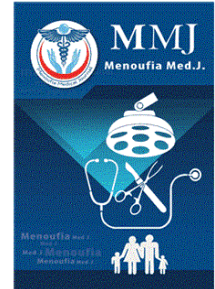




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## Time For Wound Healing After Revascularization In Patients With Critical Limb Ischemia

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## ORIGINAL STUDY

# Time for Wound Healing After Revascularization in Patients with Critical Limb Ischemia

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### Abstract

**Objectives:** This prospective observational study aimed to investigate rates of wound healing, survival analysis of wound healing time, and predictors of wound healing in patients undergoing revascularization for critical limb ischemia.

**Background:** Wound healing after revascularization procedures is crucial for patients with critical limb ischemia (CLI) to prevent limb loss and improve outcomes.

**Patients and methods:** A total of 114 patients with CLI were included in the study. Demographic data, comorbidities, laboratory investigations, tissue loss characteristics, and wound healing rates were recorded. Survival analysis of wound healing time was conducted using Kaplan–Meier curves. Multivariate sequential logistic regression was performed to identify predictors of wound healing.

**Results:** The median age of patients was 60 years, with a predominance of males (64.9%) and smokers (45.6%). The majority of patients had diabetes (77.2%) and underwent endovascular intervention (85.96%). Tissue loss characteristics revealed a high prevalence of gangrene (51.8%) and ulcers (42.1%). The overall wound healing rate was 43%, with a median healing duration of 112 days. Multivariate analysis identified age younger than 60 years, ambulatory status, and absence of wound infection as significant predictors of wound healing.

**Conclusion:** This study provides valuable insights into the factors associated with wound healing after revascularization for CLI. The findings underscore the importance of early intervention and targeted management strategies to optimize wound healing outcomes in this high-risk patient population. Further research is warranted to validate these findings and develop tailored approaches to improve limb salvage and patient quality of life in CLI.

**Keywords:** Amputation, Critical limb ischemia, Peripheral arterial disease, Revascularization, Wound healing

## 1. Introduction

Critical limb ischemia (CLI) is a severe condition characterized by limb pain at rest or impending limb loss due to compromised blood flow [1]. Like peripheral arterial occlusive disease, CLI results from a chronic lack of blood supply, leading to rest pain or trophic lesions in the legs. The international consensus defines CLI as chronic ischemic rest pain, ulcers, or gangrene caused by objectively proven arterial occlusive disease [2]. CLI is considered the ‘end stage’ of peripheral arterial

disease (PAD), and patients are classified in severe stages of Fontaine or Rutherford classifications [3].

Recent evidence challenges the traditional progression of CLI through these classifications, showing that CLI may manifest in asymptomatic patients or deviate from expected patterns [4]. Regardless, CLI patients suffer from the most severe form of PAD, with significant morbidity and cardiovascular event rates surpassing those with symptomatic coronary artery disease [5].

Despite advancements in revascularization, amputations still occur, partly due to late referrals to

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vascular surgeons and the absence of a consensus on defining a non-salvageable limb [6]. The focus on physician-oriented outcomes, such as graft patency and limb salvage, is shifting towards patient-oriented outcomes research, recognizing that limb amputation may improve the quality of life in certain populations [7].

Diagnosing CLI involves vascular examination, ankle-brachial index (ABI) [8], and various imaging modalities. However, the optimal clinical management, whether surgical or medical, remains unclear [9,10]. This study aimed to comprehensively evaluate and compare the demographics, comorbidities, laboratory findings, and clinical outcomes of patients diagnosed with CLI who undergo either endovascular revascularization or open surgery. The primary objectives include examining the impact of different revascularization interventions on patient characteristics, wound healing rates, re-intervention frequencies, and major amputation occurrences. Additionally, the study aimed to identify predictors of wound healing to inform clinical decision-making and enhance the understanding of factors influencing the outcomes in patients with critical limb ischemia.

