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FM UP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

CLINICAL AND IMAGIOLOGICAL PREDICTORS OF PROGNOSIS IN EXTENSIVE AORTOILIAC DISEASE

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TESE DE DOUTORAMENTO APRESENTADA
À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO EM
MEDICINA

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CLINICAL AND IMAGIOLOGICAL PREDICTORS OF PROGNOSIS IN EXTENSIVE AORTOILIAC DISEASE

Preditores Clínicos e Imagiológicos de Prognóstico na Doença Aortoilíaca Extensa

Thesis to obtain the Degree of Doctor from the Faculty of the University of Porto

Dissertação para obtenção do Grau de Doutor
Apresentada a Faculdade de Medicina da Universidade do Porto

Porto, 2025

TITLE/TÍTULO

Clinical and imagiological predictors of prognosis in extensive aortoiliac disease

Preditores clínicos e imagiológicos de prognóstico na doença aortoilíaca extensa

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ACKNOWLEDGMENTS/AGRADECIMENTOS

Este trabalho representa o culminar natural de um percurso académico e profissional exigente, e é com enorme satisfação e sentido de realização que dou este passo.

Antes de mais, quero expressar o meu profundo agradecimento ao meu orientador, Prof. Doutor João Rocha Neves, que desde o momento em que nos conhecemos me prestou um apoio científico inestimável e me fez crescer como médico, cirurgião, académico e investigador. A tudo isto aliou um companheirismo e uma amizade inquebrantáveis, sem os quais não estaria hoje onde estou.

Agradeço igualmente ao meu co-orientador, Professor Doutor José Paulo Andrade, Professor Catedrático de mérito incontestável, cujo rigor científico e exigência foram determinantes para a concretização desta tese. Agradeço também o apoio institucional e humano proporcionado pela Unidade de Anatomia do Departamento de Biomedicina, que tão bem representa.

Ao Serviço de Angiologia e Cirurgia Vascular da ULS São João, manifesto o meu sincero reconhecimento. Em particular, ao meu orientador de internato, Dr. Alfredo Cerqueira, que foi peça essencial no meu desenvolvimento profissional, sempre com um apoio incondicional ao longo dos anos, sendo exemplo máximo de profissionalismo e de uma amizade genuína. À Dra. Isabel Vilaça, que me acompanhou de forma próxima, quase como se fosse seu interno, ensinando-me, apoiando-me e brindando-me também com a sua amizade, exprimo-lhe a minha enorme gratidão.

Agradeço ainda ao Dr. José Teixeira e ao Professor Doutor Armando Mansilha, que assumiram a Direção do Serviço de Angiologia e Cirurgia Vascular da ULS São João durante o meu percurso e, por isso, garantes das condições que me permitiram igualmente a concretização deste projeto.

Quero ainda expressar um agradecimento especial ao Serviço de Angiologia e Cirurgia Vascular da ULS Tâmega e Sousa, pela contribuição imprescindível e relevantíssima para esta tese, nomeadamente através da colaboração do seu atual Diretor, Dr. José Vidoedo, e do Doutor Luís Gamas, colegas e amigos, cujo apoio e empenho foram determinantes para a elaboração deste projeto.

Quero deixar uma palavra de apreço aos meus colegas e amigos Prof. Doutora Mariana Fragão-Marques, Prof. Doutor Hugo Ribeiro, Doutora Juliana Macedo, Mestre Leandro Nóbrega, Mestre Lara Dias, Mestre Tiago Pereira e Prof. Doutora Marina Dias Neto, que colaboraram em muitas das publicações realizadas e têm acompanhado o meu percurso científico, alguns desde o início, partilhando desafios, aprendizagens e sucessos, num crescimento verdadeiramente mútuo.

Por último, mas de forma muito especial, agradeço à minha esposa, Carolina, pelo apoio incondicional desde o momento em que nos conhecemos, pela alegria e motivação que me transmite e que tornam todos os desafios da vida alcançáveis. À minha família — mãe, pai e irmã — que, mesmo longe, está sempre presente, com um apoio inabalável em qualquer projeto ou fase da minha vida.

DECLARAÇÃO

No cumprimento do código de ética de conduta académica da Universidade do Porto (UP), aprovado em dezembro de 2017, e das recomendações da Comissão de Ética da mesma Universidade, declaro, sob minha honra, que participei na conceção e na execução do trabalho empírico, nomeadamente no planeamento de cada um dos quatro estudos aqui apresentados (dois como autor e dois como co-autor), recolha de dados, análise e interpretação de resultados, redação dos artigos resultantes, bem como na sua revisão, aprovação final e submissão.

Neste sentido, confirmo que não incorri em plágio. Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram devidamente referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a fonte bibliográfica.

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Assinatura conforme cartão de identificação:

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ABBREVIATION LIST

ABBREVIATION LIST

ABF	Aortobifemoral Bypass
ABI	Ankle-Brachial Index
AHF	Acute Heart Failure
aHR	Adjusted Hazard Ratio
AID	Aortoiliac Peripheral Artery Disease
AMI	Acute Myocardial Infarction
CAC	Coronary Artery Calcium score
CAD	Coronary Artery Disease
CERAB	Covered Endovascular Reconstruction Of Aortic Bifurcation
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLTI	Chronic Limb-Threatening Ischemia
CTA	Computed Tomography Angiography
DM	Diabetes Mellitus
HF	Heart Failure
HIC	High- income countries
HR	Hazard Ratio
ICS	Iliac Calcium Score
IQR	Interquartile Range
LMIC	Low- and middle-income countries
MACE	Major Adverse Cardiovascular Events
MALE	Major Adverse Limb Events
mFI-5	Modified Frailty Index 5 Factors
MHR	Monocyte-to-HDL cholesterol ratio
MINS	Myocardial Injury After Noncardiac Surgery
OR	Odds Ratio
PAD	Peripheral Artery Disease
QoL	Quality Of Life
TASC	TransAtlantic Inter-Society Consensus

ABSTRACT

ABSTRACT

INTRODUCTION

Extensive aortoiliac disease, classified as TransAtlantic Inter-Society Consensus II [TASC II] type D lesions, continues to present a significant role in predicting outcomes after revascularization. Although endovascular and surgical techniques have evolved substantially, considerable variability persists in patient outcomes, including major adverse cardiovascular events (MACE), major adverse limb events (MALE), and amputation. The identification of robust and clinically applicable prognostic tools remains an urgent clinical need to optimize patient selection and personalize therapeutic strategies in complex aortoiliac revascularization.

OBJECTIVES

This thesis aimed to validate clinical, hematological, and imaging markers as independent predictors of perioperative and long-term outcomes in patients with complex aortoiliac disease undergoing elective revascularization. Specifically: (1) to validate the Modified Frailty Index-5 (mFI-5) as a prognostic tool; (2) to evaluate absolute monocyte count as a predictor of limb outcomes; (3) to examine the relationship between chronic kidney disease (CKD) and cardiovascular or limb outcomes; and (4) to develop and validate an Iliac Calcification Scoring (ICS) system derived from computed tomography as a prognostic tool.

METHODS

Consecutive patients undergoing elective revascularization for TASC II type D aortoiliac disease were prospectively enrolled at two centers between January 2013 and January 2024. Demographic, clinical, and procedural data were obtained from electronic health records and institutional vascular registries. Follow-up assessment included clinical evaluation and non-invasive hemodynamic studies at one month, 12 months, and annually thereafter. Predefined clinical endpoints included MACE (myocardial infarction, stroke, acute heart failure, all cause-mortality), MALE (reintervention, acute limb ischemia, major amputation, occlusion without reintervention), and all-cause mortality. Survival analysis included multivariate Cox regression modelling and Kaplan-Meier survival analysis.

RESULTS

MFI-5 scores >2 were independently associated with long-term MACE (hazard ratio [HR] 2.469; 95% confidence interval [CI] 1.267–4.811; P=0.008) and all-cause mortality (HR 2.585; 95% CI 1.270–5.260; P=0.009), but not with 30-day complications. Five-year MACE-free survival was significantly worse in frail patients (50.8±9.3% vs. 77.6±5.4%; P=0.006).

Patients with CKD demonstrated higher rates of perioperative myocardial injury (54.5%; P=0.014) and were independently associated with acute heart failure (HR 4.88; P=0.007), MACE (HR 2.99; P=0.002), and mortality (HR 3.30; P<0.001).

An absolute monocyte threshold >0.720 × 10^9/L was identified as a significant predictor of 30-day MALE (OR 7.14; P=0.013) and long-term MALE (aHR 2.149; P=0.022), with independent association to increased major amputation and reduced secondary patency.

An iliac calcification score ≥37 was independently associated with 2.3-fold higher risk of MACE and 7.5-fold higher risk of major amputation. At 60 months, amputation-free survival was markedly inferior in the high calcification group (74.5% vs. 97.8%; P=0.002), as was MACE-free survival (47.3% vs. 73.4%; P=0.005) and overall survival (54.6% vs. 77.0%, P=0.013).

CONCLUSION

Simple and clinically available markers—mFI-5, CKD status, preoperative absolute monocyte count, and CT-derived ICS—provide complementary and independent prognostic information that improves patient selection, procedural planning, and follow-up intensity in complex aortoiliac disease. Integration of these markers into preoperative risk stratification may refine risk assessment and enable more personalized decision-making in TASC II type D aortoiliac revascularization, while also guiding intensified surveillance strategies in high-risk patients.

RESUMO

RESUMO

INTRODUÇÃO

A doença aortoilíaca extensa, classificada como lesões do tipo D segundo o *TransAtlantic Inter-Society Consensus II* (TASC II), continua a desempenhar um papel significativo na previsão dos resultados após revascularização. Apesar da evolução substancial das técnicas endovasculares e cirúrgicas, persiste uma variabilidade considerável nos resultados clínicos, incluindo eventos cardiovasculares adversos major (MACE), eventos adversos major do membro (MALE) e amputação. A identificação de ferramentas prognósticas robustas e clinicamente aplicáveis continua a ser uma necessidade urgente, de modo a otimizar a seleção de doentes e a personalizar as estratégias terapêuticas em casos complexos de revascularização aortoilíaca.

OBJETIVOS

Esta tese teve como objetivo validar marcadores clínicos, hematológicos e imagiológicos como preditores independentes de resultados perioperatórios e a longo prazo em doentes com doença aortoilíaca complexa submetidos a revascularização eletiva. Especificamente: (1) validar o *Modified Frailty Index-5* (mFI-5) como ferramenta prognóstica; (2) avaliar a contagem absoluta de monócitos como preditor de resultados dos membros inferiores; (3) analisar a relação entre doença renal crónica (DRC) e resultados cardiovasculares e do membro; e (4) desenvolver e validar um sistema de pontuação de calcificação ilíaca (*Iliac Calcification Score*, ICS) obtido por tomografia computorizada (TC).

MÉTODOS

Foram prospetivamente incluídos doentes consecutivos submetidos a revascularização eletiva por doença aortoilíaca tipo D (TASC II) em dois centros, entre janeiro de 2013 e janeiro de 2024. Dados demográficos, clínicos e do procedimento foram obtidos a partir de registos eletrónicos e bases de dados institucionais. O seguimento incluiu avaliação clínica e estudos hemodinâmicos não invasivos ao primeiro mês, aos 12 meses e, posteriormente, de forma anual. Os resultados clínicos pré-definidos incluíram MACE (enfarte do miocárdio, acidente vascular cerebral, insuficiência cardíaca aguda, mortalidade por todas as causas), MALE (reintervenção, isquemia aguda do membro, amputação major, oclusão sem reintervenção) e mortalidade. A análise de sobrevivência incluiu modelos de regressão de Cox multivariada e análise de sobrevivência de Kaplan-Meier.

RESULTADOS

Valores de mFI-5 superiores a 2 associaram-se de forma independente a MACE a longo prazo (*hazard ratio* [HR] 2,469; intervalo de confiança [IC] 95%: 1,267–4,811; P=0,008) e mortalidade (HR 2,585; IC 95%: 1,270–5,260; P=0,009), mas não a complicações nos primeiros 30 dias. A sobrevivência livre de MACE aos cinco anos foi significativamente inferior em doentes frágeis (50,8±9,3% vs. 77,6±5,4%; P=0,006).

Os doentes com DRC apresentaram taxas mais elevadas de lesão miocárdica perioperatória (54,5%; P=0,014) e apresentaram maior risco de agudização de insuficiência cardíaca (HR 4,88; P=0,007), MACE (HR 2,99; P=0,002) e mortalidade por todas as causas (HR 3,30; P<0,001).

Uma contagem absoluta de monócitos superior a 0,720 × 10^9/L foi identificada como preditor significativo de MALE aos 30 dias (*odds ratio* [OR] 7,14; P=0,013) e a longo prazo (aHR 2,149; P=0,022), com associação independente a maior taxa de amputação *major* e menor patência secundária.

Um valor de ICS ≥37 associou-se de forma independente a um risco 2,3 vezes superior de MACE e 7,5 vezes superior de amputação *major*. Aos 60 meses, a sobrevivência livre de amputação foi significativamente inferior no grupo com elevada calcificação (74,5% vs. 97,8%; P=0,002), tal como a sobrevivência livre de MACE (47,3% vs. 73,4%; P=0,005) e a sobrevivência livre de mortalidade de todas as causas (54.6% vs. 77.0%, P=0.013).

CONCLUSÃO

Marcadores simples e clinicamente acessíveis — mFI-5, presença de DRC, contagem absoluta de monócitos pré-operatória e ICS — fornecem informação prognóstica complementar e independente que melhora a seleção dos doentes, o planeamento do procedimento e o seguimento na doença aortoilíaca complexa. A integração destes marcadores na estratificação pré-operatória do risco pode refinar a avaliação prognóstica e permitir uma tomada de decisão mais personalizada na revascularização aortoilíaca TASC II tipo D, orientando simultaneamente estratégias de vigilância mais intensivas em doentes de alto risco.

INTRODUCTION

INTRODUCTION

Definition and relevance peripheral artery disease

Peripheral arterial disease (PAD) of the lower extremities is defined as an obstructive disease of the arteries extending from the distal aorta to the foot. In about 95% of cases, atherosclerosis is the cause leading to arterial stenosis or occlusion which impairs blood flow to one or both lower limbs and can be identified by clinical symptoms, physical signs, or abnormalities on vascular testing or imaging. Aortoiliac PAD is defined by atherosclerosis that affects the infrarenal aorta and the iliac arteries. Aortoiliac disease typically occurs in younger individuals and is more rapidly progressive than distal artery disease (1).

Lower limb PAD is most commonly diagnosed through measurement of the ankle-brachial index (ABI), with values outside the normal range (0.91–1.39) indicating disease. Importantly, even in asymptomatic individuals, a reduced ABI serves as a marker of elevated risk for future adverse cardiovascular outcomes. A large meta-analysis comprising 480,325 person-years of follow-up demonstrated that men with a low ABI (≤0.90) had a 10-year cardiovascular mortality of 18.7% (95% confidence interval [CI], 13.3–24.1%) compared with 4.4% (95% CI, 3.2–5.7%) in those with a normal ABI (1.11–1.40), corresponding to a hazard ratio (HR) of 4.2 (95% CI, 3.3–5.4). Among women, the respective figures were 12.6% (95% CI, 6.2–19.0%) and 4.1% (95% CI, 2.2–6.1%), with an HR of 3.5 (95% CI, 2.4–5.1) (2). The hallmark clinical manifestation of PAD is intermittent claudication, which may not initially interfere with daily activities. However, in advanced stages, patients may develop functionally limiting claudication or even chronic limb-threatening ischemia (CLTI) (rest pain or tissue loss [ulceration or gangrene]), conditions associated with a significant reduction in quality of life, increased risk of limb loss, and elevated morbi-mortality (3).

The global burden of PAD has risen substantially over recent decades, from an estimated 163 million cases in 2000, to 202 million in 2010, and 237 million in 2015—a 45% increase in just 15 years, largely attributed to population aging and the growing prevalence of cardiovascular risk factors, in particular diabetes mellitus (DM) (4, 5). At younger ages, prevalence was slightly higher in low- and middle-income countries (LMIC) compared with high-income countries (HIC), but the age-related increase was steeper in HIC, leading to higher prevalence at older ages. In HIC, PAD was also somewhat more frequent in women than men until age 75, whereas in LMIC the prevalence was similar between sexes. Overall, the global prevalence of PAD in adults aged ≥25 years is estimated at 5.6% (95% CI, 3.8–8.6), higher in HIC (7.4% vs. 5.1%). However, prevalence is rising more rapidly in LMIC (22.6% relative increase vs. 4.5% in HIC), a trend likely related to demographic shifts, tobacco use patterns, improved screening and expanded access to cardiovascular care (4, 5). Ethnicity also influences PAD prevalence, with higher rates observed in Black individuals compared to Whites, whereas Asians and Hispanics tend to have lower prevalence (6, 7). The underlying reasons remain uncertain, as it is unclear whether these

differences are primarily genetic or reflect varying exposure to traditional risk factors. However, the observation that disease risk profiles shift with migration suggests that environmental and lifestyle factors may play a greater role than genetic predisposition (8).

The global rise in PAD prevalence, in contrast to other forms of ischemic cardiovascular disease, is associated not only with increased mortality but also with years of life lost, years lived with disability, and higher disability-adjusted life years (9). Although cardiovascular disease is widely recognized as a leading health concern, the prognosis of patients with PAD is considerably worse. Evidence from recent studies indicates a five-year mortality ranging between 13% and 50%, markedly exceeding the six-year mortality of 13% reported in patients following myocardial infarction (8).

Pathophysiology and risk factors of peripheral artery disease

Atherosclerosis is now understood as a chronic, immune-driven process of arterial wall injury and repair. Endothelial dysfunction (due to risk factors like hyperlipidemia, hypertension or smoking) allows plasma lipoproteins, especially oxidized Low-density Lipoprotein, to accumulate in the intima. These lipids trigger local inflammation: circulating monocytes adhere to the injured endothelium and migrate into the vessel wall, where they differentiate into macrophages and ingest oxidized Low-density Lipoprotein, becoming foam cells. Foam cells secrete pro-inflammatory cytokines and chemokines (e.g. Interleukin -1β, Interleukin-6, Tumor necrosis factor α) that recruit additional immune cells and perpetuate a vicious cycle of inflammation (10, 11). Plaque macrophages and foam cells release matrix metalloproteinases and procoagulant factors, thinning the cap and promoting thrombosis when plaques rupture (10, 11). Vascular smooth muscle cells also migrate from the media into the intima and synthesize collagen to form the fibrous cap of the plaque. Proteolytic degradation of this cap further weakens plaque stability, increasing its propensity to rupture (12).

PAD represents the manifestation of this same atherosclerotic process in the arteries of the lower limbs (13, 14). Just as in coronary disease, atherosclerotic plaques form in peripheral vessels under the influence of lipid deposition and inflammation. In PAD, chronic ischemia from occlusive plaques leads to skeletal muscle injury, mitochondrial dysfunction and oxidative stress, which in turn amplify local inflammatory signalling (13). Repeated episodes of ischemia and reperfusion in these tissues further aggravate oxidative damage and provoke progressive loss of muscle, ultimately resulting in limb functional impairment (15, 16). Importantly, and as mentioned above, inflammation represents a key factor in the pathogenesis of atherosclerosis (17) and that role in PAD is no exception. Elevated systemic inflammation has been reported and epidemiologic studies have confirmed that higher levels of C-reactive protein strongly predict the risk of developing symptomatic PAD, even after accounting for conventional risk factors (18, 19), or that homocysteine levels are higher among several case-control PAD cohort studies (19, 20).

Regarding PAD risk factors, these are commonly categorized as non-modifiable and modifiable. Among the non-modifiable and demographic determinants, the prevalence of PAD rises sharply with advancing age, varies across ethnic groups and regions, and shows only modest sex-related differences as mentioned above (5). By contrast, the contribution of family history and genetic predisposition remains less clearly defined, with available data suggesting only a minor or uncertain impact (21, 22).

Concerning modifiable risk factors, cigarette smoking is the single strongest modifiable risk factor for PAD (23). Furthermore, has been shown to confer a disproportionately high risk for PAD when compared with other atherosclerotic outcomes (23). In a large prospective cohort, duration and intensity of smoking both demonstrated strong dose–response associations: current smokers with a smoking history of ≥35 years exhibited HRs of 5.56 (95% CI 4.26–7.26) for PAD, higher than HR of 2.30 (95% CI 1.98–2.66) for coronary artery disease (CAD) or the HR of 1.92 (95% CI 1.58–2.33) for stroke, compared to never smokers. Likewise, those consuming ≥1 pack/day had HRs of 5.36 (95% CI 4.16–6.91) for PAD, 2.37 (95% CI 2.07–2.72) for CAD, and 1.88 (95% CI 1.57–2.26) for stroke (24). Importantly, patients who quit smoking achieve better outcomes, although the excess risk of PAD associated with prior smoking may persist for up to 30 years (24-26). Moreover, smoking has been particularly linked to the development of proximal atherosclerotic disease, most notably affecting the aortoiliac segment, in contrast to DM, which more often involves infrapopliteal and distal arteries (27). DM is another major driver: people with DM have roughly 2-3 times higher PAD prevalence than non-diabetics (5, 28). The relationship between DM and PAD is particularly complex, as diabetic patients not only face higher rates of PAD development but also experience more severe adverse events, with lower success rates following revascularization procedures and increased risk of amputation (23, 29, 30). The anatomical distribution of PAD in diabetic patients differs markedly from that in non-diabetic individuals, with DM showing preferential involvement of the distal vessels, particularly the infrapopliteal segment, creating a pattern of below-the-knee disease that presents a unique therapeutic challenge (27). Chronic kidney disease (CKD), particularly in its end-stage form, is a powerful risk factor for PAD and subsequent limb loss. Its impact is especially pronounced when coexisting with DM and, similarly, predominantly involves distal arterial segments (5, 19). Both DM and CKD are strongly associated with accelerated vascular calcification, particularly within the media arterial layer, and confer a markedly worse prognosis in patients with PAD (31-34). Dyslipidemia and hypertension also contribute to the incidence of PAD, although their relative impact is less pronounced than that of smoking or DM (5, 35). The presence of other cardiovascular diseases (multivessel disease) further elevates the risk of developing PAD (5, 36).

Patient selection criteria for lower limb revascularization

Patient selection for lower limb revascularization should be guided by an understanding of the natural history of PAD. While most patients remain asymptomatic or their intermittent claudication display stable symptoms, recent meta-analyses reveal that between 1.1% and 36.7% (pooled rate ≈15%)

of claudicants eventually progress to CLTI over an average follow-up of approximately 5 years (37). Factors such as advanced age, DM, smoking, and renal replacement therapy are significant predictors of more rapid disease progression (37, 38). CLTI is associated with poor outcomes as untreated patients face a 22% one-year risk of major amputation (95% CI, 2%-42%) and mortality (95% CI, 12%-33%) (39).

The European Society for Vascular Surgery guidelines for PAD and CLTI (8, 36), emphasize the importance of distinguishing between CLTI and lifestyle-limiting claudication when considering revascularization. For patients with CLTI, the primary objective of intervention is limb salvage, relieving rest pain, promoting wound healing, and preventing amputation and mortality, accompanied by best medical therapy and multidisciplinary evaluation (8). In contrast, for patients with disabling claudication, the goal is to improve quality of life (QoL), and revascularization is appropriate only after the optimization of medical and exercise therapies (36).

Ultimately, patient selection for revascularization must be individualized and led by multifactorial clinical assessment rather than imaging alone (8, 36). Decisions should incorporate the severity of symptoms, signs, comorbidities and anatomical factors to perform a risk–benefit analysis. Critically, the patient's preferences and overall objectives, whether limb salvage in CLTI or symptom improvement and QoL in severely claudicant patients must be taken into account.

Overview of surgical options in extensive aortoiliac disease

Within the spectrum of aortoiliac peripheral disease (AID), both open surgical, typically aortobifemoral bypass (ABF), and endovascular techniques, such as angioplasty and stenting, including covered endovascular reconstruction of aortic bifurcation (CERAB) configurations, are well-established therapeutic options.

ABF has long been regarded as the gold standard due to its durability (23), with ten-year patency rates of approximately 80–90% even though it achieves perioperative mortality rates between 3-5%, relevant perioperative morbidity, and a delay in the return to normal routine (40). Conversely, contemporary endovascular approaches have demonstrated high technical success rates (86–100%) and low perioperative morbidity (1.2–6.7% mortality, with most complications managed percutaneously) (41). Primary patency at one-year ranges from 70% to 97%, with secondary patency as high as 98–100% at long-term follow-up (41-43). Notably, the CERAB technique also offers excellent three-year patency and limb-salvage outcomes, with primary and secondary patency exceeding 82% and 97%, respectively (44).

A meta-analysis indicates that although surgical revascularization yields superior primary patency, endovascular procedures, especially when combined with common femoral endarterectomy, achieve equivalent limb salvage rates, albeit with reintervention trade-offs (40). Moreover, endovascular

strategies provide significant short-term advantages such as reduced complication rates, shorter hospital stays, and lower costs when compared to open surgery (42, 45, 46).

The increasing expertise level among vascular surgeons associated with device development led to more frequent utilization of endovascular approaches (47, 48), with experienced centers proposing an "endovascular-first" approach (43, 48, 49). This recommendation is further supported on the premise that an unsuccessful endovascular attempt does not preclude subsequent ABF (50, 51). Age and lesion complexity directly influence strategy choice since younger patients may experience superior long-term outcomes with surgical bypass, while older ones often fare better with endovascular therapy (52, 53). Currently, consensus among vascular surgeons and guidelines advocate an "endovascular-first" approach for TASC II A-C lesions, with surgical revascularization reserved for more extensive TASC C–D disease or failed endovascular attempts, especially in patients with low-risk with long life expectancy (36). There remains a role for extra-anatomical bypass procedures, most commonly femorofemoral crossover or axillofemoral bypass, in patients who are not suitable candidates for endovascular, hybrid, or standard anatomical surgical revascularization (36).

Current challenges

Current challenges in the management of complex AID focus on the reliable prediction of both cardiovascular and limb-related outcomes. This information influences three key decisions: (1) which patients will truly benefit from revascularization; (2) which revascularization strategy (endovascular, open, hybrid or extra-anatomical) optimally balances durability and perioperative risk for an individual; and finally (3) who requires intensified peri- and post-procedural surveillance to prevent major adverse cardiovascular events (MACE), major adverse limb events (MALE) and amputation.

Existing selection frameworks rely heavily on anatomy, general comorbidity scores and clinical judgment, but they perform poorly, given the increasing fragility and cumulative burden of comorbidities among contemporary patients, turning clinical profiles markedly heterogeneous (54, 55). This uncertainty might lead to both overtreatment and undertreatment: some high-risk patients undergo interventions with limited long-term benefit, while others who might benefit from earlier or different technical approaches are not identified (56). These gaps create an urgent need for validated, practical prognostic tools that integrate clinical, laboratory and imaging biomarkers to enable personalized and refined decision-making.

THESIS OVERVIEW

THESIS OVERVIEW

Despite significant advances in both endovascular and surgical approaches to AID, contemporary clinical practice faces several persistent challenges that complicate optimal patient management and outcomes. These challenges span diagnostic accuracy, risk stratification, treatment selection, and long-term prognosis, particularly in TASC II type D lesions.

One of the most significant challenges in current practice is the accurate prediction of outcomes following aortoiliac revascularization. Traditional clinical assessment alone has proven insufficient for optimal patient selection, leading to variable outcomes despite technically successful procedures (54). The need for improved risk stratification tools is particularly acute given the growing adoption of an "endovascular-first" approach, where precise patient selection becomes crucial for balancing expected benefits with procedural risks (46).

The integration of frailty assessment represents an emerging challenge in patient evaluation (57). With frailty prevalence estimated at 48% among PAD patients, and significantly higher rates in those with CLTI (54%), the identification and quantification of frailty status have become essential (58). However, standardized frailty assessment in vascular surgery remains challenging due to the lack of consensus on optimal measurement tools. Traditional phenotypic measurements may be skewed in PAD patients due to ischemic pain that impairs mobility, while comprehensive frailty indices require substantial resources and expertise that are not universally available (58). Furthermore, recent research has identified several promising prognostic markers that address current gaps in risk prediction. Arterial calcification assessment through CT-based scoring systems has emerged as a valuable tool for predicting both cardiovascular and limb-related outcomes. However, the standardization of calcium scoring methodology remains inconsistent across institutions, and the additional time required for calcification analysis may limit widespread adoption in routine clinical practice (59). Similarly, inflammatory biomarkers, namely monocyte count, have demonstrated significant prognostic value (60, 61). Despite the availability and cost-effectiveness of complete blood count analysis, the clinical integration of monocyte-based risk stratification requires validation across diverse patient populations and institutional settings. Moreover, the management of patients with CKD presents unique challenges in aortoiliac revascularization as this population demonstrates markedly worse outcomes, with higher rates of MACE, amputation, and mortality (62, 63). The complex pathophysiology involving accelerated atherosclerosis, chronic inflammation, and vascular calcification in CKD patients requires specialized management approaches that are often not standardized across institutions (62, 63).

These contemporary challenges in AID management underscore the need for continued research, standardization of assessment tools, and development of evidence-based care protocols that can be effectively implemented across diverse clinical settings. The work presented in this thesis aims to address several of these challenges through the validation of novel prognostic markers and risk stratification tools in complex aortoiliac disease.

Specific aims

In light of these premises, this thesis aimed to:

1.

Validate the modified frailty index-5 (mFI-5) as a prognostic tool for postoperative outcomes in patients with TASC II D aorto-iliac occlusive disease undergoing elective revascularization.

• Nóbrega L, **Pereira-Neves A,** Duarte-Gamas L, Dias PP, Azevedo-Cerqueira A, Ribeiro H, Vidoedo J, Teixeira J, Rocha-Neves J. Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease.(64)

Ann Vasc Surg. 2022 Feb;79:153-161. doi: 10.1016/j.avsg.2021.06.049.

Impact Factor: 1.5 (2022)

Quartile: Q2 (Scimago, 2022); Q3 (JCR, 2022)

2.

Assess whether preoperative absolute monocyte count predicts early and long-term limb-related outcomes in patients with TASC II D aorto-iliac lesions undergoing elective revascularization.

• **Pereira-Neves A,** Dias L, Fragão-Marques M, Vidoedo J, Ribeiro H, Andrade JP, Rocha-Neves J. Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization.(65)

J Clin Med. 2024 Oct 26;13(21):6412. doi: 10.3390/jcm13216412.

Impact Factor: 2.9 (2024)

Quartile: Q1 (Scimago, 2024); Q1 (JCR, 2024)

3.

To examine the relationship between chronic kidney disease and both perioperative and long-term outcomes in patients treated with aorto-iliac revascularization for TASC II D disease.

• Alves M, Pias AD, Marques J, Miranda C, **Pereira-Neves A,** Shahat M, Vidoedo J, Andrade JP, Rocha-Neves J, Marreiros A. Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study.(66)

J Cardiovasc Surg (Torino). 2025 Apr;66(2):109-119. doi: 10.23736/S0021-9509.24.13135-7.

Impact Factor: 1.5 (2024)

Quartile: Q2 (Scimago, 2024); Q3 (JCR, 2024)

4.

Evaluate whether a CT-derived Iliac Calcium Score (ICS) predicts adverse limb and/or cardiovascular events in patients with TASC II D aorto-iliac disease undergoing elective revascularization.

• **Pereira-Neves A,** Rocha-Neves J, Costa-Pereira T, Ribeiro H, Dias LR, Duarte-Gamas L, Andrade JP. Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease.(67)

Front Med (Lausanne). 2025 Sep 17;12:1655229. doi: 10.3389/fmed.2025.1655229.

Impact Factor: 3.0 (2024)

Quartile: Q1 (Scimago, 2024); Q1 (JCR, 2024)

1. Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease

Reference to the published version:

Nóbrega L, Pereira-Neves A, Duarte-Gamas L, Dias PP, Azevedo-Cerqueira A, Ribeiro H, Vidoedo J, Teixeira J, Rocha-Neves J. Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease.

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Impact Factor: 1.5 (2022)

Quartile: Q2 (Scimago, 2022); Q3 (JCR, 2022)

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JID: AVSG [mNS;November 17, 2021;17:47]

Clinical Research, Basic Science

Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease

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OBJECTIVES: Vascular surgery patients commonly have several comorbidities that cumulatively lead to a frailty status. The cumulative comorbidities disproportionately increase the risk of adverse events and are also associated with worsened long-term prognosis. In recent years, several tools have been elaborated with the objective of quantifying a patient's frailty. One of them is the modified frailty index-5 (mFI-5), a simplified and easy to use index. There is scarce data regarding its value as a prognostic factor in aortoiliac occlusive disease. The aim of this work is to validate mFI-5 as a potential postoperative prognostic indicator in this population.
METHODS: From January 2013 to January 2020, 109 patients who underwent elective revascularizations, either endovascular or open surgery, having Trans-Atlantic Inter-Society Consensus II type D aortoiliac lesions in a tertiary and a regional hospital were selected from a prospective vascular registry. Demographic data was collected including diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, arterial hypertension requiring medication and functional status. The 30-d and subsequent long-term surveillance outcomes were also collected including major adverse cardiovascular events (MACE), major adverse limb events (MALE) and all-cause mortality were assessed in the 30-d post-procedure and in the subsequent long-term surveillance period. The mFI-5 was applied to this population to evaluate the prognostic impact of this frailty marker on mortality and morbidity.
RESULTS: In the long-term follow-up, mFI-5 was significantly associated with MACE (hazard ratio [HR] 2.469; 95% confidence interval [CI]: 1.267−4.811; $P = .008$) and all-cause mortality (HR 2.585; 95% CI: 1.270−5.260; $P = .009$). However, there was no significant association with 30-day outcomes. Along with the presence of chronic kidney disease, mFI-5 was the prognostic factor better able of predicting MACE. No prognostic value was found regarding short-term outcomes.
CONCLUSION: The mFI-5 index may have a role in predicting long term outcomes, namely MACE and all-cause mortality, in the subset of patients with extensive aortoiliac occlusive disease. Its ease of use can foster its application in risk stratification and contribute for the decision-making process.

