more prevalent in female patients).

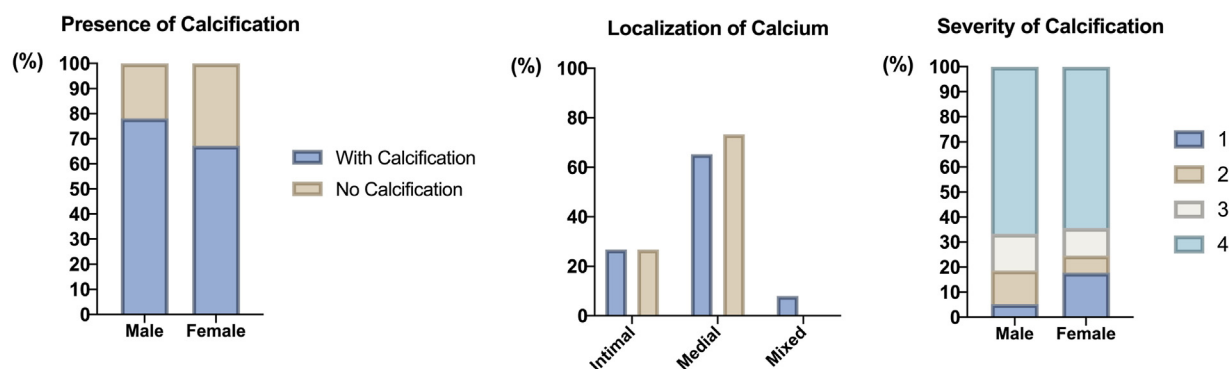


Fig 5. Calcification characteristics, including presence, severity, and localization of calcification. No significant sex-based differences were noted across lesions.

concentrations than males, which is associated with increased platelet reactivity and heightened likelihood of thrombotic events in female patients.²⁵ The sex-based disparities observed in PAD manifestation and endovascular treatment outcomes may be attributed to the increased platelet concentration and reactivity observed in female patients. Previous literature has shown that female patients have higher platelet

reactivity measured as maximum amplitude indicating high clot strength compared with male patients. Also, females showed greater platelet aggregation and less platelet inhibition in response to antiplatelet medication compared with males, indicating stronger thrombotic propensity and resulting in worse outcomes. These poorer outcomes occur even when taking the same standard of care antiplatelet medications as men, indicating

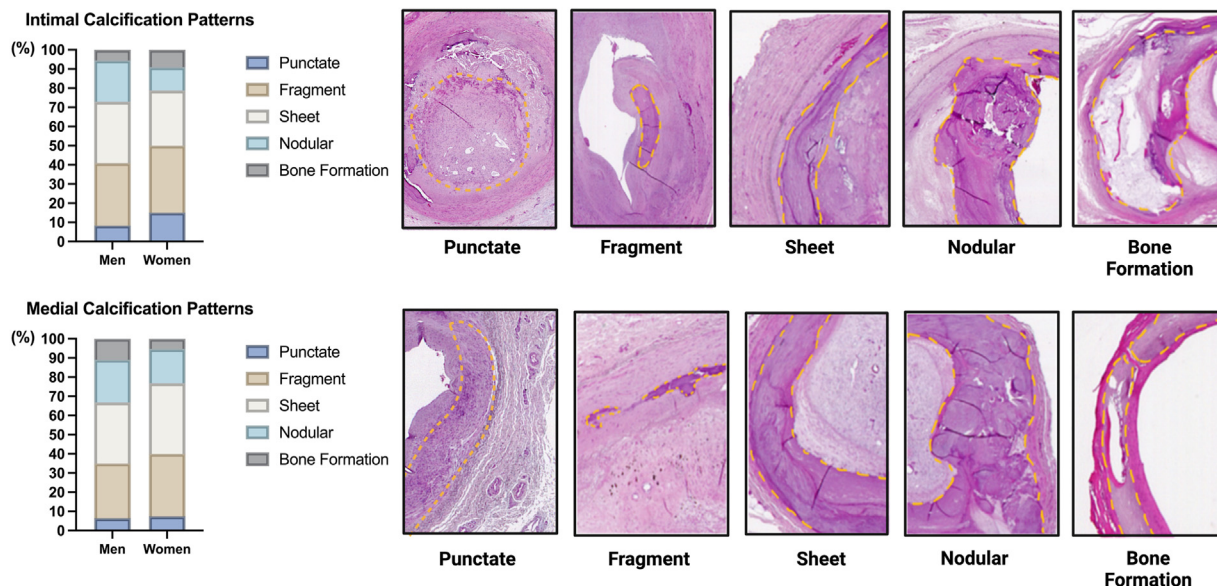


Fig 6. Observed sex-based differences across intimal and medial calcification patterns, including punctate, fragment, sheet, nodular, and bone calcification. Results are comparable between male and female patients with no significant sex-based differences. Histological cross-sections illustrate examples corresponding with the listed calcification types. The yellow dashed line represents calcification in each sample.

