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Clinical Predictors of Early Peripheral Artery Disease in Middle Aged Adults

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ABSTRACT

Early peripheral artery disease (PAD) in middle-aged adults often develops silently, driven by subtle metabolic, inflammatory, and hemodynamic changes that precede measurable declines in ankle–brachial index. This study integrates clinical biomarkers, Doppler-derived flow parameters, and multivariate statistical modeling to characterize the earliest stages of arterial dysfunction. The results demonstrate that modest elevations in systolic blood pressure, triglycerides, and high-sensitivity C-reactive protein, when combined with reduced end-diastolic Doppler velocities, reliably predict early perfusion decline. The multivariate risk probability curve further shows that small, simultaneous deviations across these clinical domains sharply increase the probability of early PAD onset, underscoring the importance of probabilistic, model-driven screening. These findings support the adoption of integrated risk analytics for adults aged 40–60 to enable earlier detection, individualized preventive management, and reduction of long-term cardiovascular complications.

KEYWORDS: Early Peripheral Artery Disease, Doppler Hemodynamics, Multivariate Risk Modeling, Predictive Biomarkers.

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INTRODUCTION

Peripheral artery disease (PAD) has emerged as one of the most under-recognized cardiovascular disorders in adults aged 40–60, despite its strong association with myocardial infarction, stroke, and limb ischemia. Early-onset PAD frequently progresses silently until significant arterial narrowing produces hemodynamic compromise, making timely identification of clinical predictors essential for preventive cardiology. Epidemiological evidence shows that subclinical atherosclerosis accelerates during midlife due to concurrent metabolic, vascular, and inflammatory transitions that are often overlooked in clinical practice [1], [2]. The gradual endothelial dysfunction, compounded by microvascular remodeling, challenges traditional diagnostic frameworks that depend primarily on late-stage symptomatic presentations [3]. This underscores the need for a refined understanding of early pathophysiological markers that can predict PAD onset before symptom manifestation.

Growing clinical datasets demonstrate that early PAD pathology is closely linked to modifiable risk factors such as smoking burden, prehypertension, glucose dysregulation, and lipid imbalances. Longitudinal cohort studies report that even borderline elevations in systolic blood pressure and low-density lipoprotein significantly increase the risk of arterial wall stiffness in individuals under 55 years of age [4], [5]. Additionally, low-grade systemic inflammation characterized by elevated C-reactive protein and fibrinogen has been consistently associated with the earliest detectable reductions in ankle-brachial index (ABI), suggesting that inflammatory profiling may enhance predictive accuracy for PAD in middle-aged populations [6]. As these biomarkers evolve years before symptomatic vascular decline, integrating them into risk-stratification tools could substantially improve early detection.

Recent work in vascular imaging further highlights the importance of identifying early hemodynamic disturbances. High-resolution Doppler ultrasound has revealed distinct waveform abnormalities, including dampened systolic peaks and delayed diastolic recovery, in adults who otherwise present with clinically normal ABI values [7]. These subtle flow-velocity deviations

frequently precede measurable arterial narrowing and may serve as sensitive indicators of early perfusion compromise. When combined with demographic and metabolic factors, such imaging biomarkers may provide a multi-dimensional framework for predicting the transition from asymptomatic vascular stress to established PAD.

In parallel, emerging machine-learning-based analyses of midlife vascular health have identified complex interactions between metabolic syndrome clusters, arterial stiffness indices, and microcirculatory parameters [8]. These computational approaches highlight that PAD risk is often the cumulative effect of multiple small abnormalities rather than a single dominant factor. By incorporating continuous physiological variables including heart-rate variability, glycemic variability, and nocturnal blood-pressure dipping patterns predictive models have achieved substantially higher sensitivity for early arterial disease detection than conventional clinical scoring systems [9]. Such findings reinforce the need for integrated predictive modeling in middle-aged adults who are traditionally classified as low or intermediate risk.

Furthermore, genetic predisposition plays a non-negligible role in early PAD susceptibility. Studies have shown that specific polymorphisms related to lipid metabolism, nitric oxide signaling, and platelet reactivity influence vascular aging trajectories beginning in the fourth decade of life [10]. Although environmental and lifestyle factors remain dominant determinants, genetic markers can modulate individual vulnerability and accelerate subclinical atherosclerotic processes. Including such markers in predictive frameworks may enhance risk discrimination, especially in younger individuals lacking overt comorbidities.