Declaration of Competing Interest: The authors have no conflict of interest to disclosure.

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Ann Vasc Surg 2021; 000: 1–9
https://doi.org/10.1016/j.avsg.2021.06.049
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Manuscript received: December 31, 2020; manuscript revised: June 27, 2021; manuscript accepted: June 30, 2021; published online: xxx

Please cite this article as: Nóbrega *et al.*, Annals of Vascular Surgery(2021), https://doi.org/10.1016/j.avsg.2021.06.049

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JID: AVSG [mNS;November 17, 2021;17:47]

INTRODUCTION

The treatment of aortoiliac atherosclerotic disease has changed over the last few years. Whereas previously there was a debate over the choice of treatment modality now the recommendations are balancing towards an endovascular approach.[1] For TASC II D lesions despite the endovascular approach being broadly considered a good option, open surgery is still recommended for complex anatomic cases or when endovascular intervention fails.[2-4] This brings challenges for the surgical team and the anesthesiologist regarding the ability of the patient to withstand an open surgical repair.

Cardiovascular diseases are associated with a wide range of risk factors, including aging. This combination is a common trait in many vascular surgery patients and can lead to frailty. One possible definition for frailty is a physiologic decline associated with aging, vulnerability to adverse events and poor prognosis.[5] Frailty has been associated with short- and long-term mortality after major vascular surgery in elderly patients.[6] Furthermore, it can also lead to an increase in health care costs for surgical patients.[7]

The subjectivity of frailty has been an obstacle for a consensus definition and it has been the subject of broad debate in the last few decades.[5] As a result, several indexes have been elaborated with the objective to quantify frailty and its prognostic value. Regarding the Canada Study of Health and Aging Frailty Index, the original consisted of 70 items that were posteriorly reduced to an 11 items index, the modified frailty index 11 (mFI-11).[8] This simplified version has been associated with early readmission rates and increased morbidity and mortality across several surgical specialties.[9, 10]

There are also several studies that show the prognostic value of mFI-11 in vascular surgery patients and is the multi-domain tool with the best available evidence albeit with moderate quality.[6] It has been associated with adverse events such as postoperative wound infections, higher likelihood of non-home discharge and mortality.[11, 12] There is also evidence suggesting association with increased risk of postoperative stroke, myocardial infarction (MI), prolonged in-hospital stays and higher readmission rates.[13] Lastly, mFI-11 was a better discriminator for mortality after carotid endarterectomy (CEA) and open abdominal aortic aneurysm (AAA) repair than Lee Cardiac Risk Index (LCRI) and the American Society of Anesthesiologists (ASA) score, while also being a better discriminator for major complications after both open and endovascular AAA repair.[14]

In recent years, a more pragmatic version, named modified frailty index 5 (mFI-5), was elaborated. It retained only 5of the previous 11 variables which were diabetes mellitus, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), arterial hypertension and functional status.[15] The available evidence suggests that the mFI-5 is an equally effective predictor in comparison with mFI-11 for mortality, postoperative complications and unplanned 30-day readmission across several surgical specialties.[16] This was also verified in patients undergoing CEA.[17] In a recent prospective study with 184 patients undergoing CEA, mFI-5 was associated with increased risk of long-term MI, acute heart failure (AHF), major adverse cardiovascular events (MACE) and mortality.[18] On itself, mFI-5 was also a strong predictor for mortality, postoperative complications and unplanned 30-day readmission.[16, 17]

The prognostic value of the mFI-5 has not yet been evaluated in patients with extensive aortoiliac disease undergoing revascularization. This study aims to determine the prognostic value of the mFI-5 upon associated short and long-term adverse outcomes including MI, related major adverse cardiovascular events (MACE and mortality), in patients undergoing revascularization of the aortoiliac sector with extensive and complex disease. MACE was the primary outcome of this analysis, while stroke, MI, AHF, MALE, and all-cause mortality were secondary outcomes.

METHODS

Patient Selection

A total of 109 consecutive patients (103 males, 6 females; mean age 62.61±9.5 years) from a tertiary and a community hospital who underwent elective revascularization for aortoiliac TASC II type D lesions[2] between January 2013 and January 2020 were included in this prospective cohort study. A detailed review of the clinical records of the patients using the vascular registry was made to retrieve demographic and clinical characteristics of the patients, cardiovascular risk factors, procedural, and lesion-specific details.[19]

Two independent and experienced observers (JRN and APN) reviewed the preoperative imaging and the TASC II classification was used to categorize disease patterns.[2]

In the 30-days post-procedure and in the subsequent long-term surveillance period, patients related events as AHF, MI, stroke and mortality, and

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limb related events as reintervention, acute limb ischemia or occlusion without intervention were assessed. Patient informed consent was handled according to the observational nature of data, and all data processing was anonymous. This study was reported according to the STROCSS criteria.[20] The study protocol was approved by the local Ethics Committee and respects the Declaration of Helsinki (protocol number 246-18).

Surgical Technique

Treatment approach, either open surgery or endovascular procedure, was decided in a shared decision between patient and surgeon, also in accordance with the surgeon and the institution experience and preferences. Technical success was defined as maintained patency at 24 hr after the procedure. Clinical evaluation, Doppler ultrasound, and non-invasive Doppler arterial study with ankle brachial index (ABI) measurements were used for postoperative follow-up and surveillance. The ABI measurements were usually performed at 1 and 12 months, followed by biannual follow-up.[19] Patency was defined according to reporting standards.[21]

Transperitoneal aortobifemoral bypass surgery was done under general anesthesia. In all the bilateral aortoiliac reconstructions a double woven polyester graft was used. All patients were under acetylsalicylic acid (100 mg/day) and a statin before intervention and with indication for long-term use. All open procedures were monitored in an Intensive Care Unit at least for the first 24hr.

Regarding endovascular procedures, they were performed by a vascular surgeon under local anesthesia. Endovascular procedures seldom needed intensive care. After stent implantation, acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) were prescribed for 1 month. At the end of 1-month, acetylsalicylic acid (100 mg/day) was recommended for lifelong use.

Low-molecular-weight heparin for thromboembolic prophylaxis was prescribed in all patients during hospital stay. If a patient had an independent indication for long-term anticoagulation, simultaneous anti-aggregation would be prescribed in the postoperative period. In the long-term, anticoagulation was privileged.

Definitions

The retrieved data was recorded according to the Society for Vascular Surgery reporting standard for lower extremity ischemia. Symptoms of chronic lower extremity ischemia were classified according to the Rutherford classification.[2]

The mFI-5 was calculated according to previously published studies.[16] MACE was defined as a composite outcome, including MI, AHF, and all-cause mortality.[22] MALE was defined as the merged events of reintervention, including due to primary assisted patency, secondary patency and major amputation of the revascularized artery segment, and occlusion without intervention.[23]

Statistical Analysis

The necessary sample for a survival test was calculated resorting to WinPepi® V11.65, aiming for statistical power (β) of 80% and an $\alpha < 0.05$. The sample was estimated (72) for a hazard ratio of 2 between groups and a predicted survival at the end of follow-up of 80% although higher event rate differences are described.[24, 25] Due to the low rate of 30-day-events, an increased sample size would be necessary to detect 30-day differences in outcome (nine MACE at 30 days). A previously described binary analysis was performed to increase short-term statistical power, creating mFI5.2, which divides patients with different scores in two groups.[24, 26]

For statistical purposes, SPSS (IBM Corp., released 2019. IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA) was used. Student's t-test was preferred for normaly-distributed continuous variables and Mann-Whitney-U for variables whose normal distribution could not be assumed, presenting median and range or as mean and standard deviation as appropriate. Analysis of categoric variables was performed, resorting to Qui-square test. The results were considered significant at the $P < 0.05$ level.

Multivariate logistic regression analysis was performed to determine independent clinical and demographic factors associated with mFI-5. The stepwise dimension reduction method was used, and variables with $P < 0.10$ were included. The Log Rank estimator was applied to test the effect of the mFI-5 in time-dependent variables. Multivariate Cox regression analysis was performed for independent predictors of long-term MACE and all-cause mortality, by the stepwise dimension reduction method.

RESULTS

Patients' demographics and comorbidities are displayed in Table I. The mean age was 62.6±9.51 years and the majority of patients were male (94.5%). The median follow-up was 66 months (interquartile range 25 to75% [30 −96]). Smoking

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Table I. Patients demographics and comorbidities

*Characteristics**	Totaln = 109	MFI 5 ≤2(n = 73)	MFI 5 >2(n = 36)	*P*	
Age, years	62.61±9.51	60.7±8.4	66.4±10.5	**0.003**	NC
Sex, male	103 (94.5)	71 (97.3)	32 (88.9)	0.071	0.129 (0.017−0.951) $P = 0.044$
Hypertension	71 (65.1)	38 (52.1)	33 (91.7)	—	
Smoking history	98 (89.9)	69 (94.5)	29 (80.6)	**0.023**	NC
Diabetes	35 (32.1)	7 (9.6)	28 (77.8)	—	
Dyslipidemia	68 (62.4)	41 (56.2)	27 (75)	0.056	NC
CKD	14 (12.8)	2 (2.7)	12 (33.3)	**<0.001**	12.35 (2.319−65.79) $P = 0.03$
CAD	27 (24.8)	10 (13.7)	17 (47.2)	**<0.001**	NC
COPD	27 (24.8)	4 (5.5)	8 (22.2)	—	
CHF	13 (11.9)	1 (1.4)	12 (33.3)	—	
ASA				**<0.001**	4.065
2	43 (39.4)	36 (49.3)	7 (19.4)		(1.487−11.11)
3	60 (55.0)	37 (50.7)	23 (63.9)		$P = 0.006$
4	6 (5.5)	0	6 (16.7)		
Status				—	
Dependent	100 (91.7)	71 (97.3)	29 (80.6)		
Partially	6 (6.4)	0	7 (19.4)		
Dependent	2 (1.8)	2 (2.7)	0		
Independent					
Pre-op Hb (g/L)	13.1 ± 1.86	13.1 ± 1.86	13.1±1.89	0.986	
SFA disease, n (%)	62 (58.4)	37 (52.1)	25 (71.4)	0.058	NC
Rutherford Classification, mean ±SD	4.05±0.90	4.1±0.89	4.0±0.94	0.705	
Iliac Stenting vs. ABF, n (%)	61 (56) vs. 48 (44)	30 (41.1) vs. 43 (58.9)	18 (50) vs. 18 (50)	0.378	
MFI5	1.21±1.03	0.63±0.514	2.39±0.766	—	—

ABF, aortobifemoral bypass; ASA, American Society of Anesthesiologists; CAD, Coronary artery disease; CHF, Cardiac heart failure; CKD, Chronic kidney disease (creatinine = 1.5 mg/dL); COPD, Chronic obstructive pulmonary disease; Pre-op Hb, pre-operative hemoglobin; PAD, Peripheral artery disease; mFI-5, Modified Frailty index - 5
*Variables are presented as N (%) if categorical, mean±standard deviation if continuous and median (interquartile range if ASA).

history (89.9%) was the most prevalent comorbidity followed by hypertension (65.1%) and dyslipidemia (62.4%). Chronic kidney disease (CKD) and coronary artery disease (CAD) were present in 12.8% and 24.8% of the patients, respectively. The median ASA score was 3. Most of the patients were elective and presented Critical limb-threatening ischemia (71 − 66%)

Two groups were identified according to mFI-5 score. First group consisted of 73 (67%) patients with mFI-5≤2 and 36 (33.0%) patients with mFI-5>2 (18). Patients with mFI-5>2 were less likely to be male (adjusted Odds Ratio [aOR] 0.129 [0.017−0.951] $P = 0.044$) and more likely to have CKD (aOR:12.35 [2.319−65.79] $P = 0.03$) and higher ASA score (aOR:4.065 [1.487−11.11] $P = 0.006$). The patients in this latter group were also significantly older 60.7±8.4 vs. 66.4±10.5 ($P = 0.003$) although not confirmed on multivariable analysis.

Regarding the short-term prognostic value of mFI-5, in the univariate analysis it was not significantly associated with myocardial injury after non-cardiac surgery (MINS), MACE, MALE, intensive care unit or hospital stay (Table II).

Regarding survival analysis, the Kaplan-Meier survival plots (Fig. 1) revealed that a mFI-5 score >2 was a good predictor of 5 Year Major adverse cardiovascular events (77.6% SE 5.4% vs. 50.8% SE 9.3%, $P = 0.006$)

On the other hand, in the long-term analysis a mFI-5 score >2 was significantly associated with MACE (hazard ratio [HR] 2.469; 95% confidence interval [CI]: 1.267−4.811; $P = 0.008$) and all-cause mortality (HR 2.585; 95% CI 1.270−-5.260; $P = 0.009$) in multivariable analysis. There was no

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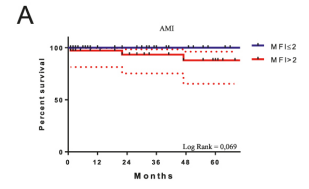
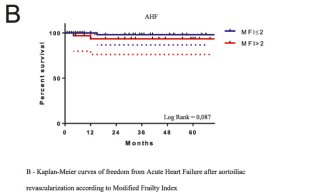


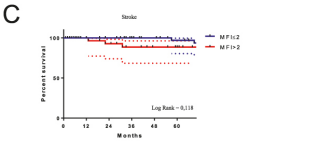
A - Kaplan-Meier curves of freedom from Acute Myocardial Infarction after aortoiliac revascularization according to Modified Frailty Index. SE – Standard Error

	30d	12	24	36	48	60
MFI5≤2	95.9% SE: 2.3% 3 64	95.9% SE: 2.3% 3 49	95.9% SE: 2.3% 3 47	95.9% SE: 2.3% 3 39	95.9% SE: 2.3% 3 36	95.9% SE: 2.3% 3 31
MFI5≥3	94.4% SE: 3.8% 2	94.4% SE: 3.8 2	90.7% SE: 5.2% 3	90.7% SE: 5.2% 3	85.3% SE: 7.1% 4	85.3% SE: 7.1% 4
	34	27	24	19	16	13



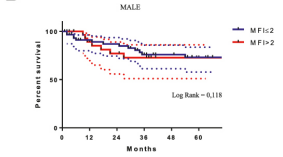
B - Kaplan-Meier curves of freedom from Acute Heart Failure after aortoiliac revascularization according to Modified Frailty Index

	30d	12	24	36	48	60
MFI5≤2	- SE: - 0	- SE: - 0	98.0% SE: 2.0% 1	98.0% SE: 2.0% 1	98.0% SE: 2.0% 1	98.0% SE: 2.0% 1
	66	50	48	40	36	31
MFI5≥3	97.2% SE: 2.7% 1 34	90.8% SE: 5.1% 3 27	90.8% SE: 5.1% 3 26	90.8% SE: 5.1% 3 20	90.8% SE: 5.1% 3 16	90.8% SE: 5.1% 3 13



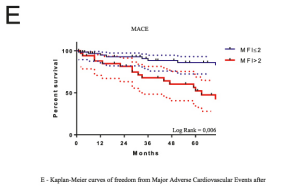
C - Kaplan-Meier curves of freedom from Stroke after aortoiliac revascularization according to Modified Frailty Index

	30d	12	24	36	48	60
MFI5≤2	- SE: - 0	- SE: - 0	- SE: - 0	- SE: - 0	- SE: - 0	97% SE: 3.0% 1
	66	50	48	40	36	32
MFI5≥3	97.2% SE: 2.7% 1 34	97.2% SE: 2.7% 1 28	90.1% SE: 5.4% 3 25	86% SE: 6.6% 4 19	86% SE: 6.6% 4 15	86% SE: 6.6% 4 12



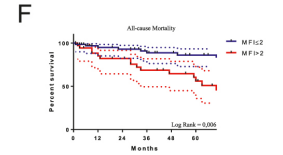
D - Kaplan-Meier curves of freedom from Major Adverse Limb Events after aortoiliac revascularization according to Modified Frailty Index

	30d	12	24	36	48	60
MFI5≤2	91.7% SE: 3.3% 6 59	83.5% SE: 4.6% 11 44	79.7% SE: 5.1% 13 40	71.5% SE: 6.0% 17 32	71.5% SE: 6.0% 17 28	78.8% SE: 6.3% 18 23
MFI5≥3	88.9% SE: 5.2% 4 31	79.1% SE: 7.1% 7 23	68.5% SE: 8.0 10 19	64.7% SE: 8.7% 11 17	64.7% SE: 8.7% 11 12	64.7% SE: 8.7% 11 9



E - Kaplan-Meier curves of freedom from Major Adverse Cardiovascular Events after aortoiliac revascularization according to Modified Frailty Index

	30d	12	24	36	48	60
MFI5≤2	89.0% SE: 3.7% 8 63	85.7% SE: 4.2% 10 49	84.0% SE: 4.5% 11 47	80.0% SE: 5.1% 13 39	80.0% SE: 5.1% 13 36	77.7% SE: 5.4% 14 31
MFI5≥3	97.2% SE: 2.7% 1 34	85.4% SE: 6.0% 5 28	79.2% SE: 7.0% 7 25	66.0% SE: 8.4% 11 20	58.7% SE: 8.9% 13 16	50.8% SE: 9.3% 15 13



F - Kaplan-Meier curves of freedom from all-cause mortality after aortoiliac revascularization according to Modified Frailty Index

	30d	12	24	36	48	60
MFI5≤2	93.1% SE: 3.0% 5 66	89.8 SE: 3.7% 7 50	87.9% SE: 4% 8 48	83.8% SE: 4.8% 10 40	83.8% SE: 4.8% 10 36	81.4% SE: 5.2% 11 31
MFI5≥3	- SE: - 0 35	85.2 SE: 6.1% 5 28	82.1 SE: 6.6% 6 26	68.7% SE: 8.3% 10 20	64.6% SE: 8.7% 11 16	56 % SE: 9.5% 13 13

Fig. 1. Survival plots. 60 months follow-up Kaplan Meier survival plots for different clinical events post elective aortoiliac revascularization, for groups with or without mFI-5>2.

Please cite this article as: Nóbrega *et al.*, Annals of Vascular Surgery(2021), https://doi.org/10.1016/j.avsg.2021.06.049

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Table II. Patients 30-day outcomes according to mFI-5 and mFI5.2 scores

30 Day	MINS	*P* =	MACE	*P* =	MALE	*P* =	ICU (days)	*P* =	Hospital (days)	*P* =
MFI 5	17 (28)	0.187	10 (9.2)		12 (11.0)	0.304	-	-	-	-
MFI5 ≤2	11 (25)	0.842	7 (9.6)	0.831	8 (11)	0.981	2 [0−3]	0.146	7 [3−16.5]	0.319
MFI5 >2	6 (27.3)		3 (8.3)		4 (11)		1 [0−3]		8.5 [4.25−21]	

MACE, Major Adverse Cardiovascular Event at 30 Days; MALE, Major Adverse Limb Events; mFI, Modified Frailty index – 5 items; MINS, Myocardial Injury after non-cardiac surgery

Table III. Cox multivariate regression proportional hazard ratio for each outcome

	Non-adjusted Hazard Ratios	95% Confidence interval	*P*-Value
AMI	3.460	0.825−14.508	0.090
AHF	5.726	0.595−55.071	0.131
Stroke	3.140	0.694−14.205	0.137
MALE	1.047	0.505−2.174	0.902
MACE	2.469	1.267−4.811	0.008
All-cause mortality	2.585	1.270−5.260	0.009

AMI, Acute Myocardial Infarction; AHF , Acute Heart Failure; MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events.

Table IV. Cox proportional hazard multivariable analyses of prognostic factors for MACE and All-cause Mortality

MACE	aHR	95% CI	*P* =
SEX	0.488	0.163-1.465	0.201
CKD	2.485	1.137-5.434	0.023
ASA	1.286	0.578-2.860	0.530
MFI5.2	2.485	1.003-5.434	0.049
All-cause Mortality			
SEX	0.909	0.207-3.983	0.899
CKD	2.559	1.124-5.825	0.025
ASA	1.394	0.585-3.324	0.453
MFI5.2	1.958	1.122-4.251	0.037

ASA, American Society of Anesthesiologists; CKD, Chronic kidney disease; mFI-5, Modified Frailty index – 5.

statistical significance regarding the occurrence of MI, AHF, stroke or MALE (Table III).

As shown in Table IV, mFI-5 score > 2 was the only prognostic factor, besides CKD, significantly associated with MACE (aHR: 2.485; 95% CI 1.003−5.434; $P = 0.049$) and with all-cause mortality (aHR: 1.958; 95% CI 1.122−4.251; $P = 0.037$).

DISCUSSION

Results in this cohort demonstrate the predictive value of mFI-5 for patients undergoing revascularization for extensive aortoiliac disease. Patients with a higher mFI-5 score, and therefore greater frailty status, revealed poorer outcomes in long-term follow-up. These outcomes corroborate the literature and reflect the clinical value of this index in decision making.

Together with mFI-5, CKD was also able to predict increased risk for MACE and all-cause mortality in the long-term for this subpopulation. This result is also in accordance with the scientific evidence till date. A recent systematic review with meta-analysis found that the mean reported prevalence of frailty in CKD patients is 41.8% and that it is associated with increased risk of all-cause mortality, all-cause hospitalizations and falls.[27] Another study found that frailty in a CKD population is associated with higher symptom-burden and worse quality of life.[28] There are studies currently underway to assess potential measures to improve frailty status in CKD patients.[29] On the other hand, CKD is a known risk factor for cardiovascular disease.[30] CKD has also been associated with increased risk of MACE in other studies,[31, 32] including in patients that underwent lower extremity revascularization.[33] There is investigation concerning potential serum markers for cardiovascular risk in CKD patients.[34] It is also important to take in consideration that some CKD risk factors are mFI-5 components and therefore confounding cannot be totally excluded.

As stated previously, frailty has been associated with adverse outcomes and increased mortality across several surgical specialties.[9, 10, 16] Although

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JID: AVSG [mNS;November 17, 2021;17:47]

scarce, there is already some evidence regarding its prognostic importance in vascular surgery.[6] In the carotid stenosis setting, frailty has been associated with increased morbidity and mortality among patients that underwent CEA.[35] On the other hand, both in open and endovascular AAA elective repair, mFI-5 was associated with increased short and long-term mortality while also increasing the risk of 30-day mortality, morbidity and failure to rescue rate independently of other risk factors.[36, 37]

There is also some evidence on the effect of frailty in peripheral artery disease (PAD). In patients with stable claudication, frailty increased the risk of MACE.[38] In another study with 24,645 patients who underwent infra-inguinal procedures, frailty was independently associated with increased mortality and major complications and the risk was higher in frail women.[39] Likewise, in a population of 4,704 patients who underwent infra-inguinal arterial bypass, frailty was a risk factor for mortality and postoperative complications.[40] This was also verified in a population of 431 male patients with first-time revascularizations where frailty independently predicted2-year major amputation and mortality[41]. Lastly, in patients after major lower extremity amputation, preoperative frailty was a significant predictor of 30-day readmission and non-ambulatory status,[42, 43] although recently this was not verified in an Asian population[44].

The results in the population of our study are in line with the available evidence and highlights the potential of mFI-5 as a prognostic index. In a population that underwent elective revascularization for extensive aortoiliac disease, mFI-5 was able to predict long-term adverse outcomes such as MACE and all-cause mortality. These are expected results based on pathophysiology, considering that cardiovascular risk markers are used to calculate mFI-5 and, simultaneously, are inherent to the studied adverse outcomes.

However, in this subpopulation, no significant association was found regarding short-term outcomes. One possible explanation for this may be the selection bias, that patients with more comorbidities and less physiological reserve usually are considered for less invasive procedures or even excluded for revascularization. Nevertheless, in this study there were no significant differences between patients that underwent open repair and endovascular treatment. The contemporary improvement of pre-operative study, the implementation of pre-emptive measures according to patients' comorbidities, improvement of peri-operative anesthetic care and better short-term monitoring can help explain this lack of differences. Nevertheless, patient distribution was uneven and can explain our findings. The lower levels, mFI5 0 to 3, comprised 96.3% of the total sample, as patients subjectively considered with the decreased physiologic reserve are less likely to be selected for invasive surgical procedures. These may be the reasons that justify the inability to predict short-term outcomes as previously found.

Due to the higher prevalence of male patients, it was not possible to verify any interaction with sex as in other studies,[39] probably because of the demographic epidemiology inherent to aortoiliac disease. In the long-term, although not significant, there was a trend for mFI-5 to predict MI. In a recent study, myocardial injury (MINS) after aortoiliac revascularization for extensive disease was significantly associated with myocardial infarction, stroke, MACE, MALE, and all-cause mortality.[24] However, in our population mFI-5 was not able to predict MINS. Globally, and considering the fact that some cardiovascular markers are an integral part of mFI-5 and that cardiovascular markers such as CAD or CKD are also risk factors for the studied outcomes, the results of this study are in agreement with the published evidence.

The use of tools like mFI-5 could further enhance patient stratification. In turn, the stratifying of patients can help to optimize management approaches while also trying to achieve the best possible outcome given the available resources. The results of the present study indicate that frailer patients may benefit from less invasive procedures while also may need strict and tailored long-term follow-up to better approach possible complications, although the validity of interventions on this subgroup is still lacking validation. There are several advantages in the use of the mFI-5. It is an objective index and its 5 components are easily gathered by history taking and clinical examination. Physical phenotype-based models are time-consuming and complex in training and required equipment towards frailty data gathering, despite presenting decent reproducibility.[45, 46] This also means that it is easy and quickly applicable in the daily practice for long-term stratification of different populations of patients. This furthermore opens the possibility of identifying patients in whom efforts should be made to improve frailty in order to improve results. These can be nutritional and exercise interventions that can lead to improved prognosis in vascular interventions.[47]

There are some limitations inherent to this study that need consideration. There is a possible

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selection bias since patients with more comorbidities and worse clinical condition possibly not tangible in our variables, may have been selected for less invasive procedures or even excluded from revascularization. The current recommended guidelines also consider that open surgery should be considered on fit patients and that an endovascular-first approach should be considered in patients with severe comorbidities (1). As a 2 center study, and and with a small sample size, t there can be a limitation to its general applicability as well as the above mentioned overrepresentation of male sex.

On the other hand, the prospective design, extended follow-up and the similarity of the aortoiliac lesions are some of the strengths of the current study. This study includes patients from a large academic teaching institution and from a community referral hospital, which increases the external validity of the results and make it more similar to "real world" practice.

CONCLUSION

The mFI-5 index revealed potential as a stratifying tool and as a predictor for long-term MACE and mortality in a population with extensive aortoiliac atherosclerotic disease. Besides CKD, the mFI-5 was also the only prognostic factor independently associated with MACE and mortality in the long-term. However, the prognostic value of the mFI-5 upon short-term outcomes was not apparent in our patients.

Besides the potential patent in this study, the mFI-5 also has the advantage of being an objective and quickly applicable tool since its components are easily accessed through the clinical history and physical exam. It can help physicians to implement preventive measures to improve prognosis while also predicting which patients are at high risk of adverse outcomes.

The ability to predict short-term and long-term postoperative outcomes is of immeasurable importance. Tools like the mFI-5 can help optimize healthcare resources and medical outcomes. Continuous research is necessary to better understand and validate the prognostic value of the mFI-5 while attempting to improve frailty status.

FUNDING SOURCES

This study received no funding from any external source

REFERENCES

1 Aboyans V, Ricco J-B, Bartelink M-LEL, et al. Editor's Choice; 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55(3):305–68.
2 Norgren L, Hiatt W, Dormandy J. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(1):S5–S67.
3 Jaff M, White C, Hiatt W, et al. An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-the-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Endovasc Ther 2015;22(5):663–77.
4 Dorigo W, Piffaretti G, Benedetto F, et al. A comparison between aortobifemoral bypass and aortoiliac kissing stents in patients with complex aortoiliac obstructive disease. J Vasc Surg 2017;65(1):99–107.
5. Abellan van Kan G, Rolland Y, Houles M. The assessment of frailty in older adults. Clin Geriatr Med 2010;26(2):275–86.
6. Wang J, Zou Y, Zhao J, et al. The impact of frailty on outcomes of elderly patients after major vascular surgery: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2018;56(4):591–602.
7. Wilkes J, Evans J, Prato B. Frailty cost: economic impact of frailty in the elective surgical patient. J Am Coll Surg 2019;228(6):861–70.
8. Velanovich V, Antoine H, Swartz A. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res 2013;183(1):104–10.
9. Panayi A, Orkaby A, Sakthivel D, et al. Impact of frailty on outcomes in surgical patients: A systematic review and meta-analysis. Am J Surg 2019;218(2):393–400.
10 Wahl T, Graham L, Hawn M, et al. Association of the modified frailty index with 30-day surgical readmission. JAMA Surg 2017;152(8):749–57.
11 Karam J, Tsiouris A, Shepard A. Simplified frailty index to predict adverse outcomes and mortality in vascular surgery patients. Ann Vasc Surg 2013;27(7):904–8.
12 Arya S, Long C, Brahmbhatt R, et al. Preoperative frailty increases risk of nonhome discharge after elective vascular surgery in home-dwelling patients. Ann Vasc Surg 2016;35:19–29.
13 Czobor N, Lehot J, Holndonner-Kirst E. Frailty in patients undergoing vascular surgery: a narrative review of current evidence. Therap Clin Risk Manag 2019;15:1217–32.
14 Ehlert B, Najafian A, Orion K. Validation of a modified Frailty Index to predict mortality in vascular surgery patients. J Vasc Surg 2016;63(6):1595–601 e2.
15 Traven S, Reeves R, Slone H. Frailty predicts medical complications, length of stay, readmission, and mortality in revision hip and knee arthroplasty. JArthroplasty 2019;34(7):1412–16.
16 Subramaniam S, Aalberg J, Soriano R. New 5-Factor Modified Frailty Index Using American College of Surgeons NSQIP Data. J Am Coll Surg 2018;226(2):173–81 e8.
17 Pandit V, Zeeshan M, Nelson P, et al. Frailty Syndrome in patients with carotid disease: simplifying how we calculate frailty. Ann Vasc Surg 2020;62:159–65.
18 Araújo-Andrade L, Rocha-Neves J, Duarte-Gamas L, et al. Prognostic effect of the new 5-factor modified frailty index in patients undergoing carotid endarterectomy with

Please cite this article as: Nóbrega *et al.*, Annals of Vascular Surgery(2021), https://doi.org/10.1016/j.avsg.2021.06.049

ARTICLE IN PRESS
JID: AVSG [mNS;November 17, 2021;17:47]

regional anesthesia – A prospective cohort study. Int J oSurg 2020;80:27–34.
19 Rocha-Neves J, Ferreira A, Sousa J, et al. Endovascular approach versus aortobifemoral bypass grafting: outcomes in extensive aortoiliac occlusive disease. Vasc Endovasc Surg 2019;54(2):102–10.
20. Agha R, Abdall-Razak A, Crossley E, et al. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. Int J Surg 2019;72:156–65.
21 Stoner M, Calligaro K, Chaer R, 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.
22 Thygesen K, Alpert J, Jaffe A, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72(18):2231–64.
23 Fashandi A, Mehaffey J, Hawkins R. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. J Vasc Surg 2018;68(6):1817–23.
24. Pereira-Macedo J, Machado N, Pereira-Neves A, et al. Myocardial injury after aortoiliac revascularization for extensive disease: A survival analysis. Turk gogus kalp damar cerrahisi dergisi 2020;28(3):426–34.
25. Rocha-Neves J, Ferreira A, Sousa J, et al. Endovascular Approach versus aortobifemoral bypass grafting: outcomes in extensive aortoiliac occlusive disease. Vasc Endovascular Surg 2020;54(2):102–10.
26 Segal D, Wilson J, Staley C. The 5-Item modified frailty index is predictive of 30-day postoperative complications in patients undergoing kyphoplasty vertebral augmentation. World Neurosurg 2018;116:e225–ee31.
27. Mei F, Gao Q, Chen F, et al. Frailty as a predictor of negative health outcomes in chronic kidney disease: a systematic review and meta-analysis. J Am Med Direct Assoc
28 Kosaka S, Ohara Y, Naito S, et al. Association among kidney function, frailty, and oral function in patients with chronic kidney disease: a cross-sectional study. BMC Nephrol 2020;21(1):357.
29. Nixon AC, Bampouras TM, Gooch HJ, et al. The EX-FRAIL CKD trial: a study protocol for a pilot randomised controlled trial of a home-based EXercise programme for pre-frail and FRAIL, older adults with Chronic Kidney Disease. BMJ Open 2020;10(6):e035344.
30 Cabrera CS, Lee AS, Olsson M, et al. Impact of CKD progression on cardiovascular disease risk in a contemporary UK cohort of individuals with diabetes. Kidney Int Rep 2020;5(10):1651–60.
31 Cherney DZI, Repetto E, Wheeler DC, et al. Impact of cardio-renal-metabolic comorbidities on cardiovascular outcomes and mortality in type 2 diabetes mellitus. Am J Nephrol 2020;51(1):74–82.
32 Chen S, Hsu W-y, Lin Y-N. Incidence and risk of major adverse cardiovascular events in middle-aged patients with chronic kidney disease: a population-based cohort study. Int Urol Nephrol 2019;51(7):1219–27.
33. Smilowitz NR, Bhandari N, Berger JS. Chronic kidney disease and outcomes of lower extremity revascularization for peripheral artery disease. Atherosclerosis 2020;297:149–56.
34. Feldreich T, Nowak C, Carlsson AC, et al. The association between plasma proteomics and incident cardiovascular disease identifies MMP-12 as a promising cardiovascular risk marker in patients with chronic kidney disease. Atherosclerosis 2020;307:11–15.
35 Pandit V, Lee A, Zeeshan M, et al. Effect of frailty syndrome on the outcomes of patients with carotid stenosis. J Vasc Surg 2020;71(5):1595–600.
36 Barbey S, Scali S, Kubilis P, et al. Interaction between frailty and sex on mortality after elective abdominal aortic aneurysm repair. J Vasc Surg 2019;70(6):1831–43.
37 Arya S, Kim SI, Duwayri Y, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. J Vasc Surg 2015;61(2):324–31.
38 Schaller M, Ramirez J, Gasper W. Frailty is associated with an increased risk of major adverse cardiac events in patients with stable claudication. Ann Vasc Surg 2018;50:38–45.
39 Brahmbhatt R, Brewster L, Shafii S, Rajani R, Veeraswamy R, Salam A, et al. Gender and frailty predict poor outcomes in infrainguinal vascular surgery. JSurg Res 2016;201(1):156–65.
40 Ali T, Lehman E, Aziz F. Modified Frailty Index Can Be Used to Predict Adverse Outcomes and Mortality after Lower Extremity Bypass Surgery. Ann Vasc Surg 2018;46:168–77.
41 Gonzalez L, Kassem M, Owora A, et al. Frailty and biomarkers of frailty predict outcome in veterans after open and endovascular revascularization. J Surg Res 2019;243:539–52.
42. Fang Z, Hu F, Arya S. Preoperative frailty is predictive of complications after major lower extremity amputation. J Vasc Surg 2017;65(3):804–11.
43. Chopra A, Azarbal AF, Jung E, et al. Ambulation and functional outcome after major lower extremity amputation. J Vasc Surg 2018;67(5):1521–9.
44. D'Cruz R, Chong T, Tan T, et al. The modified frailty index does not predict mortality after major lower extremity amputation for peripheral arterial disease in an asian population. Ann Vasc Surg 2020;69:298–306.
45. Bouillon K, Sabia S, Jokela M, et al. Validating a widely used measure of frailty: are all sub-components necessary? Evidence from the Whitehall II cohort study. Age (Dordr) 2013;35(4):1457–65.
46. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. J Am Geriatr Soc 2012;60(8):1478–86.
47. Hsieh T, Su S, Chen C, et al. Individualized home-based exercise and nutrition interventions improve frailty in older adults: a randomized controlled trial. Int J Behav Nutr Phys Act 2019;16(1):119.

