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Editor's Choice – Impact of Endovascular Pedal Artery Revascularisation on Wound Healing in Patients With Critical Limb Ischaemia

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WHAT THIS PAPER ADDS

Pedal arch patency has been associated with improved wound healing after revascularisation. However, limited data exist regarding the impact of endovascular pedal artery revascularisation (PAR) on clinical outcomes of patients with critical limb ischaemia (CLI). This study demonstrates that successful PAR in patients with CLI achieved higher rates of wound healing and freedom from major amputation than infrapopliteal revascularisation without PAR. Thus, efforts should be made to revascularise the pedal arteries, especially when the pedal arch is completely absent in patients with CLI.

Objective: The present study investigated the impact of endovascular pedal artery revascularisation (PAR) on the clinical outcomes of patients with critical limb ischaemia (CLI).

Methods: This retrospective analysis of a single centre cohort included 239 patients who underwent endovascular revascularisation of infrapopliteal arteries for a chronic ischaemic wound. PAR was attempted in 141 patients during the procedure. After propensity score matching, there were 87 pairs of patients with and without PAR.

Results: After the matching, the two groups showed balanced baseline clinical and lesion characteristics. PAR was achieved in 60.9% of the PAR group. Direct angiosome flow was more frequently obtained in the PAR group than in the non-PAR group (81.6% *vs.* 34.5%; $p < .001$). Subintimal angioplasty (47.1% *vs.* 29.9%; $p = .019$) and pedal–plantar loop technique (18.4% *vs.* 0%; $p < .001$) were more frequent in the PAR group. At the one year follow up, the PAR group showed greater freedom from major amputation (96.3% *vs.* 84.2%; $p = .009$). The wound healing rate, overall survival, major adverse limb event, and freedom from re-intervention did not differ significantly between the two groups. However, the patient subgroup with successful PAR showed a higher wound healing rate than the non-PAR group (76.0% *vs.* 67.0%; $p = .031$). In a multivariable Cox proportional hazards regression model, successful PAR (hazard ratio [HR] 1.564, 95% confidence interval [CI] 1.068–2.290; $p = .022$) was identified as an independent factor associated with improved wound healing, whereas gangrene (HR 0.659, 95% confidence interval [CI] 0.471–0.923; $p = .015$), C reactive protein >3 mg/dL (HR 0.591, 95% CI 0.386–0.904; $p = .015$), and pre-procedural absence of pedal arch (HR 0.628, 95% CI 0.431–0.916; $p = .016$) were associated with impaired wound healing.

Conclusion: Successful PAR significantly improved wound healing in patients with CLI. Thus, efforts should be made to revascularise the pedal arteries, especially when the pedal arch is completely absent.

Keywords: Critical limb ischaemia, Endovascular treatment, Peripheral artery disease
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INTRODUCTION

Revascularisation is the cornerstone of critical limb ischaemia (CLI) treatment for lower limb preservation. Endovascular revascularisation is the favoured approach in many centres because of its lower morbidity and mortality than open surgery.[1] Recent studies have suggested that direct revascularisation of an ischaemic wound area based on the angiosome concept produces better wound healing

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than indirect revascularisation.[2–4] However, the effectiveness of angiosome based revascularisation strategies is controversial. Most previous studies were retrospective, and their comparative groups were not well controlled.[5,6] Other investigators suggested that the revascularisation of multiple infrapopliteal vessels instead of a single angiosome related artery might be more advantageous for wound healing and limb salvage.[7–9] The quality of the pedal arch is also considered to be an important factor affecting perfusion of ischaemic areas in the distal lower limb.[10,11] The pedal arch connects the anterior and posterior circulation of the foot and is the main blood supply to the forefoot. Pedal arch patency has been associated with improved wound healing after revascularisation.[10–12] However, limited data exist regarding the impact of endovascular pedal artery revascularisation (PAR) on the clinical outcomes of patients with CLI. In the present study, the effects of endovascular revascularisation of the pedal arteries on wound healing in patients with CLI due to chronic infrapopliteal arterial disease and incomplete pedal arch was investigated.

MATERIALS AND METHODS

Study population

The electronic medical records of 415 patients who underwent endovascular treatment for chronic infrapopliteal arterial disease at Severance Cardiovascular Hospital, Yonsei University Health System, from January 2009 to December 2016, were evaluated retrospectively. Patients without CLI ($n = 40$) or a lower extremity wound (Rutherford category 4, $n = 70$); patients with Buerger disease ($n = 30$), previous bypass surgery ($n = 18$), or an intact pedal arch (type 1, $n = 4$); and patients lost to follow up after discharge ($n = 14$) were excluded. The final analysis included 239 patients with 239 target limbs (Fig. 1). All included patients had Rutherford category 5 or 6 CLI and a pre-procedural pedal arch classified as type 2 or 3. Pedal arch types were classified into type 1 (both the dorsalis pedis and lateral plantar arteries were patent), type 2 (either the dorsalis pedis artery or the lateral plantar artery was patent), and type 3 (neither the dorsalis pedis artery nor the lateral plantar artery were patent) (Fig. 2).[10] Patients were evaluated before endovascular revascularisation by physical examination, ankle brachial index (ABI), and an imaging study, such as a computed tomography (CT) scan or colour Duplex ultrasound. The wounds were primarily examined and treated by orthopaedic surgeons. Data were collected regarding baseline medical history, medications, revascularisation procedure, and immediate and late outcomes. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board approved the study and waived the requirement for patient informed consent because of the study's retrospective nature.