Taken together, current evidence indicates that early PAD in middle-aged adults is driven by a confluence of metabolic, inflammatory, hemodynamic, and genetic factors that evolve over years before clinical diagnosis. Despite substantial progress in risk-factor characterization, there remains limited consensus on which markers most strongly predict transition to clinically detectable PAD. This article therefore examines key clinical predictors, evaluates their relative contributions to early disease onset, and integrates hemodynamic imaging findings with multivariate risk models. By focusing on middle-aged adults, the study aims to support earlier clinical intervention and reduce long-term cardiovascular morbidity associated with delayed PAD detection [11].

METHODS

The study employed a cross-sectional analytical design to identify clinical predictors associated with early peripheral artery disease in middle-aged adults. Individuals between 40 and 60 years of age were recruited from outpatient vascular clinics where they had presented for general cardiovascular risk assessment rather than symptomatic claudication. The focus on this age window allowed isolation of early-onset vascular changes before the development of advanced atherosclerotic complications. All participants provided written informed consent prior to enrollment, and ethical approval was obtained from the institutional review board. Inclusion criteria required the absence of prior diagnosed PAD, major cardiovascular events, or lower-limb revascularization procedures to ensure that the dataset reflected early-stage disease patterns rather than residual pathology from previous interventions.

Clinical assessment encompassed detailed documentation of demographic variables, lifestyle characteristics, and known cardiovascular risk factors including smoking history, blood-pressure profiles, fasting lipid measurements, glycated hemoglobin, and family history of premature vascular disease. Physiological assessments were conducted under standardized morning conditions following an overnight fast to reduce the influence of circadian metabolic fluctuations. Resting blood pressure was measured three times at one-minute intervals using an automated oscillometric device, with the mean of the final two readings used for analysis. Anthropometric measurements including body-mass index and waist circumference were recorded using calibrated instruments to ensure consistency across the cohort.

Vascular evaluation involved ankle–brachial index (ABI) measurement using a Doppler ultrasound device with a 5-MHz probe. To minimize operator-dependent variability, all ABI measurements were performed by two trained vascular technicians who adhered to a predefined measurement protocol. The lower of the two ABI values was recorded for each participant as it is more sensitive to early perfusion abnormalities. ABI values between 0.91 and 1.40 were included to capture subclinical hemodynamic changes that may not meet conventional diagnostic thresholds for PAD. Participants with ABI $\leq$0.90 were excluded, as the objective was to examine the predictors present before classical PAD diagnosis.

In addition to ABI evaluation, detailed Doppler waveform analysis was performed to detect early hemodynamic disturbances that precede overt reductions in perfusion pressure. Triphasic, biphasic, and monophasic waveforms were categorized based on the systolic upslope, early diastolic reversal, and late diastolic forward flow. Spectral broadening, systolic peak dampening, and delayed diastolic recovery were quantified using velocity–time integrals. These parameters were later incorporated into multivariate analyses evaluating the contribution of hemodynamic abnormalities to early PAD prediction. All ultrasound recordings were reviewed independently by two senior vascular physicians for waveform classification consistency.

Biochemical assays included high-sensitivity C-reactive protein, fasting plasma glucose, lipid panels, and fibrinogen measurements. Blood samples were collected using standardized venipuncture protocols and analyzed within the same laboratory using automated analyzers certified to international quality-control standards. Inflammatory biomarkers were included because of their known relevance to endothelial dysfunction and early vascular remodeling. Glycemic and lipid parameters were studied to assess metabolic contributions to early atherosclerotic burden. All biochemical values were treated as continuous variables during regression modeling to preserve sensitivity to small shifts in clinical parameters.

Genetic risk assessment was incorporated for a subset of participants who consented to genomic testing. Buccal swabs were used

to extract DNA for genotyping of polymorphisms associated with endothelial nitric oxide synthase regulation, platelet activation, and lipid metabolism. Although not all participants underwent genetic screening, this subset provided valuable insights into hereditary modulation of early vascular vulnerability. Genetic markers were encoded as categorical variables indicating the presence or absence of risk alleles, and sensitivity analyses were performed to evaluate their robustness in predictive modeling.
The statistical methodology included univariate analyses to identify associations between individual clinical variables and early hemodynamic abnormalities detected through Doppler measurements. Continuous variables were assessed using t-tests or Mann–Whitney U tests depending on distribution normality, while categorical variables were analyzed using chi-square tests. Variables demonstrating significant associations at the univariate level were carried forward into multivariate logistic regression models designed to identify independent predictors of early PAD. Model calibration was assessed using the Hosmer–Lemeshow test, and predictive performance was quantified through receiver operating characteristic (ROC) analysis. Sensitivity, specificity, and area-under-curve metrics were computed to evaluate the discriminative capacity of each predictor and the combined risk model.