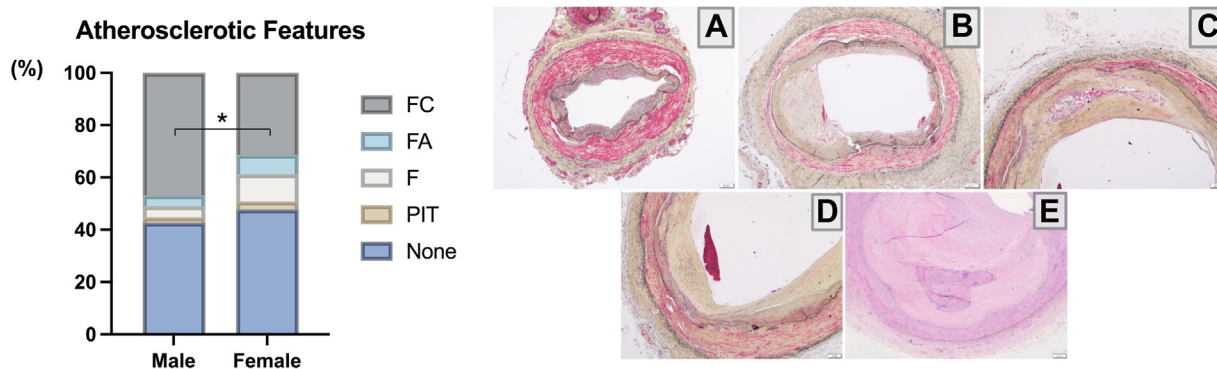


Fig 7. Sex-based differences observed in atherosclerotic lesion features. Fibrocalcific plaque (FC) was significantly more prevalent in males than females. Histological examples of atherosclerotic features are displayed. (A) Adaptive intimal thickening. (B) Pathological intimal thickening (PIT). (C) Fibroatheroma (FA). (D) Fibrous plaque (F). (E) Fibrocalcific plaque (FC).

that current standard-of-care antiplatelet regimens may be inadequate for female patients. This result was consistent with the findings in this study where male and female patients had similar antiplatelet regimens, yet females had more intraluminal thrombus (Table II). Prior studies also showed that female patients showed significantly higher occlusion in the area of intervention than males on aspirin, indicating that the medication did not decrease platelet activity in female patients to the same level as in males.²⁶⁻²⁹ This reported physiological variation between the sexes might explain the increased sensitivity of female patients to severe PAD progression, despite a lack of traditional risk factor presentation, as has been observed in previous studies.

Although there were no significant differences noted in calcification patterns for the general cohort, the segment-based analysis between tibial and popliteal arteries showcased increasingly severe calcification (stages III and IV) in the tibial arteries compared with the popliteal group. The calcification distribution was also measured, with tibial arteries displaying predominantly medial calcification while intimal calcification was more prevalent in the popliteal segments. Intimal calcification typically presents within atherosclerotic plaque in the intima layer of medium- and large-sized arteries and is associated with plaque rupture and hyperlipidemia.^{30,31} Medial calcification, in contrast, is considered nonatherosclerotic in nature and is associated with