## 2. Patients and methods

This study is a prospective observational investigation conducted at Vascular Surgery departments in Menofia University Hospitals and Shebin El-Kom Teaching Hospital spanning from February 2022 to August 2022. The primary focus involved 114 patients diagnosed with CLI exhibiting foot tissue loss, who subsequently underwent open or endovascular revascularization procedures. Decision-making for the intervention was guided by the TASC II classification, directing endovascular approaches for type A lesions and surgical bypass for type D lesions. Lesions situated between classes B and C prompted collaborative discussions among surgeons to formulate optimal plans for achieving complete revascularization.

Patients were comprehensively informed about procedural details, potential benefits, associated risks, possible complications, and alternative interventions, obtaining informed consent for participation.

In terms of methodology, the inclusion criteria encompassed all patients with CLI and tissue loss, regardless of whether the revascularization procedure was open or endovascular. Exclusion criteria were applied to patients failing to attend regular follow-up visits for three months or those experiencing unsuccessful revascularization attempts.

Patient enrollment involved a systematic approach, beginning with detailed history-taking covering personal information, complaints, and relevant medical and treatment histories. Clinical examinations incorporated both general and local assessments, including pulse, blood pressure, cardiovascular evaluation, and specific examinations for color changes, gangrene, ischemic ulcers, tissue loss, deformities, and infections. Laboratory investigations covered a range of parameters, including complete blood count, INR (International Normalized Ratio), kidney function tests, liver functions tests, serum albumin, and wound swab cultures.

Non-invasive investigations included ABI interpretation, duplex scanning for spectral waveform analysis, and computed tomography (CT) angiography for a comprehensive assessment of the vascular status.

Postoperative follow-up procedures were rigorous, involving intra-operative and post-operative verification of successful revascularization through hemodynamic measurements. Clinical and duplex scanning assessments were regularly conducted throughout a six-month follow-up period initiated in February 2022.

Follow-up procedures comprised weekly visits during the initial three months, transitioning to monthly visits thereafter. Wounds were diligently examined, photographed, and dressed, with debridement performed when necessary. Monthly wound swabs and hemodynamic measurements were obtained, forming the basis for statistical analyses assessing risk factors associated with each patient (Figs. 1–3).

The time required for wound healing was a critical aspect, calculated from the revascularization procedure day until complete healing and epithelialization of ulcers/wounds. The primary endpoint was the achievement of complete healing, with healing rates calculated for each case.

Wound measurements were conducted using standard rulers marked in centimeters, documenting



Fig. 1. Wound of patient no. 13 pre and post Healing, which took 5 weeks.



Fig. 2. Wound of patient no. 19 pre and post healing showing 83% healing by end of follow-up period.



Fig. 3. Wound of patient no. 39 pre and post healing by 5 weeks' duration.

sizes at various follow-up visits. These measurements, alongside regular photographic documentation, provided a comprehensive visual log for subsequent statistical analyses.

The assessment of risk factors was a key component of the study, involving the analysis of relationships between wound healing time (WHT) and categorical risk factor variables using Kaplan–Meier curves. Detailed risk factor data were collected from each patient, guiding subsequent statistical analyses.

### 2.1. Ethical considerations

This study adhered to the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the Faculty of Medicine, Menoufia University (code no.). Patient consent was secured, and strict anonymity and confidentiality were maintained throughout the study.

### 2.2. Statistical analysis

Descriptive statistics characterized the study population. Kaplan–Meier curves visually represented the probability of wound healing over time. Additionally, Cox proportional hazards regression

models assessed the simultaneous impact of multiple risk factors on WHT, calculating hazard ratios and confidence intervals. All analyses maintained a significant level of 0.05, utilizing statistical software IBM SPSS 25 for processing and analysis.

## 3. Results

The study enrolled 114 patients diagnosed with CLI, characterized by a median age of 60 years [interquartile range ((IQR), 55–65], with a majority being males (64.9%) and smokers (45.6%). Common comorbidities included diabetes (77.2%), hypertension (45.6%), and chronic kidney disease (42.1%) in different stages of chronic kidney disease not requiring regular hemodialysis, with no significant differences observed between the groups. The majority of patients underwent endovascular intervention (85.96%), while a smaller proportion opted for open surgery (14.04%) (Table 1).