Please cite this article as: Nóbrega *et al.*, Annals of Vascular Surgery(2021), https://doi.org/10.1016/j.avsg.2021.06.049

2. Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization

Reference to the published version:

Pereira-Neves A, Dias L, Fragão-Marques M, Vidoedo J, Ribeiro H, Andrade JP, Rocha-Neves J. Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization.

J Clin Med. 2024 Oct 26;13(21):6412. doi: 10.3390/jcm13216412.

Impact Factor: 2.9 (2024)

Quartile: Q1 (Scimago, 2024); Q1 (JCR, 2024)

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Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization

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Abstract: Background/Objectives: Atherosclerosis is a leading cause of death, especially in the developed world, and is marked by chronic arterial inflammation and lipid accumulation. As key players in its progression, monocytes contribute to plaque formation, inflammation, and tissue repair. Understanding monocyte involvement is crucial for developing better therapeutic approaches. The objective of this study is to assess the prognostic value of monocytes for limb-related outcomes following revascularization for complex aortoiliac lesions, thereby emphasizing the central role of monocytes in atherosclerosis. **Methods:** This prospective cohort study-enrolled patients who had undergone elective aortoiliac revascularization at two hospitals between January 2013 and December 2023. Patients with TASC II type D lesions were included, excluding those with aneurysmal disease. Demographic, clinical, and procedural data were gathered, and patients were monitored for limb-related outcomes. Preoperative complete blood counts were analyzed, and statistical analyses, including multivariable Cox regression, were conducted to identify predictors of major adverse limb events (MALE). **Results:** The study included 135 patients with a mean age of 62.4 ± 9.20 years and predominantly male (93%). Patients were followed for a median of 61 IQR [55.4–66.6] months. Smoking history (91%) was the most prevalent cardiovascular risk factor. Preoperative monocyte count >0.720 × 10^9/L was associated with worse 30-day limb-related outcomes (MALE: OR 7.138 95% CI: 1.509–33.764, $p = 0.013$) and long-term outcomes, including secondary patency ($p = 0.03$), major amputation ($p = 0.04$), and MALE ($p = 0.039$). Cox regression analysis confirmed an elevated monocyte count as an independent predictor of MALE (adjusted hazard ratio 2.149, 95% CI: 1.115–4.144, $p = 0.022$). **Conclusions:** This study demonstrated that patients with a higher absolute monocyte count may be more exposed to the risk of MALE in patients with aortoiliac TASC II type D lesions undergoing revascularization, with predictive accuracy in both the short and long term. Additionally, it was an independent predictor of major amputation. This new marker has the potential to serve as a cost-effective and easily available tool for risk stratification, helping identify patients at higher risk of MALE.

Keywords: aortoiliac disease; peripheral artery disease; amputation; inflammation mediators; biomarker; hematologic

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Citation: Pereira-Neves, A.; Dias, L.; Fragão-Marques, M.; Vidoedo, J.; Ribeiro, H.; Andrade, J.P.; Rocha-Neves, J. Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization. *J. Clin. Med.* **2024**, *13*, 6412. https://doi.org/10.3390/jcm13216412

Academic Editor: Carlo Setacci

Received: 30 August 2024
Revised: 20 October 2024
Accepted: 24 October 2024
Published: 26 October 2024

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1. Introduction

Despite advancements in interventional and pharmacological treatments, atherosclerotic disease remains the leading cause of death in the developed world [1]. This highlights the necessity for developing more effective therapeutic strategies, which requires a more comprehensive understanding of the molecular mechanisms and pathophysiology underlying the disease [2]. Atherosclerosis is defined by persistent low-grade, chronic inflammation within the arterial wall, characterized by the progressive buildup of lipids and inflammatory cells, notably including several subsets of monocyte-derived macrophages, T lymphocytes, and mast cells, within developing atherosclerotic plaques [3]. Blood-derived myeloid cells that infiltrate developing atherosclerotic lesions also comprise monocyte-derived dendritic cells, different subsets of B lymphocytes, and neutrophils, particularly in advanced, frequently thrombotic lesions [4,5].

As understanding of the molecular pathways involved in atherosclerosis advances, the critical role of monocytes in this process becomes increasingly evident [6]. Circulating monocytes attach to and migrate into the vascular endothelial wall, a process enabled by pro-inflammatory cytokines and adhesion molecules [7]. In addition to accumulating lipids and forming atherogenic foam cells, monocytes promote the progression of atherosclerotic plaques by further producing inflammatory cytokines, matrix metalloproteinases, and reactive oxidative species [6,8]. Monocyte subsets are also involved in intraplaque angiogenesis and tissue repair mechanisms [6,8].

The earliest detectable atherosclerotic change is pathological intimal thickening [9], which is considered to be an early surrogate marker for atherosclerosis, while pathological neovascularization is connected to both the early and late stages of the disease [10,11]. Plaque enlargement leads to intraplaque hypoxia, which induces the infiltration of inflammatory cells, subsequently driving local neovascularization [10]. For instance, experimental studies on hypercholesterolemia have demonstrated that adventitial neovascularization in the coronary arteries occurs before the development of plaque protrusion into the lumen [10].

Monocytes, which have been described as key players in the innate immune system, significantly influence the initiation, propagation, and progression of atherosclerosis, as well as plaque thrombosis [2,12]. Experimental data suggest that monocytes are also involved in acute coronary syndromes and post-infarction outcomes; however, human research remains limited [2].

Monocytes' prognostic value has been previously demonstrated across various medical fields, either as an absolute count or as part of a ratio, and even by subtypes [13–15]. For instance, in cancer, the lymphocyte-to-monocyte ratio (LMR), when compared with other inflammatory response markers, had the strongest ability to predict the survival of patients with gastric cancer, with lower values of LMR connected to reduced survival following gastrectomy with a curative intention [13]. Several studies have already been conducted in cardiology, which is more closely related to vascular surgery [16,17]. Monocyte to HDL cholesterol ratio (MHR), an inflammation-based marker, was associated with the severity of coronary artery disease and future cardiovascular events in patients with acute coronary syndrome (ACS) [16]. A recent meta-analysis showed that higher MHR values were associated with higher in-hospital mortality and major adverse cardiovascular events (MACE) in ST-elevated myocardial infarction (STEMI) patients who had undergone a primary percutaneous intervention [17]. Moreover, dynamic changes in monocyte subsets predict MACE and left ventricular function after STEMI [18], and the absolute counts of monocytes are predictive of MACE in patients with coronary artery disease (CAD) [14].

This study aimed to evaluate monocytes' predictive ability for limb-related outcomes following revascularization due to complex aortoiliac lesions.

2. Methods

2.1. Patient Selection

Patients who had undergone elective aortoiliac revascularization were consecutively included in a prospective cohort study maintained between two centers, a tertiary hospital and a community hospital, from January 2013 to December 2023. Selection criteria included aortoiliac TransAtlantic Inter-Society Consensus (TASC) II type D lesions, excluding those with aortoiliac aneurysmal disease [19]. The choice between open surgery or an endovascular procedure was taken in a shared decision-making process that included the patient and the surgeon, bearing in mind both the surgeon and the institution's experience and preferences.

Demographic and clinical characteristics of the patients, including cardiovascular risk factors, procedural details, and lesion-specific information, were obtained through a comprehensive review of their medical records, which also included data from computed tomography scans [20]. Lesion type was described according to TASC II document recommendations [19]. TASC II classifies aortoiliac TASC D lesions as the most complex, including infrarenal aortic occlusion and diffuse iliac disease affecting at least two from the common to the external iliac arteries, such as stenosis of both common and external iliac arteries on the same axis or occlusion of both external iliac arteries.

All aortoiliac procedures were performed using the same type of material to ensure consistency. Specifically, the aortobifemoral grafts that were used were Dacron grafts (Maquet Cardiovascular, model #102687, Aortobifemoral Y graft, 14 × 7 mm and 16 × 8 mm), and this material was consistently applied across all patients. Additionally, the iliac stents were predominantly Cordis SMART stents (Cordis Endovascular, model #SEV-8-100-120, 6–11 mm diameter, 40–120 mm length). Patients were evaluated within the first 30 days following the procedure, as well as during the extended surveillance period. Clinical records from outpatient visits were reviewed to document relevant outcomes, including patient-specific events such as MACE, stroke, and limb-related events, including reinterventions for primary or secondary patency, acute limb ischemia, major amputations, and occlusion without intervention. This study followed the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2019 Guideline [21] and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [22]. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional revision board/Ethics Committee of Comissão de Ética para a Saúde do *CHUSJ* (Project identification code 246-18 on July of 2018). Each patient's informed consent was handled accordingly.

2.2. Definitions

Data collection followed the Reporting Standards of the Society for Vascular Surgery for lower extremity ischemia [23]. The Rutherford Classification system was employed to categorize the severity and symptoms of chronic lower extremity ischemia [24].

Major adverse cardiovascular events (MACE) were defined as a composite outcome, including acute myocardial infarction (AMI), acute heart failure (AHF), and all-cause mortality [25]. The technical success of the procedure was defined as maintained target vessel patency 24 h postoperatively. Major adverse limb events (MALE) were defined as a composite of reinterventions, including those for primary assisted patency, secondary patency, major amputation of the revascularized artery segment, or occlusion without intervention [26].

2.3. Analytical Parameters

All patients had at least one preoperative complete blood count sample available in the two weeks prior to the intervention. When several blood samples per patient met the inclusion criteria, the sample closest to the time of surgery was selected for analysis. Blood analyses were conducted using a Sysmex® XE-2100D (Sysmex Corporation, Kobe, Japan) automated hematology analyzer.

2.4. Statistical Analysis

The sample size for a survival analysis for the primary endpoint was determined using online Sample Size Calculators for Designing Clinical Research (https://sample-size.net/sample-size-survival-analysis/; access date: 28 April 2024). The calculation aimed for a statistical power (β) of 90% and an $\alpha < 0.05$. An estimated sample size of 122 patients was obtained, based on a hazard ratio of 1.8 between groups and an anticipated survival rate of 80% at the conclusion of the follow-up, although higher hazards have been described [20,27,28].

For statistical analysis, SPSS (IBM Corp., released 2023. IBM SPSS Statistics for Windows, version 29.0.2.0, Armonk, NY, USA) was utilized. The Student's *t*-test was applied for continuous variables normally distributed, with results expressed as mean and standard deviation. For non-normally distributed variables, the Mann–Whitney U test was employed, and results were reported as median and interquartile range. Categorical variables were analyzed using the Chi-squared test. Statistical significance was defined as $p < 0.05$.

To facilitate the interpretation and clinical application of monocyte levels, the authors established a threshold, with the optimal cut-off determined through an optimal binning procedure using MALE as the reference outcome. A multivariate logistic regression analysis was conducted to identify independent clinical and demographic factors associated with 30-day events. The Log Rank estimator was employed to assess the impact of time-dependent variables, and the Wilcoxon test was applied whenever deemed necessary for additional comparisons. Multivariate Cox regression analysis was performed to determine independent predictors of long-term MALE. The backward and forward stepwise regression approach was applied, including variables with a p value < 0.10.

3. Results

The patients' demographics and comorbidities are described in Table 1. The cohort included 135 patients with a mean age of 62.4 ± 9.20 years old, with a clear male predominance (93%) and a median follow-up of 61 months (interquartile range 25%–75% [55.4–66.6] months). The most prevalent cardiovascular risk factor was smoking history (current or past), present in 123 patients (91%), followed by dyslipidemia (68%), and hypertension (66%). Diabetes was present in 30% of the cohort. More than 70% of the patients were revascularized due to chronic limb-threatening ischemia (CLTI), while a minority were due to lifestyle-limiting claudication (<30%). Concerning the revascularization method, 43.7% were revascularized through endovascular techniques, while 56.3% were revascularized with open surgery. The mean ABI before revascularization was 0.31 ± 0.13.

Table 1. Patient's demographics and comorbidities.

Characteristics	Total *n* = 135 (%)	Monocytes ≤ 0.720 *n* = 63	Monocytes > 0.720 *n* = 72	*p* Value
Age, years (mean ± SD)	62.4 ± 9.20	59.9 ± 9.25	64.6 ± 8.66	0.003
Gender, male	126 (93.3)	58 (92.1)	68 (94.4)	0.580
Hypertension	89 (65.9)	43 (68.3)	46 (63.9)	0.593
Smoking history	123 (91.1)	57 (90.5)	66 (91.7)	0.808
Diabetes	40 (29.9)	22 (34.9)	18 (25.4)	0.227
Dyslipidemia	91 (67.9)	43 (69.4)	48 (66.7)	0.740
CKD	17 (12.6)	7 (11.1)	10 (13.9)	0.627
CAD	37 (27.4)	17 (27.0)	20 (27.8)	0.918
COPD	15 (11.1)	5 (7.9)	10 (13.9)	0.272
CHF	16 (11.9)	8 (12.7)	8 (11.1)	0.776

Table 1. *Cont.*

Characteristics	Total n = 135 (%)	Monocytes ≤ 0.720 n = 63	Monocytes > 0.720 n = 72	p Value
ASA				
II	53 (39.3)	27 (42.9)	26 (36.1)	0.392
III	74 (54.8)	31 (49.2)	43 (59.7)	
IV	8 (5.9)	5 (7.9)	3 (4.2)	
Rutherford Classification				
III	37 (27.6)	23 (36.5)	14 (18.3)	0.163
IV	53 (39.6)	23 (36.5)	30 (42.3)	
V	36 (26.9)	14 (22.2)	22 (31.0)	
VI	8 (6.0)	3 (4.8)	5 (7.0)	
Endovascular technique	59 (43.7)	21 (33.3)	38 (52.8)	0.023
Open surgery	76 (56.3)	42 (66.7)	34 (47.2)	
SFA disease	83 (61.5)	36 (57.1)	47 (65.3)	0.333
ABI, (mean ± SD)	0.31 ± 0.13	0.33 ± 0.12	0.30 ± 0.14	0.253

Variables are presented as n (%) unless otherwise specified. ABI—Ankle-Brachial; ASA—American Society of Anesthesiologists; CAD—Coronary Artery Disease; CHF—Chronic Heart Failure; CKD—Chronic Kidney Disease (creatinine = 1.5 mg/dL); COPD—Chronic Obstructive Pulmonary Disease; SD—Standard Deviation; SFA—Superficial Femoral Artery Atherosclerotic Disease.

When analyzing patients' demographics and comorbidities concerning monocyte count, the group with monocytes ≤0.720 included 63 patients, while the group with monocytes >0.720 included 72 patients. Patients with a monocyte count >0.72 were older (64.6 ± 8.66 vs. 59.9 ± 9.25 years old, p = 0.003) and were more likely to be submitted to endovascular revascularization (p = 0.023) when compared to patients with a monocyte count ≤0.72. No other demographic variables or comorbidities differed significantly between the groups. Hematological parameters are described in detail in Supplemental Table S1.

Regarding 30-day outcomes, the only statistically significant difference between the groups was MALE, with patients having preoperative monocyte counts >0.720 experiencing the worst limb-related outcomes (OR = 7.138 CI 1.509–33.764, p = 0.013). Even though 30-day MACE and mortality were higher in the group with elevated monocyte counts, the difference did not reach significance (Table 2).

Table 2. Patients' 30-day outcomes according to monocyte count.

	Total n = 135 (%)	Monocytes ≤ 0.720 n = 63	Monocytes > 0.720 n = 72	p Value
AKI	10 (8.6)	4 (6.7)	6 (10.7)	0.438
ABI Δ, (mean ± SD)	0.45 ± 0.24	0.45 ± 0.241	0.41 ± 0.234	0.398
Rutherford Δ (mean ± SD)	2.5 ± 1.42	2.5 ± 1.39	2.6 ± 1.58	0.826
Prosthetic infection #	7 (5.3)	4 (6.3)	3 (4.3)	0.608
ICU (days) (median IQR)	2 [0–3]	2 [0–3]	2 [0–3]	0.388 *
Enfermary (days) (median—IQR)	8 [3.25–19]	7 [4–11.25]	10.5 [3–24]	0.095 *
MALE	15 (11.1)	2 (3.2)	13 (18.1)	0.006
MACE	11 (8.1)	3 (4.8)	8 (11.1)	0.179
Death	7 (5.2)	2 (3.2)	5 (6.9)	0.324

Variables are presented as N (%) unless otherwise specified. ABI Δ —Ankle-Brachial Index—postoperative minus preoperative; AKI—Acute Kidney Injury; ICU—stay in intensive care unit; IQR—Interquartile Range; MACE—Major Adverse Cardiovascular Event; Rutherford chronic ischemia Δ—preoperative minus postoperative; * Non-parametric test; # Prothesis infection at 1 year of follow-up.

When evaluating long-term outcomes using Kaplan–Meier curves, patients with a monocyte count >0.720 had worse outcomes when compared with patients with a monocyte count ≤0.720, including lower secondary patency (p = 0.03), higher major amputation (p = 0.04), and higher MALE (p = 0.039). Even though this same group also showed worse primary patency, it did not reach a statistically significant result (Figures 1–4). This result was further corroborated by Cox multivariable regression, with a monocyte count >0.720 being associated with an adjusted hazard ratio (aHR) of 2.149 (95% CI [1.115–4.144], p = 0.022) for MALE during follow-up (Table 3).

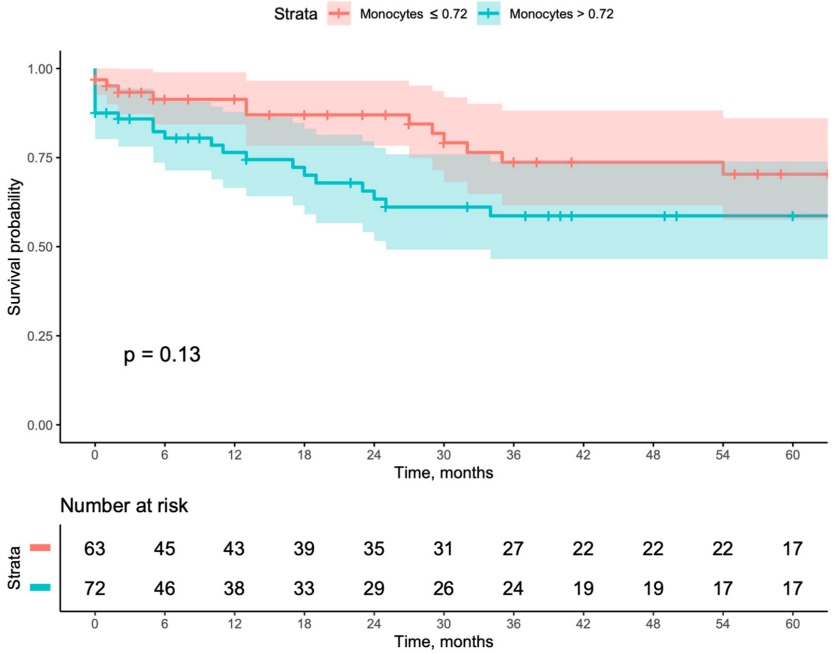

Figure 1. Kaplan–Meyer survival curves and number-at-risk stratified according to a monocyte count of ≤0.72 or >0.72 for primary patency.

Table 3. Cox multivariable regression proportional hazard ratio for Major Adverse Limb Events.

	Non-Adjusted Hazard Ratios	95% Confidence Interval	*p*-Value	Adjusted Hazard Ratios	95% Confidence Interval	*p* Value
Age	1.009	0.976–1.043	0.606	NC		
Monocytes (*n*) >0.720 × 10 ^{9}/L	2.696 * 2.149 #	1.077–6.746 1.115–4.144	0.034 0.022	2.696 2.149	1.077–6.746 1.115–4.144	0.034 0.022
Platelets	1.0	1.0–1.0	0.134	NC		
Mean Platelet Value	1.001	0.998–1.005	0.473	NC		
Preoperative Rutherford	1.148	0.806–1.636	0.444	NC		
Open Surgery (vs. endo)	1.384	0.747–2.562	0.301	NC		

NC—not confirmed. *—continuous variable; #—categorical variable.

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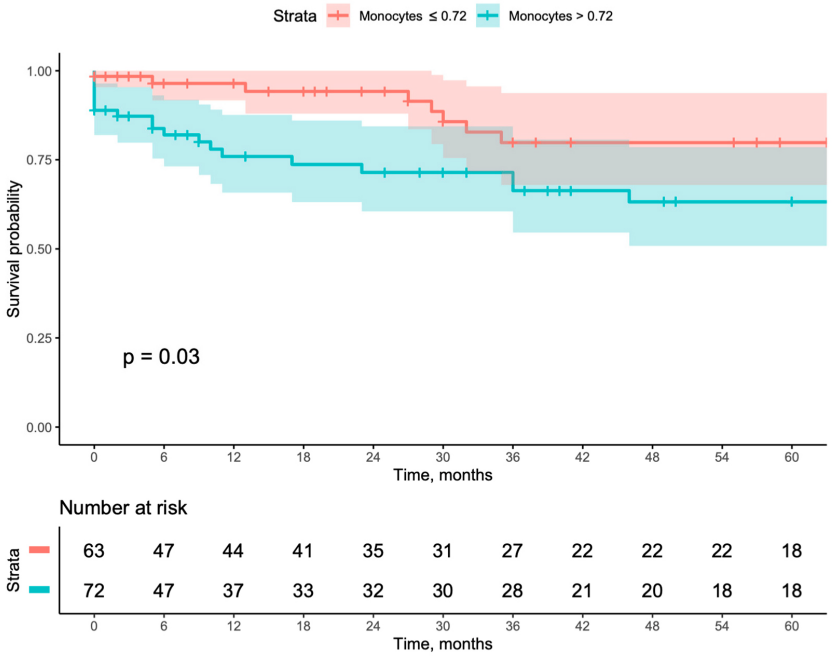

Figure 2. Kaplan–Meyer survival curves and number-at-risk stratified according to monocyte count of ≤0.72 or >0.72 for secondary patency.

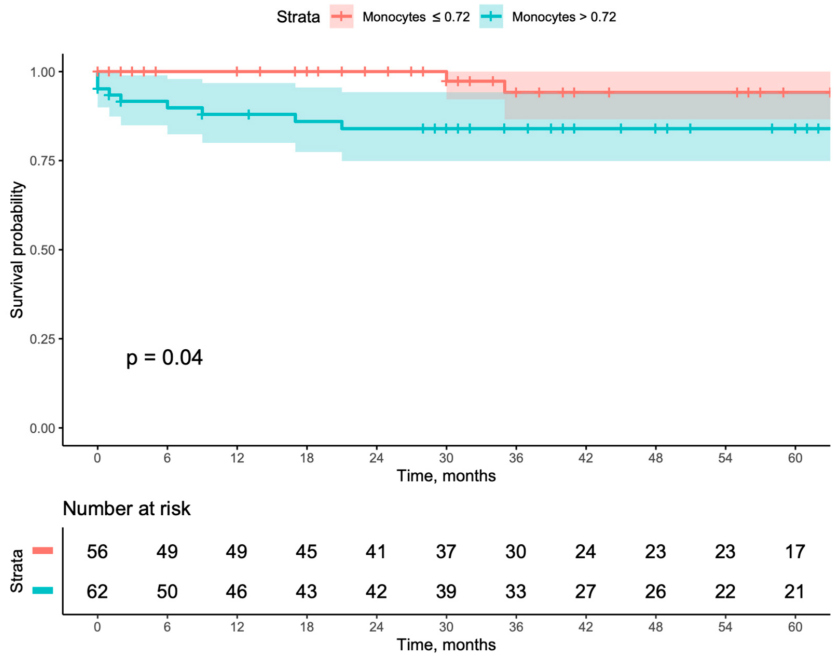

Figure 3. Kaplan–Meyer survival curves and number-at-risk stratified according to a monocyte count of ≤0.72 or >0.72 for amputation.

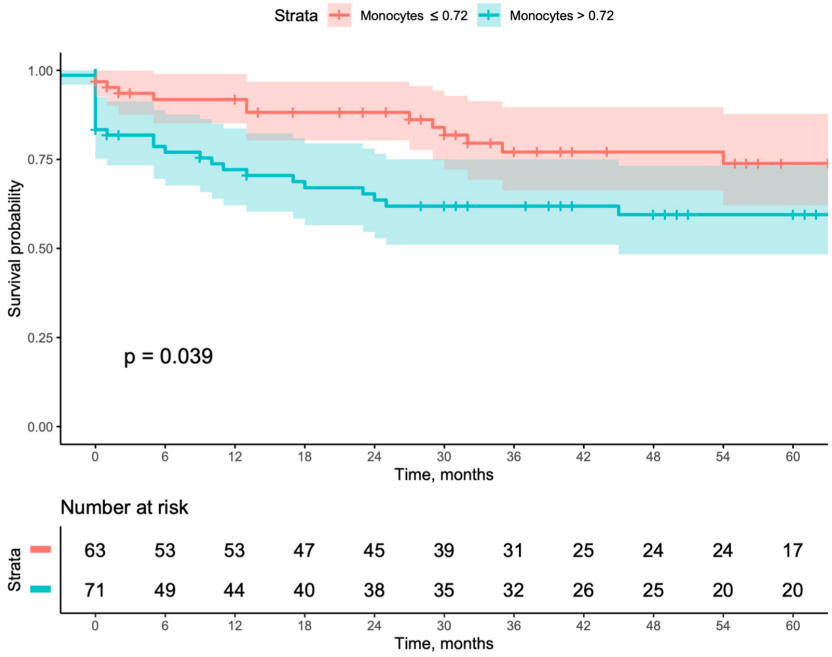

Figure 4. Kaplan–Meyer survival curves and number-at-risk stratified according to a monocyte count of ≤0.72 or >0.72 for major adverse limb events.

4. Discussion

This study showed that the absolute monocyte count can predict MALE in a cohort of patients with aortoiliac TASC D type II lesions submitted to revascularization. This predictive ability was shown both in the short and long term. Furthermore, it could predict a higher risk of major amputation and lower secondary patency.

Inflammation plays a key factor in the pathogenesis of atherosclerosis [8]. Evidence points out that monocytes seem to have a particular role in atherogenesis. Inflammatory macrophages, the dominant immune cells within atherosclerotic plaques, derive from circulating monocytes that attach to activated endothelial cells and migrate into the intimal layer, as well as from the local proliferation of resident macrophages [29,30]. The importance of monocytes is further highlighted by the observation that lesion generation is significantly reduced when circulating monocytes are inhibited from attaching to endothelial cells [31]. Macrophages drive atherosclerosis progression within the plaque by absorbing oxidized low-density lipoprotein particles (oxLDL) and forming foam cells. Moreover, when stimulated by danger-associated molecular patterns such as oxLDL and proteoglycans present in the atherosclerotic environment, macrophages produce a variety of pro-atherogenic cytokines and chemokines [32]. They also impact plaque stability by regulating collagen production and secreting proteases like matrix metalloproteinases [33,34]. The infiltration of macrophages is a crucial initial step in atherosclerotic plaque formation [35]. The apoptosis or death of these macrophages largely contributes to the formation of a necrotic core in the plaque, with accumulating free cholesterol causing its expansion [36]. Plaque destabilization is a complex process involving an imbalance in the production of inflammatory cytokines, angiogenic factors, and growth factors that promote pathological plaque neovascularization [37]. Matrix metalloproteinases (MMPs) degrade various extracellular matrix proteins, ultimately leading to the rupture of the fibrous cap of the plaque and the formation of an intracoronary thrombus [36]. While the mechanisms driving plaque destabilization are primarily internal to the plaque, circulating peripheral blood monocytes

can produce and release mediators that influence key factors involved in this process, such as inflammation, matrix degradation, and thrombogenesis [38]. Additionally, specific monocyte subpopulations have vigorous in vitro angiogenic properties and are a key component of endothelial progenitor cells (EPCs) [25,38]. Therefore, monocytes are crucial in atherogenesis by mediator production, macrophage signaling, foam cell formation, and influencing plaque stability and thrombus formation.

Few studies have assessed monocytes' impact and predictive ability in vascular surgery, and most existing research utilizes monocytes in ratios. In a cross-sectional study of 216 Type 2 Diabetes (DM) patients without PAD and 218 Type 2 DM patients with PAD, the levels of monocyte/HDL ratio (MHR) were higher in Type 2 DM with PAD patients (vs. without PAD), and they were independently linked with its clinical severity [39]. In this study, although it did not reach statistical significance, patients with elevated monocyte count also presented with worse clinical grades as assessed by the Rutherford Classification. Even though monocyte count was not able to reach statistical significance in predicting primary patency ($p = 0.13$), it showed a predictive ability in secondary patency ($p = 0.03$) during follow-up. The relationship between monocyte count and patency has also been highlighted in vascular access by Caifang Li et al. [40]. This study included 120 patients who submitted arteriovenous fistula (AVF) construction and divided them into three groups based on monocyte count. After a median follow-up of 20 months, 31 AVF failure events occurred. Patients with a baseline monocyte count $\geq 0.51 \times 10^9$/L had the lowest patency rate of AVF. After adjusting for primary clinical data and biochemical indicators, there were statistically significant differences in the AVF patency rates of the three groups (hazard ratio [HR]: 2.774, 95% CI [1.092–7.043]).

The role of immune cells, particularly monocytes and T cells, in the context of peripheral arterial disease (PAD) has been the focus of extensive research by Pawel Maga et al. [41,42] In a study of 45 patients with Rutherford 3–4 PAD undergoing percutaneous transluminal angioplasty (PTA), the author observed an acute reduction in CD8+ T cell subsets immediately following the procedure. This included a significant drop in pro-atherosclerotic, immunosenescent effector T cells, likely due to their adhesion to the vascular wall at the site of injury. These findings suggest a key involvement of T cells in the early immune response to vascular trauma [41]. In a complementary study involving 61 patients with Rutherford 3–4 PAD, monocyte subpopulations were monitored before and after PTA. The results showed a significant reduction in monocyte counts post-procedure, with only subtle signs of monocyte activation, primarily indicated by changes in CD45RA and β-integrins. Interestingly, no direct correlation was found between these monocyte changes and long-term clinical outcomes [42]. These studies highlight the acute immune responses to PTA in PAD, while suggesting that these immune markers may not serve as reliable predictors of long-term adverse events. On the other hand in alignment with the results of this study, in a retrospective study with a cohort of 203 patients submitted to revascularization due to PAD, the cut-off value for the prediction of amputation was 2.55 for the lymphocyte-to-monocyte ratio (LMR) (LMR; sensitivity, 56.25%; specificity, 66.88%) with a decrease ratio being associated with a higher rate of amputation after revascularization [43]. Moreover, in patients undergoing embolectomy for acute lower extremity ischemia, patients with a higher MHR have a significantly higher amputation rate, with MHR being an independent predictor on multivariate analysis (HR: 1.547, CI [1.003–2.387], $p = 0.04$) [44].