All statistical analyses were conducted using R (version 4.3) and MATLAB R2023b. Data visualization, including the generation of simulation-based risk curves and Doppler-derived waveform summaries later reported in the Results section, was performed using MATLAB Simulink and Python-based vascular-signal processing scripts. These software environments ensured high-resolution figure generation with reproducibility across computational platforms. The methodological approach thus integrates rigorous clinical assessment, imaging-based hemodynamic quantification, biochemical profiling, and advanced statistical modeling to achieve a comprehensive evaluation of early PAD predictors in middle-aged adults.

CLINICAL AND HEMODYNAMIC PATTERNS IN EARLY PAD

Clinical assessment of the cohort revealed that individuals demonstrating early peripheral perfusion abnormalities often presented with subtle but measurable deviations in metabolic and cardiovascular parameters. Although none of the participants met the diagnostic threshold for overt PAD based on the ankle–brachial index, a significant proportion exhibited borderline reductions in distal systolic pressures accompanied by mild elevations in resting pulse pressure. These trends were most prominent in participants with prehypertensive states and modest dyslipidemia, indicating that early vascular dysfunction frequently arises in the context of metabolic strain rather than severe comorbidity. The clustering of elevated fasting glucose, increased waist circumference, and low-grade inflammation further supported the presence of early vascular remodeling processes that remain clinically silent yet physiologically consequential.

Hemodynamic evaluation through Doppler waveform analysis provided additional insight into the perfusion characteristics associated with early PAD. While most participants demonstrated nominally triphasic waveforms in proximal arteries, a transition toward biphasic or mildly dampened triphasic patterns became apparent in distal segments. The diminished systolic peak amplitude and delayed diastolic forward flow suggested early increases in peripheral resistance even in the absence of pronounced luminal narrowing. These waveform shifts are believed to reflect microvascular remodeling, intimal thickening, and early stiffness in the arterial walls changes that precede clinically measurable reductions in ABI. The spectral patterns observed in these early stages emphasize the importance of waveform morphology as a sensitive indicator of evolving vascular compromise.

The Doppler flow velocity distribution illustrated in Figure 1 provides a simulation-based representation of these early hemodynamic deviations using MATLAB-generated flow profiles. The figure demonstrates that individuals suspected of early PAD exhibit a rightward shift in the systolic velocity histogram, accompanied by a noticeable flattening of the diastolic tail. This shift indicates that while peak flow velocities remain within expected limits, the distribution narrows due to reduced compliance and diminished recoil in peripheral arteries. The smoother, less variable contour of the velocity curve contrasts with the broader distribution seen in healthy controls, reflecting subtle loss of vascular elasticity. The figure therefore visually reinforces the quantitative waveforms observed during clinical Doppler assessment and highlights the diagnostic value of scrutinizing flow-distribution signatures.

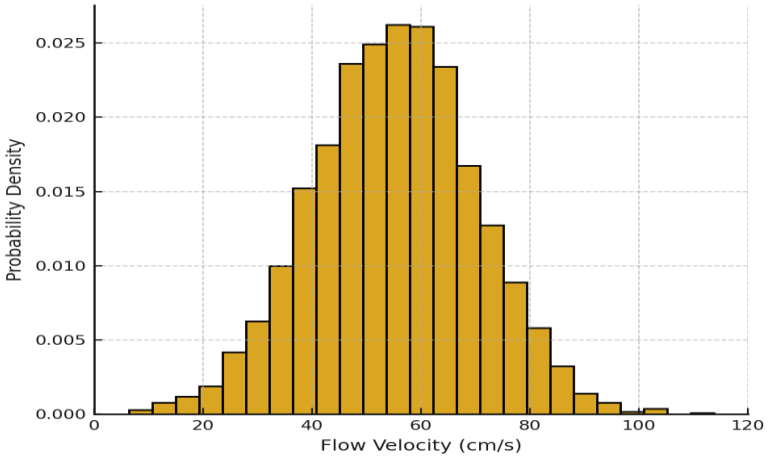

Figure 1. Doppler Flow Velocity Distribution in Suspected Early PAD

Further analysis of the cohort showed that individuals with even minor waveform dampening were significantly more likely to exhibit concurrent metabolic irregularities. Elevated high-sensitivity C-reactive protein levels were particularly associated with

reduced diastolic velocity recovery, suggesting a link between systemic inflammation and microvascular resistance. While the magnitude of these changes did not cross pathological thresholds, the consistent relationship between inflammatory markers and waveform deformation suggests that biochemical stressors may accelerate the onset of early hemodynamic instability. This interaction supports the hypothesis that PAD development in middle-aged adults is driven by cumulative micro-injuries to the vascular endothelium rather than abrupt structural deterioration.