Laboratory investigations revealed a median hemoglobin level of 11.5 g/dl (IQR, 9.9–12.5), total leukocytic count (TLC) of  $9 \times 10^9/l$  (IQR, 7–11.3), and C-reactive protein positivity in 88.6% of patients, with a median level of 24 mg/dl (IQR, 12–48). The median serum albumin level was 2.9 g/dl (IQR, 2.7–3.1).

Regarding tissue loss and wound characteristics, gangrene was present in 51.8% of patients, ulcers in 42.1%, and minor amputations in 6.1%. The majority of patients had single wounds (89.5%), primarily located in the toe (58.8%). Wound infections were noted in 50.9% of cases.

Wound healing rates varied significantly among different patient groups. Ambulant patients exhibited a higher rate of successful wound healing (47.2%) compared to bedridden patients (63%). Moreover, patients without wound infections demonstrated a substantially higher healing rate (89%) compared to those with infections (54%). Wounds located at the heel site showed a slower

Table 1. Demographics and comorbidities in patients undergoing revascularization (N = 114) for critical limb ischemia.

Parameters	N (%) or mean $\pm$ SD (N = 114)
Age (years)	60 (55–65)
Male sex	74 (64.9)
Smoker	52 (45.6)
DM	88 (77.2)
HTN	52 (45.6)
CAD	37 (32.5)
RD	48 (42.1)
Ambulatory status	
Ambulant	89 (78.1)
Bed ridden	25 (21.9)

DM, diabetes mellitus; HTN, hypertension; CAD: coronary artery disease; RD: Renal Dialysis.

healing rate (67%) compared to wounds at other sites (88%).

At the end of the follow-up period, complete wound healing was documented in 43% of patients, with a median healing duration of 112 days. Major amputation was required in 5.2% of cases, while 8.8% of patients died during the study period (Table 2).

Survival analysis using Kaplan–Meier curves showed that only 6.1% of patients had healed wounds at 2 months, increasing to 33.3% at 4 months, and reaching 43% after 6 months (Table 3).

Multivariate logistic regression identified several predictors of wound healing. Patients aged younger than 60 years had significantly higher odds of

Table 2. Tissue loss and wound characteristics in patients undergoing revascularization (N = 114) for critical limb ischemia.

Parameters	Total (N = 114), N (%)
Tissue loss	
Ulcer	48 (42.1)
Gangrene	59 (51.8)
Minor amputation	7 (6.1)
No. wounds	
Single wound	102 (89.5)
>1 wound	12 (10.5)
Wound site	
Heel	34 (29.8)
Foot	13 (11.4)
Toe	67 (58.8)
Wound infection	58 (50.9)

Table 3. Wound healing achievement in different study groups within the follow-up period in cm.

Parameters	Wound healing rate (%)	P value
Intervention		
Open	75	<0.001*
Endovascular	92	
DM		
Yes	72	0.585
No	86	
CAD		
Yes	76	0.363
No	85	
Ambulatory status		
Ambulant	85	0.002*
Bed ridden	63	
Wound infection		
Yes	54	<0.001*
No	89	
Heel-site wound		
Yes	67	0.009*
No	88	
Neuropathic pain		
Yes	78	0.365
No	81	

DM, diabetes mellitus; CAD: coronary artery disease.

Table 4. Predictors of wound healing using multivariate sequential logistic regression (N = 114).

Variable	AOR	95% CI	P value
Age <60 years	2.1	1.1–3.2	0.045 <sup>a</sup>
Male sex	1.2	0.8–4.3	0.159
HTN	0.8	0.4–1.9	0.444
DM	0.7	0.3–2.1	0.610
Bed ridden	0.4	0.2–0.9	0.034
Heel-site wound	0.8	0.3–1.7	0.162
Wound infection	0.3	0.1–0.6	0.013 <sup>a</sup>

AOR, adjusted odds ratio; DM, diabetes mellitus; HTN, hypertension.

<sup>a</sup> Statistically significant difference.

complete wound healing [odds ratio (OR) = 2.1; P = 0.045] while being bedridden (OR = 0.4; P = 0.034) and having wound infections (OR = 0.3; P = 0.013) were associated with lower odds of healing (Table 4).