A higher circulating monocyte count may reflect not only an increased systemic inflammatory response but also persistent monocyte production, suggesting a broader inflammatory burden that contributes to vascular injury and atherogenesis, thus serving as a potential marker for heightened cardiovascular risk. Monocytes, as representatives of the innate immune system, play a significant role in atherosclerosis initiation, propagation, and progression from a stable to an unstable state [2]. One approach would be to continue investigating the potential presence of various subtypes of monocytes and their specific receptors and roles in cardiovascular disease. Hopefully, this would be useful for develop-

ing new therapeutic targets to prevent the progression of atherosclerotic disease and its complications [6].

This study has certain limitations that warrant consideration. Selection bias may have been introduced, as patients with more severe comorbidities and worse clinical conditions, which may not have been fully accounted for by the variables analyzed, could have been preferentially selected for best medical therapy, excluded from revascularization, or directed towards palliative care. Although the findings are valuable, the relatively small sample size of this two-center study, driven by the severity of the selected lesions, limits its generalizability and presents challenges for robust statistical analysis. Furthermore, the predominance of male patients in the cohort restricts the extrapolation of results to the female population, despite their smaller representation in this clinical context. External validation of our findings, particularly the specific monocyte count cut-off, is necessary to ensure broader applicability and confirm the robustness of our results. Furthermore, the detailed survival tables included in the manuscript capture all relevant events, which will aid future meta-analyses of long-term outcomes and provide further insights into the prognostic value of monocyte counts. Another limitation of this study is the lack of longitudinal analysis of monocyte counts, as we only assessed preoperative values. Future research should aim to incorporate both pre- and postoperative monocyte measurements to better understand the temporal dynamics and predictive value of these markers in surgical outcomes.

Conversely, this study's strengths include its prospective design, extended follow-up period, and homogeneity of the patients' aortoiliac lesions. By including patients from a large academic teaching institution and a community referral hospital, the external validity of our results is enhanced. However, additional studies are needed to confirm these findings.

5. Conclusions

In conclusion, this study demonstrated that patients with a higher absolute monocyte count may be more exposed to the risk of MALE if they have aortoiliac TASC D type II lesions and are undergoing revascularization, with predictive accuracy in both the short and long term. Additionally, it was an independent predictor of major amputation. This new marker can be used as a cost-effective and easily available tool for risk stratification, helping identify patients at higher risk for MALE. Further research is needed to validate this marker further and understand the mechanism of the monocyte effect and its potential for pharmacological manipulation, enabling the individualization of targeted therapy to mitigate the onset, progression, and complications of atherosclerosis in peripheral artery disease.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13216412/s1, Table S1: Hematological parameters; Figure S1: Kaplan-Meyer notarial tables and number-at-risk stratified according to monocytes count $\leq$0.72 or >0.72 for primary patency. Figure S2: Kaplan-Meyer notarial tables and number-at-risk stratified according to monocytes count $\leq$0.72 or >0.72 for secondary patency. Figure S3: Kaplan-Meyer notarial tables and number-at-risk stratified according to monocytes count $\leq$0.72 or >0.72 for amputation. Figure S4: Kaplan-Meyer notarial tables and number-at-risk stratified according to monocytes count $\leq$0.72 or >0.72 for major adverse limb events.

Author Contributions: Conceptualization, A.P.-N., J.P.A. and J.R.-N.; methodology, A.P.-N., M.F.-M., J.P.A. and J.R.-N.; software, L.D. and J.R.-N.; validation, A.P.-N., L.D., M.F.-M., J.V., J.P.A. and J.R.-N.; formal analysis, M.F.-M., J.P.A. and J.R.-N.; investigation, A.P.-N., L.D., H.R. and J.R.-N.; data curation, A.P.-N., L.D., M.F.-M., J.V. and J.R.-N.; writing—original draft, A.P.-N.; writing—review & editing, A.P.-N., L.D., M.F.-M., J.V., H.R., J.P.A. and J.R.-N.; supervision, A.P.-N., J.P.A. and J.R.-N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional revision board/Ethics Committee of Comissão de Ética para a Saúde do CHUSJ (Project identification code 246-18 approved on 8 November 2018). The patient's informed consent was handled accordingly.

Informed Consent Statement: Patient consent was waived due to the observational nature of the study (registry without intervention).

Data Availability Statement: The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Conflicts of Interest: Author Mariana Fragão Marques is employed by the company Novo Nordisk A/S. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bray, F.; Laversanne, M.; Weiderpass, E.; Soerjomataram, I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer* **2021**, *127*, 3029–3030. [CrossRef] [PubMed]
2. Ghattas, A.; Griffiths, H.R.; Devitt, A.; Lip, G.Y.; Shantsila, E. Monocytes in coronary artery disease and atherosclerosis: Where are we now? *J. Am. Coll. Cardiol.* **2013**, *62*, 1541–1551. [CrossRef] [PubMed]
3. Back, M.; Yurdagul, A., Jr.; Tabas, I.; Oorni, K.; Kovanen, P.T. Inflammation and its resolution in atherosclerosis: Mediators and therapeutic opportunities. *Nat. Rev. Cardiol.* **2019**, *16*, 389–406. [CrossRef] [PubMed]
4. Libby, P.; Ridker, P.M.; Maseri, A. Inflammation and atherosclerosis. *Circulation* **2002**, *105*, 1135–1143. [CrossRef] [PubMed]
5. Zernecke, A. Dendritic cells in atherosclerosis: Evidence in mice and humans. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 763–770. [CrossRef]
6. Jaipersad, A.S.; Lip, G.Y.; Silverman, S.; Shantsila, E. The role of monocytes in angiogenesis and atherosclerosis. *J. Am. Coll. Cardiol.* **2014**, *63*, 1–11. [CrossRef]
7. Zhou, H.; Tu, L.N.; Giachelli, C.; Nigam, V.; Scatena, M. Monocyte Adhesion and Transmigration Through Endothelium Following Cardiopulmonary Bypass Shearing is Mediated by IL-8 Signaling. *bioRxiv* **2023**. [CrossRef]
8. Pamukcu, B.; Lip, G.Y.; Devitt, A.; Griffiths, H.; Shantsila, E. The role of monocytes in atherosclerotic coronary artery disease. *Ann. Med.* **2010**, *42*, 394–403. [CrossRef]
9. de Groot, E.; van Leuven, S.I.; Duivenvoorden, R.; Meuwese, M.C.; Akdim, F.; Bots, M.L.; Kastelein, J.J. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat. Clin. Pract. Cardiovasc. Med.* **2008**, *5*, 280–288. [CrossRef]
10. Kwon, H.M.; Sangiorgi, G.; Ritman, E.L.; McKenna, C.; Holmes, D.R., Jr.; Schwartz, R.S.; Lerman, A. Enhanced coronary vasa vasorum neovascularization in experimental hypercholesterolemia. *J. Clin. Investig.* **1998**, *101*, 1551–1556. [CrossRef]
11. van Hinsbergh, V.W.; Eringa, E.C.; Daemen, M.J. Neovascularization of the atherosclerotic plaque: Interplay between atherosclerotic lesion, adventitia-derived microvessels and perivascular fat. *Curr. Opin. Lipidol.* **2015**, *26*, 405–411. [CrossRef] [PubMed]
12. Amengual, J.; Barrett, T.J. Monocytes and macrophages in atherogenesis. *Curr. Opin. Lipidol.* **2019**, *30*, 401–408. [CrossRef] [PubMed]
13. Okuno, K.; Tokunaga, M.; Yamashita, Y.; Umebayashi, Y.; Saito, T.; Fukuyo, R.; Sato, Y.; Saito, K.; Fujiwara, N.; Hoshino, A.; et al. Preoperative lymphocyte-to-monocyte ratio is the most predictive inflammatory response marker of survival in gastric cancer. *Langenbecks Arch. Surg.* **2021**, *406*, 2287–2294. [CrossRef] [PubMed]
14. Hopfner, F.; Jacob, M.; Ulrich, C.; Russ, M.; Simm, A.; Silber, R.E.; Girndt, M.; Noutsias, M.; Werdan, K.; Schlitt, A. Subgroups of monocytes predict cardiovascular events in patients with coronary heart disease. The PHAMOS trial (Prospective Halle Monocytes Study). *Hell. J. Cardiol.* **2019**, *60*, 311–321. [CrossRef] [PubMed]
15. Ribeiro, H.; Alves, R.; Jorge, J.; Goncalves, A.C.; Sarmento-Ribeiro, A.B.; Teixeira-Verissimo, M.; Andrade, J.P.; Dourado, M. Monocytes in the Characterization of Pain in Palliative Patients with Severe Dementia-A Pilot Study. *Int. J. Mol. Sci.* **2023**, *24*, 10723. [CrossRef]
16. Cetin, M.S.; Ozcan Cetin, E.H.; Kalender, E.; Aydin, S.; Topaloglu, S.; Kisacik, H.L.; Temizhan, A. Monocyte to HDL Cholesterol Ratio Predicts Coronary Artery Disease Severity and Future Major Cardiovascular Adverse Events in Acute Coronary Syndrome. *Heart Lung Circ.* **2016**, *25*, 1077–1086. [CrossRef]
17. Villanueva, D.L.E.; Tiongson, M.D.; Ramos, J.D.; Llanes, E.J. Monocyte to High-Density Lipoprotein Ratio (MHR) as a predictor of mortality and Major Adverse Cardiovascular Events (MACE) among ST Elevation Myocardial Infarction (STEMI) patients undergoing primary percutaneous coronary intervention: A meta-analysis. *Lipids Health Dis.* **2020**, *19*, 55. [CrossRef]
18. Boidin, M.; Lip, G.Y.H.; Shantsila, A.; Thijssen, D.; Shantsila, E. Dynamic changes of monocytes subsets predict major adverse cardiovascular events and left ventricular function after STEMI. *Sci. Rep.* **2023**, *13*, 48. [CrossRef]
19. Norgren, L.; Hiatt, W.R.; Dormandy, J.A.; Nehler, M.R.; Harris, K.A.; Fowkes, F.G.R. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J. Vasc. Surg.* **2007**, *45*, S5–S67. [CrossRef]

20. Rocha-Neves, J.; Ferreira, A.; Sousa, J.; Pereira-Neves, A.; Vidoedo, J.; Alves, H.; Teixeira, J.; Azevedo, A. Endovascular Approach Versus Aortobifemoral Bypass Grafting: Outcomes in Extensive Aortoiliac Occlusive Disease. *Vasc. Endovasc. Surg.* **2020**, *54*, 102–110. [CrossRef]
21. Agha, R.; Abdall-Razak, A.; Crossley, E.; Dowlut, N.; Iosifidis, C.; Mathew, G. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. *Int. J. Surg.* **2019**, *72*, 156–165. [CrossRef] [PubMed]
22. Collins, G.S.; Reitsma, J.B.; Altman, D.G.; Moons, K.G. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. *BMJ* **2015**, *350*, g7594. [CrossRef] [PubMed]
23. Stoner, M.C.; Calligaro, K.D.; Chaer, R.A.; Dietzek, A.M.; Farber, A.; Guzman, R.J.; Hamdan, A.D.; Landry, G.J.; Yamaguchi, D.J.; Society for Vascular Surgery. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J. Vasc. Surg.* **2016**, *64*, e1–e21. [CrossRef] [PubMed]
24. Conte, M.S.; Bradbury, A.W.; Kolh, P.; White, J.V.; Dick, F.; Fitridge, R.; Mills, J.L.; Ricco, J.-B.; Suresh, K.R.; Murad, M.H.; et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur. J. Vasc. Endovasc. Surg.* **2019**, *58*, S1–S109.e33. [CrossRef] [PubMed]
25. Thygesen, K.; Alpert, J.S.; Jaffe, A.S.; Chaitman, B.R.; Bax, J.J.; Morrow, D.A.; White, H.D.; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J. Am. Coll. Cardiol.* **2018**, *72*, 2231–2264. [CrossRef] [PubMed]
26. Fashandi, A.Z.; Mehaffey, J.H.; Hawkins, R.B.; Kron, I.L.; Upchurch, G.R., Jr.; Robinson, W.P. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. *J. Vasc. Surg.* **2018**, *68*, 1817–1823. [CrossRef]
27. Vieira-Cardoso, N.; Pereira-Neves, A.; Fragao-Marques, M.; Duarte-Gamas, L.; Domingues-Monteiro, D.; Vidoedo, J.; Reis, P.; Teixeira, J.; Andrade, J.P.; Rocha-Neves, J. Red blood cell distribution width as a predictor of cardiovascular outcomes in extensive aortoiliac disease. *J. Cardiovasc. Surg.* **2023**, *64*, 48–57. [CrossRef]
28. Zhu, Y.; Xu, H.; Wang, Y.; Feng, X.; Liang, X.; Xu, L.; Liang, Z.; Xu, Z.; Li, Y.; Le, Y.; et al. Risk factor analysis for diabetic foot ulcer-related amputation including Controlling Nutritional Status score and neutrophil-to-lymphocyte ratio. *Int. Wound J.* **2023**, *20*, 4050–4060. [CrossRef]
29. Moore, K.J.; Sheedy, F.J.; Fisher, E.A. Macrophages in atherosclerosis: A dynamic balance. *Nat. Rev. Immunol.* **2013**, *13*, 709–721. [CrossRef]
30. Robbins, C.S.; Hilgendorf, I.; Weber, G.F.; Theurl, I.; Iwamoto, Y.; Figueiredo, J.L.; Gorbatov, R.; Sukhova, G.K.; Gerhardt, L.M.S.; Smyth, D.; et al. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. *Nat. Med.* **2013**, *19*, 1166–1172. [CrossRef]
31. Boring, L.; Gosling, J.; Cleary, M.; Charo, I.F. Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* **1998**, *394*, 894–897. [CrossRef] [PubMed]
32. Zimmer, S.; Grebe, A.; Latz, E. Danger signaling in atherosclerosis. *Circ. Res.* **2015**, *116*, 323–340. [CrossRef] [PubMed]
33. Moore, K.J.; Tabas, I. Macrophages in the pathogenesis of atherosclerosis. *Cell* **2011**, *145*, 341–355. [CrossRef] [PubMed]
34. Groh, L.; Keating, S.T.; Joosten, L.A.B.; Netea, M.G.; Riksen, N.P. Monocyte and macrophage immunometabolism in atherosclerosis. *Semin. Immunopathol.* **2018**, *40*, 203–214. [CrossRef] [PubMed]
35. Sakakura, K.; Nakano, M.; Otsuka, F.; Ladich, E.; Kolodgie, F.D.; Virmani, R. Pathophysiology of atherosclerosis plaque progression. *Heart Lung Circ.* **2013**, *22*, 399–411. [CrossRef]
36. Schwartz, S.M.; Galis, Z.S.; Rosenfeld, M.E.; Falk, E. Plaque rupture in humans and mice. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 705–713. [CrossRef]
37. Camare, C.; Pucelle, M.; Negre-Salvayre, A.; Salvayre, R. Angiogenesis in the atherosclerotic plaque. *Redox Biol.* **2017**, *12*, 18–34. [CrossRef]
38. Shantsila, E.; Lip, G.Y. Monocytes in acute coronary syndromes. *Arterioscler. Thromb. Vasc. Biol.* **2009**, *29*, 1433–1438. [CrossRef]
39. Song, Y.; Zhao, Y.; Shu, Y.; Zhang, L.; Cheng, W.; Wang, L.; Shu, M.; Xue, B.; Wang, R.; Feng, Z.; et al. Combination model of neutrophil to high-density lipoprotein ratio and system inflammation response index is more valuable for predicting peripheral arterial disease in type 2 diabetic patients: A cross-sectional study. *Front. Endocrinol.* **2023**, *14*, 1100453. [CrossRef]
40. Li, C.; Li, Q.; Ou, J.; Li, W.; Guan, B.; Lu, Y.; Yun, C.; Hocher, B.; Hu, B.; Yin, L. Relationship between Monocytes and Stenosis-Related Autologous Arteriovenous Fistula Dysfunction. *Blood Purif.* **2022**, *51*, 226–232. [CrossRef]
41. Maga, P.; Mikolajczyk, T.P.; Partyka, L.; Siedlinski, M.; Maga, M.; Krzanowski, M.; Malinowski, K.; Luc, K.; Nizankowski, R.; Bhatt, D.L.; et al. Involvement of CD8+ T cell subsets in early response to vascular injury in patients with peripheral artery disease in vivo. *Clin. Immunol.* **2018**, *194*, 26–33. [CrossRef] [PubMed]
42. Maga, P.; Mikolajczyk, T.P.; Partyka, L.; Krzanowski, M.; Malinowski, K.P.; Nizankowski, R. Percutaneous Transluminal Angioplasty in Patients with Peripheral Arterial Disease Does Not Affect Circulating Monocyte Subpopulations. *Biomed. Res. Int.* **2016**, *2016*, 2708957. [CrossRef] [PubMed]

43. Cosarca, M.C.; Halmaciu, I.; Muresan, A.V.; Suciu, B.A.; Molnar, C.; Russu, E.; Horvath, E.; Niculescu, R.; Puscasiu, L.; Bacalbașa, N.; et al. Neutrophil-to-lymphocyte, platelet-to-lymphocyte and lymphocyte-to-monocyte ratios are associated with amputation rates in patients with peripheral arterial disease and diabetes mellitus who underwent revascularization: A Romanian regional center study. *Exp. Ther. Med.* **2022**, *24*, 703. [CrossRef] [PubMed]
44. Cicek, M.C.; Dagli, M.; Yilmaz, I.S.; Baysal, A.N.; Durgut, K. Admission monocyte to high density lipoprotein cholesterol ratio predicts amputation in patients undergoing embolectomy for acute lower extremity ischemia. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, *26*, 4735–4743.

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3. Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study

Reference to the published version:

Alves M, Pias AD, Marques J, Miranda C, Pereira-Neves A, Shahat M, Vidoedo J, Andrade JP, Rocha-Neves J, Marreiros A. Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study.

J Cardiovasc Surg (Torino). 2025 Apr;66(2):109-119. doi: 10.23736/S0021-9509.24.13135-7.

Impact Factor: 1.5 (2024)

Quartile: Q2 (Scimago, 2024); Q3 (JCR, 2024)

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The Journal of Cardiovascular Surgery 2024 mese;65(0):000–000
DOI: 10.23736/S0021-9509.24.13135-7

ORIGINAL ARTICLE
PERIPHERAL ARTERY

Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study

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ABSTRACT

BACKGROUND: Aortoiliac disease poses a significant cardiovascular (CV) risk, especially in individuals with chronic kidney disease. This study aimed to assess the predictive role of chronic kidney disease in long-term major adverse CV events in patients submitted to aortoiliac revascularization due to severe aortoiliac atherosclerotic disease.

METHODS: From 2013 to 2023, patients who underwent aortoiliac revascularization for TASC II type D lesions, including those with chronic kidney disease, were selected from a prospective cohort study. Demographic, clinical, and postoperative data were collected. Prognostic factors were evaluated for their independent impact on outcomes using survival analysis with a multivariate Cox regression model.

RESULTS: The study included 135 patients, 93.3% male, with a mean age of 62.39±9.20 years. Chronic kidney disease was associated with higher prevalence of short-term myocardial injury after noncardiac surgery (54.5%, P=0.014) and was a long-term predictor of acute heart failure (Hazard Ratio=4.884; 95% confidence interval 2.377-22.802; P=0.007), major adverse CV events (HR 2.992; 95% CI 1.498-5.975, P=0.002) and all-cause mortality (HR 3.296; 95% CI 1.626-6.682, P<0.001). The multivariable analysis revealed significant associations between major adverse CV events and the following predictors: chronic kidney disease (adjusted HR=2.416, 95% CI 1.171-4.984, P=0.017) and congestive heart failure (adjusted HR=2.633, 95% CI 1.233-5.623, P=0.012).

CONCLUSIONS: Chronic kidney disease is a recognized CV risk factor and an independent predictor of long-term acute heart failure, major adverse CV events, and all-cause mortality. These findings underscore the importance of early identification of CV complications and stricter long-term follow-up for chronic kidney disease patients undergoing aortoiliac revascularization.

(*Cite this article as:* Alves M, Pias AD, Marques J, Miranda C, Pereira-Neves A, Shahat M, *et al.* Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study. J Cardiovasc Surg 2024;65:000-000. DOI: 10.23736/S0021-9509.24.13135-7)

KEY WORDS: Peripheral arterial disease; Cardiovascular diseases; Arterial occlusive diseases; Heart disease risk factors; Survival analysis; Perioperative care.

Aortoiliac disease (AOID) is a manifestation of peripheral arterial disease (PAD) defined by a partial or total vascular obstruction caused by atherosclerosis in the common iliac arteries and infrarenal aorta.[1] Estimated to affect approximately 14% of the general population, AOID tends to occur more frequently in younger individuals than distal

artery disease.[2, 3] In advanced stages, AOID leads to severe claudication or chronic limb-threatening ischemia, reducing quality of life and increasing morbidity and mortality.[4] It is often associated with steno-occlusive disease in other key vascular territories, such as the cerebrovascular, coronary, renal, and mesenteric arteries.[4, 5]

The management of TASC II type D lesions, the most advanced form of AOID, has evolved significantly in recent years, but these patients remain at high risk for subsequent cardiovascular (CV) events.[6, 7] While an endovascular-first approach is favored due to its lower 30-day morbidity and mortality, open surgery is still necessary in cases involving more complex vascular anatomy or when prior endovascular attempts are unsuccessful. Despite offering superior long-term patency, open surgery carries increased perioperative risks, including higher mortality rates.[8] However, the role of chronic kidney disease (CKD) as a risk factor in this population has not been extensively validated.[8]

CKD is a significant risk factor for CV events. Both proteinuria and a reduction in glomerular filtration rate (GFR) can predict the development of fatal and non-fatal CV events, independently of traditional CV risk factors such as high blood pressure, smoking, cholesterol, age, and gender.[9-11] The relationship is observed even in the early stages 1 and 2 of CKD, but the risk of mortality from CV disease doubles and triples in the more advanced stages 3 and 4, respectively.[12] The high CV risk manifests itself in coronary artery disease (CAD), heart failure (HF), arrhythmias, and sudden cardiac death, and individuals with CKD are considerably more likely to suffer CV events than to develop end-stage renal disease (stage 5).[13, 14]

Patients with CKD are at a significantly increased risk of PAD[15] and experience a higher rate risk of perioperative complications after revascularization compared to patients without CKD.[16]

Considering CKD's prognostic ability, one could conjecture its relevance in predicting postoperative and long-term outcomes after aortoiliac revascularization and, therefore, help to identify patients at higher risk of adverse events.

This study aimed to evaluate the potential role of CKD in predicting long-term major adverse CV events (MACE). As secondary outcomes, the authors aimed to determine the prognostic values of CKD with CV long-term outcomes, including acute myocardial infarction (AMI), acute heart failure (AHF), stroke, major adverse lower limb events (MALE), and all-cause mortality.

Materials and methods

Patient selection

Between January 2013 and January 2023, consecutive patients who underwent elective aortoiliac revascularization were included in this prospective cohort study (Figure 1). All patients were selected from São João University Hospital, EPE, Porto, and Padre Américo Hospital, EPE, Penafiel, a tertiary and a community hospital, respectively. All patients had aortoiliac Transatlantic Inter-Society Consensus (TASC) II type D lesions, excluding those with aortoiliac aneurysmatic disease.[6] Independent vascular surgeons performed the TASC II classification of lesions. Discrepancies were resolved through a multidisciplinary meeting to ensure a consensus on the classification. Only

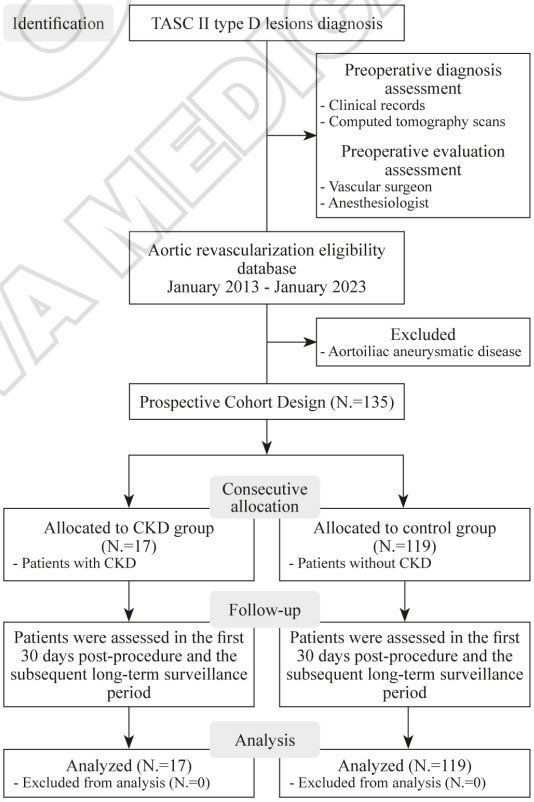

Figure 1.—Flow diagram of the designed study.
CKD: chronic kidney disease.

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TASC II D lesions were included to focus on the most complex cases, which provide clearer insights into the impact of CKD on high-risk patients. Including TASC II C lesions could introduce variability in treatment and outcomes.

Surgeons and patients shared the decision on whether to perform open surgery or an endovascular procedure, considering the surgeon's and institution's experience and preferences. For TASC II D lesions, the original standard treatment at these institutions was open surgery, although this has been challenged over the years with the completion of the endovascular learning curve. Treatment is adjusted based on patient factors, including age and comorbidities. CKD patients who face higher perioperative risks may receive more tailored care, including less invasive options and comprehensive follow-up.

An internist reviewed all patient prescriptions, ensuring that each patient received aspirin 100 mg and a high-dose statin for at least two days before the intervention. The internist meticulously assessed all prescriptions to optimize the medical treatment before the intervention. This approach aligns with international guidelines for managing CV risk. An internist overseeing each case ensured that patients were discharged with the most appropriate medical treatment tailored to their individual needs; in most cases, single antiplatelet therapy was prescribed, the preoperative regimens typically being maintained, and pain medications were provided as needed for symptom management. However, while appropriate preoperative medication was thoughtfully reviewed, detailed data on postoperative adherence to antiplatelet and statin therapy were not systematically recorded, although they were properly endorsed as institutional policy.

Patient's demographic and clinical characteristics, including their CV risk factors and their procedural and lesion-specific details, were retrieved by a detailed review of their clinical records, including computed tomography.[17] Patients were assessed in the first 30 days post-procedure and the subsequent long-term surveillance period. The outpatient clinic's clinical record was summarily reviewed for the reported outcomes, including patient-related events such as AHF, AMI, stroke, and all-cause mortality. Additionally, limb-related events such as reintervention, acute limb ischemia, major amputation, or occlusion without intervention were noted.

This cohort study is based on the Strengthening the Reporting of Cohort Studies in Surgery 2024 (STROCSS) Guideline[18] and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[19] The local Ethics Committee approved the study protocol (Protocol Number 246-18). It respects the Declaration of Helsinki and the European Union General Data Protection Regulation (GDPR). Patient informed consent was handled accordingly, and all data processing was anonymous.

The retrieved data was registered in agreement with the Reporting Standards of the Society for Vascular Surgery for lower extremity ischemia.[20] The Rutherford chronic ischemia classification was used to classify the symptoms and severity of chronic lower extremity ischemia.[21] MACE was a composite outcome, including AMI, AHF, and all-cause mortality.[22] Myocardial injury after noncardiac surgery (MINS), including myocardial infarction and ischemic myocardial injury, is defined by at least one postoperative elevation of cardiac troponins (cTn) concentration that exceeds the 99th percentile upper reference limit of the cTn assay within the first 30 days after surgery, with no requiring clinical symptoms or electrocardiographic changes.[23] MALE was defined as the combined events of reintervention, including reintervention due to primary assisted patency, secondary patency or major amputation, and occlusion without intervention.[24] Vascular prosthesis infection was defined by resorting to the Validation of the Management of Aortic Graft Infection Collaboration (MAGIC) criteria.[25] Acute kidney injury (AKI) is characterized by a significant increase in serum creatinine (SCr) levels by at least 0.3 mg/dL (≥26.5 μmol/L) within 48 hours or an increase in SCr to at least 1.5 times the baseline within the prior seven days.[26]

CKD is characterized by kidney damage or a persistent decline in function over three months. GFR and the presence of kidney injury or proteinuria stage it. Stages range from G1 (GFR≥90 mL/min/1.73 m^2) to G5 (GFR<15 mL/min/1.73 m^2), and albuminuria levels from A1 (urine protein <30 mg/g or <3 mg/mmol) to A3 (urine protein >300 mg/g or >30 mg/mmol). Stage G5 denotes kidney failure, the most severe form of CKD. An isolated GFR<60 mL/min/1.73m^2 also confirms CKD diagnosis.[27]

Statistical analysis

The sample size for a survival test was calculated using online Sample Size Calculators for Designing Clinical Research (https://sample-size.net/sample-size-survival-analysis/), with a statistical power (β) of 80% and a significance level of 0.05. The sample was estimated (131) for a hazard ratio >2 between groups and a predicted survival at the end of follow-up of 80%, although higher event rate differences are described.[14, 28]

For statistical analysis, SPSS (IBM Corp., released

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2023. IBM SPSS Statistics for Windows, version 29.0, Armonk, NY, USA) was used. Student's t-test was favored when dealing with normally distributed continuous variables. Data was presented as N. (%) or as mean and standard deviation or median and interquartile range for continuous variables. At the same time, the Mann-Whitney U Test was used privileged when working with variables whose normal distribution could not be assumed. The χ^2 test was used to analyze categorical variables. Statistically significant results were set at a P<0.05 level.

Multivariate logistic regression analysis was performed to determine independent clinical and demographic factors associated with CKD. The backward and forward stepwise regression method was applied, and variables with P<0.10 were included. The Log Rank estimator was utilized to test the effect of the score on time-dependent variables. Multivariate Cox proportional hazard analysis was performed using the backward stepwise regression method for independent predictors of long-term AHF, AMI, MACE, MALE, stroke, and all-cause mortality. The standard error of long-term results was kept below 10%.

Results

Demographic and clinical data

A total of 135 patients were included in the study population, with a male majority (93.3%), a mean age of 62.39±9.20 years and a median follow-up of 61 IQR [34-90] months. The control group comprised 118 patients, while the CKD group included 17. The CKD group presented a higher mean age of 71.76±12.82 years compared to the control group of 61.03±7.74 years (P<0.001). No significant differences between groups regarding gender were found (P=0.890).

There was a significant association between CV risk factors (Table I) and CKD for hypertension (HTN) (100% *vs.* 61%, P=0.002), CAD (64.7% *vs.* 22.0%, P<0.001), and CHF (41.2% *vs.* 7.6%, P<0.001). However, a lower percentage of smoking history was observed (58.8% *vs.* 95.8%, P<0.001) compared to the control group. The remaining CV risk factors and comorbidities for both groups were comparable.

As for the American Society of Anesthesiologists (ASA) Physical Status Classification System grade, patients with CKD presented a higher percentage of patients with grade IV (35.3% *vs.* 1.7, P<0.001), but lower percentages of grade II (17.6% *vs.* 42.4%, P<0.001) and III (47.1% *vs.* 55.9%, P<0.001) as shown in Table I. Concerning the preoperative Rutherford category as well as the Ankle-Brachial Index (ABI), aortoiliac stenting, aortobifemoral bypass (ABF), and superficial femoral disease (SFA), no differences were found between the groups. Fifteen patients in the endovascular group underwent covered stenting, also without significant impact on outcomes. Revascularization of the infrainguinal sector was also similar in both groups (P=0.085).

Predictive impact of CKD on short-term outcomes

When comparing the CKD and control groups for the 30-day incidence of MACE (11.8% *vs.* 7.6%, P=0.560), death (5.9% *vs.* 5.1%, P=0.890), prosthetic infection (0.0% *vs.* 6.0%, P=0.313), and AKI (13.3% *vs.* 7.9%, P=0.486) no differences were found (Table II). CKD patients had a greater incidence of MINS (54.5% *vs.* 20.5%) (P=0.014).

No differences were observed between groups regarding preoperative and postoperative ABI (Δ 0.44±0.25 *vs.* 0.35±0.17, P=0.214) and the Rutherford chronic ischemia classification (Δ -2.60±1.53 *vs.* -2.38±1.12, P=0.630).

Predictive impact of CKD on long-term outcomes

The survival analysis of CKD patients (Figure 2) showed a statistically significant association between CKD and AMI (log-rank=0.034), AHF (log rank<0.001), stroke (log rank=0.035), MACE (log rank=0.001) and all-cause mortality (log rank<0.001) in 36 months follow-up, revealing that CKD was a good predictor of major adverse outcomes. No association was found between CKD and MALE (log rank=0.660).

Cox proportional hazard multivariate analysis (Figure 3) demonstrated a significant association of CKD with AHF (hazard ratio [HR]=4.884; 95% confidence interval [CI]: 2.377-22.802; P=0.007), MACE (HR=2.992; 95% CI: 1.498-5.975; P=0.002), and all-cause mortality (HR=3.296; 95% CI: 1.626-6.682; P<0.001). The results were marginally significant regarding AMI (P=0.052) and stroke (P=0.051), despite presenting a non-adjusted HR of 3.974, 95% CI: 0.990-15.947 and non-adjusted HR of 3.973, 95% CI: 0.992-15.916, respectively. There was no statistical significance regarding the occurrence of MALE (P=0.796).

The multivariable analysis of prognostic factors showed a statistically significant adjusted HR (aHR) between long-term MACE and CKD (aHR=2.416, 95% CI 1.171-4.984, P=0.017) and CHF (aHR=2.633, 95% CI 1.233-5.623, P=0.012) (Table III).