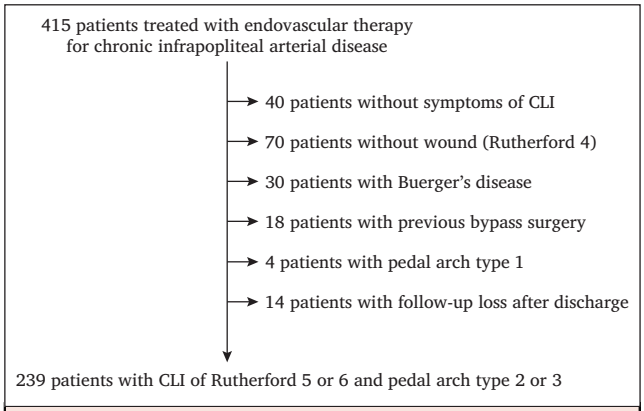


Figure 1. Patient flowchart. CLI = critical limb ischaemia.

Interventional procedure

All procedures were performed under local anaesthesia, supplemented by intravenous sedation and analgesia. Depending on the presence of combined proximal lesions, an ipsilateral antegrade approach or a contralateral crossover approach was chosen. For the ipsilateral antegrade approach, a 5 F or 6 F Ansel sheath (Cook, Bloomington, IN, USA) was introduced into the popliteal artery through the ipsilateral common femoral artery; for the contralateral crossover approach, a 6 F—8 F Balkin sheath (Cook) or 5 F or 6 F Shuttle sheath (Cook) was inserted through the contralateral femoral artery. After insertion of the sheath, unfractionated heparin (5000 units) was administered to achieve an activated clotting time of >250 s. When present, significant proximal inflow lesions were treated in the same session before endovascular treatment of the infrapopliteal lesions. For treatment of the infrapopliteal lesions, a 0.014, 0.018, or 0.035 inch guidewire plus microcatheters or supporting catheters were used via an intraluminal approach or a subintimal approach, depending on the lesion's characteristics and operator's preference. When antegrade wire passage in the tibial or peroneal arteries failed, a retrograde approach via pedal puncture, pedal plantar loop technique, or transcollateral wiring was performed. The pedal plantar loop technique refers to the creation of a loop from the dorsalis pedis artery to the lateral plantar circulation or vice versa by means of the guidewire and balloon tracking through the plantar arch of the foot.[13] The transcollateral technique is based on the retrograde recanalisation of the occluded tibial arteries by guidewire tracking through the collaterals between the different tibial arteries.[14] The decision to perform multivessel revascularisation or PAR was left to the discretion of the operators. In general, the treatment goal was to obtain at least one straight line blood flow to the ischaemic territory. In patients with ischaemic wounds, an attempt was made to revascularise as many tibial and pedal arteries as possible, whenever feasible. Wire passage for PAR was primarily performed using an antegrade approach. However, when antegrade wiring failed, retrograde wire passage by the pedal plantar loop technique was attempted. All infrapopliteal lesions were treated by angioplasty using 2—4 mm diameter balloon catheters. In the presence of flow limiting dissection despite

