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Assessing mid to long term amputation-free survival rates in chronic limb-threatening ischemia; a study of hybrid vascular techniques

Cristian Traian Paius[1,2], Vlad Denis Constantin[1,3], Alexandru Carap[1,3], Andrei Tarus[2,4*], Grigore Tinica[2,4]

[1] *St. Pantelimon Emergency Clinical Hospital, Department of Surgery, Bucharest, Romania*

[2] *Grigore T. Popa University of Medicine and Pharmacy, Department of Cardiac Surgery, Iasi, Romania*

[3] *Carol Davila University of Medicine and Pharmacy, Department of General Surgery, Bucharest, Romania*

[4] *Prof. Dr. George I.M. Georgescu Institute of Cardiovascular Diseases, Department of Cardiovascular Surgery, Iasi, Romania*

ABSTRACT

Introduction. Chronic limb-threatening ischemia (CLTI) is a debilitating condition characterized by inadequate blood supply to the lower extremities, often leading to tissue damage, ulcers, and limb loss. Amputation-free survival (AFS) serves as a crucial measure in evaluating interventions and managing CLTI, emphasizing limb preservation, functional restoration, and prevention of recurrent ischemic events. *Objectives*. This study aimed to assess mid to long term AFS in CLTI patients treated with hybrid vascular techniques. *Materials and Methods*. Conducted over 24 months at the Emergency Hospital of Saint Pantelimon in Bucharest, Romania, the study enrolled 62 adult CLTI patients, tracking them postoperatively. Kaplan Meyer survival curves were used to assess AFS rates. *Results*. Findings revealed a high prevalence of cardiovascular risk factors among participants, with most undergoing infrainguinal bypass revascularization in association with proximal and/or distal angioplasty with or without stenting. Prior to intervention, the majority of patients exhibited advanced stages of ischemia, with trophic lesions predominantly confined to the toes. Analysis of AFS revealed a decline over time, with the majority of amputations occurring within three months post-revascularization. Notably, 64.5% of patients achieved amputation free complete wound healing within the first year, with 90% of them achieving this within the first six months. Complex wounds were associated with prolonged healing. *Conclusions.* The study shows a 75.2% AFS rate at 24 months, highlighting the effectiveness of hybrid revascularization techniques and proper wound care in optimizing outcomes for CLTI patients.

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***Corresponding author:**

Andrei Tarus,

Grigore T. Popa University of Medicine and Pharmacy, Department of Cardiac Surgery, Universității St. No. 16, Iasi, Romania

E-mail: andrei.tarus@umfiasi.com

Introduction

Chronic limb-threatening ischemia (CLTI) is a severe condition characterized by inadequate blood supply to the lower extremities, leading to tissue damage, ulcers, gangrene, and ultimately, the threat of limb loss. It poses a significant challenge in vascular medicine, affecting millions worldwide and representing a major cause of morbidity and mortality while imposing substantial burdens on healthcare systems [1]. The condition arises from advanced peripheral arterial disease, often compounded by diabetes, hypertension, and other comorbidities and it manifests with severe pain, non-healing wounds and tissue necrosis. Patients with CLTI face a myriad of challenges, including impaired mobility, chronic pain, increased risk of infection, and diminished quality of life while also facing a dire prognosis, with a high risk of major amputations and mortality [2].

Amputation-free survival (AFS) serves as a metric in assessing the effectiveness of revascularization interventions and the overall management of CLTI. It encompasses not only the preservation of the affected limb but also the restoration of functionality and the prevention of recurrent ischemic events. Achieving and maintaining amputation-free survival is paramount in preventing disability, reducing healthcare costs, and improving patient well-being [3]. Timely diagnosis and intervention are essential to halt disease progression and salvage affected

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limbs. Revascularization techniques, including endovascular interventions and surgical bypass grafting, aim to restore adequate blood flow to ischemic tissues, promoting wound healing and limb salvage. Moreover, interdisciplinary approaches involving wound care, medical therapy, and lifestyle modifications are integral to optimizing outcomes in CLTI patients [4]. Despite advancements in treatment modalities, challenges persist in optimizing outcomes for CLTI patients. Access to specialized care, resource limitations, and patient factors can impact treatment efficacy and amputation-free survival rates [5]. Chronic limb-threatening ischemia represents a complex vascular disorder, posing significant challenges to patients, clinicians, and healthcare systems. Amputation-free survival serves as a critical endpoint in evaluating the success of interventions and guiding treatment strategies. By prioritizing limb preservation and optimizing vascular health, we can mitigate the devastating consequences of CLTI and enhance patients' overall well-being and longevity.