#### 4. Discussion

The present study investigated the demographics and comorbidities of patients with CLI undergoing endovascular revascularization and open surgery. A notable finding was the high percentage of smokers. This result aligns with previous studies that have suggested smoking as a potential risk factor for peripheral arterial disease.

Young and colleagues conducted a retrospective review of all patients undergoing open lower extremity revascularization for symptomatic PAD, defined as claudication (Rutherford 3) or critical limb ischemia (Rutherford 4–6), during a 5-year period (2013–2017). 693 patients were identified undergoing open lower extremity revascularization for PAD (66% critical limb ischemia; 46% diabetes). The 1-year cumulative incidence of MALEs was 29.9% (95% CI, 26.4–33.9), whereas the 1-year incidence of death was 9.8% (95% CI, 7.5–12.7). The broad classification of current and former smokers identified no statistically significant differences in any measured outcomes. Patients who smoked more than one pack/day had 1.48 (95% CI, 1.01–2.16) times increase in risk of MALEs at 1 year compared with patients who smoked one or fewer packs/day. Patients who smoked more than one pack/day also had the highest 1-year amputation incidence (12.7%) [11].

Another study by Clark and colleagues evaluated the relationship between cigarette smoking and PAD. The study included 3579 (68%) never-smokers, 986 (19%) past smokers, and 693 (13%) current smokers self-identified at baseline. After adjustment for covariates, current smokers had an increased risk of ankle-brachial index less than 1 (odds ratio,

2.2, 95% CI, 1.5–3.3) and increased risk of abdominal aortic (odds ratio, 8.4, 95% CI, 5.8–12.0) and aortoiliac calcium (odds ratio, 9.6, 95% CI, 6.7–13.7). When starting by smoking intensity, those smoking more than 20 cigarettes daily (1 pack) had higher likelihood of subclinical PAD by all of these measures compared with lower-intensity use, suggesting a dose-dependent relationship. This suggests that cigarette smoking is associated with measures of subclinical PAD in a dose-dependent manner [12].

Cha and colleagues investigated the effects of tobacco use on adverse clinical outcomes after revascularization for PAD in the Western Pacific region, where PAD cases and tobacco use are among the highest in the world. The relatively healthy cohort comprised 8 324 patients (mean age 64.7 years; 76.9% male) following revascularization for PAD. Among them, 32.7% were inactive and 26.4% were tobacco users. Tobacco users had poorer outcomes than non-users [all-cause mortality adjusted hazard ratio (adjHR) 1.279; 95% CI 1.124–1.456, major adverse outcome adjHR 1.263; 95% CI 1.124–1.418, MALE adjHR 1.291; 95% CI 1.143–1.458]. Indicating that even after receiving revascularization for PAD, a sizable proportion of patients were used tobacco, leading to adverse clinical outcomes such as death, cardiovascular morbidity, and amputation [12].

The distribution of comorbidities, including diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease.

In terms of laboratory investigations, the study revealed a high total leukocytic count (TLC). Elevated TLC may reflect a more pronounced inflammatory response, possibly due to the greater extent of tissue trauma associated with intervention. The positive C-reactive protein (CRP) levels were also high, further supporting the notion of a heightened inflammatory state following revascularization. This aligns with existing literature suggesting that the extent of the surgical procedure can impact the inflammatory response.

One study focused on 37 patients with PAD who underwent infrapopliteal vein graft and midfoot amputation. Plasma levels of various inflammatory markers were measured preoperatively and during follow-up to assess their impact on wound healing. Univariate analysis revealed that high postoperative levels of inflammatory markers (TNF- $\alpha$ , IL-6, MMP-2, and MMP-9) in PAD patients predicted wound healing failure at different time points, suggesting that inflammatory markers are dependent on the type of intervention and the extent of the surgical procedure and be used to identify patients at risk of healing failure after revascularization.

The analysis of tissue loss and wound characteristics demonstrated the diverse nature of tissue loss observed in the patients. The predominant manifestations of tissue loss were gangrene, ulceration, and minor amputation, with gangrene being the most prevalent, affecting 51.8% of the patients. This suggests a significant burden of advanced tissue damage in the study population.