Discussion

This study's primary finding is that CKD is a significant predictor of long-term outcomes, including AHF, MACE,

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TABLE I.—*Patient's demographics and comorbidities.*

	Total N.=135 (%)	Control N.=118 (%)	CKD N.=17 (%)	P value
Gender, male	126 (93.3)	110 (93.2)	16 (94.1)	0.890
Age, years (mean±SD)	62.39±9.20	61.03±7.74	71.76±12.82	<0.001
Hypertension	89 (65.9)	72 (61)	17 (100)	0.002
Smoking history	123 (91.1)	113 (95.8)	10 (58.8)	<0.001
Diabetes	40 (29.9)	32 (27.4)	8 (47.1)	0.097
Dyslipidemia	91 (67.9)	78 (66.7)	13 (76.5)	0.418
CAD	37 (27.4)	26 (22.0)	11 (64.7)	<0.001
COPD	15 (11.1)	13 (11.0)	2 (11.8)	0.927
CHF	16 (11.9)	9 (7.6)	7 (41.2)	<0.001
ASA				
II	53 (39.3)	50 (42.4)	3 (17.6)	<0.001
III	74 (54.8)	66 (55.9)	8 (47.1)	
IV	8 (5.9)	2 (1.7)	6 (35.3)	
Preoperative Rutherford Classification				
2	1 (0.7)	1 (0.9)	0	0.252
3	36 (26.9)	35 (29.9)	1 (5.9)	
4	53 (39.6)	44 (37.6)	9 (52.9)	
5	36 (26.9)	31 (26.5)	5 (29.4)	
6	8 (6.0)	6 (5.1)	2 (11.8)	
Aortoiliac stenting	59 (43.7)	50 (42.4)	9 (52.9)	0.411
ABF	76 (56.3)	68 (57.6)	8 (47.1	
ABIpre (mean±SD)	0.31±0.29	0.31±0.13	0.31±0.10	0.938
SFA Disease	83 (61.5)	71 (60.2)	12 (70.6)	0.409

Variables are presented as N. (%) if categorical, mean±standard deviation if continuous and median, interquartile range if ASA.
ABI: Ankle-brachial index preoperative; ABF: aortobifemoral bypass; ASA: American Society of Anesthesiologists; CAD: coronary artery disease; CHF: cardiac heart failure; CKD: chronic kidney disease (creatinine=1.5 mg/dL); COPD: chronic obstructive pulmonary disease; SD: standard deviation; SFA: superficial femoral artery disease.

TABLE II.—*Patient's 30-day outcome according to kidney disease status.*

	Total	Control	CKD	P value
MACE, N. (%)	11 (8.1)	9 (7.6)	2 (11.8)	0.560
Death, N. (%)	7 (5.2)	6 (5.1)	1 (5.9)	0.890
Prosthetic infection, N. (%) *	7 (5.3)	7 (6.0)	0 (0.0)	0.313
AKI	10 (8.6)	8 (7.9)	2 (13.3)	0.486
TropI [MINS]	23 (24.5)	17 (20.5)	6 (54.5)	0.014
ABI Δ, (mean±SD)	0.43±0.24	0.44±0.25	0.35±0.17	0.214
Rutherford Δ, (mean±SD)	-2.57±1.48	-2.60±1.53	-2.38±1.12	0.630
ICU (days) (median-IQR)	2 [0-3]	2 [0-3]	0 [0-3]	0.115*
Infirmary (days) (median-IQR)	8 [3.50-19.50]	8 [3-19]	10 [3.50-26.50]	0.531*

ABI Δ: Ankle-brachial Index Delta - preoperative minus postoperative; AKI: acute kidney injury; MACE: major adverse cardiovascular event at 30 Days; MINS: myocardial injury after non-cardiac surgery; prothesis infection (1 year of follow-up); Rutherford Δ: Rutherford chronic ischemia delta - preoperative minus postoperative; ICU: in stay on intensive care unit; TropI: troponin I.
*non-parametric test – Mann-Whitney U Test.

and all-cause mortality in patients who have undergone revascularization for extensive aortoiliac disease. CHF was identified as an independent predictor of MACE. Furthermore, CKD was recognized as a possible predictor of MINS.

While previous research has highlighted the association of CKD with MACE across diverse patient cohorts,[28-30] this study stands out as the first to highlight an association between CKD and long-term adverse outcomes in this subset of patients.

In the present study, age emerged as a clinical characteristic associated with CKD. The higher mean age in the CKD group compared to the control group is consistent with findings that CKD prevalence increases with age.[31] This association is likely due to the natural decline in renal function associated with aging.[32]

It was also verified that the incidence of CAD and CHF was significantly higher in the CKD group compared to the control, which was expected, given its known association with CV disease. However, the underlying mecha-

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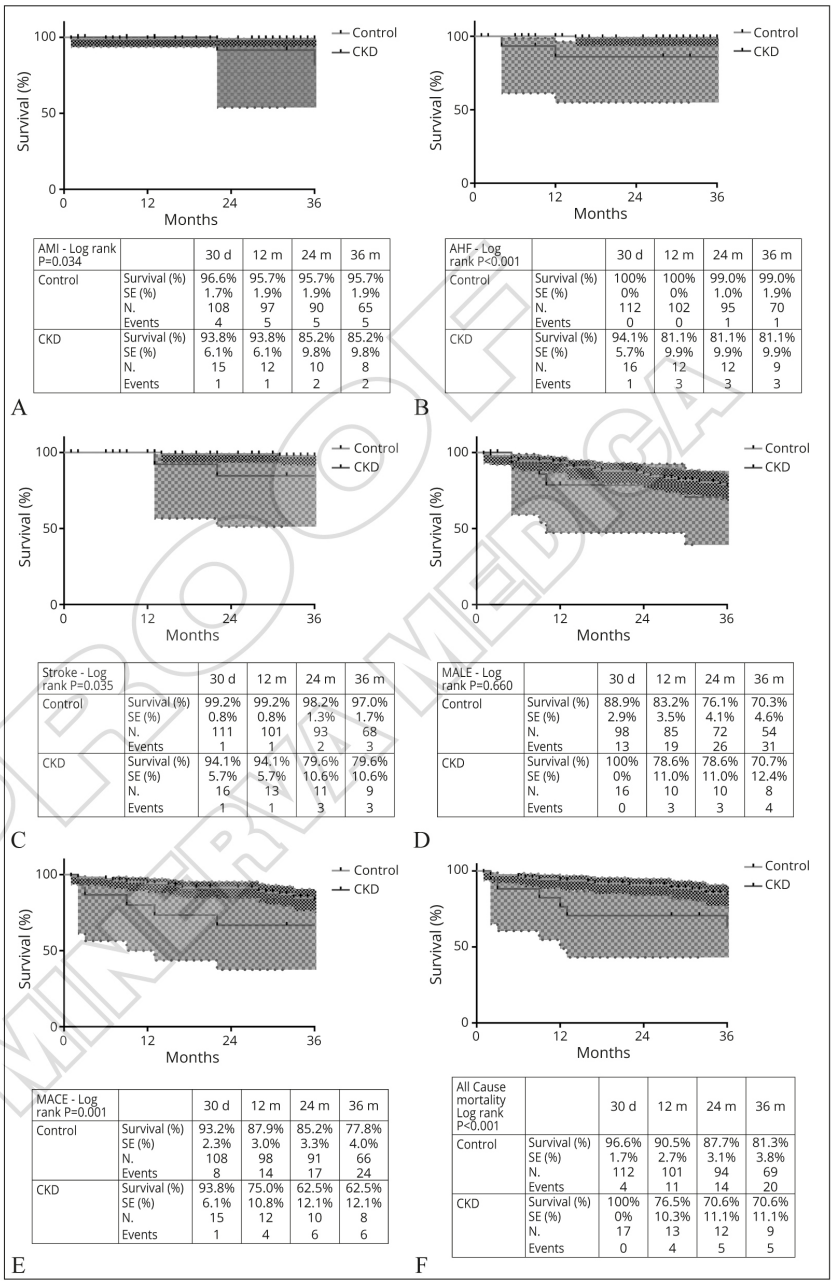
Figure 2.—Kaplan-Meyer survival curves according to CKD status.
A) acute myocardial infarction (AMI); B) acute heart failure (AHF); C) stroke; D) major adverse limb events (MALE); E) major adverse cardiac events (MACE); F) all-cause mortality.
LogRank P significance <0.05.
d: Days; m: months; SE: standard error.



AMI - Log rank P=0.034		30 d	12 m	24 m	36 m
Control	Survival (%)	96.6%	95.7%	95.7%	95.7%
	SE (%)	1.7%	1.9%	1.9%	1.9%
	N.	108	97	90	65
	Events	4	5	5	5
CKD	Survival (%)	93.8%	93.8%	85.2%	85.2%
	SE (%)	6.1%	6.1%	9.8%	9.8%
	N.	15	12	10	8
	Events	1	1	2	2

AHF - Log rank P<0.001		30 d	12 m	24 m	36 m
Control	Survival (%)	100%	100%	99.0%	99.0%
	SE (%)	0%	0%	1.0%	1.9%
	N.	112	102	95	70
	Events	0	0	1	1
CKD	Survival (%)	94.1%	81.1%	81.1%	81.1%
	SE (%)	5.7%	9.9%	9.9%	9.9%
	N.	16	12	12	9
	Events	1	3	3	3

Stroke - Log rank P=0.035		30 d	12 m	24 m	36 m
Control	Survival (%)	99.2%	99.2%	98.2%	97.0%
	SE (%)	0.8%	0.8%	1.3%	1.7%
	N.	111	101	93	68
	Events	1	1	2	3
CKD	Survival (%)	94.1%	94.1%	79.6%	79.6%
	SE (%)	5.7%	5.7%	10.6%	10.6%
	N.	16	13	11	9
	Events	1	1	3	3

MALE - Log rank P=0.660		30 d	12 m	24 m	36 m
Control	Survival (%)	88.9%	83.2%	76.1%	70.3%
	SE (%)	2.9%	3.5%	4.1%	4.6%
	N.	98	85	72	54
	Events	13	19	26	31
CKD	Survival (%)	100%	78.6%	78.6%	70.7%
	SE (%)	0%	11.0%	11.0%	12.4%
	N.	16	10	10	8
	Events	0	3	3	4

MACE - Log rank P=0.001		30 d	12 m	24 m	36 m
Control	Survival (%)	93.2%	87.9%	85.2%	77.8%
	SE (%)	2.3%	3.0%	3.3%	4.0%
	N.	108	98	91	66
	Events	8	14	17	24
CKD	Survival (%)	93.8%	75.0%	62.5%	62.5%
	SE (%)	6.1%	10.8%	12.1%	12.1%
	N.	15	12	10	8
	Events	1	4	6	6

All Cause mortality Log rank P<0.001		30 d	12 m	24 m	36 m
Control	Survival (%)	96.6%	90.5%	87.7%	81.3%
	SE (%)	1.7%	2.7%	3.1%	3.8%
	N.	112	101	94	69
	Events	4	11	14	20
CKD	Survival (%)	100%	76.5%	70.6%	70.6%
	SE (%)	0%	10.3%	11.1%	11.1%
	N.	17	13	12	9
	Events	0	4	5	5

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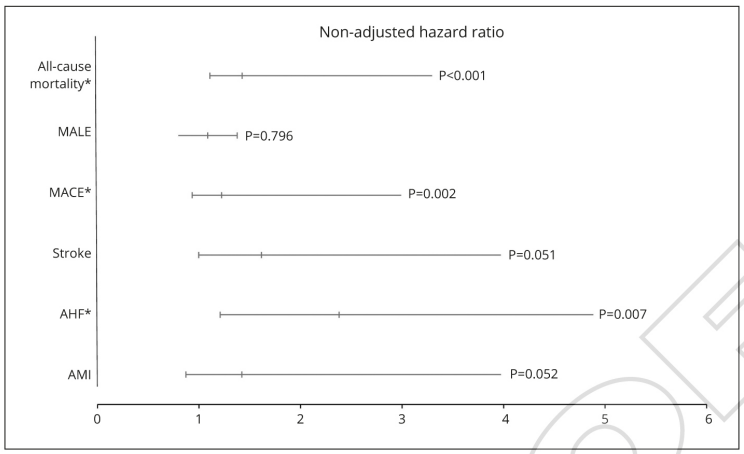

Figure 3.—Cox proportional hazard multivariable analysis of outcomes for CKD.
AMI: acute myocardial infarction; AHF: acute heart failure; CKD: chronic kidney disease; MACE: major adverse cardiovascular events.
LogRank p significance <0.05.

TABLE III.—*Cox multivariate regression proportional hazard ratio of prognostic factors for long-term.*

	Non-adjusted Hazard Ratios	95% confidence interval	P value	Adjusted Hazard Ratios	95% confidence interval	P value
Age	1.028	0.995-1.062	0.093	NC		
Hypertension	1.360	0.680-2.721	0.385	NC		
Smoking status	0.373	0.172-0.810	0.013	NC		
CAD	2.396	1.290-4.451	0.006	NC		
CHF	3.269	1.588-6.730	0.001	2.633	1.233-5.623	0.012
CKD	2.992	1.498-5.975	0.002	2.416	1.171-4.984	0.017

CAD: coronary artery disease; CHF: cardiac heart failure; CKD: chronic kidney disease (creatinine=1.5 mg/dL); MACE: major adverse cardiovascular events.

nisms must still be fully understood.[33] CKD accelerates artery stiffness and atherosclerosis, leading to CAD and CHF.[13, 34] Factors like microalbuminuria and inflammation in CKD may also contribute to heart failure.[35] Given the increased risks of MI, stroke, and heart failure, it is essential to incorporate CV risk stratification and perioperative management for CKD patients undergoing major vascular procedures.[36] In patients with CHF undergoing vascular surgery, careful preoperative stabilization is crucial to manage elevated perioperative risks. Surgery should be postponed in decompensated HF when possible, and hemodynamic monitoring such as pulmonary artery catheter is advised for high-risk patients, particularly those in NYHA classes III and IV.[37] Postoperatively, these patients require careful monitoring for complications, including pulmonary edema, ischemia, and arrhythmias. Managing fluid balance is especially important, with a focus on maintaining preoperative "dry weight" to guide diuresis and avoid fluid overload, which could worsen heart failure.[38] Continuous surveillance for ischemic events and arrhythmias is critical to minimizing postoperative morbidity and ensuring optimal recovery outcomes. Continuation of HF medications, such as beta-blockers and angiotensin-converting enzyme inhibitors, is vital to stabilize cardiac function and reduce postoperative risks.[39]

Routine screening for ischemic heart disease using coronary computed tomography angiography (CCTA) or invasive coronary angiography identifies high-risk CKD patients who lack proper evidence.[40, 41] For instance, the RENOVATE-COMPLEX-PCI trial demonstrated that intravascular imaging-guided percutaneous coronary intervention (PCI) reduces the risk of target vessel failure compared to angiography-guided PCI, particularly in patients with CKD. This underscores the value of detailed preoperative assessment and imaging in optimizing outcomes for CKD patients undergoing complex revascularization procedures.[36]

CKD is a well-established predictor of adverse long-term outcomes, including MACE, AHF, and all-cause mortality.[29, 30, 42] A study by Chen *et al.*, which included

1566 patients, 261 with CKD and 1305 without CKD, and demonstrated that patients with CKD have a higher incidence of MACE, including CHF and MI, compared to those without CKD.[43] Similarly, an overall increase in the rates of mortality, hemorrhage, hospital readmission, the risk of lower extremity amputation, and MACE was reported compared to patients without kidney disease.[16, 28]

The Coronary CTA VISION trial showed that CCTA enhances the prediction of postoperative CV death and non-fatal MI in patients with CAD risk factors. Functional assessments like fractional flow reserve (FFR) may also guide revascularization decisions, potentially improving long-term outcomes.[41, 44]

Additionally, CKD is associated with a worse prognosis in AHF cases.[43] This underscores the importance of enhanced CV risk management and thorough preoperative assessments. As renal function worsens, the prevalence and mortality rate of patients with AHF increases, which makes it an independent predictor of hospital mortality in patients with AHF.[45, 46] AHF reduces renal blood flow and causes ischemic injury, worsening CKD. Conversely, CKD affects the heart through mechanisms such as fluid overload, uremia, anemia, and left ventricular remodeling, leading to heart dysfunction.[45, 46]

While AMI and stroke showed HR indicative of increased risk in CKD patients, the statistical significance was marginal in the multivariate analysis. This result suggests other factors may influence the association between CKD and these specific events. Abramson *et al.* suggested that CKD may lead to oxidative stress, promoting atherosclerosis and increasing the risk of cerebral ischemia and stroke. CKD is also linked to left ventricular hypertrophy, a strong predictor of stroke. The study found a significant association between CKD and stroke risk, especially in patients with anemia, while the association was weaker in those without anemia.[47]

According to Li *et al.*, there is a high incidence of lower limb complications among individuals with CKD.[48] Furthermore, following surgical revascularization, patients with CKD face a significantly elevated risk of limb loss, approximately five times higher when compared to those with an earlier stage of CKD, despite a similar revascularization rate.[16, 28] Still, interestingly, in our study, there was no statistically significant association between CKD and MALE.

The incidence of MINS was higher in CKD patients, referring to the findings from the previous meta-analysis, which included 169 studies on heterogeneous noncardiac surgery that estimated an incidence of approximately 20%.[49, 50] This finding could indicate an indirect association between CKD and MINS, as both CAD and CKD are strongly correlated to CV disease, with the CKD group in this study having a significantly higher incidence of these comorbidities.

Notably, patients with hs-cTnI levels ≥60 ng/L exhibited a markedly elevated risk of adverse outcomes, highlighting its potential as a diagnostic marker for MINS.[51] However, interpreting troponin levels in CKD patients poses challenges due to chronically elevated levels and reduced renal clearance of cTn, potentially reducing the diagnostic utility of this cardiac biomarker.[52] Despite these challenges, prior studies have suggested that elevated cTn levels could predict short-term MACE in CKD patients with acute coronary syndrome, particularly among those undergoing dialysis.[53]

Optimal medical management in AIOD involves the use of antiplatelet agents, such as aspirin or clopidogrel, and statins to reduce MACE. These therapies stabilize atherosclerotic plaques and help manage risk factors, including hypertension, diabetes, and hyperlipidemia. According to the studies, integrating these treatments with endovascular or surgical interventions improves patient outcomes and reduces the need for reintervention, highlighting their critical role in comprehensive care for AIOD patients.[3, 54] Furthermore, the increased cv-specific and 30-day mortality in the CKD population highlights the importance of incorporating perioperative renal function monitoring to enhance overall outcomes.[55]

Limitations of the study

There are some limitations inherent to this study that need consideration. Possible selection bias may have occurred since patients with more comorbidities and worse clinical conditions, which might not have been entirely captured by our variables, may have been preferentially selected for less invasive procedures or even excluded from revascularization altogether. Although CKD patients present a high risk of CV disease, morbidities, and mortality, they are often excluded or poorly represented in clinical studies, which makes it difficult to obtain more in-depth and targeted knowledge for the effective and correct treatment and prevention of their complications. The competing risk of death is also a limitation, as patients who died before experiencing events like MACE may have influenced survival analyses, potentially leading to an overestimation of event-free survival. Although the results were comparable to previous reports, due to the severity of the lesions selected, this two-center study presented a small sample that

can limit its general applicability, with inherent limitations for statistical analysis. Moreover, the overrepresentation of the male gender limited the generalization to the female population, even though they consist of a minority of these patients. Additionally, the study does not track the long-term progression of CKD beyond the initial follow-up period. Future studies with extended follow-up and detailed renal function assessments would be beneficial in evaluating how CKD progresses and affects patient outcomes beyond the scope of this study. On the other hand, the prospective design, extended follow-up, and similarity of the aortoiliac lesions are strengths of the current study. Furthermore, the inclusion of patients from both a large academic teaching institution and a community referral hospital enhances the external validity of the results, making them more applicable to "real-world" practice.

Conclusions

The findings of this prospective study underscore the ability of CKD to predict long-term MACE, AHF, and all-cause mortality in a population with TASC II type D lesions who underwent elective aortoiliac revascularization.

This emphasizes the elevated CV risk faced by CKD patients, highlighting the need for tailored perioperative interventions to optimize outcomes.

Given the significant impact of CKD on long-term survival, close monitoring and personalized care strategies are crucial for managing this high-risk group. Further prospective studies are needed to confirm these findings and improve clinical guidelines for CKD patients undergoing elective aortoiliac revascularization.

References

1. Wooten C, Hayat M, du Plessis M, Cesmebasi A, Koesterer M, Daly KP, *et al.* Anatomical significance in aortoiliac occlusive disease. Clin Anat 2014;27:1264–74.

2. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: similarities and differences. Prog Cardiovasc Dis 2007;50:112–25.

3. Heaton J, Khan YS. Aortoiliac Occlusive Disease. Treasure Island, FL: StatPearls; 2024.

4. Vogt MT, Wolfson SK, Kuller LH. Segmental arterial disease in the lower extremities: correlates of disease and relationship to mortality. J Clin Epidemiol 1993;46:1267–76.

5. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–6.

6. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5–67.

7. Aboyans V, Ricco JB, Bartelink ME, Björck M, Brodmann M, Cohnert T, *et al.* Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:305–68.

8. Nordanstig J, Behrendt CA, Baumgartner I, Belch J, Bäck M, Fitridge R, *et al.*; ESVS Guidelines Committee; Document Reviewers. Editor's Choice — European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. Eur J Vasc Endovasc Surg 2024;67:9–96.

9. Provenzano M, Coppolino G, Faga T, Garofalo C, Serra R, Andreucci M. Epidemiology of cardiovascular risk in chronic kidney disease patients: the real silent killer. Rev Cardiovasc Med 2019;20:209–20.

10. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation 2021;143:1157–72.

11. Carmena R, Ascaso JF, Redon J. Chronic kidney disease as a cardiovascular risk factor. J Hypertens 2020;38:2110–21.

12. Warrens H, Banerjee D, Herzog CA. Cardiovascular Complications of Chronic Kidney Disease: an Introduction. Eur Cardiol 2022;17:e13.

13. 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;351:1296–305.

14. Cofer LB, Soomro QH, Xia Y, Luttrell-Williams E, Myndzar K, Charytan DM, *et al.* Platelet Activity and Cardiovascular Risk in CKD and Peripheral Artery Disease. Kidney Int Rep 2022;7:2242–50.

15. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2004;109:320–3.

16. Serra R, Bracale UM, Ielapi N, Del Guercio L, Di Taranto MD, Sodo M, *et al.* The Impact of Chronic Kidney Disease on Peripheral Artery Disease and Peripheral Revascularization. Int J Gen Med 2021;14:3749–59.

17. Rocha-Neves J, Ferreira A, Sousa J, Pereira-Neves A, Vidoedo J, Alves H, *et al.* Endovascular Approach Versus Aortobifemoral Bypass Grafting: Outcomes in Extensive Aortoiliac Occlusive Disease. Vasc Endovascular Surg 2020;54:102–10.

18. Rashid R, Sohrabi C, Kerwan A, Franchi T, Mathew G, Nicola M, *et al.* The STROCSS 2024 guideline: strengthening the reporting of cohort, cross-sectional, and case-control studies in surgery. Int J Surg 2024;110:3151–65.

19. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, *et al.* Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1-73.

20. Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ, *et al.* Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg 2016;64:1–21.

21. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, *et al.*; GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. Eur J Vasc Endovasc Surg 2019;58(1S):S1, 109.e33.

22. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.*; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72:2231–64.

23. Ruetzler K, Smilowitz NR, Berger JS, Devereaux PJ, Maron BA, Newby LK, *et al.* Diagnosis and Management of Patients With Myocar-

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dial Injury After Noncardiac Surgery: A Scientific Statement From the American Heart Association. Circulation 2021;144:e287–305.

24. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR Jr, Robinson WP. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. J Vasc Surg 2018;68:1817–23.

25. Anagnostopoulos A, Mayer F, Ledergerber B, Bergadà-Pijuan J, Husmann L, Mestres CA, *et al.*; VASGRA Cohort Study. Editor's Choice - Validation of the Management of Aortic Graft Infection Collaboration (MAGIC) Criteria for the Diagnosis of Vascular Graft/Endograft Infection: Results from the Prospective Vascular Graft Cohort Study. Eur J Vasc Endovasc Surg 2021;62:251–7.

26. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179–84.

27. Kidney Disease: Improving Global Outcomes CKDWG. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2024;105(4S):117–314.

28. Kotov A, Blasche DA, Peters F, Pospiech P, Rother U, Stavroulakis K, *et al.* The Impact of Chronic Kidney Disease on Mid-Term Outcomes after Revascularisation of Peripheral Arterial Occlusive Disease: Results from a Prospective Cohort Study. J Clin Med 2022;11:4750.

29. Nóbrega L, Pereira-Neves A, Duarte-Gamas L, Dias PP, Azevedo-Cerqueira A, Ribeiro H, *et al.* Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease. Ann Vasc Surg 2022;79:153–61.

30. Vieira-Cardoso N, Pereira-Neves A, Fragão-Marques M, Duarte-Gamas L, Domingues-Monteiro D, Vidoedo J, *et al.* Red blood cell distribution width as a predictor of cardiovascular outcomes in extensive aortoiliac disease. J Cardiovasc Surg 2023;64:48–57.

31. Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, *et al.* Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 2012;157:471–81.

32. Glassock RJ, Rule AD. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. Nephron 2016;134:25–9.

33. Feldreich T, Nowak C, Carlsson AC, Östgren CJ, Nyström FH, Sundström J, *et al.* The association between plasma proteomics and incident cardiovascular disease identifies MMP-12 as a promising cardiovascular risk marker in patients with chronic kidney disease. Atherosclerosis 2020;307:11–5.

34. Tanriover C, Copur S, Mutlu A, Peltek IB, Galassi A, Ciceri P, *et al.* Early aging and premature vascular aging in chronic kidney disease. Clin Kidney J 2023;16:1751–65.

35. Nayor M, Larson MG, Wang N, Santhanakrishnan R, Lee DS, Tsao CW, *et al.* The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail 2017;19:615–23.

36. Kwon W, Choi KH, Song YB, Park YH, Lee JM, Lee JY, *et al.*; RENOVATE COMPLEX-PCI Investigators. Intravascular Imaging in Patients With Complex Coronary Lesions and Chronic Kidney Disease. JAMA Netw Open 2023;6:e2345554.

37. Reginelli JP, Mills RM. Non-cardiac surgery in the heart failure patient. Heart 2001;85:505–7.

38. Upshaw J, Kiernan MS. Preoperative cardiac risk assessment for noncardiac surgery in patients with heart failure. Curr Heart Fail Rep 2013;10:147–56.

39. Smit-Fun V, Buhre WF. The patient with chronic heart failure undergoing surgery. Curr Opin Anaesthesiol 2016;29:391–6.

40. Botelho FE, Flumignan RL, Shiomatsu GY, de Castro-Santos G, Cacione DG, Leite JO, *et al.* Preoperative coronary interventions for preventing acute myocardial infarction in the perioperative period of major open vascular or endovascular surgery. Cochrane Database Syst Rev 2024;7:CD014920.

41. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, *et al.* G Ital Cardiol (Rome) 2023;24(Suppl 1):1–102.

42. Li X, Lindholm B. Cardiovascular Risk Prediction in Chronic Kidney Disease. Am J Nephrol 2022;53:730–9.

43. Llauger L, Jacob J, Miró Ò. Renal function and acute heart failure outcome. Med Clin (Barc) 2018;151:281–90.

44. Sheth T, Chan M, Butler C, Chow B, Tandon V, Nagele P, *et al.*; Coronary Computed Tomographic Angiography and Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study Investigators. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. BMJ 2015;350:h1907.

45. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, *et al.*; Conference Participants. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:1304–17.

46. Ryan DK, Banerjee D, Jouhra F. Management of Heart Failure in Patients with Chronic Kidney Disease. Eur Cardiol 2022;17:e17.

47. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int 2003;64:610–5.

48. Li K, Ferguson T, Embil J, Rigatto C, Komenda P, Tangri N. Risk of Kidney Failure, Death, and Cardiovascular Events After Lower Limb Complications in Patients With CKD. Kidney Int Rep 2020;6:381–8.

49. Smilowitz NR, Redel-Traub G, Hausvater A, Armanious A, Nicholson J, Puelacher C, *et al.* Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. Cardiol Rev 2019;27:267–73.

50. Pereira-Macedo J, Machado N, Pereira-Neves A, Ferreira V, Oliveira-Pinto J, Dias-Neto M, *et al.* Myocardial injury after aortoiliac revascularization for extensive disease: A survival analysis. Turk Gogus Kalp Damar Cerrahisi Derg 2020;28:426–34.

51. Duceppe E, Borges FK, Tiboni M, Pearse R, Chan MT, Srinathan S, *et al.* High-Sensitivity Cardiac Troponin I Thresholds to Identify Myocardial Injury After Noncardiac Surgery: A Cohort Study. Can J Cardiol 2023;39:311–8.

52. Kampmann J, Heaf J, Backer Mogensen C, Pedersen AK, Granhøj J, Mickley H, *et al.* Troponin Cut-Offs for Acute Myocardial Infarction in Patients with Impaired Renal Function-A Systematic Review and Meta-Analysis. Diagnostics (Basel) 2022;12:276.

53. Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, *et al.* Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. Ann Intern Med 2014;161:502–12.

54. Paisley MJ, Adkar S, Sheehan BM, Stern JR. Aortoiliac occlusive disease. Semin Vasc Surg 2022;35:162–71.

55. Huber M, Ozrazgat-Baslanti T, Thottakkara P, Scali S, Bihorac A, Hobson C. Cardiovascular-Specific Mortality and Kidney Disease in Patients Undergoing Vascular Surgery. JAMA Surg 2016;151:441–50.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Mariana Alves, Ana-Daniela Pias, Joana Marques, Conceição Miranda and João Rocha-Neves have participated to drafting of the manuscript; Mariana Alves, Ana-Daniela Pias, Joana Marques, Conceição Miranda, António Pereira-Neves, Mohammed Shahat, José Vidoedo, José P. Andrade, João Rocha-Neves and

Ana Marreiros provided critical revisions; João Rocha-Neves have given substantial contribution to the conception and the design of the manuscript and helped supervised the project; Mariana Alves, Ana-Daniela Pias, Joana Marques, Conceição Miranda, João Rocha-Neves and Ana Marreiros verified the analytical methods and analysed the data; Mariana Alves and Ana-Daniela Pias equally contributed to this paper as first authors. All authors read and approved the final version of the manuscript.

History
Article first published online: _____. - Manuscript accepted: December 4, 2024. - Manuscript revised: November 7, 2024. - Manuscript received: June 19, 2024.

Supplementary data
For supplementary materials, please see the HTML version of this article at www.minervamedica.it

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4. Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease

Reference to the published version:

Pereira-Neves A, Rocha-Neves J, Costa-Pereira T, Ribeiro H, Dias LR, Duarte-Gamas L, Andrade JP. Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease.

Front Med (Lausanne). 2025 Sep 17;12:1655229. doi: 10.3389/fmed.2025.1655229.

Impact Factor: 3.0 (2024)

Quartile: Q1 (Scimago, 2024); Q1 (JCR, 2024)

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TYPE Original Research
PUBLISHED 17 September 2025
DOI 10.3389/fmed.2025.1655229

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RECEIVED 27 June 2025
ACCEPTED 05 September 2025
PUBLISHED 17 September 2025

CITATION
Pereira-Neves A, Rocha-Neves J, Costa-Pereira T, Ribeiro H, Dias LR, Duarte-Gamas L and Andrade JP (2025) Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease. *Front. Med.* 12:1655229. doi: 10.3389/fmed.2025.1655229

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Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease

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Introduction: Extensive lower limb arterial calcification complicates revascularization and is linked to poor outcomes, including limb loss and cardiovascular events. Standardized scoring systems are lacking, particularly in aortoiliac TASC II D lesions. This study evaluated the prognostic value of a CT-based Iliac Calcium Score (ICS) in predicting major adverse limb events (MALE), cardiovascular events (MACE), and all-cause mortality in patients with severe aortoiliac disease.

Methods: In this prospective cohort (2013–2024), 109 patients with TASC II D aortoiliac occlusive disease underwent elective revascularization and preoperative CT angiography. Iliac artery calcification was scored semiquantitatively by morphology, circumference, and lesion length. Patients were stratified into low ($\leq$ 36) and high ($\geq$ 37) ICS groups. Outcomes included MALE, MACE, and mortality, analyzed using Kaplan-Meier and Cox regression.

Results: The study included 109 patients (95.4% male) with a median follow-up of 67 months. Baseline characteristics were similar across ICS groups, though ICS $\geq$ 37 was associated with more advanced Rutherford stages (p = 0.035). At 30 days, both groups improved clinically, but Rutherford class improvement was greater in the ICS $\leq$ 36 group (p = 0.013), with no other significant differences. At 1 year, MALE was more frequent in patients with ICS $\geq$ 37 (48.1% vs. 27.3%; p = 0.024). At 60 months, this group showed significantly lower amputation-free (74.5% vs. 97.8%; p = 0.002), MACE-free (47.3% vs. 73.4%; p = 0.005), and overall survival (54.6% vs. 77.0%; p = 0.013). Acute heart failure occurred only in the high ICS group (p = 0.015), while patency rates were similar. ICS $\geq$ 37 remained an independent predictor of MACE (aHR 2.30; p = 0.008) and major amputation (aHR 7.52; p = 0.008) in multivariable analysis.

Conclusion: In patients with extensive TASC II D aortoiliac occlusive disease, an ICS $\geq$ 37 was independently associated with increased long-term risk of MACE,

MALE, and reduced overall survival, despite similar short-term outcomes. These findings support the integration of preoperative calcium scoring as a simple, lesion-specific tool for risk stratification, procedural planning, and personalized postoperative surveillance in complex peripheral arterial disease.