Our objective was to assess the mid to long term amputation free survival rate for patients with chronic limb-threatening ischemia treated by hybrid techniques.

Materials and Methods

An observational study took place at the Emergency Hospital of Saint Pantelimon in Bucharest, Romania, from 2019 to 2022. This study enrolled 62 adult patients diagnosed with CLTI treated by hybrid vascular techniques (either infrainguinal bypass or common femoral thromboendarterectomy associated with distal and/or proximal balloon angioplasty with or without stenting) who were followed postoperatively for a period of 24 months. Standard follow-up appointments were scheduled at 3, 6, 12, and 24 months after revascularization.

Data collection took place both before revascularization and during follow-up examinations thereafter. Upon admission, general demographics, risk factors, and associated morbidities were evaluated. The incidence of subsequent minor and major amputations was closely monitored as the primary endpoint of this study. Minor amputations are defined as below the ankle amputations and major amputations include transtibial and transfemoral amputations.

We included adult patients diagnosed with CLTI presenting trophic ulcers or gangrene, with disease staging following international standards by using the Fontaine and WIFi classifications. The patients enrolled in this study also demonstrated effective communication and decision-making abilities and lacked any other documented conditions that significantly impaired their mobility such as paralysis, spinal cord injury, multiple sclerosis, cerebral palsy, et cetera.

Data analysis utilized the Kaplan-Meier survival function for assessing AFS. It's important to acknowledge that the collected data only pertains to moderate to high-risk patients who underwent hybrid revascularization techniques, which could introduce bias.

Approval for this study was granted by the research ethics committee of the Emergency Hospital of Saint Pantelimon in Bucharest, Romania.

Results

The average age was 74.5 years, with significantly more male participants. There was a high prevalence of cardiovascular risk factors and pre-existing conditions, most notably hypertension (82.3%), dyslipidemia (77.4%), smoking (69.4%) and diabetes (48.4%). All patients were classified as Fontaine stage IV at admission and more than two thirds underwent infrainguinal bypass revascularization with associated transluminal angioplasty with or without stenting. Detailed demographics, associated morbidities and risk factors can be found in Table 1.

Table 1. General demographics, associated morbidities and risk factors (n = 62)

Age, mean (SD)	74.5 (10.1)
Sex, male - n (%)	39 (62.9)
Associated morbidities and risk factors - n (%)	
Smoking	43 (69.4)
Diabetes	30 (48.4)
Dyslipidemia	48 (77.4)
Hypertension	51 (82.3)
Heart failure	29 (46.8)
Coronary artery disease	14 (22.6)
Cerebrovascular disease	23 (37.1)
Stroke	13 (21)
COPD	10 (16.1)
Chronic kidney disease (GFR< 30)	2 (3.2)
Intervention performed - n (%)	
Bypass + angioplasty/stenting	43 (69.4)
TEA + angioplasty/stenting	19 (30.6)

Abbreviations: GFR - Glomerular Filtration Rate, COPD - Chronic Obstructive Pulmonary Disease, TEA - Thromboendarterectomy

Prior to revascularization, patients were classified using the WIFi system to estimate amputation risk and revascularization benefit (Tables 2 and 3). Out of our 62 patients with trophic lesions, 71% were at a high risk of amputation without treatment, 27.4% had a moderate risk, and only one patient was deemed to have a low risk. More

than three-quarters exhibited advanced stages of ischemia, with 16.1% showing moderate ischemia and 6.5% demonstrating mild ischemia. The majority of patients had trophic lesions confined to their toes, while another 12.9% had extensive lesions on the forefoot. In 9.7% of cases, lesions were severe, extending to the ankle joint or heel. A significant benefit from revascularization was anticipated for the vast majority of patients, while a moderate benefit was expected for the remaining 6.4%. No patients fell into the categories of minor or minimal benefit.