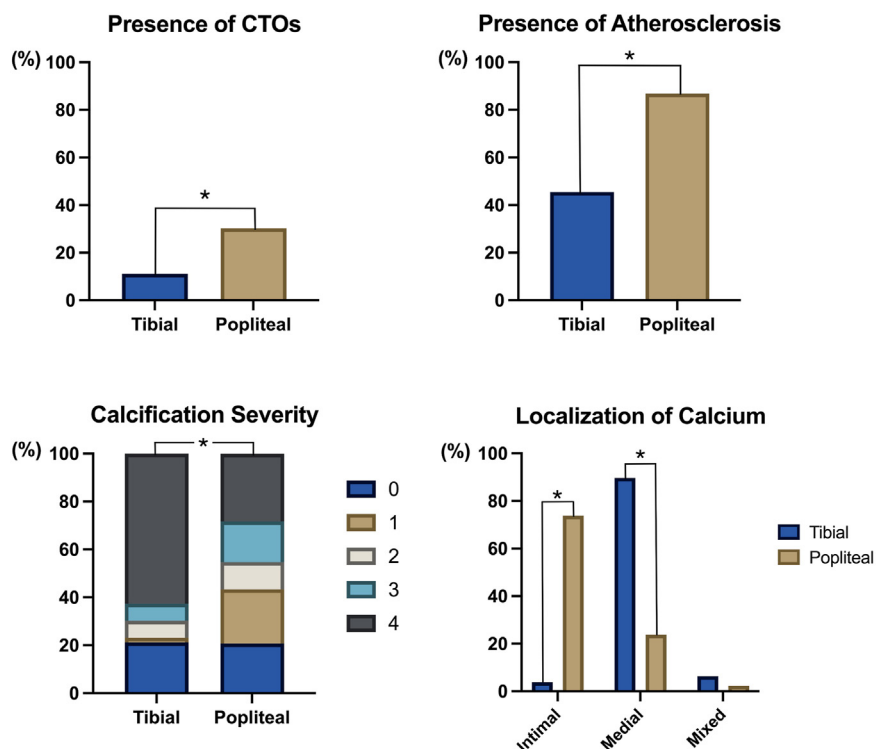


Fig 8. Differences observed between popliteal and tibial arteries in presence of chronic total occlusions (CTOs), atherosclerosis, calcification severity, and calcium localization. Popliteal arteries demonstrate significantly greater presence of CTOs, atherosclerosis, and intimal calcification. Tibial arteries display significantly more severe and medial calcification in stage 4.

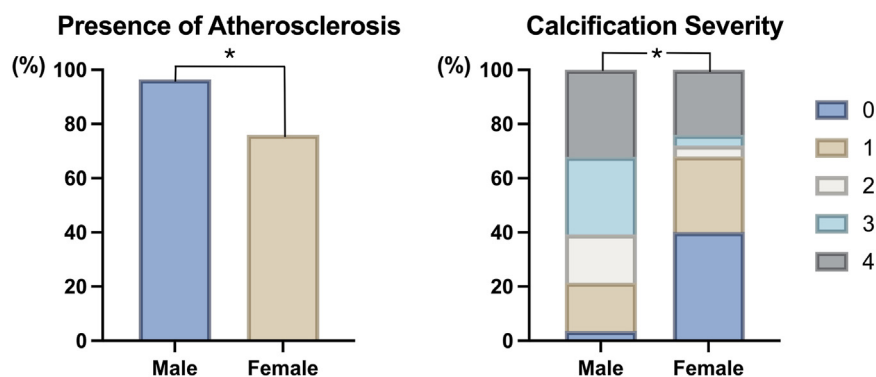


Fig 9. Sex-based differences observed in the popliteal arteries. Male patients appear significantly more likely to display severe calcification (stages III and IV) and atherosclerosis compared to female patients.

reduced vessel wall compliance. The presence of calcium in the media layer is more often seen in small- and medium-sized arteries and can alter vessel hemodynamics significantly owing to increased vascular stiffness.³² Popliteal segments also had significantly more CTO formation than tibial, indicating greater occlusion of blood flow.

Sex-based differences were observed within the popliteal group, including heightened atherosclerosis and calcification severity in male patients compared with females.

Limitations. This study includes patients who were enrolled in an ongoing MRI study at our institution. Although the participating patients were selected for various MRI end points, any selection bias was applied equally to male and female patient groups. Additionally, segments with prior ipsilateral intervention were not excluded from the study and may have impacted some of the evaluated measures. However, there were no significant differences observed in prior intervention between male and female patient groups, indicating equal bias.

Because this study is conducted with amputation models, it is important to note that concrete conclusions regarding occlusive disease cannot be made based on this group. Rather, this study hopes to validate existing sex-based differences in PAD presentation and treatment in patients with end-stage PAD while generating additional hypotheses to advance research in the field.

CONCLUSIONS

The clinical characteristics of male and female patients with end-stage PAD seem to converge with extended disease progression, indicating a potential final common pathway for both male and female patients. However, the sex-based disparities that are observed in presentation and treatment outcomes may be associated with the increased platelet reactivity and coagulation observed in female patients, which is correlated to heightened prevalence of luminal thrombosis. Further studies are needed to evaluate how the effects of luminal thrombus, in addition to severe calcification and atherosclerotic plaque, may affect therapeutic decision-making and the outcome of endovascular procedures.

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AUTHOR CONTRIBUTIONS

Conception and design: FK, DV, JC, BB, TR
Analysis and interpretation: FK, DV, JC, BB, SS, AD, TR
Data collection: FK, DV, JC, BB, TR
Writing the article: FK, JC, TR
Critical revision of the article: FK, DV, JC, BB, SS, AD, TR
Final approval of the article: FK, DV, JC, BB, SS, AD, TR
Statistical analysis: FK, JC, BB
Obtained funding: TR
Overall responsibility: FK

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DISCLOSURES

None.

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