KEYWORDS

peripheral artery disease, arterial calcification, TASC II, revascularization, amputation, cardiovascular outcomes

Highlights

- Calcium score $\geq$ 37 independently predicted limb loss and cardiovascular mortality, with a 7.5-fold higher amputation risk and 2.3-fold higher major adverse cardiovascular event risk ($p < 0.01$).
- Late divergence in survival curves (e.g., acute heart failure and mortality after 24 months) suggests calcification may contribute to progressive systemic vascular dysfunction.
- Primary/secondary patency pattern similarities suggest that calcification impacts long-term clinical outcomes more than procedural success, highlighting the need for post-intervention monitoring.

Introduction

Coronary artery calcium (CAC) scoring has become a cornerstone in coronary heart disease risk stratification, with robust evidence supporting its incremental prognostic value beyond traditional risk factors and also for cardiovascular risk stratification (1, 2). Moreover, a systematic review and meta-analysis demonstrated that CAC scoring improves discrimination for cardiovascular events [pooled C-statistic gain: 0.036 (95% CI 0.020–0.0520)] while highlighting limitations in cost-benefit ratios for routine use (3). Coronary artery calcium (CAC) scores were significantly associated with biological aging, with scores > 400 adding up to 30 years to predicted age in younger individuals, while scores < 10 reduced biological age by up to 10 years in older patients; calcium-adjusted age reclassified 55% of low-risk and 45% of intermediate-risk individuals (by Framingham score) into higher-risk categories, improving mortality prediction beyond observed age ($p < 0.0001$) (4).

In peripheral artery disease (PAD), extensive aortoiliac occlusive disease, classically classified as TransAtlantic Inter-Society Consensus (TASC) II type D aortoiliac lesions, presents unique challenges. While open surgery remains the gold standard, endovascular and hybrid approaches show comparable mid-term patency rates (85% at 5 years) with lower perioperative risks in high-comorbidity patients (5–7). In this complex aortoiliac disease, characterized by extensive occlusions or calcifications involving the distal aorta and bilateral iliac arteries, vascular calcification exacerbates technical challenges during revascularization, especially with endovascular techniques.

The pathophysiology of lower limb arterial calcification (LLAC) in aortoiliac disease involves both intima and media layers, with distinct clinical implications. While intimal calcification is classically linked to atherosclerosis and inflammatory processes, predominating in patients with traditional risk factors (e.g., smoking, hyperlipidemia), medial calcification is systematically regulated and linked to diabetes, chronic kidney disease (CKD), and aging-related reduction in arterial compliance, exacerbating hemodynamic impairment and limb ischemia (8–11).

In the iliac arteries, calcification predominantly localizes to the intima in atherosclerotic plaques, but medial calcification coexists in patients with metabolic comorbidities, amplifying cardiovascular risk (9, 10). This dual calcification pattern mirrors findings in femoral and tibial arteries, where medial calcification correlates strongly with advanced ischemia severity and limb-related morbidity (11–13).

Emerging evidence suggests that scoring LLAC could refine PAD management. Studies in PAD populations associate elevated calcium scores with limb-related events, including major amputations (12, 14), but also with cardiovascular events, including all-cause mortality (15).

Despite its clinical relevance to revascularization outcomes and amputation risk, LLAC lacks standardized quantification. Current methods range from qualitative visual scores like Peripheral Arterial Calcium Scoring System (PACSS) to adapted Agatston protocols, creating heterogeneity in research and clinical applications (9, 14, 16, 17). Furthermore, despite their complexity and clinical relevance, no validated calcium scoring system currently exists for TASC II type D aortoiliac lesions.

This study aims to evaluate the prognostic value of a standardized lower limb calcium scoring system in predicting outcomes such as major adverse limb events (MALE), MACE, and all-cause mortality, helping to optimize risk stratification and guide therapeutic decisions in this high-risk population.

Materials and methods

Patient selection

A total of 180 consecutive patients who underwent elective aortoiliac revascularization between January 2013 and January 2024 were included in a prospective cohort. All patients were selected from a tertiary and a community hospital and had aortoiliac TASC II type D lesions, excluding those with aortoiliac aneurysmatic

disease (18). The choice between open surgery and an endovascular procedure was made by a shared decision between the patient and the surgeon, considering the surgeon and the institution's experience and preferences.

A *post hoc* analysis was performed, including only patients who had undergone preoperative computed tomography (CT). Of the initial 180 patients, only 109 had preoperative CT and were included in the final analysis (Figure 1). Among baseline comorbidities, the only statistically significant difference between included and excluded patients was a higher prevalence of smoking in the included cohort (95.4% vs. 85.9%, $p = 0.024$) (Supplementary Table 1).

The patients' demographic and clinical profiles — encompassing cardiovascular risk factors as well as procedural and lesion-specific information — were obtained through a review of their medical records, including data on whether a CT scan had been performed (7). Further information regarding the type of lesion is described elsewhere (18). Patients underwent evaluation during the initial 30 days following the procedure and throughout the subsequent long-term follow-up period, which included regular clinical and hemodynamic assessments in an outpatient setting. This study is under the framework of the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2019 Guideline (19).

The local Ethics Committee approved the study protocol and respects the Declaration of Helsinki. Patient informed consent was handled accordingly, and all data processing was anonymous (Protocol Number 246-18). It respects the European Union General Data Protection Regulation (GDPR).

Definitions and outcomes

Retrieved data was registered in agreement with the *Reporting Standards* of the *Society for Vascular Surgery* for lower extremity ischemia (20). The Rutherford chronic ischemia classification was used to classify the symptoms and severity of chronic lower extremity ischemia (21).

The primary outcome was long-term MACE, defined as a composite outcome, including myocardial infarction (MI), acute heart failure (AHF), and all-cause mortality (22). MALE was described as a composite of reintervention, including reintervention due to primary assisted patency, secondary patency, major amputation of the revascularized artery segment, and occlusion without intervention (23).

Imagiological parameters

Iliac artery calcification was quantified by two independent operators using a validated CT-based semiquantitative scoring system, which evaluates three distinct features: morphology, circumferential involvement, and length of calcification. Axial CT images with 5 mm slice thickness and bone window settings (width 3077 HU; level 570 HU) were analyzed by experienced vascular surgeons and non-contrast CT slices acquired before contrast injection were used for quantification. Each iliac arterial segment (common and external, bilaterally) was scored separately. Morphology was graded from 0 to 3, with 0 indicating no calcification, 1 representing thin linear calcifications $\leq$ 1 mm ("eggshell" type), two corresponding to thick linear calcifications $>$ 1 mm with convex margins, and 3 indicating bulky calcifications $>$ 2 mm with convex luminal margins. Circumferential and length involvement were each scored from 0 to 4, based on percentage involvement (0 = none; 1 = 1%–25%; 2 = 26%–50%; 3 = 51%–75%; 4 = 76%–100%). The highest value in each segment was recorded (24). The final score by patient was calculated by adding the scores from each of the four iliac segments.

Statistical analysis

The sample size for a survival test was calculated using online Sample Size Calculators for Designing Clinical Research,[1] with a statistical power (β) of 80% and a significance level of 0.05. The sample size (95 patients) was estimated based on an expected hazard ratio of 2, for cardiovascular events, between groups and a projected 80% event-free survival rate at the end of follow-up (7, 25, 26).

Statistical analyses were performed using SPSS (IBM Corp., released 2023. IBM SPSS Statistics for Windows, version 29.0.2.0, Armonk, NY, United States). Continuous variables were assessed for normality using histograms and skewness. Normally distributed variables were reported as mean ± standard deviation (SD), and comparisons between groups were performed using the independent samples *t*-test. Non-normally distributed continuous variables were reported as median and interquartile range (IQR), and compared using the Mann-Whitney U test. When appropriate, categorical variables were presented as frequencies and percentages and compared using the chi-square or Fisher's exact test.

To facilitate the interpretation and clinical applicability of the Iliac Calcium Score (ICS), dichotomization was performed using visual binning rather than Receiver Operating Characteristic (ROC) analysis. A threshold of 36.5 was selected based on observed data distribution and clinical reasoning, corresponding to the point of greatest contrast in event rates (MACE) between groups. This cut-off was then used to stratify patients into low ($\leq$ 36) and high ($\geq$ 37) ICS groups for further analysis.

Kaplan-Meier survival analyses were conducted to evaluate time-to-event outcomes, including MACE, MALE, and all-cause mortality. Log-rank tests were used to compare survival curves between groups.

The Log Rank estimator was utilized to test the effect of the ICS on time-dependent variables. Multivariate Cox regression analysis was performed for independent predictors of long-term MACE and all-cause mortality, using the backward stepwise regression method. The backward stepwise regression method was applied, and variables with $p < 0.20$ were included.

All statistical tests were two-sided; a p-value < 0.05 was considered statistically significant.

1 https://sample-size.net/sample-size-survival-analysis/

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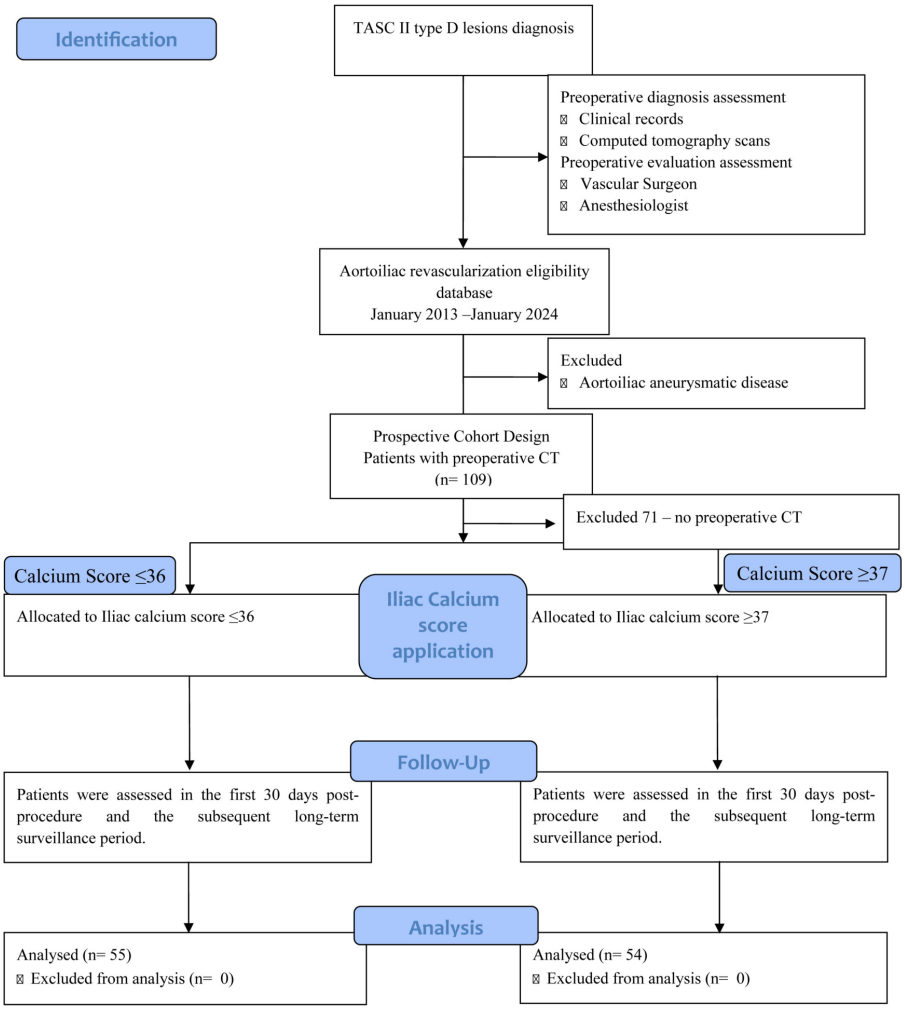

FIGURE 1
Flowchart of patient selection and cohort allocation.

Results

Population data

The cohort included 109 patients with a median follow-up of 67 (IQR 56.2–77.8) months. Table 1 presents the baseline characteristics of the patients included, stratified by ICS ($\leq$ 36 vs. $\geq$ 37), with 55 patients and 54 patients, respectively. Most patients were male (95.4%), with similar distribution between groups (92.7% vs. 98.1%; p = 0.363). Although the two groups did not differ significantly in most comorbidities, patients with higher calcium scores ($\geq$ 37) presented a trend for hypertension (77.8% vs. 61.8%; p = 0.070) and had a higher prevalence of chronic kidney disease (13.0% vs. 5.5%; p = 0.175) and chronic heart failure (CHF) (13.0% vs. 5.5%; p = 0.175), albeit without reaching statistical significance.

Notably, a significant difference was observed in the distribution of Rutherford classification (p = 0.035), with advanced stages (V and VI) being more frequent in the higher calcium score group. Overall, approximately 75% of the cohort presented with chronic limb-threatening ischemia.

The majority of procedures were open surgery (64.2%), followed by endovascular (26.6%) and hybrid (9.2%), with no significant differences between ICS groups (p = 0.103). The mean preoperative ABI was 0.30 $\pm$ 0.120, slightly higher in the ICS $\leq$ 36 group (0.31 $\pm$ 0.133) than in the ICS $\geq$ 37 group (0.29 $\pm$ 0.107; p = 0.065).

TABLE 1 Patient's demographics and comorbidities.

Characteristics	Total n = 109 (%)	Iliac Calcium Score ≤ 36 n = 55	Iliac Calcium Score ≥ 37 n = 54	P-value
Age, years (mean ± SD)	62.0 ± 8.70	59.8 ± 8.55	64.2 ± 8.33	0.989
Gender, male	104 (95.4)	51 (92.7)	53 (98.1)	0.363
Smoking history	104 (95.4)	54 (98.2)	50 (92.6)	0.206
Hypertension	76 (69.7)	34 (61.8)	42 (77.8)	0.070
Dyslipidemia	79 (72.5)	39 (70.9)	40 (74.1)	0.711
Diabetes	29 (26.6)	12 (21.8)	17 (31.5)	0.254
CKD	10 (9.2)	3 (5.5)	7 (13.0)	0.175
CAD	29 (26.6)	12 (21.8)	17 (31.5)	0.254
CVD	16 (14.7)	8 (14.5)	8 (14.8)	0.968
COPD	12 (11.0)	7 (12.5)	5 (9.3)	0.563
CHF	10 (9.2)	3 (5.5)	7 (13.0)	0.175
ASA				
III	46 (42.2)	23 (41.8)	23 (42.6)	0.356
IV	58 (53.2)	31 (56.4)	27 (50.0)	
V	5 (4.6)	1 (1.8)	4 (7.4)	
Rutherford classification				
3	28 (25.7)	18 (32.7)	10 (18.5)	**0.035**
4	45 (41.3)	24 (43.6)	21 (38.9)	
5	29 (26.6)	13 (23.6)	16 (29.6)	
6	7 (6.4)	0 (0.0)	7 (13.0)	
Open surgery	70 (64.2)	39 (70.9)	31 (57.4)	0.103
Endovascular technique	29 (26.6)	14 (25.5)	15 (27.8)	
Hybrid surgery	10 (9.2)	2 (3.6)	8 (14.8)	
ABI, (mean ± SD)	0.30 ± 0.120	0.31 ± 0.133	0.29 ± 0.107	0.065

Variables are presented as N (%) unless otherwise specified. ABI, Ankle-brachial index (preoperative); ASA, American Society of Anesthesiologists Physical Status Classification System; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease (creatinine = 1.5 mg/dl); COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; SD, standard deviation. Bold value represents statistically significant results ($p < 0.05$).

TABLE 2 Patient's 30 days outcomes according to iliac calcium score.

	Total n = 109 (%)	Iliac Calcium Score ≤ 36 n = 55	Iliac Calcium Score ≥ 37 n = 54	P-value
AKI	13 (11.9)	6 (10.9)	7 (13.0)	0.765
ABI Δ, (mean ± SD)	0.43 ± 0.235	0.48 ± 0.241	0.37 ± 0.218	0.167
Rutherford Δ, (mean ± SD)	2.6 ± 1.41	−2.9 ± 1.10	−2.4 ± 1.61	**0.013**
ICU (days), (median–IQR)	2 (0–3)	2 (0.5–3)	1 (0–3)	0.710*
Ward (days), (median–IQR)	7 (4–17.75)	6 (3–11.5)	10 (4–21)	0.131*
MINS	19 (17.4)	9 (16.4)	10 (18.5)	0.645
MALE	24 (22.0)	9 (16.4)	15 (27.8)	0.150
MACE	11 (10.1)	7 (12.7)	4 (7.4)	0.357
All cause-mortality	6 (5.5)	4 (7.3)	2 (3.7)	0.679

*Non-parametric test. Variables are presented as N (%) unless otherwise specified. ABI, Ankle-brachial index Δ - postoperative minus preoperative; AKI, Acute kidney injury; Rutherford chronic ischemia Δ, preoperative minus postoperative; MACE, major adverse cardiovascular event; MALE, major adverse limb event; MINS, myocardial injury after non-cardiac surgery;ICU, in stay on intensive care unit; IQR, interquartile range. Bold value represents statistically significant results ($p < 0.05$).

Thirty-day outcomes according to ICS

Table 2 summarizes the 30 days outcomes. The mean change in ABI was 0.43 ± 0.235 (0.48 ± 0.241 in ICS ≤ 36 vs. 0.37 ± 0.218 in ICS ≥ 37; p = 0.167). Although both groups showed clinical improvement in the Rutherford chronic ischemia classification (Δ = −2.6 ± 1.41), patients with lower calcium scores exhibited a significantly greater mean improvement (Δ = −2.9 ± 1.10 vs. −2.4 ± 1.61, p = 0.013). Median intensive care unit (ICU) stay was 2 days (IQR 0–3), with no significant difference between groups (p = 0.710). Median ward stay was seven days (IQR 4–17.75), also similar between groups (p = 0.131).

TABLE 3 Patient's 1 year outcomes according to iliac calcium score.

	Total n = 109 (%)	Iliac Calcium Score ≤ 36 n = 55	Iliac Calcium Score ≥ 37 n = 54	P-value
Prosthetic infection	6 (5.5)	3 (5.5)	3 (5.5)	0.981
MALE	41 (37.6)	15 (27.3)	26 (48.1)	**0.024**
MACE	22 (20.2)	9 (16.4)	13 (24.1)	0.316
All cause-mortality	18 (16.5)	7 (12.7)	11 (20.4)	0.283

Variables are presented as N (%) unless otherwise specified. MACE, major adverse cardiovascular event; MALE, major adverse limb event. Bold value represents statistically significant results ($p < 0.05$).

TABLE 4 Cox multivariable regression proportional hazard ratio for major adverse cardiovascular events and major lower limb amputation.

	Non-adjusted hazard ratios	95% confidence interval	P-value	Adjusted hazard ratios	95% confidence interval	P-value
MACE						
Hypertension	1.325	0.768–2.286	0.312	NC	–	–
CKD	2.708	1.478–4.962	< 0.001	NC	–	–
CHF	3.485	1.954–6.215	< 0.001	2.604	1.147–5.908	0.022
ICS ≥ 37	2.310	1.256–4.250	0.007	2.296	1.246–4.229	0.008
ICS (cont)	1.035	1.005–1.066	0.021	1.036	1.006–1.068	0.020
MLLA						
Hypertension	2.424	0.714–8.242	0.156	NC	–	–
CKD	2.521	0.841–7.560	0.099	NC	–	–
CHF	1.693	0.494–5.803	0.402	NC	–	–
ICS ≥ 37	7.521	1.693–33.409	0.008	7.521	1.693–33.409	0.008
ICS (cont)	1.142	1.030–1.26	0.011	1.142	1.030–1.26	0.011

CHF chronic heart failure; CKD, chronic kidney disease (creatinine = 1.5 mg/dl); ILC, Iliac Calcium Score; MACE, major adverse cardiovascular event; MLLA, major lower limb amputation; NC, not confirmed; cont, continuous variable.

The incidence of acute kidney injury (AKI) was 11.9% overall (10.9% vs. 13.0%; $p = 0.765$). The incidence of myocardial injury after non-cardiac surgery (MINS) was 17.4% (16.4% vs. 18.5%; $p = 0.645$), MALE 22.0% (16.4% vs. 27.8%; $p = 0.150$), MACE 10.1% (12.7% vs. 7.4%; $p = 0.357$), and all cause-mortality 5.5% (7.3% vs. 3.7%; $p = 0.679$).

One-year outcomes according to ICS

Table 3 shows the 1 year outcomes. Prosthetic infection occurred in 5.5% of patients, equally distributed between groups (5.5% vs. 5.5%; $p = 0.981$). Patients with higher ICS (≥ 37) experienced a significantly greater incidence of MALE compared to those with lower scores (48.1% vs. 27.3%, $p = 0.024$). Although higher rates of MACE and all-cause mortality were observed in the high ICS group (24.1% vs. 16.4% and 20.4% vs. 12.7%, respectively), these differences were not statistically significant ($p = 0.316$ and $p = 0.283$, respectively).

Multivariable analysis of predictors for MACE and major lower limb amputation

Table 4 presents the Cox proportional hazards regression analysis results for MACE and major lower limb amputation (MLLA).

For MACE, unadjusted analysis revealed that CKD (HR 2.708, 95% CI 1.478–4.962, $p < 0.001$), CHF (HR 3.485, 95% CI 1.954–6.215, $p < 0.001$), and an ICS ≥ 37 (HR 2.310, 95% CI 1.256–4.250, $p = 0.007$) were significant predictors. After adjustment, CHF (adjusted HR 2.604, 95% CI 1.147–5.908, $p = 0.022$) and calcium score ≥ 37 (adjusted HR 2.296, 95% CI 1.246–4.229, $p = 0.008$) remained independently associated with increased MACE risk.

For MALE, CHF was a significant predictor (adjusted HR 2.116, 95% CI 1.105–4.052, $p = 0.024$), while calcium score did not reach statistical significance in the adjusted model.

For MLLA, ICS ≥ 37 was strongly associated with increased risk both in unadjusted (HR 7.521, 95% CI 1.693–33.409; $p = 0.008$) and adjusted models (aHR 7.521, 95% CI 1.693–33.409; $p = 0.008$).

The continuous calcium score variable was also significant for MACE (aHR 1.035, 95% CI 1.005–1.066; $p = 0.021$) and MLLA (aHR 1.142, 95% CI 1.030–1.260; $p = 0.011$).

Survival analysis

Limb-related outcomes

Kaplan-Meier analysis revealed significantly lower amputation-free survival in patients with calcium scores ≥ 37 vs. ≤ 36 (log-rank $p = 0.002$), with 60 months rates of 74.5% vs. 97.8% (Figure 2A). MALE trended higher in the ≥ 37 group (50.8% vs. 62.5% survival; $p = 0.139$) (Figure 2D), while primary/secondary patency rates showed no significant differences (Figures 2B, C).

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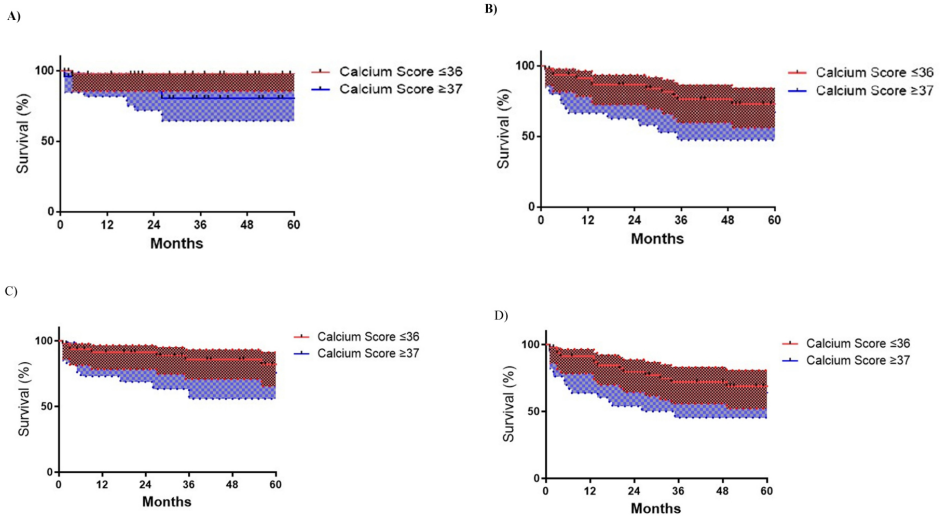

FIGURE 2
Kaplan-Meyer limb outcomes survival curves according to Iliac Calcium Score cut-off ≥ 37 status. **(A)** Major Lower limb amputation (MLLA) ($p = 0.002$); **(B)** Primary patency ($p = 0.193$); **(C)** Secondary patency ($p = 0.233$); **(D)** Major adverse limb events (MALE) ($p = 0.139$).

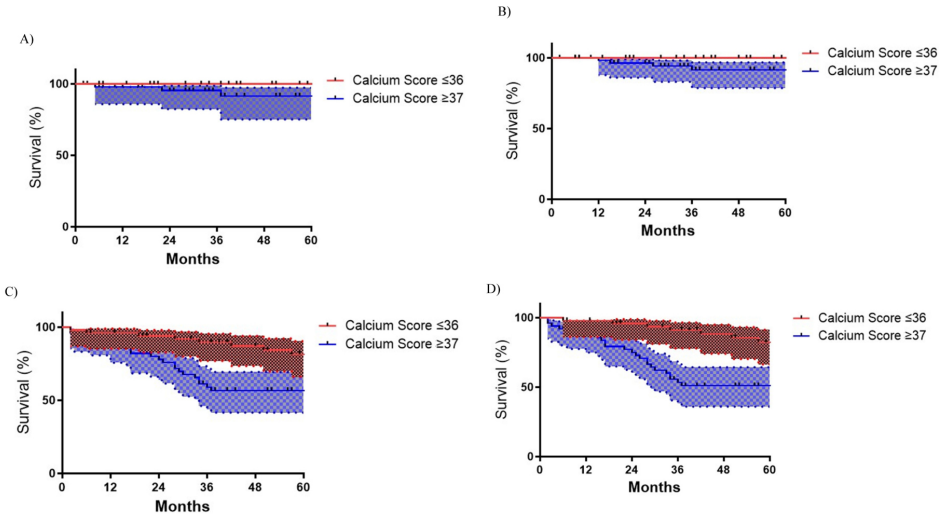

FIGURE 3
Kaplan-Meyer cardiovascular outcomes survival curves according to Iliac Calcium Score cut-off ≥ 37 status. **(A)** Acute myocardial infarction (AMI) ($p = 0.407$); **(B)** Acute heart failure (AHF) ($p = 0.015$); **(C)** All-cause mortality ($p = 0.013$); **(D)** Major adverse cardiac events (MACE) ($p = 0.005$).

Cardiovascular outcomes

Patients with ICS ≥ 37 exhibited significantly worse cardiovascular outcomes, including a higher risk of MACE (log-rank $p = 0.005$), with 60-month MACE-free survival rates of 47.3% compared to 73.4% in the ≤ 36 group (Figure 3D) and higher risk of all-cause mortality (log-rank, $p = 0.013$), with 60-month survival rates of 54.6% versus 77.0% (Figure 3C). Notably, AHF occurred exclusively in the ≥ 37 group, where AHF-free survival at 60 months was 87.7% compared to 100% in the ≤ 36 group ($p = 0.015$) (Figure 3B). Acute myocardial injury (AMI) rates showed no significant differences (Figure 3A).

Discussion

This study demonstrates that a standardized ICS ≥ 37 could be considered a prognostic marker for 1 year and midterm adverse limb and cardiovascular outcomes in patients with TASC D aortoiliac disease undergoing revascularization. However, calcium burden does not seem to significantly impact short-term survival and perioperative complications. Elevated calcium burden was independently associated with a 2.3-fold increased risk of MACE and a striking 7.5-fold higher risk of major lower limb amputation over time. The threshold effect was particularly pronounced in longitudinal outcomes, with patients scoring ≥ 37 in the ICS exhibiting significantly reduced amputation-free survival (74.5% vs. 97.8% at 60 months) and cardiovascular event-free survival (47.3% vs. 73.4%). Notably, calcium burden correlated with advanced baseline ischemia severity and attenuated clinical improvement in Rutherford classification, underscoring its dual role as both a marker of anatomical complexity and a predictor of functional recovery.

The findings that higher calcium scores are associated with more advanced Rutherford stages (5 and 6) are consistent with previous studies that have identified a link between arterial calcification and the severity of limb ischemia. In a study of 116 patients, increasing Rutherford categories were independently associated with higher calcification scores, even after adjusting for cardiovascular risk factors and the extent of occlusive disease (11). Similarly, another study demonstrated that patients with Rutherford stages 5–6 had significantly higher iliac calcification scores compared to those with milder ischemia (stages 1–2) (13). Huang et al. (8) also reported that patients with more advanced Fontaine stages tended to have significantly higher calcification scores, further supporting the association between calcification burden and clinical severity. These findings reinforce the prognostic significance of calcium scoring in assessing lower limb ischemia.

At 30 days follow-up, the cohort with higher calcification score demonstrated attenuated improvement in Rutherford classification post-revascularization, with no significant differences in other limb-related outcomes or adverse cardiovascular events. These results are partially consistent with those of Megale et al. (12), who also reported no significant association between aortic calcium scores and 30 days mortality ($p = 0.679$), patency ($p = 0.167$), or technical success ($p = 0.103$) across 14 interventions in 11 patients. However, in contrast to our findings, Megale et al. observed a significantly higher calcium score in patients who required amputation (5,767.6 vs. 805.3; $p = 0.02$) or underwent subsequent revascularization (3,686.8 vs. 645.2; $p = 0.008$) within 30 days. These comparisons suggest that while calcification burden may influence early clinical recovery, its association with short-term major events remains inconsistent.

While no procedural preference differences were found ($p = 0.103$), this may reflect center-specific strategies rather than calcium's technical irrelevance. Our cohort's high open surgery rate (64.2%) might mask this relationship, as bypass grafting may circumvent calcification-related challenges. While Megale et al. (15) also did not find any statistical difference, Kang et al. on the other hand, in a cohort with 124 patients, reported that technical success of infra-popliteal angioplasty was significantly lower in patients with extensive tibial artery calcification (71.1%) compared to those with minimal (95.3%) or intermediate calcification (91.7%) ($p = 0.001$), with extensive calcification emerging as an independent predictor of technical failure ($p = 0.014$) (10).

In this study, no significant differences were observed in primary or secondary patency rates between patients with high versus low calcium scores, both in short-term (30 days) and long-term follow-up (up to 60 months), which may reflect our high open surgery rate (64.2%) but aligning with the findings of Megale et al., which included patients submitted to both open and endovascular techniques, who also reported no significant association between calcium score and patency at any time point (12, 15). However, a more anatomically focused study which included 733 limbs submitted to drug-coated balloon (DCB) angioplasty for *de novo* femoropopliteal lesions, demonstrated that femoropopliteal lesions with bilateral calcification ≥ 5 cm [peripheral artery calcification scoring system (PACSS) 4] had significantly lower 1 year primary patency (82.6%; $p < 0.001$), with PACSS 4 emerging as an independent predictor of restenosis (HR 1.82; 95% CI 1.15–2.87; $p = 0.010$), suggesting that the pattern and extent of calcification may play a relevant role in long-term durability of revascularization with DCB (27).

Regarding amputation, this study data showed robust association with a significantly lower major amputation-free survival in patients with calcium scores ≥ 37 (74.5% vs. 97.8% at 60 months; log-rank $p = 0.002$), in agreement with previous studies linking extensive calcification to worse limb outcomes, albeit some exceeding rates likely reflecting our cohort's critical ischemia severity. For instance, Huang et al. (8) reported a 2.88-fold increased risk of amputation in patients in the highest calcium score quartile (95% CI 1.18–12.72; $p = 0.03$), and Kang et al. (10) found that patients with extensive tibial calcification had significantly lower 2 years amputation-free survival (Extensive Calcification: 58.9% vs. Minimal Calcification: 79.0% vs. Intermediate Calcification: 95.3%; $p < 0.001$), with extensive calcification being an independent predictor (HR 9.90; 95% CI 2.05–47.75; $p = 0.004$). Similarly, Dong et al. (28) identified tibial artery annular calcification as an independent predictor of unplanned amputation (HR 3.74; 95% CI 1.71–8.19; $p = 0.001$), reinforcing the importance of the calcification pattern.

In terms of MALE, a significantly higher incidence was observed at 1 year in patients with higher calcium scores (48.1% vs. 27.3%; $p = 0.024$), although this association did not remain significant in adjusted analysis. These results likely reflect the persistent significance of major amputations over time, while the lack of sustained differences in primary/secondary patency rates may have diluted the composite MALE outcome's statistical significance in adjusted models. This suggests that calcification's strongest prognostic impact, measured through ICS, lies in irreversible limb loss rather than revascularization-dependent endpoints in the aortoiliac population, and since distal vessel disease were not systematically included in the analysis, ICS may serve as a reflection of the overall systemic arterial calcification burden, including in the lower limbs. This trend is supported by findings from Megale et al., where higher below-the-knee calcium scores were associated with MALE both at 30 days (679.4 vs. 158.9; $p = 0.019$) and 1 year (910.1 vs. 12.3; $p = 0.002$) (12).