Furthermore, a considerable proportion of patients were presented with single wounds (89.5%), whereas a smaller yet notable subset had multiple wounds (10.5%). This distribution underscores the complexity of managing tissue loss in this patient cohort, as multiple wounds may pose distinct challenges in terms of treatment and healing. In terms of anatomical distribution, the majority of wounds were localized to the toes (58.8%) and heels (29.8%), with a smaller percentage affecting the foot (11.4%). This distribution aligns with the common sites of tissue breakdown observed in individuals with peripheral vascular disease or diabetic neuropathy. Moreover, nearly half of the patients (50.9%) exhibited signs of wound infection, emphasizing the critical role of infection control measures in the management of tissue loss. Addressing wound infection promptly is paramount not only for promoting wound healing but also for preventing systemic complications and reducing the risk of limb loss.

Pherson and colleagues utilized nationwide Vascular Quality Initiative (VQI) data from 2003 to 2017 to analyze the association between surgical site infection (SSI) and outcomes in open lower extremity bypass procedures for symptomatic peripheral arterial disease. The cohort comprised 21 639 adult patients with at least one follow-up record. Of the patients, 5% (1155) experienced SSI within 30 days of surgery, and those with SSI were more likely to be obese. After adjusting for demographic and patient characteristic differences, patients with SSI were nearly twice as likely to undergo major amputation by 6 months, and this association persisted at 1 year. The increased amputation rates associated with SSI were consistent across different preoperative Rutherford classes. While SSI did not show a statistically significant association with 1-year mortality, the study concluded that SSI is more common in obese patients and significantly increases the risk of limb amputation after open lower extremity revascularization [12].

The clinical outcomes of revascularization interventions in patients with critical limb ischemia were assessed, shedding light on various important parameters. The targeted arteries for revascularization

included femoropopliteal (FP), below knee (BK), and infrapopliteal vessels, with combinations of FP and BK vessels in some cases.

The study revealed that complete wound healing was more frequent in the endovascular group compared to the open surgery group, with a shorter median duration for wound healing in the endovascular group. Moreover, major amputation rates were significantly higher in the open surgery group, underscoring the potential advantage of endovascular interventions in preserving limb viability. These findings align with previous research emphasizing the benefits of endovascular approaches in terms of reduced morbidity and faster recovery.

In the BASIL-2 trial which spanned from July 2014 to November 2020, 345 patients with chronic limb-threatening ischemia were randomly assigned to either a vein bypass group or the best endovascular treatment group. The primary outcome was amputation-free survival, and at a median follow-up of 40 months, 63% of the vein bypass group and 53% of the endovascular treatment group experienced no amputation-free survival. The adjusted hazard ratio was 1.35, indicating a significantly higher risk for the vein bypass group. Secondary outcomes included overall survival, major amputation, 30-day morbidity, and mortality, among others. There were no significant differences in 30-day morbidity and mortality, major adverse limb events, major adverse cardiac events, or health-related quality of life between the two treatment groups. However, the vein bypass group had a higher rate of major amputation or death, with an adjusted hazard ratio of 1.23. Overall survival was also lower in the vein bypass group, with an adjusted hazard ratio of 1.37. The study concluded that, in patients with chronic limb-threatening ischemia, best endovascular treatment resulted in better outcomes than vein bypass in terms of amputation-free survival and overall survival [12].

The analysis of wound healing rates according to different groups provided valuable insights into factors influencing outcomes. Ambulant patients demonstrated significantly higher rates of successful wound healing compared to bedridden patients, emphasizing the importance of mobility and post-operative ambulation in the healing process. Additionally, the presence of wound infection was associated with significantly lower wound healing rates, highlighting the need for effective infection control measures in the management of critical limb ischemia patients.

The Global Vascular Guidelines (GVG) for chronic limb-threatening ischemia (CLTI) provide recommendations for infection control and overall

management of the condition. Following revascularization, long-term limb surveillance is advised. The guidelines stress the importance of multidisciplinary teams and centers of excellence for amputation prevention as a key health system initiative. Non-revascularization therapies' effectiveness, such as spinal stimulation, pneumatic compression, prostanoids, and hyperbaric oxygen, is not established. Regenerative medicine approaches for CLTI should be restricted to well-conducted randomized clinical trials. The GVG promotes standardization of study designs and endpoints for clinical trials in CLTI [2].