Table 2. WIFi classification - Estimate risk of amputation at 12 months in the absence of treatment

	Ischemia 1 (6.5%)				**Ischemia 2** (16.1%)				**Ischemia 3** (77.4%)			
Wound 0 -												
Wound 1 (77.4%)		1.6%	4.8%			4.8%	8.1%		1.6%	16.1%	37.1%	3.2%
Wound 2 (12.9%)								1.6%	1.6%	1.6%	8.1%	
Wound 3 (9.7%)							1.6%		1.6%	1.6%	4.8%	
	Fi 0	Fi 1	Fi 2	Fi 3	Fi 0	Fi 1	Fi 2	Fi 3	Fi 0	Fi 1	Fi 2	Fi 3
Fi - Foot infection	very low risk -			low risk (1.6%)			moderate risk (27.4%)		high risk (71%)			

Table 3. WIFi classification - Revascularization benefit

	Ischemia 1 (6.5%)				**Ischemia 2** (16.1%)				**Ischemia 3** (77.4%)			
Wound 0 -												
Wound 1 (77.4%)		1.6%	4.8%			4.8%	8.1%		1.6%	16.1%	37.1%	3.2%
Wound 2 (12.9%)								1.6%	1.6%	1.6%	8.1%	
Wound 3 (9.7%)							1.6%		1.6%	1.6%	4.8%	
	Fi 0	Fi 1	Fi 2	Fi 3	Fi 0	Fi 1	Fi 2	Fi 3	Fi 0	Fi 1	Fi 2	Fi 3
Fi - Foot infection	minimum benefit -			low benefit -			medium benefit (6.4%)		high benefit (93.6%)			

We tracked limb amputation-free survival in our patients and found that the majority required amputations before the 3-month mark, leaving only 83.9% (95% CI: 0.72 - 0.91) of patients free from amputation. There was a moderate decrease at the 6 and 12-month intervals to 82.2% (95% CI: 0.70 - 0.90) and 75.2% (95% CI: 0.62 - 0.84), respectively. Following this interval, a plateau phase ensued during which no additional amputations occurred (Figure 1). A total of 27 amputations were performed, including 7 major amputations and 20 minor ones. Intraoperatively, 12 amputations of one or more digits were performed in addition to the revascularization procedure, with no transtibial or transfemoral amputations conducted. The remaining 15 amputations occurred within the first year postoperatively. Of the major amputations, more than half occurred within the first 30 days following revascularization, with three more within a 12-month interval.

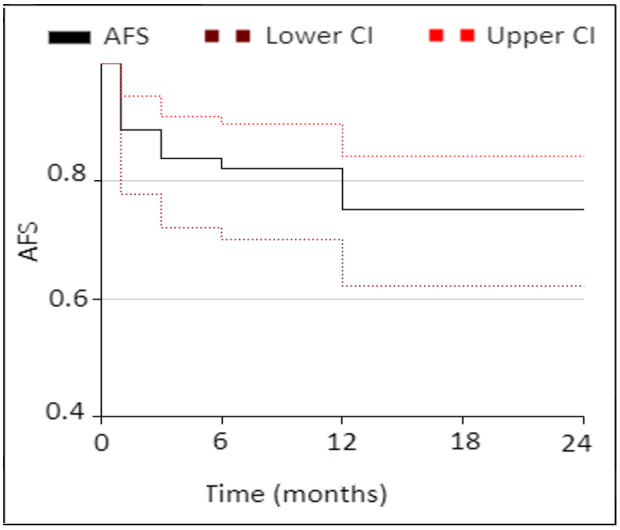


Figure 1. Amputation free survival at 24 months

Table 4. Total amputations

Time	Major amputations		Minor amputations	
	During	After	During	After
	Revascularization			
	0	7 (5.5%)	12 (9.4%)	8 (6.3%)
1 month	-	4	-	3
3 months	-	1	-	2
6 months	-	1	-	0
12 months	-	1	-	3
24 months	-	0	-	0