Patients with higher ICS (≥ 37) experienced significantly worse cardiovascular outcomes over time in this cohort. At 5 years,

10.3389/fmed.2025.1655229

MACE-free survival was markedly lower in the high calcium group compared to those with lower scores (47.3% vs. 73.4%; log-rank $p = 0.005$), and all-cause mortality was also higher (54.6% vs. 77.0%; log-rank $p = 0.013$). Notably, acute heart failure (AHF) occurred exclusively in the high calcium group, with 60 months heart failure-free survival rates of 87.7% versus 100% in the lower calcium group ($p = 0.015$). Although rates of acute myocardial injury did not differ significantly between groups, as opposite to AHF and all-cause mortality, multivariable analysis confirmed that a calcium score ≥ 37 remained an independent predictor of MACE (adjusted HR 2.30, 95% CI 1.25–4.23; $p = 0.008$), even after adjusting for comorbidities. These findings underscore the prognostic value of arterial calcification for long-term cardiovascular morbidity and mortality in this population. In the study published by Huang et al. (8), patients in the highest calcium score quartile had a 5.16-fold (95% CI 1.13–21.61, $p = 0.04$) increased risk of death compared to those in the lowest quartile. Similarly, annular tibial artery calcification has been identified as a robust predictor of all-cause mortality (HR = 3.19) (28), and complete annular calcification in crural or femoropopliteal arteries independently predicted 10 years mortality (29). Kang et al. (10) also reported that survival free of MACE was significantly higher in the lowest calcification score group ($p = 0.028$). More recently, Megale et al. (15) reported among 72 patients and 88 lower limb revascularizations that the calcium score of the operated limb was higher in patients who died within 30 days and 6 months (6571 vs. 2590.6; $p = 0.026$) and (5227.8 vs. 2335.3; $p = 0.036$). Additionally, in a cohort of 84 patients, higher ICS had significantly lower left ventricular ejection fraction, with a moderate inverse correlation between the two ($r = -0.54$; $p < 0.0001$) (13). Collectively, these data reinforce the prognostic value of arterial calcification as a marker of systemic cardiovascular risk in this patient population.

As above described, several studies have demonstrated that peripheral arterial calcium scores, including those of the iliac and femoral arteries, are associated with increased severity of PAD and worse cardiovascular outcomes in symptomatic patients (30) and additionally in this study ICS demonstrated to be an independent prognostic value by stratifying long-term cardiovascular and limb-related risk in patients undergoing revascularization for complex aortoiliac disease, suggesting it may serve as a global marker of systemic atherosclerosis. may serve as a reflection of the overall systemic arterial calcification burden. However, the use of these calcium scores as a stratification and prevention tool in asymptomatic and claudicant populations remains underexplored. Future prospective research could focus on the potential value of iliac calcium scoring for early risk stratification and cardiovascular prevention in these patient groups, similar to the role already established for coronary artery calcium scoring in primary prevention settings (31, 32).

This study has several important limitations. Although it was conducted across two centers — a large academic institution and a community referral hospital, which enhances external validity — the sample size remains relatively small. Additionally, the marked predominance of male patients (95.4%) significantly limits the generalizability of findings to the broader population, particularly to women. To mitigate potential selection bias arising from the inclusion of only patients with available CT imaging, a sensitivity analysis was performed (Supplementary Table 1). Second, the *post hoc* design introduces inherent limitations, including the possibility of selection bias: patients with significant comorbidities or unfavorable clinical status may have been more likely to undergo less invasive procedures or to be excluded from revascularization altogether. This is particularly relevant given that current guidelines recommend open surgery for healthier patients with extensive aortoiliac disease. At the same time, an endovascular-first approach is often favored in those with higher operative risk (33). Third, although significant associations were found between calcium scores and clinical outcomes, causality cannot be established due to the study's observational nature. In addition, variability in the measurement of calcium scores may have influenced patient classification into high-score vs. low-score groups, and absolute score values are known to be affected by age, sex, and ethnicity—factors not fully controlled for in this cohort, despite the limited ethnic diversity in the region. Finally, the pattern of arterial calcification was not evaluated (intima layer vs. media layer) or specific morphological features such as circumferential characteristics or thickness of the artery, which recent studies have identified as potentially relevant predictors of outcomes (28, 29).

Despite these limitations, the study's strengths include its prospective data collection, extended follow-up period, and the relative homogeneity of aortoiliac lesions, all of which support the robustness of the observed associations. Further prospective cohort studies with larger and more diverse populations are needed to validate these findings.

Conclusion

This study introduces the ICS as a lesion-specific tool capable of stratifying long-term cardiovascular and limb-related risk in patients undergoing revascularization for complex aortoiliac disease. The ICS demonstrated independent prognostic value beyond perioperative outcomes, highlighting its relevance for long-term clinical decision-making. By quantifying arterial calcification in a standardized manner, the score enhances preoperative risk assessment, informs procedural planning, and supports individualized surveillance strategies. Further prospective cohort studies are needed to confirm the reproducibility and generalizability of these findings across broader populations and to explore the impact of ICS-guided interventions on clinical outcomes.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Unidade Local de Saúde de São João. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or

the participants' legal guardians/next of kin because observational study without change in therapeutic options.

Author contributions

AP-N: Supervision, Writing – original draft, Formal analysis, Writing – review & editing, Investigation, Methodology, Conceptualization. JR-N: Methodology, Writing – review & editing, Funding acquisition, Supervision, Investigation, Writing – original draft, Conceptualization, Formal analysis. TC-P: Writing – review & editing. HR: Writing – review & editing. LD: Writing – review & editing. LD-G: Writing – review & editing. JA: Writing – review & editing, Funding acquisition, Supervision.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This article was supported by National Funds through FCT - Fundação para a Ciência e a Tecnologia, I.P., within CINTESIS, R&D Unit (reference UIDB/4255/2020).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1655229/full#supplementary-material

References

1. Khan S, Post W, Guo X, Tan J, Zhu F, Bos D, et al. Coronary artery calcium score and polygenic risk score for the prediction of coronary heart disease events. *JAMA*. (2023) 329:1768–77. doi: 10.1001/jama.2023.7575

2. Nguyen H, Liu J, Del Castillo M, Shah T. Role of coronary calcium score to identify candidates for ASCVD prevention. *Curr Atheroscler Rep*. (2019) 21:53. doi: 10.1007/s11883-019-0812-8

3. Bell K, White S, Hassan O, Zhu L, Scott A, Clark J, et al. Evaluation of the incremental value of a coronary artery calcium score beyond traditional cardiovascular risk assessment: a systematic review and meta-analysis. *JAMA Intern Med*. (2022) 182:634–42. doi: 10.1001/jamainternmed.2022.1262

4. Shaw L, Raggi P, Berman D, Callister T. Coronary artery calcium as a measure of biologic age. *Atherosclerosis*. (2006) 188:112–9. doi: 10.1016/j.atherosclerosis.2005.10.010

5. Freyermuth M, Roisin S, Saidak Z, Matray L, Sevestre M, Reix T, et al. Contemporary minimally invasive surgery for TASC-D aorto-iliac lesions: analysis of outcomes and risk factors for primary and secondary patency. *Ann Vasc Surg*. (2023) 97:367–74. doi: 10.1016/j.avsg.2023.05.018

6. Gabel J, Kiang S, Abou-Zamzam A, Oyoyo U, Teruya T, Tomihama R. Trans-atlantic inter-society consensus class D aortoiliac lesions: a comparison of endovascular and open surgical outcomes. *AJR Am J Roentgenol*. (2019) 213:696–701. doi: 10.2214/AJR.18.20918

7. Rocha-Neves J, Ferreira A, Sousa J, Pereira-Neves A, Vidoedo J, Alves H, et al. Endovascular approach versus aortobifemoral bypass grafting: outcomes in extensive aortoiliac occlusive disease. *Vasc Endovascular Surg*. (2020) 54:102–10. doi: 10.1177/1538574419888815

8. Huang C, Wu I, Wu Y, Hwang J, Wang S, Chen W, et al. Association of lower extremity arterial calcification with amputation and mortality in patients with symptomatic peripheral artery disease. *PLoS One*. (2014) 9:e90201. doi: 10.1371/journal.pone.0090201

9. Dong Y, Liu Y, Cheng P, Liao H, Jiang C, Li Y, et al. Lower limb arterial calcification and its clinical relevance with peripheral arterial disease. *Front Cardiovasc Med*. (2023) 10:1271100. doi: 10.3389/fcvm.2023.1271100

10. Kang I, Lee W, Choi B, Choi D, Hong M, Jang Y, et al. Semiquantitative assessment of tibial artery calcification by computed tomography angiography and its ability to predict infrapopliteal angioplasty outcomes. *J Vasc Surg*. (2016) 64:1335–43. doi: 10.1016/j.jvs.2016.04.047

11. Zettervall S, Marshall A, Fleser P, Guzman R. Association of arterial calcification with chronic limb ischemia in patients with peripheral artery disease. *J Vasc Surg*. (2018) 67:507–13. doi: 10.1016/j.jvs.2017.06.086

12. Megale A, Wolosker N, Kalil V, Nigro J, Wakisaka C, Dias B, et al. Aortic calcium score predicts early outcomes in aortoiliac revascularization. *Einstein*. (2025) 23:eAO0527. doi: 10.31744/einstein_journal/2025AO0527

13. Jeremias Z, Rat N, Benedek I, Rapolti E, Ratiu M, Muresan A, et al. High iliac calcium score is associated with increased severity and complexity of peripheral arterial disease and predicts global atherosclerotic burden. *Vasa*. (2018) 47:377–86. doi: 10.1024/0301-1526/a000718

14. Lee S, Kalra K, Kashikar A, Redpath B, Bernheim A, Brewster L, et al. Evaluation of lower extremity calcium score as a measure of peripheral arterial disease burden and amputation risk. *Ann Vasc Surg*. (2023) 95:154–61. doi: 10.1016/j.avsg.2023.02.009

15. Megale A, Wolosker N, Kalil V, Nigro J, Wakisaka C, Dias B, et al. Calcium score predicts mortality after revascularization in critical limb ischemia. *J Endovasc Ther*. (2022) 29:438–43. doi: 10.1177/15266028211059911

16. Okuno S, Iida O, Shiraki T, Fujita M, Masuda M, Okamoto S, et al. Impact of calcification on clinical outcomes after endovascular therapy for superficial femoral artery disease: assessment using the peripheral artery calcification scoring system. *J Endovasc Ther*. (2016) 23:731–7. doi: 10.1177/1526602816656612

17. Rocha-Singh K, Zeller T, Jaff M. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv*. (2014) 83:E212–20. doi: 10.1002/ccd.25387

18. Norgren L, Hiatt W, Dormandy J, Nehler M, Harris K, Fowkes F, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. (2007) 45(Suppl S):S5–67. doi: 10.1016/j.jvs.2006.12.037

19. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, et al. STROCSS 2019 Guideline: strengthening the reporting of cohort studies in surgery. *Int J Surg*. (2019) 72:156–65. doi: 10.1016/j.ijsu.2019.11.002

20. Stoner M, Calligaro K, Chaer R, Dietzek A, Farber A, Guzman R, 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:e1–21. doi: 10.1016/j.jvs.2016.03.420

21. Conte M, Bradbury A, Kolh P, White J, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. (2019) 58:S1–S109.e33. doi: 10.1016/j.ejvs.2019.05.006.

22. Thygesen K, Alpert J, Jaffe A, Chaitman B, Bax J, Morrow D, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. (2018) 72:2231–64. doi: 10.1016/j.jacc.2018.08.1038

23. Fashandi A, Mehaffey J, Hawkins R, Kron I, Upchurch G, Robinson W. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg*. (2018) 68:1817–23. doi: 10.1016/j.jvs.2018.06.193

24. Davis B, Marin D, Hurwitz L, Ronald J, Ellis M, Ravindra K, et al. Application of a Novel CT-based iliac artery calcification scoring system for predicting renal transplant outcomes. *AJR Am J Roentgenol*. (2016) 206:436–41. doi: 10.2214/AJR.15.14794

25. Werlin E, Braun H, Walker J, Freise J, Amara D, Liu I, et al. Utility of a simplified iliac artery calcium scoring system to guide perioperative management for renal transplantation. *Front Med*. (2021) 8:606835. doi: 10.3389/fmed.2021.606835

26. TerBush M, Rasheed K, Young Z, Ellis J, Glocker R, Doyle A, et al. Aortoiliac calcification correlates with 5-year survival after abdominal aortic aneurysm repair. *J Vasc Surg*. (2019) 69:774–82. doi: 10.1016/j.jvs.2018.05.242

27. Mori S, Takahara M, Nakama T, Tobita K, Hayakawa N, Iwata Y, et al. Impact of calcification on clinical outcomes after drug-coated balloon angioplasty for superficial femoral artery disease: assessment using the peripheral artery calcification scoring system. *Catheter Cardiovasc Interv*. (2023) 101:892–9. doi: 10.1002/ccd.30622

28. Dong Y, Liu Y, Liao H, Cheng P, Liu X, Huang W, et al. Circumferential degree of tibial artery calcification is associated with infrapopliteal endovascular revascularization outcomes in patients with chronic limb-threatening ischemia. *Int Angiol*. (2023) 42:528–36. doi: 10.23736/S0392-9590.23.05130-1

29. Konijn L, Takx R, de Jong P, Spreen M, Veger H, Mali W, et al. Arterial calcification and long-term outcome in chronic limb-threatening ischemia patients. *Eur J Radiol*. (2020) 132:109305. doi: 10.1016/j.ejrad.2020.109305

30. Devia-Rodriguez R, Derksen M, El Moumni M, de Groot K, Vedder I, Zeebregts C, et al. Association of Iliofemoral calcium score and major vascular complications within the first year after lower limb endovascular revascularization. *Ann Vasc Surg*. (2025) 111:290–8. doi: 10.1016/j.avsg.2024.11.009

31. Hussain B, Mahmood A, Flynn M, Alexander T. Coronary artery calcium scoring in asymptomatic patients. *HCA Healthc J Med*. (2023) 4:341–52. doi: 10.36518/2689-0216.1565

32. Gupta A, Bera K, Kikano E, Pierce J, Gan J, Rajdev M, et al. Coronary artery calcium scoring: current status and future directions. *Radiographics*. (2022) 42:947–67. doi: 10.1148/rg.210122

33. Aboyans V, Ricco J, Bartelink M, Björck M, Brodmann M, Cohnert T, et al. Editor's Choice - 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. (2018) 55:305–68. doi: 10.1016/j.ejvs.2017.07.018

DISCUSSION

DISCUSSION

Study population

Consecutive patients who underwent elective revascularization for complex AID (defined as TransAtlantic Inter-Society Consensus II [TASC II] type D lesions) at two participating centers — a tertiary referral hospital (Centro Hospitalar Universitário São João, now known as Unidade Local de Saúde de São João) and a community hospital (Centro Hospitalar do Tâmega e Sousa, now known as Unidade Local de Saúde do Tâmega e Sousa) — were prospectively enrolled between January 2013 and January 2024. Patients with concomitant aortoiliac aneurysmal disease were excluded.

Demographic, clinical and procedural data were obtained by extensive and methodical review of electronic medical records and local vascular registries. Extracted variables included age, sex, standard cardiovascular risk factors, relevant comorbidities, lesion anatomy and procedural details. Two experienced observers independently reviewed preoperative imaging to confirm TASC II classification and lesion characteristics; discrepancies were resolved by consensus. Lesion descriptions and classification follow the TASC II recommendations for AID (23).

Treatment modality (open surgical versus endovascular revascularization) was determined by a shared decision-making process involving the operating surgeon and the patient and was informed by lesion anatomy, patient comorbidity and institutional/surgeon expertise. To enhance procedural comparability, ABF grafts were consistently Dacron prostheses (Maquet Cardiovascular, ABF Y graft, 14×7 mm and 16×8 mm), and iliac stents were predominantly Cordis S.M.A.R.T.® stents (Cordis Endovascular). Technical success was defined as maintenance of target vessel patency at 24 hours after the procedure (46).

Patients were assessed during the early postoperative period (30 days) and subsequently at regular outpatient follow-up visits. Routine surveillance comprised clinical evaluation and non-invasive hemodynamic studies (ABI and duplex ultrasound), typically at one and 12 months postoperatively and thereafter at one-year intervals unless a different schedule was clinically indicated. Prespecified clinical endpoints captured during follow-up included MACE, MALE, and all-cause mortality (46).

The study protocol was approved by the local Institutional Review Board / Ethics Committee (Comissão de Ética para a Saúde do CHUSJ; protocol no. 246-18). Data collection and processing adhered to the Declaration of Helsinki and applicable data-protection regulations (European General Data Protection Regulation); the observational nature of the study guided informed-consent procedures and all data were handled anonymously. Reporting follows the Strengthening the reporting of cohort studies in surgery 2019 guideline (68).

Clinical predictors of prognosis in extensive aortoiliac disease

The accurate prediction of outcomes following aortoiliac revascularization remains a fundamental challenge in vascular surgery practice. While technical success rates have improved with both endovascular and open surgical techniques, substantial variability in patient outcomes persists, underscoring the need for robust prognostic tools beyond traditional anatomical and procedural considerations. Two complementary clinical predictors - CKD and the mFI-5 - have emerged from this thesis as independent markers of long-term adverse outcomes in patients with extensive TASC II type D aortoiliac disease, while differing in their short-term predictive performance and mechanistic signal.

Frailty represents a multidimensional syndrome characterized by diminished physiological reserve and increased vulnerability to adverse health outcomes (69). In vascular surgery populations, frailty prevalence ranges from 20% to 60%, significantly exceeding rates observed in general surgical cohorts (70). The mFI-5, a simplified frailty assessment tool comprising five readily obtainable clinical variables—diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, hypertension requiring medication, and functional status—offers a pragmatic approach to preoperative risk stratification, using cumulative comorbidities (70).

The prospective analysis of patients undergoing elective revascularization for extensive aortoiliac disease demonstrated that mFI-5 scores greater than 2 independently predicted long-term MACE with a HR of 2.469 (95% CI: 1.267-4.811; P=0.008) and all-cause mortality with a HR of 2.585 (95% CI: 1.270-5.260; P=0.009) (64). Importantly, the prognostic value of mFI-5 was maintained in multivariable analysis after adjusting for other clinical factors, with frailty emerging, alongside CKD, as one of only two independent predictors of long-term MACE and all-cause mortality. Kaplan-Meier survival analysis revealed that patients with mFI-5 ≥ 2 demonstrated significantly worse five-year freedom from MACE (50.8% ± 9.3% vs. 77.6% ± 5.4%; P=0.006) (64).

The absence of association between mFI-5 and short-term outcomes in the study`s cohort likely reflects several factors inherent to contemporary vascular practice. Selection bias might play a role, as patients with more severe comorbidities and limited physiologic reserve are increasingly directed toward less invasive endovascular procedures or medical management, and the surgeon's experience and judgment in patient selection may further influence overall outcomes. Additionally, improvements in perioperative care, including enhanced preoperative optimization, refined anesthetic techniques, and intensive postoperative monitoring, might have attenuated the impact of frailty on immediate perioperative complications. The distribution of mFI-5 scores in our population, with 96.3% of patients scoring between 0 and 3, confirms that severely frail individuals (scores 4-5) are often deemed unsuitable for revascularization procedures altogether.

The mFI-5 predictive ability has been tested across several vascular areas. It has been associated with higher short- and long-term worse outcomes after carotid endarterectomy (71, 72) and in both open

and endovascular elective abdominal aortic aneurysm repair (73, 74). Evidence in PAD is concordant, with frailty increasing the risk of MACE in patients with stable claudication (75). Also, in those submitted to infra-inguinal interventions, frailty has shown to independently predict mortality and major complications, with a disproportionately higher risk among frail women as reported in a large series (76). Other authors confirm associations with frailty and postoperative complications after infra-inguinal bypass (77). Smaller cohorts have likewise found frailty to predict two-year major amputation and mortality following first-time revascularization (78), and preoperative frailty has also been identified as a risk factor for 30-day readmission and loss of ambulation after major lower-limb amputation (79, 80), although an Asian series did not replicate these findings (81). Also, a recent cohort of aortoiliac patients where frailty was measured using mFI did not show statistical significance in re-intervention, amputation, or death rates (82). Overall, as above succinctly described, the published literature supports the prognostic relevance of frailty and of mFI-5 in particular across vascular populations; in this aorto-iliac cohort, mFI-5 similarly predicted worse long-term MACE and mortality but did not predict 30-day outcomes, a pattern that aligns with some prior reports while differing from the abdominal aortic aneurysm and carotid literature where short-term risk increases have been observed.

It was also demonstrated that CKD is associated with a markedly increased incidence of perioperative myocardial injury after noncardiac surgery (MINS) (54.5%; P=0.014) and is an independent predictor of several long-term cardiovascular endpoints. In Cox regression models, CKD carried large effect sizes for acute heart failure (AHF) (HR 4.88; P=0.007), MACE (HR 2.99; P=0.002 unadjusted; adjusted HR 2.42; P=0.017) and all-cause mortality (HR 3.30; P<0.001) (66). CKD patients also showed numerically worse event-free survival for acute myocardial infarction (AMI) and stroke on Kaplan–Meier analysis. These findings support the interpretation of CKD as a potent systemic risk amplifier in the aortoiliac population and underscore the importance of targeted cardiorenal assessment and optimization in the preoperative pathway (83, 84). Furthermore, the study demonstrated age was a key clinical correlate of CKD: patients with CKD were older on average, consistent with the well-established increase in CKD prevalence with advancing age (85, 86). CKD patients also had a higher burden of CAD and HF, findings that mirror the known epidemiologic and pathophysiologic links between renal dysfunction and cardiovascular disease (87). Mechanistically, CKD promotes arterial stiffness and accelerates atherosclerosis, processes that plausibly underlie the higher rates of CAD and HF observed in this population (88, 89); additional pathways such as microalbuminuria and systemic inflammation may further contribute to myocardial vulnerability and progressive cardiac dysfunction in CKD (90). CKD and PAD therefore share common risk determinants and pathogenic mechanisms, reinforcing the concept of a systemic atherosclerotic background (91).

Published data show that PAD is associated with increased all-cause mortality, cardiovascular events and lower-limb complications, and that these risks escalate with advancing CKD stage, most markedly in dialysis patients (84, 92). Although revascularization can improve outcomes irrespective of baseline estimated glomerular filtration rate, patients with advanced CKD nevertheless experience substantially higher rates of amputation, mortality, reintervention and perioperative complications after

revascularization (63). By contrast, in this aortoiliac cohort, CKD was a strong predictor of cardiovascular adverse outcomes but did not predict limb-related adverse events, a discrepancy that may reflect differences in sample size, event rates, patient selection or follow-up protocols and warrants further investigation (66).

Taken together, the two studies deliver a coherent clinical message but also raise important interpretative points. First, both CKD and mFI-5 converge on the prediction of long-term MACE and mortality, but each captures different aspects of risk: CKD appears to predict both perioperative MINS and long-term cardiac decompensation (suggesting active cardiorenal pathophysiology), whereas mFI-5 indexes a broader, cumulative physiologic vulnerability that manifests as poorer long-term cardiovascular resilience. The partial overlap between predictors is important: patients with higher mFI-5 scores had a markedly higher prevalence of CKD in the mFI-5 cohort, raising the aggregation of risk factors or shared pathways (inflammation, multimorbidity) that amplify risk. Incorporating both markers (both readily obtainable), into preoperative evaluation may enhance risk stratification and permit more personalised choices of technique and follow-up intensity. However, wider validation and interventional studies are required before routine use can be recommended as guideline-changing practice.

Hematological predictors of prognosis in extensive aortoiliac disease

The growing recognition of inflammation as a central mechanism in atherosclerosis (93) has shifted attention toward readily available hematological parameters as potential prognostic biomarkers in PAD. Monocytes, as key players in the innate immune system, contribute significantly to atherosclerosis initiation, propagation, and plaque destabilization through multiple mechanisms including macrophage infiltration, foam cell formation, pro-inflammatory cytokine production, and matrix metalloproteinase secretion (17, 94-96). Beyond their well-established pathophysiological role, circulating monocyte counts have demonstrated prognostic value across various cardiovascular conditions, including acute coronary syndromes and CAD (17, 94). These observations prompted investigation into whether absolute monocyte count could serve as a simple, cost-effective predictor of outcomes following revascularization for complex AID.

In this prospective cohort of patients undergoing elective aortoiliac revascularization for TASC II type D lesions, preoperative absolute monocyte count emerged as a significant predictor of both short-term and long-term MALE. Using optimal binning procedures with MALE as the reference outcome, a threshold of 0.720×10^9/L was identified. Patients with preoperative monocyte counts exceeding this threshold demonstrated substantially worse 30-day limb-related outcomes (MALE: Odds Ratio [OR] 7.138, 95% CI 1.509–33.764, P=0.013). This short-term predictive capacity is particularly valuable, as it may enable targeted perioperative monitoring and early intervention strategies in high-risk individuals (65).

The prognostic value of elevated monocyte count extended throughout long-term follow-up, with a median surveillance period of 61 months (Interquartile range [IQR] 55.4–66.6 months). Kaplan-Meier survival analysis revealed that patients with monocyte counts greater than 0.720 × 10^9/L experienced significantly lower secondary patency (P=0.03), higher rates of major amputation (P=0.04), and increased overall MALE (P=0.039) compared to those with counts at or below the threshold. Multivariable Cox regression analysis confirmed an elevated monocyte count as an independent predictor of long-term MALE, with an adjusted HR of 2.149 (95% CI 1.115–4.144, P=0.022). This independent association persisted after adjustment for potential confounding variables (65).

Interestingly, patients with elevated monocyte counts in this cohort were significantly older (64.6±8.66 vs. 59.9±9.25 years; P=0.003) and were more frequently selected for endovascular revascularization rather than open surgery (52.8% vs. 33.3%; P=0.023) (65). This pattern probably reflects clinical decision-making processes wherein older patients with higher inflammatory burden are preferentially directed toward less invasive endovascular approaches, despite potentially having more complex disease biology that predisposes to adverse limb outcomes.

The predictive utility of monocyte-based markers in PAD has been previously explored, though most existing studies have utilized monocyte count as part of composite ratios rather than as an absolute value. In a cross-sectional study of 434 patients with Type 2 DM, elevated monocyte-to-HDL cholesterol ratio (MHR) was independently associated with the presence and clinical severity of PAD (97). Similarly, in vascular access surgery, Li et al. demonstrated that patients with baseline monocyte counts ≥0.51 × 10^9/L exhibited significantly lower arteriovenous fistula patency rates, with an aHR of 2.774 (95% CI 1.092–7.043) for fistula failure (98).

Regarding amputation outcomes specifically, Cosarca et al. reported that the lymphocyte-to-monocyte ratio (LMR) predicted amputation following revascularization for PAD, with a cut-off value of 2.55 (sensitivity 56.25%; specificity 66.88%) and lower ratios associated with higher amputation rates (99). Additionally, in a larger cohort of 563 patients with CLTI, the MHR was significantly elevated in those requiring amputation compared to those treated with revascularization or medical management (15.7±1.52 vs. 12.8±1.45, P<0.001), with MHR emerging as an independent predictor of amputation risk in multivariable regression analysis (P<0.001) (60). This finding further reinforces the prognostic importance of monocyte-based indices in predicting limb loss across different PAD populations and disease severities. Furthermore, among patients undergoing embolectomy for acute lower extremity ischemia, elevated MHR emerged as an independent predictor of amputation on multivariate analysis (HR 1.547, 95% CI 1.003–2.387, P=0.04) (61).

In summary, absolute monocyte count emerges as a clinically useful and biologically plausible biomarker in the prognosis of extensive AID. Its ease of measurement through routine complete blood counts provides an inexpensive and accessible means of risk stratification, enabling identification of patients prone to early graft failure, MALE, and amputation. The mechanistic link between circulating monocytes and vascular injury is strongly supported by experimental and clinical evidence, as these cells

orchestrate pro-inflammatory and pro-thrombotic pathways that destabilize atherosclerotic plaques and impair vascular healing (17, 94-96). From a clinical perspective, incorporating monocyte count into preoperative assessment may refine patient selection and guide tailored management in complex aortoiliac revascularization, particularly in those at heightened risk for restenosis or occlusion, while its prognostic value highlights a potential link between innate immune activation and limb outcomes that warrants further investigation.

Imagiological predictors of prognosis in extensive aortoiliac disease

Arterial calcification has emerged as an important prognostic marker across the spectrum of cardiovascular disease, with coronary artery calcium (CAC) scoring now established as a cornerstone of risk stratification in CAD (100, 101). The incremental prognostic value of CAC beyond traditional risk factors has been well documented, with systematic reviews demonstrating improved discrimination for cardiovascular events and meaningful reclassification of intermediate-risk patients (102). In PAD, particularly in the context of extensive AID, vascular calcification complicates revascularization procedures and has been increasingly recognized as a predictor of adverse limb and cardiovascular outcomes (59, 103, 104). However, despite its clinical relevance, standardized and validated quantification of lower limb arterial calcification remains lacking, with considerable heterogeneity in measurement approaches ranging from qualitative visual scores to adapted Agatston protocols (103, 105). Notably, no validated calcium scoring system has been specifically developed for TASC II type D aortoiliac lesions, the most complex anatomical presentation requiring revascularization.

In this prospective cohort of patients with TASC II type D aortoiliac occlusive disease undergoing elective revascularization, a standardized CT-based Iliac Calcium Score (ICS) system, previously used on renal transplant patients, was adapted and evaluated. Iliac artery calcification was quantified semiquantitatively using three distinct features: morphology (graded 0-3 based on thickness and convexity), circumferential involvement (scored 0-4 by percentage), and length of calcification (scored 0-4 by percentage) (106). Each iliac arterial segment (common and external, bilaterally) was scored separately, with the final ICS calculated by summing the scores from all four segments. Using visual binning based on observed data distribution and clinical reasoning, patients were stratified into low (ICS ≤36) and high (ICS ≥37) calcium burden groups, corresponding to the point of greatest contrast in MACE rates (67).

The cohort comprised predominantly male patients (95.4%) with a median follow-up of 67 months, and approximately 75% presented with CLTI. Baseline characteristics were largely similar between ICS groups, though patients with ICS ≥37 demonstrated significantly more advanced Rutherford stages (particularly stages V and VI; P=0.035), along with trends toward higher prevalence of hypertension, CKD and HF. At 30 days post-revascularization, both groups showed clinical improvement in Rutherford

classification, but patients with lower calcium scores exhibited significantly greater mean improvement (-2.9±1.10 vs. -2.4±1.61, P=0.013). No significant differences were observed in short-term complications, including acute kidney injury, MINS, MALE, MACE, or all-cause mortality (67).

However, the prognostic significance of elevated ICS became evident during longer-term follow-up. At one year, patients with ICS ≥37 experienced significantly higher rates of MALE compared to those with lower scores (48.1% vs. 27.3%, Logrank P=0.024). At 60 months, patients in the high calcium group demonstrated markedly worse outcomes across multiple domains: amputation-free survival was substantially lower (74.5% vs. 97.8%; Logrank P=0.002), MACE-free survival was reduced (47.3% vs. 73.4%; Logrank P=0.005), and overall survival was significantly diminished (54.6% vs. 77.0%; Logrank P=0.013). Notably, AHF occurred exclusively in the high ICS group, with 60-month AHF-free survival of 87.7% compared to 100% in the low ICS group (Logrank P=0.015). In contrast, primary and secondary patency rates showed no significant differences between groups, suggesting that calcification's impact on clinical outcomes may extend beyond purely mechanical factors affecting immediate procedural success (67).

Multivariate Cox regression analysis confirmed the independent prognostic value of elevated ICS. An ICS ≥37 remained independently associated with a 2.30-fold increased risk of MACE (aHR 2.296, 95% CI 1.246-4.229, P=0.008) and a striking 7.52-fold elevated risk of major lower limb amputation (aHR 7.521, 95% CI 1.693-33.409, P=0.008). When analyzed as a continuous variable, each incremental increase in ICS also demonstrated independent associations with both MACE (adjusted HR 1.036, 95% CI 1.006-1.068, P=0.020) and major amputation (aHR 1.142, 95% CI 1.030-1.260, P=0.011).

These findings align with and extend previous observations linking arterial calcification to adverse outcomes in PAD. Huang et al. reported that patients in the highest calcium score quartile had a 2.88-fold increased risk of amputation (95% CI 1.18-12.72, P=0.03) and a 5.16-fold increased risk of death (95% CI 1.13-21.61, P=0.04) compared to the lowest quartile (107). In the infrapopliteal territory, a study demonstrated that extensive tibial artery calcification was associated with lower technical success of angioplasty (71.1% vs. 95.3% in minimal calcification, P=0.001), reduced two-year amputation-free survival (58.9% vs. 79.0% vs. 95.3% across calcification grades, P<0.001), and emerged as an independent predictor of amputation (HR 9.90, 95% CI 2.05-47.75, P=0.004) (108). Dong et al. similarly identified tibial artery annular calcification as an independent predictor of unplanned amputation (HR 3.74, 95% CI 1.71-8.19, P=0.001) (109), while Konijn et al. reported that complete annular calcification in crural or femoropopliteal arteries independently predicted 10-year mortality (110). Zettervall et al. found that increasing Rutherford categories were independently associated with higher calcification scores even after adjusting for cardiovascular risk factors (111), consistent with this cohort observation, of more advanced Rutherford stages in the high ICS group.

In the specific context of aortoiliac disease, Megale et al. reported that aortic calcium scores were higher in patients requiring amputation (5,767.6 vs. 805.3, P=0.02) or subsequent revascularization (3,686.8 vs. 645.2, P=0.008) within 30 days, though they found no significant association with patency or

technical success (59), paralleling the findings from this cohort regarding patency. More recently, the same group demonstrated that calcium scores of the operated limb were significantly higher in patients who died within 30 days and six months (6,571 vs. 2,590.6, P=0.026 and 5,227.8 vs. 2,335.3, P=0.036, respectively) (104). However, in this other study, no statistically significant relation was found concerning amputation, patency, and technical success in any of the periods analysed (104). Jeremias et al. additionally reported that high iliac calcium scores were associated with lower left ventricular ejection fraction (moderate inverse correlation r=-0.54, P<0.0001), suggesting that iliac calcification may serve as a marker of global atherosclerotic burden and systemic cardiovascular dysfunction (112).