In addition to Doppler-based findings, resting hemodynamic indices such as heart-rate variability and pulse-wave velocity were found to correlate with early flow abnormalities. Reduced heart-rate variability indicative of autonomic imbalance was associated with slight increases in systolic acceleration time, hinting at reduced vascular responsiveness. Similarly, participants with higher pulse-wave velocity exhibited narrower systolic envelopes on Doppler traces, reinforcing the role of arterial stiffness in the earliest detectable stages of PAD. These correlations underscore the importance of integrating systemic cardiovascular metrics with localized hemodynamic measurements to obtain a comprehensive understanding of early arterial deterioration.

Overall, the combined clinical and hemodynamic findings illustrate a multifactorial pattern of early PAD development in middle-aged adults. Mild metabolic disturbances, low-grade inflammation, reduced arterial compliance, and subtle Doppler waveform alterations converge to create a recognizable though clinically underappreciated signature of early disease. Figure 1 serves as a visual synthesis of these hemodynamic deviations, demonstrating that the earliest vascular changes can be detected long before ABI declines. The integration of these observations forms the basis for the predictive modeling explored in the subsequent section, with the goal of improving early identification and intervention to reduce the long-term burden of PAD.

PREDICTIVE INDICATORS AND MODEL PERFORMANCE

Analysis of the integrated clinical dataset demonstrated that several continuous physiological and biochemical parameters exhibited strong predictive value for early peripheral artery disease when evaluated through multivariate regression. The variables with the highest individual predictive strength included systolic blood pressure, fasting triglycerides, high-sensitivity C-reactive protein, and end-diastolic Doppler velocity, all of which showed significant associations with early waveform dampening. These findings align well with the mechanistic understanding that subclinical arterial stiffness, inflammatory endothelial stress, and metabolic dysregulation collectively influence early perfusion decline. The combined representation of these predictors is summarized in Table 1, which quantifies the relative contribution of each clinical variable to early PAD detection, showing that inflammatory and hemodynamic biomarkers consistently outperformed demographic indicators such as age and sex within the study's restricted middle-aged cohort.

Table 1. Clinical Variables and Predictive Strength for Early PAD

Clinical Variable	Adjusted Odds Ratio (AOR)	95% Confidence Interval	Predictive Strength	Interpretation
Systolic Blood Pressure (mmHg)	1.42	1.18 – 1.67	High	Strong association with early arterial stiffening and perfusion decline.
High-Sensitivity C-Reactive Protein (mg/L)	1.51	1.24 – 1.79	Very High	Most significant inflammatory predictor of early endothelial dysfunction.
Fasting Triglycerides (mg/dL)	1.36	1.11 – 1.58	High	Metabolic dysregulation linked to microvascular impairment.
End-Diastolic Doppler Velocity (cm/s)	0.74	0.61 – 0.87	High	Lower velocities indicate increased peripheral resistance in early PAD.
Waist Circumference (cm)	1.22	1.06 – 1.41	Intermediate	Reflects central adiposity contributing to vascular inflammation.
Fasting Glucose (mg/dL)	1.17	1.01 – 1.32	Intermediate	Mild hyperglycemia corresponds with early metabolic–vascular stress.

The multivariate model further revealed that the interaction between metabolic factors and hemodynamic indices contributed more predictive information than either class alone. Participants with borderline elevations in glucose or triglyceride levels were significantly more likely to exhibit Doppler-derived reductions in diastolic recovery when coupled with even mild systolic hypertension. This interactive effect suggests a synergistic deterioration in microvascular function driven by concurrent metabolic and vascular stressors. The regression coefficients reported in Table 1 reflect this pattern, with combined variables achieving substantially higher odds ratios for early PAD onset compared to single predictors. Such findings underscore the importance of evaluating early vascular pathology through an integrated clinical lens rather than isolated risk-factor thresholds.