Wound sites also played a role in healing outcomes, with heel-site wounds associated with significantly lower healing rates compared to other sites. This observation suggests that wounds located on the heel may pose specific challenges in terms of vascularization and tissue perfusion, warranting further investigation into tailored treatment strategies for this subgroup of patients.

The Kaplan–Meier survival analysis provided a comprehensive overview of wound healing time over the 180-day follow-up period.

Morisaki and colleagues reported that in their cohort the multivariable analysis revealed that wound, ischemia and foot infection stage (HR 1.34; 95% CI 1.07–1.68;  $P = 0.012$ ), Global Limb Anatomical Staging System stage (HR 1.31; 95% CI 1.01–1.72;  $P = 0.043$ ), EVT (HR 1.90; 95% CI 1.31–2.74;  $P < 0.001$ ), were risk factors for the composite endpoint. Concluding that Bypass surgery is superior to EVT with respect to the composite endpoint wound healing [2].

On the other hand, a study involving 1355 patients with CLTI undergoing first-time revascularization to the infrageniculate arteries, the adjusted rate of 30-day MALE was not significantly different between the bypass-first and endovascular-first revascularization cohorts (9% vs. 11.2%; OR, 0.73; 95% CI, 0.50–1.08). The incidence of transtibial or proximal amputation was lower in the bypass-first cohort compared to the endovascular-first cohort (4.3% vs. 7.4%; OR, 0.60; CI, 0.36–0.98). Patients with bypass-first revascularization had higher wound complication rates (9.7% vs. 3.7%; OR, 2.75; CI, 1.71–4.42) compared with patients in the endovascular-first cohort. The incidence of 30-day major adverse cardiovascular events (MACE) was significantly higher in bypass-first patients compared to the endovascular-first cohort (6.9% vs. 2.6%; adjusted OR, 3.88; CI, 2.18–6.88) [13].

Multivariate sequential logistic regression identified several predictors of wound healing. Patients younger than 60 years old and those undergoing

endovascular revascularization had significantly higher odds of complete wound healing. On the contrary, being bedridden and having a wound infection was associated with significantly lower odds of healing. These findings suggest that age, mobility status, and infection control are crucial factors influencing the success of wound healing in critical limb ischemia patients. The higher odds of healing in the endovascular group align with the observed better outcomes in terms of wound healing and major amputation rates.

Antonopoulos and colleagues investigated predictors of wound healing following revascularization for CLTI and reported that predictors included local wound factors, wound depth, patient's comorbidities, medications, smoking and alcohol abuse, poor vessel runoff, and direct versus indirect revascularization. Among the clinical biomarkers, platelet-derived growth factor, transforming growth factor  $\beta$ , basic fibroblast growth factor, tumor necrosis factor  $\alpha$ , interleukin (IL) 1, and IL-6 have been proposed as potential predictors.

Another retrospective study aimed to assess wound outcomes 2 years post-intervention for atherosclerotic femoropopliteal lesions in patients with ischemic tissue loss reported that Among 135 first-time endovascular procedures, 56.3% demonstrated complete wound healing without recurrence at the 2-year follow-up, but 8.1% developed new wounds on the same foot after initial healing. Persistent or recurring tolerable wounds at the same site occurred in 22.2%, and 13.3% required major amputations. Independent factors hindering wound healing without recurrence included renal insufficiency, ankle pressure less than 50 mmHg or flat forefoot PVR, and functional performance less than 4 metabolic equivalents [13].

#### 4.1. Conclusion

The observed differences in re-intervention rates, wound healing outcomes, and predictors of healing highlight the need for a nuanced and patient-specific approach in selecting the optimal revascularization method. The higher rates of complete wound healing and lower major amputation rates underscore their potential advantages in preserving limb viability. These findings, coupled with identified predictors such as age, mobility status, and infection control, contribute to the growing body of knowledge guiding clinicians in personalized decision-making for critical limb ischemia patients. Future research with larger cohorts and extended follow-up periods is imperative to validate these results and refine our understanding of the

nuanced factors influencing outcomes in this patient population.

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