Table 5. Healed trophic lesions

	Amputations during revascularization		Re-amputations	
Trophic lesions at admission	Minor	Major	Minor	Major
62	12	0	3	2
Postoperative trophic lesions	Amputations after revascularization (total)		41.7%	
	Minor	Major		
50	5	5		
Healed trophic lesions				
40 (64.5%)				

Among the 8 postoperative minor amputations, 3 occurred within the first month, 2 within the first 3 months, and 3 more by the end of the first year (Table 4). The healing of trophic lesions played a crucial role in limb amputation-free survival. Of 12 limbs with amputations associating revascularization procedures, 41.7% required additional amputation. Of the remaining 50 patients with trophic lesions, 40 healed completely, representing 64.5% of the total wounds at admission (Table 5). All remaining lesions healed completely within the first year postoperatively. More than half healed within the first 3 months, and 90% of them within the first 6 months (Figure 2). Difficult, prolonged healing was associated with complex wounds involving deep fascia, tendons, and foot joints (Figures 3 and 4).

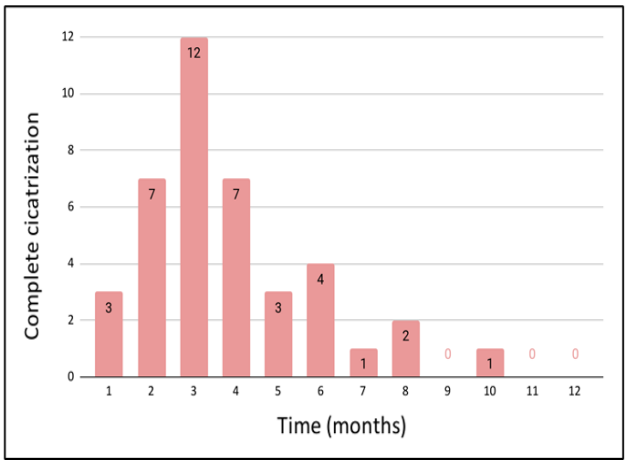


Figure 2. Complete cicatrization time

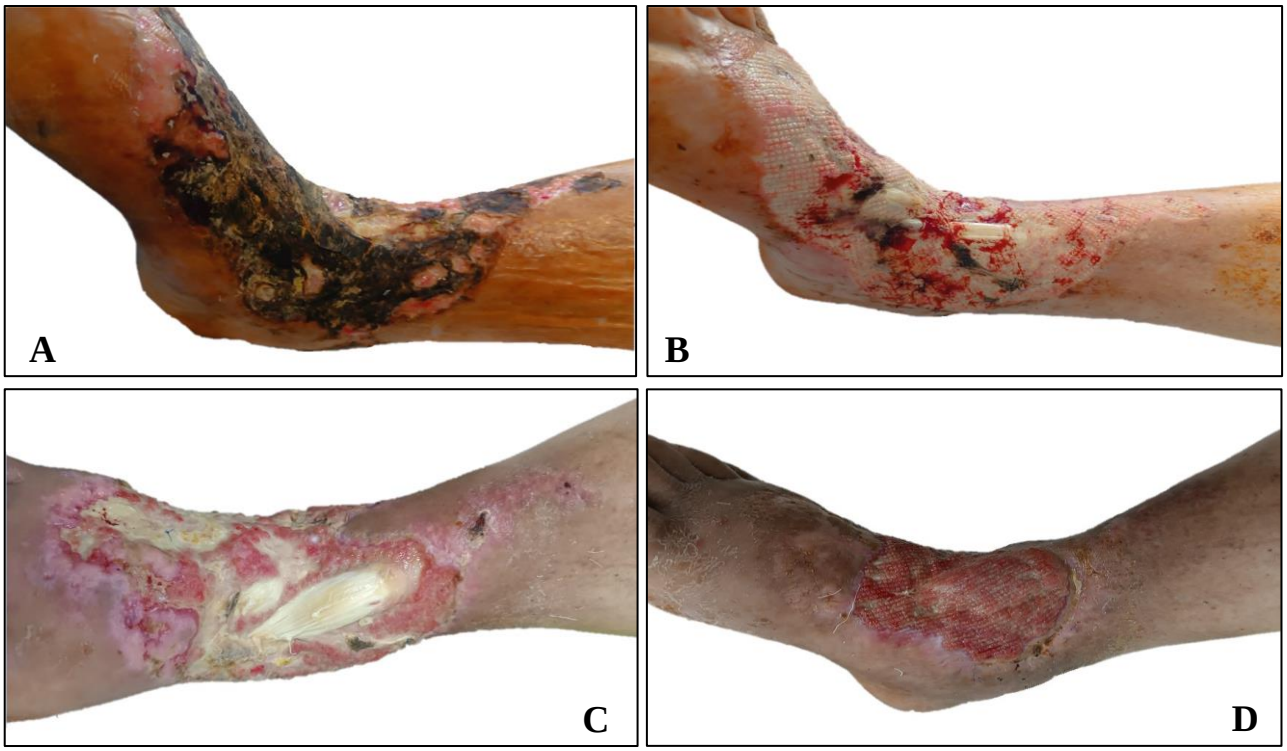


Figure 3. Complex trophic lesions complete healing: immediately after revascularization (A), postoperative (B), 1 month (C), 3 months (D)

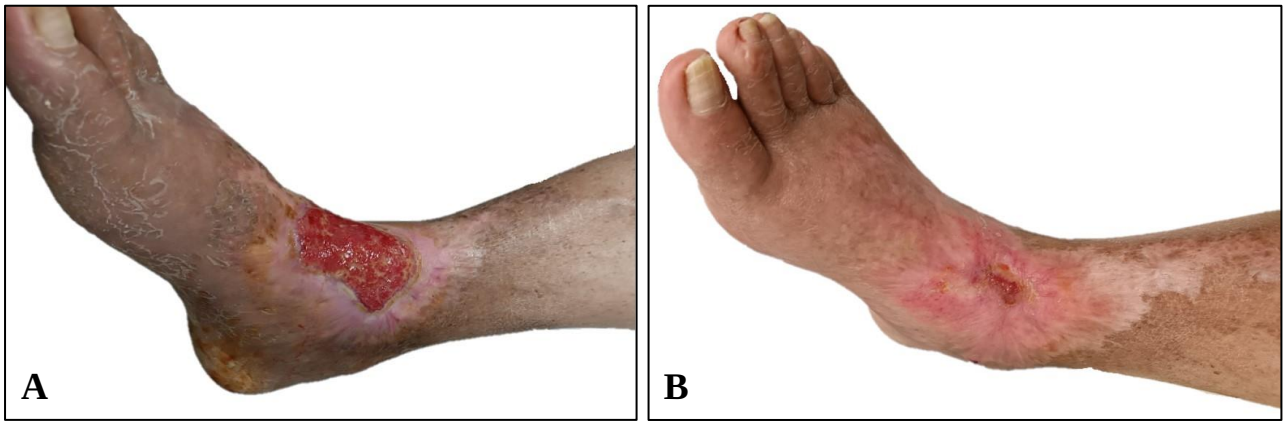


Figure 4. Complex trophic lesions complete healing: after 6 months (A) and after 7 months (B)

Discussions

Amputations represent a significant burden on patients, impacting them functionally, socially, and psychologically. Therefore, the primary aim of arterial vascular surgery is to prevent such procedures whenever possible. Patients afflicted with severe limb ischemia accompanied by gangrene or ulcers face a daunting amputation risk, which can soar up to 50% within the initial year without timely revascularization [6]. Major amputations, such as above or below the knee, have far-reaching implications for individuals afflicted by CLTI. Beyond the physical loss of limb, amputations engender profound psychological distress, functional impairment, and social isolation. Moreover, major amputations serve as an independent risk factor, contributing to an alarming rise in perioperative mortality by as much as 20%, with a staggering 85% mortality rate within five years [7].

The spectrum of amputation-free survival spans a range of factors, influenced by multiple independent variables. Interestingly, this metric doesn't always align with measures of primary, secondary, or assisted patency, underscoring the complexity of vascular outcomes. Furthermore, intriguing observations reveal that certain patients with previously healed trophic lesions following revascularization may remain asymptomatic even when re-occlusion of treated segments occurs, thanks to the compensatory mechanism of collateral circulation.