As a preoperative risk stratification tool, the ICS provides lesion-specific prognostic information that complements traditional clinical risk assessment, enabling more accurate identification of patients at elevated risk for limb loss and cardiovascular events despite technically successful revascularization. This information can inform shared decision-making conversations with patients regarding realistic outcome expectations, guide selection between open surgical versus endovascular approaches in borderline cases, and support individualized surveillance intensity based on stratified risk. The semiquantitative methodology employed, evaluating morphology, circumferential involvement, and length, can be readily and reproducibly performed by experienced vascular surgeons using standard CT-angiography (CTA), requiring no additional imaging or specialized software. Furthermore, the threshold effect observed at ICS ≥37 provides a clinically actionable dichotomization point, though the continuous association between calcium score and adverse outcomes suggests that risk increases progressively across the spectrum of calcification burden.

Limitations

The findings presented in this thesis should be interpreted within the context of several methodological limitations inherent to the study design and cohort characteristics. All four studies draw from prospectively maintained registry spanning two centers: a large tertiary academic institution and a regional referral hospital, which enhances real-world applicability and external validity. Most notably, the cohorts exhibit marked male predominance (93-95% across studies), reflecting the demographic profile typical of extensive AID but significantly limiting the generalizability of findings to female populations. Sex-related differences in atherosclerotic patterns, calcification morphology, inflammatory responses, and comorbidity profiles may influence outcomes differently in women, warranting cautious extrapolation of the identified prognostic thresholds and risk estimates.

Sample size considerations further constrain statistical power and precision of effect estimates, particularly for less frequent endpoints. In the CKD analysis, the absolute number of CKD cases (n=17) was modest, resulting in wide confidence intervals around certain estimates and borderline statistical significance for some cardiovascular endpoints such as AMI and stroke, raising the susceptibility to type-

II error. Similarly, the mFI-5 cohort (n=109) and the ICS study (n=109) involved relatively small patient numbers that may limit detection of associations in subgroup analyses and affect the stability of multivariable models. The monocyte count investigation (n=135) likewise reflects modest sample size with potential constraints on generalizability of the identified cutoff value of >0.720 × 10^9/L.

Across all studies, selection bias represents an acknowledged limitation as patients with severe comorbidities, advanced frailty, or prohibitive surgical risk may have been preferentially directed toward less invasive endovascular procedures, optimal medical therapy alone, or excluded from revascularization consideration altogether. This mechanism likely attenuates observed differences in short-term outcomes and may affect the distribution of risk factors and biomarker values in the analysed cohorts.

Study-specific limitations warrant additional consideration. The mFI-5 analysis demonstrated a skewed distribution of frailty scores, with 96.3% of patients scoring between 0 and 3 and few severely frail individuals (scores 4-5), likely reflecting exclusion of the frailest patients from revascularization procedures. This restricted range may underestimate the true prognostic impact of severe frailty and limits assessment of dose-response relationships across the full spectrum. Furthermore, overlap between mFI-5 components and traditional cardiovascular risk factors introduces potential residual confounding that multivariable adjustment may not fully address. In the monocyte count study, reliance on a single preoperative measurement precludes assessment of longitudinal monocyte dynamics, intra-individual variability, or the prognostic value of serial postoperative measurements. Additionally, the study did not differentiate monocyte subsets (classical, intermediate, and non-classical), which recent evidence suggests may have distinct roles in atherosclerosis progression and differential associations with clinical outcomes. For the ICS investigation, the semiquantitative scoring methodology, while standardized and reproducible (106), did not distinguish between intimal and medial calcification patterns, nor did it account for density variations that may influence biomechanical properties and clinical significance (109, 110). Moreover, only patients with available preoperative CTA were included, introducing imaging-dependent selection bias, and the scoring variability may have been influenced by operator-dependent interpretation despite protocol standardization, optimization and training.

Finally, the observational design across all studies precludes definitive causal inference since identified biomarkers and risk factors may function as markers of systemic disease burden rather than direct mediators/risk factors of adverse outcomes.

Despite these limitations, the extended median follow-up periods (61-67 months), focus on a homogeneous anatomical subset (TASC II type D aortoiliac disease), and consistent use of standardized endpoint definitions support the robustness of observed associations and provide a foundation for future validation studies in larger, more diverse populations.

Future Perspectives

The current "endovascular-first" paradigm, while generally appropriate for TASC II A-C lesions, faces challenges in the management of TASC II D disease. The decision-making process becomes increasingly complex when considering factors such as patient age, anatomical complexity, institutional expertise, and long-term durability expectations. Young patients with extensive disease may benefit from surgical bypass for superior long-term primary patency, while older individuals often fare better with endovascular approaches despite higher reintervention rates (59).

The prognostic markers identified in this thesis (CKD, mFI-5, monocyte count, and the ICS) represent complementary tools that address distinct dimensions of cardiovascular and limb-related risk in extensive AID. Their clinical implementation requires systematic integration into perioperative decision-making pathways and further validation to maximize potential impact on patient outcomes.

From a practical standpoint, CKD status should trigger focused cardiorenal protection strategies, including rigorous volume management, nephrotoxin avoidance, and heightened perioperative cardiac monitoring given the demonstrated associations with myocardial injury and subsequent AHF events. The mFI-5, as a rapid bedside assessment tool, enables identification of patients with limited physiologic reserve who may benefit from tailored decision-making regarding open versus endovascular revascularization, structured secondary prevention programs, and realistic goal-setting conversations when life expectancy constraints exist. Elevated preoperative monocyte counts warrant consideration of intensified antiplatelet therapy, closer imagiologic surveillance for early graft dysfunction, and lower thresholds for reintervention. The ICS provides lesion-specific prognostic information that can inform procedural planning, guide selection between surgical and endovascular approaches in borderline cases, and stratify patients for individualized surveillance.

Key research priorities include external validation of these prognostic markers in larger, multicenter cohorts to confirm generalizability across diverse populations and practice settings. Formal assessment of incremental predictive value, through net reclassification improvement (decision trees and random forest) and integrated discrimination indices, is needed to determine whether combining these markers with conventional risk models meaningfully enhances risk stratification beyond established tools. Prospective interventional studies should test whether management modifications guided by these predictors, such as preoperative rehabilitation programs for frail patients, aggressive cardiorenal optimization protocols, anti-inflammatory strategies targeting elevated monocyte counts, or calcium-directed procedural technique modifications, translate into improved hard endpoints including amputation-free survival, freedom from MACE, and all-cause mortality.

The potential expansion of the ICS warrants particular attention. Analogous to CAC scoring, which has revolutionized primary cardiovascular prevention by providing individualized risk estimates beyond traditional calculators (102), the ICS may also serve as a widely applicable marker of systemic

atherosclerotic burden and cardiovascular risk. Future investigation should explore whether ICS opportunistic assessment in asymptomatic or claudicant populations, even those not requiring revascularization, could enhance cardiovascular risk stratification and guide intensity of medical therapy.

Mechanistic research linking CKD-associated inflammation, myocardial vulnerability, and accelerated atherosclerosis progression would further clarify causal pathways and identify potential therapeutic targets, while investigations of monocyte subset dynamics (classical, intermediate, and non-classical monocytes) may reveal specific cellular populations amenable to targeted immunomodulation.

The broader challenge extends to systematic healthcare delivery improvements. Current practice often lacks standardized approaches to address the multifactorial nature of adverse outcomes in extensive AID, including inadequate attention to frailty optimization, insufficient anti-inflammatory strategies, and suboptimal management of heavily calcified lesions. Multidisciplinary care teams incorporating vascular surgeons, cardiologists, nephrologists, geriatricians, and rehabilitation specialists remain underutilized despite demonstrated benefits (113). Development of institution-specific quality metrics for complex aortoiliac revascularization, standardization of perioperative protocols incorporating the identified prognostic markers, and establishment of benchmarking networks would facilitate systematic quality improvement efforts. Ultimately, translating these research findings into routine clinical workflows requires organizational commitment to protocol development, staff education, and infrastructure investment, challenges that must be addressed for evidence-based risk stratification to improve outcomes at the populational level.

MAIN FINDINGS

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1) Modified Frailty Index-5

- mFI-5 was significantly associated with long-term MACE (HR 2.469, 95% CI 1.267–4.811; P=.008) and long-term all-cause mortality (HR 2.585, 95% CI 1.270–5.260; P=.009).
- No significant association between mFI-5 and 30-day postoperative outcomes.
- A simple frailty score helps predict long-term cardiovascular risk after complex aorto-iliac revascularization, but is not useful for predicting immediate perioperative events.

2) Chronic Kidney Disease

- CKD patients had higher rates of short-term MINS (54.5%, P=0.014).
- CKD was an independent long-term predictor of AHF (HR 4.884; P=0.007), MACE (HR 2.992; P=0.002) and all-cause mortality (HR 3.296; P<0.001).
- Multivariable analysis confirmed CKD (aHR ≈2.4) and HF as independent predictors of MACE.
- CKD confers both short- and long-term cardiovascular risk after aorto-iliac revascularization and should prompt tailored perioperative cardiorenal management and closer long-term surveillance.

3) Preoperative Absolute Monocyte Count

- Preoperative monocyte count >0.720 × 10^9/L was associated with worse 30-day limb outcomes (MALE OR 7.138, 95% CI 1.509–33.764; P=0.013) and with long-term adverse limb outcomes (worse secondary patency, higher major amputation and MALE rates).
- Elevated monocyte count was an independent predictor of MALE (aHR 2.149; 95% CI 1.115–4.144; P=0.022).
- A low-cost, widely available inflammatory biomarker can stratify limb-specific risk and identify patients at high risk of early and late limb events.

4) Iliac Calcium Score

- An ICS ≥ 37 identified patients with worse outcomes: higher 1-year MALE (48.1% vs 27.3%; Logrank P=0.024) and, at 60 months, lower amputation-free survival (74.5% vs. 97.8%; Logrank P=0.002), lower MACE-free survival (47.3% vs. 73.4%; Logrank P=0.005) and lower overall survival (54.6% vs. 77.0%; Logrank P=0.013).
- ICS ≥ 37 remained an independent predictor of MACE (aHR 2.30; P=0.008) and major amputation (aHR 7.52; P=0.008).
- Short-term clinical improvement was similar across groups, but long-term prognosis was markedly worse with high iliac calcification.

- A lesion-specific CT calcium score provides objective, procedure-relevant risk stratification that can influence technical planning and follow-up, encompassing surveillance for limb-related outcomes as well as broader cardiovascular events.

Conclusion

This thesis shows that simple, complementary and clinically available markers provide distinct and actionable prognostic information for patients with complex aortoiliac disease. A higher mFI-5 score was associated with approximately 2.5-fold increased long-term risk of MACE and all-cause mortality, whereas CKD independently predicted short-term myocardial injury and substantially higher long-term risks of AHF, MACE and death. Preoperative absolute monocyte count (>0.720×10^9/L) was an independent predictor of early (30-day) and long-term MALE and major amputation, and a CT-derived ICS (ICS ≥37) identified patients with markedly worse 1- and 5-year MALE/MACE rates and survival. Together, these markers support a multimodal, personalized approach to patient selection, procedural planning and intensity of follow-up.

REFERENCES

REFERENCES

1. Aboyans V, Lacroix P, Criqui MH. Large and Small Vessels Atherosclerosis: Similarities and Differences. Prog Cardiovasc Dis. 2007;50(2):112-25.
2. Ankle Brachial Index C, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197-208.
3. Vogt MT, Wolfson SK, Kuller LH. Segmental arterial disease in the lower extremities: Correlates of disease and relationship to mortality. Journal of Clinical Epidemiology. 1993;46(11):1267-76.
4. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382(9901):1329-40.
5. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7(8):e1020-e30.
6. Forbang NI, Hughes-Austin JM, Allison MA, Criqui MH. Peripheral artery disease and non-coronary atherosclerosis in Hispanics: another paradox? Prog Cardiovasc Dis. 2014;57(3):237-43.
7. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010;56(18):1506-12.
8. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. Eur J Vasc Endovasc Surg. 2019;58(1S):S1-S109 e33.
9. Eid MA, Mehta K, Barnes JA, Wanken Z, Columbo JA, Stone DH, et al. The global burden of peripheral artery disease. J Vasc Surg. 2023;77(4):1119-26 e1.
10. Ajoolabady A, Pratico D, Lin L, Mantzoros CS, Bahijri S, Tuomilehto J, et al. Inflammation in atherosclerosis: pathophysiology and mechanisms. Cell Death Dis. 2024;15(11):817.
11. Zimmer S, Grebe A, Latz E. Danger signaling in atherosclerosis. Circ Res. 2015;116(2):323-40.
12. Alonso-Herranz L, Albarran-Juarez J, Bentzon JF. Mechanisms of fibrous cap formation in atherosclerosis. Front Cardiovasc Med. 2023;10:1254114.
13. Sfyri P, Matsakas A. Crossroads between peripheral atherosclerosis, western-type diet and skeletal muscle pathophysiology: emphasis on apolipoprotein E deficiency and peripheral arterial disease. J Biomed Sci. 2017;24(1):42.
14. Djahanpour N, Ahsan N, Li B, Khan H, Connelly K, Leong-Poi H, et al. A Systematic Review of Interleukins as Diagnostic and Prognostic Biomarkers for Peripheral Artery Disease. Biomolecules. 2023;13(11).
15. Ferreira J, Carneiro A, Vila I, Silva C, Cunha C, Longatto-Filho A, et al. Inflammation and Loss of Skeletal Muscle Mass in Chronic Limb Threatening Ischemia. Ann Vasc Surg. 2023;88:164-73.
16. Paradis S, Charles AL, Georg I, Goupilleau F, Meyer A, Kindo M, et al. Aging Exacerbates Ischemia-Reperfusion-Induced Mitochondrial Respiration Impairment in Skeletal Muscle. Antioxidants (Basel). 2019;8(6).
17. Pamukcu B, Lip GY, Devitt A, Griffiths H, Shantsila E. The role of monocytes in atherosclerotic coronary artery disease. Ann Med. 2010;42(6):394-403.
18. Khawaja FJ, Kullo IJ. Novel markers of peripheral arterial disease. Vasc Med. 2009;14(4):381-92.
19. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116(9):1509-26.
20. Khandanpour N, Loke YK, Meyer FJ, Jennings B, Armon MP. Homocysteine and peripheral arterial disease: systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2009;38(3):316-22.
21. Prushik SG, Farber A, Gona P, Shrader P, Pencina MJ, D'Agostino RB, Sr., et al. Parental intermittent claudication as risk factor for claudication in adults. Am J Cardiol. 2012;109(5):736-41.

22. Wassel CL, Lamina C, Nambi V, Coassin S, Mukamal KJ, Ganesh SK, et al. Genetic determinants of the ankle-brachial index: a meta-analysis of a cardiovascular candidate gene 50K SNP panel in the candidate gene association resource (CARe) consortium. Atherosclerosis. 2012;222(1):138-47.
23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:S1-75.
24. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, et al. Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases. J Am Coll Cardiol. 2019;74(4):498-507.
25. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1991;20(2):384-92.
26. Bullen C. Impact of tobacco smoking and smoking cessation on cardiovascular risk and disease. Expert Rev Cardiovasc Ther. 2008;6(6):883-95.
27. Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg. 2006;31(1):59-63.
28. 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):738-43.
29. Soyoye DO, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: A review. World J Diabetes. 2021;12(6):827-38.
30. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008;51(5):747-55.
31. Ortega MA, De Leon-Oliva D, Gimeno-Longas MJ, Boaru DL, Fraile-Martinez O, Garcia-Montero C, et al. Vascular Calcification: Molecular Networking, Pathological Implications and Translational Opportunities. Biomolecules. 2024;14(3).
32. Ho CY, Shanahan CM. Medial Arterial Calcification: An Overlooked Player in Peripheral Arterial Disease. Arterioscler Thromb Vasc Biol. 2016;36(8):1475-82.
33. Kim TI, Guzman RJ. Medial artery calcification in peripheral artery disease. Front Cardiovasc Med. 2023;10:1093355.
34. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res. 2011;109(6):697-711.
35. Martinez-Aguilar E, Orbe J, Fernandez-Montero A, Fernandez-Alonso S, Rodriguez JA, Fernandez-Alonso L, et al. Reduced high-density lipoprotein cholesterol: A valuable, independent prognostic marker in peripheral arterial disease. J Vasc Surg. 2017;66(5):1527-33 e1.
36. Nordanstig J, Behrendt CA, Baumgartner I, Belch J, Back M, Fitridge R, et al. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. Eur J Vasc Endovasc Surg. 2024;67(1):9-96.
37. Froud JLJ, Landin M, Wafi A, White S, Bearne L, Patel A, et al. Rate and Predictors of Disease Progression in Patients with Conservatively Managed Intermittent Claudication: A Systematic Review. Ann Vasc Surg. 2025;112:183-92.
38. Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S. Long-term survival and fate of the leg in de novo intermittent claudication. Eur Heart J Qual Care Clin Outcomes. 2017;3(3):208-15.
39. Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. J Vasc Surg. 2015;62(6):1642-51 e3.
40. Premaratne S, Newman J, Hobbs S, Garnham A, Wall M. Meta-analysis of direct surgical versus endovascular revascularization for aortoiliac occlusive disease. J Vasc Surg. 2020;72(2):726-37.
41. Jongkind V, Akkersdijk GJ, Yeung KK, Wisselink W. A systematic review of endovascular treatment of extensive aortoiliac occlusive disease. J Vasc Surg. 2010;52(5):1376-83.

42. Yang M, Zhang B, Niu G, Yan Z, Tong X, Zou Y. Long-term results of endovascular reconstruction for aortoiliac occlusive disease. Quant Imaging Med Surg. 2021;11(4):1303-12.
43. Piffaretti G, Fargion AT, Dorigo W, Pulli R, Gattuso A, Bush RL, et al. Outcomes From the Multicenter Italian Registry on Primary Endovascular Treatment of Aortoiliac Occlusive Disease. J Endovasc Ther. 2019;26(5):623-32.
44. Taeymans K, Groot Jebbink E, Holewijn S, Martens JM, Versluis M, Goverde P, et al. Three-year outcome of the covered endovascular reconstruction of the aortic bifurcation technique for aortoiliac occlusive disease. J Vasc Surg. 2018;67(5):1438-47.
45. Indes JE, Mandawat A, Tuggle CT, Muhs B, Sosa JA. Endovascular procedures for aorto-iliac occlusive disease are associated with superior short-term clinical and economic outcomes compared with open surgery in the inpatient population. J Vasc Surg. 2010;52(5):1173-9, 9 e1.
46. Rocha-Neves J, Ferreira A, Sousa J, Pereira-Neves A, Vidoedo J, Alves H, et al. Endovascular Approach Versus Aortobifemoral Bypass Grafting: Outcomes in Extensive Aortoiliac Occlusive Disease. Vasc Endovascular Surg. 2020;54(2):102-10.
47. Leville CD, Kashyap VS, Clair DG, Bena JF, Lyden SP, Greenberg RK, et al. Endovascular management of iliac artery occlusions: extending treatment to TransAtlantic Inter-Society Consensus class C and D patients. J Vasc Surg. 2006;43(1):32-9.
48. Bekken JA, Jongsma H, de Vries JP, Fioole B. Self-expanding stents and aortoiliac occlusive disease: a review of the literature. Med Devices (Auckl). 2014;7:99-105.
49. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2017.
50. Sachwani GR, Hans SS, Khoury MD, King TF, Mitsuya M, Rizk YS, et al. Results of iliac stenting and aortofemoral grafting for iliac artery occlusions. J Vasc Surg. 2013;57(4):1030-7.
51. Danczyk RC, Mitchell EL, Petersen BD, Edwards J, Liem TK, Landry GJ, et al. Outcomes of open operation for aortoiliac occlusive disease after failed endovascular therapy. Arch Surg. 2012;147(9):841-5.
52. Madigan MC, Farber A, Rybin DV, Doros G, Robinson WP, 3rd, Siracuse JJ, et al. Younger patients have worse outcomes after peripheral endovascular interventions for suprainguinal arterial occlusive disease. J Vasc Surg. 2021;73(5):1715-22.
53. Schneider PA. Endovascular or open surgery for aortoiliac occlusive disease? Cardiovasc Surg. 2002;10(4):378-82.
54. Perez S, Thandra S, Mellah I, Kraemer L, Ross E. Machine Learning in Vascular Medicine: Optimizing Clinical Strategies for Peripheral Artery Disease. Curr Cardiovasc Risk Rep. 2024;18(12):187-95.
55. Smolderen KG, Alabi O, Collins TC, Dennis B, Goodney PP, Mena-Hurtado C, et al. Advancing Peripheral Artery Disease Quality of Care and Outcomes Through Patient-Reported Health Status Assessment: A Scientific Statement From the American Heart Association. Circulation. 2022;146(20):e286-e97.
56. Beckman JA, Schneider PA, Conte MS. Advances in Revascularization for Peripheral Artery Disease: Revascularization in PAD. Circ Res. 2021;128(12):1885-912.
57. Butala NM, Raja A, Xu J, Strom JB, Schermerhorn M, Beckman JA, et al. Association of Frailty With Treatment Selection and Long-Term Outcomes Among Patients With Chronic Limb-Threatening Ischemia. J Am Heart Assoc. 2021;10(24):e023138.
58. Wang Y, Wu X, Hu X, Yang Y. Prevalence of frailty in patients with lower extremity peripheral arterial disease: A systematic review and meta-analysis. Ageing Res Rev. 2022;82:101748.
59. Megale AB, Wolosker N, Kalil VM, Nigro JM, Wakisaka CS, Dias BO, et al. Aortic calcium score predicts early outcomes in aortoiliac revascularization. Einstein (Sao Paulo). 2025;23:eAO0527.

60. Ceyhun G, Engin MC. The Monocyte/High Density Lipoprotein Cholesterol Ratio (MHR) as an Indicator of the Need for Amputation in Patients With Peripheral Artery Disease Developing Critical Limb Ischemia. Angiology. 2021;72(3):268-73.
61. Cicek MC, Dagli M, Yilmaz IS, Baysal AN, Durgut K. Admission monocyte to high density lipoprotein cholesterol ratio predicts amputation in patients undergoing embolectomy for acute lower extremity ischemia. Eur Rev Med Pharmacol Sci. 2022;26(13):4735-43.
62. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes. Adv Chronic Kidney Dis. 2014;21(6):460-71.
63. Serra R, Bracale UM, Ielapi N, Del Guercio L, Di Taranto MD, Sodo M, et al. The Impact of Chronic Kidney Disease on Peripheral Artery Disease and Peripheral Revascularization. Int J Gen Med. 2021;14:3749-59.
64. Nobrega L, Pereira-Neves A, Duarte-Gamas L, Dias PP, Azevedo-Cerqueira A, Ribeiro H, et al. Outcome Analysis Using the Modified Frailty Index-5 in Patients With Complex Aortoiliac Disease. Ann Vasc Surg. 2022;79:153-61.
65. Pereira-Neves A, Dias L, Fragao-Marques M, Vidoedo J, Ribeiro H, Andrade JP, et al. Monocyte Count as a Predictor of Major Adverse Limb Events in Aortoiliac Revascularization. J Clin Med. 2024;13(21).
66. Alves M, Pias AD, Marques J, Miranda C, Pereira-Neves A, Shahat M, et al. Chronic kidney disease as a predictor of long-term adverse cardiovascular outcomes in patients with aortoiliac disease: a prospective cohort study. J Cardiovasc Surg (Torino). 2025;66(2):109-19.
67. Pereira-Neves A, Rocha-Neves J, Costa-Pereira T, Ribeiro H, Dias LR, Duarte-Gamas L, et al. Iliac Calcium Score thresholds predict cardiovascular and limb-related outcomes in TASC D aortoiliac disease. Front Med (Lausanne). 2025;12:1655229.
68. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, et al. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. Int J Surg. 2019;72:156-65.
69. Doody P, Lord JM, Greig CA, Whittaker AC. Frailty: Pathophysiology, Theoretical and Operational Definition(s), Impact, Prevalence, Management and Prevention, in an Increasingly Economically Developed and Ageing World. Gerontology. 2023;69(8):927-45.
70. Welsh SA, Pearson RC, Hussey K, Brittenden J, Orr DJ, Quinn T. A systematic review of frailty assessment tools used in vascular surgery research. J Vasc Surg. 2023;78(6):1567-79 e14.
71. Araujo-Andrade L, Rocha-Neves JP, Duarte-Gamas L, Pereira-Neves A, Ribeiro H, Pereira-Macedo J, et al. Prognostic effect of the new 5-factor modified frailty index in patients undergoing carotid endarterectomy with regional anesthesia - A prospective cohort study. Int J Surg. 2020;80:27-34.
72. Li R, Sidawy A, Nguyen BN. The 5-Factor Modified Frailty Index is a Concise and Effective Predictor of 30-Day Adverse Outcomes in Carotid Endarterectomy. J Surg Res. 2024;296:507-15.
73. Barbey SM, Scali ST, Kubilis P, Beck AW, Goodney P, Giles KA, et al. Interaction between frailty and sex on mortality after elective abdominal aortic aneurysm repair. J Vasc Surg. 2019;70(6):1831-43.
74. Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. J Vasc Surg. 2015;61(2):324-31.
75. Schaller MS, Ramirez JL, Gasper WJ, Zahner GJ, Hills NK, Grenon SM. Frailty Is Associated with an Increased Risk of Major Adverse Cardiac Events in Patients with Stable Claudication. Ann Vasc Surg. 2018;50:38-45.
76. Brahmbhatt R, Brewster LP, Shafii S, Rajani RR, Veeraswamy R, Salam A, et al. Gender and frailty predict poor outcomes in infrainguinal vascular surgery. J Surg Res. 2016;201(1):156-65.
77. Ali TZ, Lehman EB, Aziz F. Modified Frailty Index Can Be Used to Predict Adverse Outcomes and Mortality after Lower Extremity Bypass Surgery. Ann Vasc Surg. 2018;46:168-77.
78. Gonzalez L, Kassem M, Owora AH, Seligson MT, Richards CY, Monita MM, et al. Frailty and Biomarkers of Frailty Predict Outcome in Veterans After Open and Endovascular Revascularization. J Surg Res. 2019;243:539-52.
79. Fang ZB, Hu FY, Arya S, Gillespie TW, Rajani RR. Preoperative frailty is predictive of complications after major lower extremity amputation. J Vasc Surg. 2017;65(3):804-11.

80. Chopra A, Azarbal AF, Jung E, Abraham CZ, Liem TK, Landry GJ, et al. Ambulation and functional outcome after major lower extremity amputation. J Vasc Surg. 2018;67(5):1521-9.
81. D'Cruz R T, Chong TT, Tan TF, Ting ZYP, Lee QWS, Wong TH, et al. The Modified Frailty Index Does Not Predict Mortality After Major Lower Extremity Amputation for Peripheral Arterial Disease in an Asian Population. Ann Vasc Surg. 2020;69:298-306.
82. Zambetti BR, Plant J, Liang W, Toursavadkohi S. Impact of operative approach and patient frailty on outcomes for aorto-iliac occlusive disease with critical limb threatening ischemia. Vascular. 2025;33(4):853-60.
83. Jankowski J, Floege J, Fliser D, Bohm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-72.
84. Nathan DP, Tang GL. The impact of chronic renal insufficiency on vascular surgery patient outcomes. Semin Vasc Surg. 2014;27(3-4):162-9.
85. Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157(7):471-81.
86. Glassock RJ, Rule AD. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. Nephron. 2016;134(1):25-9.
87. Feldreich T, Nowak C, Carlsson AC, Ostgren CJ, Nystrom FH, Sundstrom J, et al. The association between plasma proteomics and incident cardiovascular disease identifies MMP-12 as a promising cardiovascular risk marker in patients with chronic kidney disease. Atherosclerosis. 2020;307:11-5.
88. Tanriover C, Copur S, Mutlu A, Peltek IB, Galassi A, Ciceri P, et al. Early aging and premature vascular aging in chronic kidney disease. Clin Kidney J. 2023;16(11):1751-65.
89. 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):1296-305.
90. Nayor M, Larson MG, Wang N, Santhanakrishnan R, Lee DS, Tsao CW, et al. The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail. 2017;19(5):615-23.
91. Jia XB, Hou XH, Ma QB, Cai XW, Li YR, Mu SH, et al. Assessment of Renal Function and Risk Factors for Chronic Kidney Disease in Patients With Peripheral Arterial Disease. Angiology. 2017;68(9):776-81.
92. Bourrier M, Ferguson TW, Embil JM, Rigatto C, Komenda P, Tangri N. Peripheral Artery Disease: Its Adverse Consequences With and Without CKD. Am J Kidney Dis. 2020;75(5):705-12.
93. Back M, Yurdagul A, Jr., Tabas I, Oorni K, Kovanen PT. Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. Nat Rev Cardiol. 2019;16(7):389-406.
94. Ghattas A, Griffiths HR, Devitt A, Lip GY, Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? J Am Coll Cardiol. 2013;62(17):1541-51.
95. Jaipersad AS, Lip GY, Silverman S, Shantsila E. The role of monocytes in angiogenesis and atherosclerosis. J Am Coll Cardiol. 2014;63(1):1-11.
96. Zhou H, Scatena M, Tu LN, Giachelli CM, Nigam V. Monocyte adhesion to and transmigration through endothelium following cardiopulmonary bypass shearing is mediated by IL-8 signaling. Front Cardiovasc Med. 2024;11:1454302.
97. Song Y, Zhao Y, Shu Y, Zhang L, Cheng W, Wang L, et al. Combination model of neutrophil to high-density lipoprotein ratio and system inflammation response index is more valuable for predicting peripheral arterial disease in type 2 diabetic patients: A cross-sectional study. Front Endocrinol (Lausanne). 2023;14:1100453.
98. Li C, Li Q, Ou J, Li W, Guan B, Lu Y, et al. Relationship between Monocytes and Stenosis-Related Autologous Arteriovenous Fistula Dysfunction. Blood Purif. 2022;51(3):226-32.
99. Cosarca MC, Halmaciu I, Muresan AV, Suciu BA, Molnar C, Russu E, et al. Neutrophil-to-lymphocyte, platelet-to-lymphocyte and lymphocyte-to-monocyte ratios are associated with amputation rates in patients with peripheral arterial disease and diabetes mellitus who underwent revascularization: A Romanian regional center study. Exp Ther Med. 2022;24(5):703.

100. Khan SS, Post WS, Guo X, Tan J, Zhu F, Bos D, et al. Coronary Artery Calcium Score and Polygenic Risk Score for the Prediction of Coronary Heart Disease Events. JAMA. 2023;329(20):1768-77.
101. Nguyen HL, Liu J, Del Castillo M, Shah T. Role of Coronary Calcium Score to Identify Candidates for ASCVD Prevention. Curr Atheroscler Rep. 2019;21(12):53.
102. Bell KJL, White S, Hassan O, Zhu L, Scott AM, Clark J, et al. Evaluation of the Incremental Value of a Coronary Artery Calcium Score Beyond Traditional Cardiovascular Risk Assessment: A Systematic Review and Meta-analysis. JAMA Intern Med. 2022;182(6):634-42.
103. Lee S, Kalra K, Kashikar A, Redpath B, Bernheim A, Brewster L, et al. Evaluation of Lower Extremity Calcium Score as a Measure of Peripheral Arterial Disease Burden and Amputation Risk. Ann Vasc Surg. 2023;95:154-61.
104. Megale A, Wolosker N, Kalil V, Nigro J, Wakisaka C, Dias B, et al. Calcium Score Predicts Mortality After Revascularization in Critical Limb Ischemia. J Endovasc Ther. 2022;29(3):438-43.
105. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv. 2014;83(6):E212-20.
106. Davis B, Marin D, Hurwitz LM, Ronald J, Ellis MJ, Ravindra KV, et al. Application of a Novel CT-Based Iliac Artery Calcification Scoring System for Predicting Renal Transplant Outcomes. AJR Am J Roentgenol. 2016;206(2):436-41.
107. Huang CL, Wu IH, Wu YW, Hwang JJ, Wang SS, Chen WJ, 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.
108. Kang IS, Lee W, Choi BW, Choi D, Hong MK, Jang Y, et al. Semiquantitative assessment of tibial artery calcification by computed tomography angiography and its ability to predict infrapopliteal angioplasty outcomes. J Vasc Surg. 2016;64(5):1335-43.
109. Dong Y, Liu Y, Liao H, Cheng P, Liu X, Huang W, et al. Circumferential degree of tibial artery calcification is associated with infrapopliteal endovascular revascularization outcomes in patients with chronic limb-threatening ischemia. Int Angiol. 2023;42(6):528-36.
110. Konijn LC, Takx RA, de Jong PA, Spreen MI, Veger HT, Mali WP, et al. Arterial calcification and long-term outcome in chronic limb-threatening ischemia patients. Eur J Radiol. 2020;132:109305.
111. Zettervall SL, Marshall AP, Fleser P, Guzman RJ. Association of arterial calcification with chronic limb ischemia in patients with peripheral artery disease. J Vasc Surg. 2018;67(2):507-13.
112. Jeremias Z, Rat N, Benedek I, Rapolti E, Ratiu M, Muresan A, et al. High iliac calcium score is associated with increased severity and complexity of peripheral arterial disease and predicts global atherosclerotic burden. Vasa. 2018;47(5):377-86.
113. Kojima S, Tokuda T, Tanaka A, Yoshioka N, Yamaguchi K, Yanagiuchi T, et al. One-year clinical outcomes of delayed referral and subsequent management in chronic limb-threatening ischemia. J Vasc Surg. 2025.