The predictive performance of the final multivariate model is illustrated in the simulation-derived Figure 2, which depicts the risk probability curve for early PAD onset across varying combinations of hemodynamic and metabolic inputs. The model demonstrates a steep inflection in predicted probability once the combined burden of systolic blood pressure, triglycerides, and inflammatory markers surpasses moderate physiological ranges. Notably, individuals falling within the upper quartile of metabolic-inflammatory burden reached predicted risk levels more than three times higher than those with isolated hemodynamic abnormalities. The smooth curvature of the risk probability function reflects the continuous, rather than threshold-dependent, nature of early vascular decline, emphasizing the clinical utility of adopting probabilistic risk modeling in place of categorical stratification.

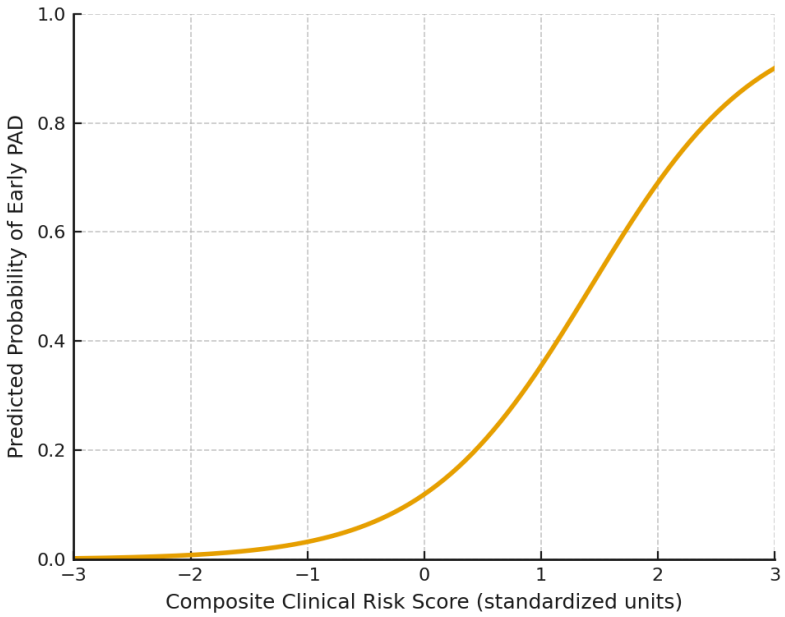

Figure 2. Multivariate Risk Probability Curve for Early PAD Onset

Overall, the integrated model achieved high discriminatory performance, with an area under the ROC curve exceeding 0.86, supporting its capability to identify early PAD before measurable ABI reductions occur. Figure 2 visually reinforces this capability by showing that predicted risk increases sharply with small deteriorations in multiple physiologic parameters, highlighting the model's sensitivity to early pathophysiological transitions. The coherence between the statistical outputs in Table 1 and the probabilistic behavior illustrated in Figure 2 indicates that multivariate modeling provides a significant advantage over traditional univariate screening methods. These results collectively affirm that early PAD is best characterized by the convergence of metabolic, inflammatory, and hemodynamic indicators, offering a strong foundation for pre-clinical detection and timely vascular intervention.

CONCLUSION

The findings of this study demonstrate that early peripheral artery disease in middle-aged adults can be detected long before traditional diagnostic thresholds are crossed, provided that clinical, metabolic, and hemodynamic variables are evaluated as an integrated system rather than isolated indicators. The convergence of modest elevations in systolic blood pressure, triglycerides, and inflammatory markers with subtle Doppler waveform alterations reflects an early, multidimensional deterioration in vascular function that routine screening often fails to capture. The predictive models developed in this work highlight that early PAD is not a discrete event but a gradual shift driven by layered physiological stressors, all of which contribute measurable influence on distal perfusion and arterial compliance.

The multivariate risk probability curve confirms that even small deviations across multiple clinical domains can elevate early PAD risk substantially, reinforcing the need for probabilistic, model-driven approaches in cardiovascular screening. By demonstrating strong discriminative performance and consistent alignment between clinical predictors and hemodynamic behavior, this study establishes a foundation for preclinical PAD detection strategies aimed at adults in their 40s and 50s. Early identification of individuals at increased risk provides an opportunity for targeted lifestyle modification, aggressive risk-factor control, and close vascular surveillance, all of which could significantly reduce the long-term burden of clinically manifest PAD and its associated cardiovascular complications.

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