To contextualize our findings, we embarked on an extensive review of relevant studies investigating amputation-free intervals among individuals grappling with critical ischemia. Our analysis sought to categorize these studies based on the modality of revascularization employed, shedding light on the efficacy and nuances of different treatment approaches. For instance, one study meticulously tracking 111 patients who underwent endovascular revascularization revealed a sobering outcome: merely 59% ± 1% retained viable limbs after the span of twelve months [8]. In a separate investigation involving a sizable cohort of 3505 patients with chronic limb-threatening ischemia, revascularization emerged as a crucial determinant of amputation-free survival. Notably, the two-year amputation-free survival rate stood at 63.7% for endovascular interventions and 67.8% for surgical interventions, suggesting a noteworthy correlation with oncological factors [9]. Adding depth to our understanding, landmark trials like the BASIL study provided invaluable insights through a randomized controlled trial involving 452 patients with infrainguinal arterial lesions treated either surgically or endovascularly. The results delineated an intricate pattern of amputation-free survival rates at various intervals, showcasing the nuanced interplay between treatment modalities and patient outcomes [10]. Furthermore, a breadth of literature underlines the pivotal role of endovascular revascularization in securing favorable amputation-free survival rates, with reports citing impressive figures such as a two-year amputation-free survival rate of 75.4% [11]. These findings are echoed by other studies, which corroborate the sustained efficacy of endovascular approaches over extended periods, underscoring their potential to mitigate the burden of critical ischemia [12,13].

In our patient cohort, we observed an amputation-free survival rate of 75.2%, mirroring and even exceeding the trends identified in existing literature. This convergence with established data reinforces the validity and generalizability of our findings, offering optimism for improved patient outcomes in the realm of arterial vascular surgery.

Wound healing in CLTI patients is crucial for improving AFS and is influenced by multiple factors, including impaired perfusion, tissue hypoxia, inflammation, infection, and comorbidities such as diabetes and renal disease [14,15]. The compromised blood flow to the affected limb impedes the delivery of oxygen, nutrients, and immune cells essential for proper wound healing, resulting in delayed or non-healing ulcers and a heightened risk of infection and amputation [16-18]. CLTI-associated

wounds present unique challenges due to the underlying vascular pathology and the presence of multiple comorbidities. These wounds often exhibit poor granulation tissue formation, impaired epithelialization, and a protracted inflammatory phase, making them resistant to standard wound care interventions [19]. Moreover, the chronic nature of CLTI exacerbates wound complexity and diminishes the likelihood of spontaneous healing, necessitating aggressive and multidisciplinary approaches to wound management and, in some cases, not requiring revascularization [20,21]. After revascularization, wound care strategies should be tailored for each patient. Advanced wound care modalities, including negative pressure wound therapy, bioengineered skin substitutes, growth factors, and hyperbaric oxygen therapy, play a pivotal role in augmenting wound healing in CLTI patients [22-25]. These interventions aim to create a conducive wound environment, stimulate cellular proliferation and angiogenesis, and expedite tissue regeneration [18]. Furthermore, addressing comorbidities such as diabetes, hypertension, and renal insufficiency is critical for optimizing wound healing outcomes [14,26]. Glycemic control, blood pressure management, and aggressive infection control measures are integral components of a comprehensive treatment strategy aimed at mitigating risk factors and promoting wound resolution [26,27]. Future research endeavors should focus on refining diagnostic algorithms, exploring novel therapies, and addressing healthcare disparities to improve CLTI management and outcomes globally.

Conclusions

The amputation-free survival rate at 24 months was 75.2%, with over half of the major amputations occurring within the initial 30 days following revascularization. Within the first year, 64.5% of patients attained amputation-free full wound healing after revascularization, with 90% of them achieving this milestone within the first 6 months.

Highlights

- ✓ The study on chronic limb-threatening ischemia underscores the paramount importance of amputation-free survival as a critical outcome measure in vascular surgery.
- ✓ It highlights the efficiency of hybrid revascularization techniques for limb loss prevention as well as its role in complex wound healing.

Contributions

Conceptualization: Cristian Paius and Alexandru Carap; Data curation: Cristian Paius; Formal analysis: Alexandru Carap; Investigation: Cristian Paius; Methodology: Vlad Denis Constantin, Cristian Paius; Project administration: Grigore Tinica, Vlad Denis Constantin; Resources: Andrei Tarus; Supervision: Grigore Tinica; Validation: Vlad Denis Constantin and Grigore Tinca; Visualization: Alexandru Carap, Andrei Tarus; Writing—original draft: Cristian Paius; Writing—review and editing: Andrei Tarus.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

References

1. Duff S, Mafilios MS, Bhounsule P, Hasegawa JT. The burden of critical limb ischemia: a review of recent literature. *Vasc Health Risk Manag*. 2019;15:187-208. doi:10.2147/VHRM.S209241
2. Wübbeke LF, Naves CCLM, Daemen JHC, Jacobs MJ, Mees BME. Editor's Choice - Mortality and Major Amputation after Revascularisation in Octogenarians Versus Non-Octogenarians with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg*. 2020;60(2):231-241. doi:10.1016/j.ejvs.2020.04.027
3. Ventoruzzo G, Mazzitelli G, Ruzzi U, Liistro F, Scatena A, Martelli E. Limb Salvage and Survival in Chronic Limb-Threatening Ischemia: The Need for a Fast-Track Team-Based Approach. *J Clin Med*. 2023; 12(18):6081. Published 2023 Sep 20. doi:10.3390/jcm12186081
4. Hawkins BM, Li J, Wilkins LR, Carman TL, Reedet AB, al. SCAI/ACR/APMA/SCVS/SIR/SVM/SVS/VESS Position Statement on Competencies for Endovascular Specialists Providing CLTI Care. *Vasc Med*. 2022;27(4):405-414. doi:10.1177/1358863X221095278
5. Berchiolli R, Bertagna G, Adami D, Canovaro F, Torri L, Troisi N. Chronic Limb-Threatening Ischemia and the Need for Revascularization. *J Clin Med*. 2023;12(7):2682. Published 2023 Apr 4. doi:10.3390/jcm12072682
6. Benoit E, O'Donnell TF Jr, Kitsios GD, Iafrati MD. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J Vasc Surg*. 2012;55(3):781-789. doi:10.1016/j.jvs.2011.10.089
7. Verwer MC, Wijnand JGJ, Teraa M, Verhaar MC, de Borst GJ. Long Term Survival and Limb Salvage in Patients With Non-Revascularisable Chronic Limb Threatening Ischaemia. *Eur J Vasc Endovasc Surg*. 2021;62(2):225-232. doi:10.1016/j.ejvs.2021.04.003
8. Joshi GS, Zhang SM, Wang K, et al. Predictors of Amputation-free Survival after Endovascular Intervention for Chronic Limb-Threatening Ischemia in the Modern era. *Ann Vasc Surg*. 2022;86: 268-276. doi:10.1016/j.avsg.2022.04.052
9. Miyata T, Kumamaru H, Mii S, et al. Prediction Models for Two Year Overall Survival and Amputation Free Survival After Revascularisation for Chronic Limb Threatening Ischaemia

[published correction appears in Eur J Vasc Endovasc Surg. 2023 Apr;65(4):616]. *Eur J Vasc Endovasc Surg*. 2022;64(4):367-376. doi:10.1016/j.ejvs.2022.05.038

10. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg*. 2010;51(5 Suppl):5S-17S. doi:10.1016/j.jvs.2010.01.073
11. Adams GL, Lichtenberg M, Wissgott C, et al. Twenty-Four Month Results of Tack-Optimized Balloon Angioplasty Using the Tack Endovascular System in Below-the-Knee Arteries. *J Endovasc Ther*. 2023;30(3):393-400. doi:10.1177/15266028221083462
12. Strøm M, Konge L, Lönn L, Schroeder TV, Rørdam P. Amputation-Free Survival after Crural Percutaneous Transluminal Angioplasty for Critical Limb Ischemia. *Scand J Surg*. 2016;105(1):42-48. doi: 10.1177/1457496915571403
13. Lebreton O, Fels A, Compagnon A, et al. Amputation-free survival in the long-term follow-up and gender-related characteristics in patients revascularized for critical limb ischemia. *J Med Vasc.* 2023;48(3-4): 105-115. doi:10.1016/j.jdmv.2023.10.002
14. Chang H, Rockman CB, Jacobowitz GR, et al. Interplay of Diabetes Mellitus and End-Stage Renal Disease in Open Revascularization for Chronic Limb-Threatening Ischemia. *Ann Vasc Surg*. 2021;72:552-562. doi:10.1016/j.avsg.2020.10.003
15. Conte MS, Bradbury AW, Kolh P, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia [published correction appears in Eur J Vasc Endovasc Surg. 2020 Mar;59(3):492-493] [published correction appears in Eur J Vasc Endovasc Surg. 2020 Jul;60(1):158-159]. *Eur J Vasc Endovasc Surg*. 2019;58(1S):S1-S109.e33. doi:10.1016/j.ejvs.2019.05.006
16. Paius CT, Constantin VD, Carap A, Tarus A, Tinica G. Revascularization impact: quality of life enhancement in chronic limb-threatening ischemia. *J Mind Med Sci*. 2023;10(2):321-329. doi:10.22543/2392-7674.1441
17. Karimi A, Lauria AL, Aryavand B, Neville RF. Novel Therapies for Critical Limb-Threatening Ischemia. *Curr Cardiol Rep*. 2022;24(5): 513-517. doi:10.1007/s11886-022-01669-6
18. Constantin VD, Socea B, Gaspar BS, Epistatu D, Paunica I, Dumitriu AS, Paunica S, Silaghi A. Limb amputations; etiopathogenesis, diagnosis and the multidisciplinary therapeutic approach. *J Mind Med Sci*. 2022;9(2):209-223. doi: 10.22543/2392-7674.1361
19. Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care*. 2012;25(7):304-314. doi: 10.1097/01.ASW.0000416006.55218.d0
20. Gabel J, Bianchi C, Possagnoli I, et al. Multidisciplinary approach achieves limb salvage without revascularization in patients with mild to moderate ischemia and tissue loss. *J Vasc Surg*. 2020;71(6):2073-2080.e1. doi:10.1016/j.jvs.2019.07.103
21. Tanasescu D, Moisin A, Fleaca R, Popa C, Bacila C, Mohor C, Gherman CD, Gaspar B, Tanasescu C. Modern therapeutic options in diabetic foot ulcer. *J Mind Med Sci*. 2022;9(2):285-293. doi: 10.22543/2392-7674.1351
22. Huerta CT, Voza FA, Ortiz YY, Liu ZJ, Velazquez OC. Mesenchymal stem cell-based therapy for non-healing wounds due to chronic limb-threatening ischemia: A review of preclinical and clinical studies. *Front Cardiovasc Med*. 2023;10:1113982. Published 2023 Feb 1. doi:10.3389/fcvm.2023.1113982
23. Chinaroonchai K. Oxygen Therapy to Enhance Wound Healing After Revascularization. *Int J Low Extrem Wounds*. 2024;23(1):49-54. doi:10.1177/15347346231215201
24. Chiang N, Rodda OA, Sleigh J, Vasudevan T. Effects of topical negative pressure therapy on tissue oxygenation and wound healing in vascular foot wounds. *J Vasc Surg*. 2017;66(2):564-571. doi: 10.1016/j.jvs.2017.02.050
25. Gormley S, Hart O, French S, O'Shea C, Khashram M. The use of fetal bovine acellular dermal matrix in severe diabetic foot ulceration and threatened limbs with tissue loss the use of FBADM as an adjunct for complex wounds. *Vascular*. Published online November 22, 2022. doi:10.1177/17085381221141115
26. Vivekanand V, Motukuru V, Kolalu S, Rangaswamy GK, Jain P. Effect of Comorbidities on Outcomes of Infrapopliteal Angioplasty in Patients with Chronic Limb-Threatening Ischemia. *Innovations (Phila)*. 2022;17(5):392-400. doi:10.1177/15569845221123327
27. Campbell DB, Sobol CG, Stacy MR, et al. Revascularization Outcomes Stratified by Glycemic Control in Patients with Diabetes Mellitus and Chronic Limb-Threatening Ischemia. *Ann Vasc Surg*. 2024;100:91-100. doi:10.1016/j.avsg.2023.10.018