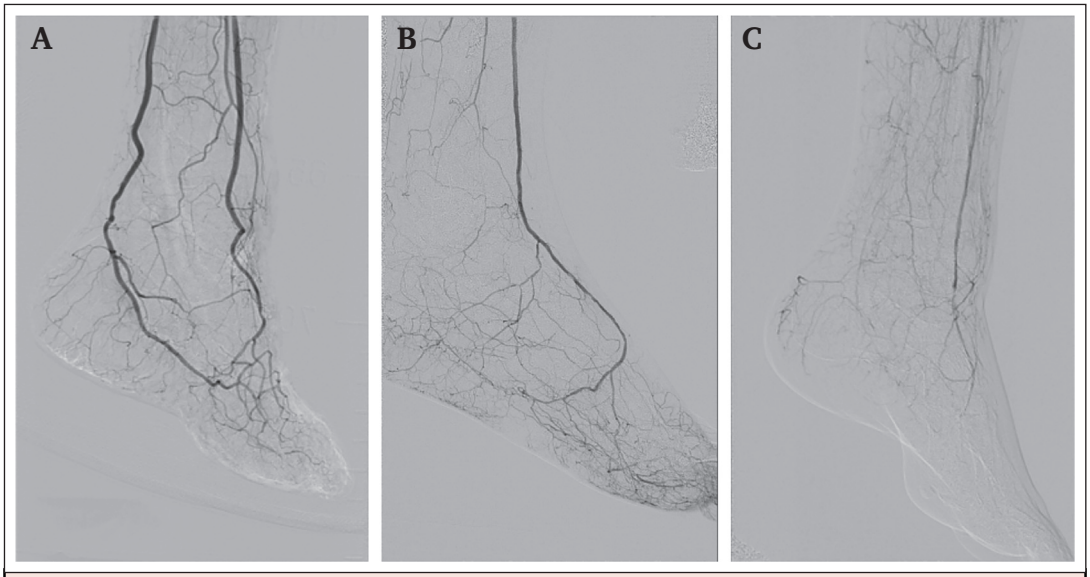


Figure 2. Pedal arch types: (A) type 1, both the dorsalis pedis and plantar arteries are patent; (B) type 2, either the dorsalis pedis artery or the plantar artery is patent; and (C) type 3, neither the dorsalis pedis artery nor the plantar artery is patent.

multiple balloon dilations, bailout stenting was performed with a self panding bare metal stent of 3—4 mm diameter and 60—80 mm length (Maris Deep; Medtronic, Minneapolis, MN, USA). Drug eluting stents and drug eluting balloons were not available for infrapopliteal lesions. No stents were implanted below the ankle. After successful recanalisation, the patients generally received a combination of aspirin (100 mg/day) and either clopidogrel (75 mg/day) or cilostazol (200 mg/day) for at least one year.

Post-procedural follow up

After the procedure, the patients were followed by orthopaedic surgeons or cardiologists at one month intervals until wound healing was complete. After complete wound healing, clinical follow up was scheduled every three to six months. Follow up ABI was routinely performed before discharge from hospital and at six and 12 months after the procedure. A follow up imaging study using duplex ultrasound or CT angiography was performed in patients with symptoms or worsening wounds.

Study end points and definitions

The primary end point was the rate of wound healing 12 months after the index endovascular procedure. The secondary end points included overall survival, freedom from major amputation, major adverse limb event (MALE), and freedom from re-intervention. Wound healing was defined as complete epithelialisation of all wounds without major amputation. Major amputation was defined as an above ankle amputation. MALE was defined as a major amputation or any surgical or endovascular re-intervention according to the Peripheral Academic Research Consortium.[15] Direct flow was considered present when an angiosome based straight line to the wound was achieved by endovascular therapy. The previously described definition of angiosome based recanalisation was adopted.[3] According to the angiosome concept, the anterior tibial artery supplies the dorsal aspect of the toe and dorsal foot; the posterior tibial artery supplies the plantar aspect of the toe, web space of the toes, plantar foot, and the inside of the heel; and the peroneal artery supplies lateral ankle and the outside of the heel. All wounds were assessed using the Rutherford classification system and the Wound, Ischaemia, and foot Infection (WIfI) classification. Rutherford category 5 was defined as minor tissue loss. Rutherford category 6 was defined as major tissue loss extending above the transmetatarsal level. Detailed definitions of the WIfI system have been described in the literature.[16]

Statistical analysis

Data are expressed as *n* (%) or mean ± standard deviation (SD). Baseline characteristics and procedural data were compared between the PAR and the non-PAR groups using the Student's *t* test and the chi square test as appropriate. Propensity score matching was performed to reduce selection bias and potential confounder effects and create balanced groups. The following variables were used for matching: age, sex, hypertension, diabetes mellitus, chronic kidney disease, body mass index, baseline lipid profiles, and current medication (anticoagulant, antiplatelet, and number of antihypertensive agents). After matching, validation was performed according to the standardised mean difference of all baseline covariates, using a threshold of 0.1 to indicate imbalance.

The rates of wound healing and "freedom from" secondary end points were analysed using the Kaplan—Meier method and compared among patient subgroups using the log rank test.

Table 1. Baseline clinical characteristics before and after propensity score matching

	Before matching			After matching		
	PAR (n = 141)	Non-PAR (n = 98)	p value	PAR (n = 87)	Non-PAR (n = 87)	p value
Male sex	109 (77.3)	73 (74)	.615	64 (74)	65 (75)	.863
Age, y	67.2 ± 10.5	67.4 ± 10.3	.869	67.1 ± 10.9	67.8 ± 9.4	.668
BMI, kg/m^2	22.4 ± 3.6	22.7 ± 3.3	.495	22.3 ± 3.9	22.5 ± 3.3	.632
Hypertension	105 (74.5)	74 (75)	.855	64 (74)	65 (75)	.863
Diabetes mellitus	120 (85.1)	86 (88)	.559	74 (85)	76 (87)	.660
Hypercholesterolaemia	60 (42.6)	47 (48)	.408	37 (42)	42 (48)	.446
CKD	55 (39.0)	45 (46)	.287	34 (39)	40 (46)	.358
ESRD	43 (30.5)	34 (35)	.495	28 (32)	31 (36)	.631
CAD	51 (36.2)	46 (47)	.095	37 (42)	39 (45)	.760
Stroke	15 (10.6)	7 (7)	.358	8 (9)	7 (8)	.787
Smoking	72 (51.1)	52 (53)	.761	42 (48)	49 (56)	.288
Previous angioplasty	36 (25.5)	22 (22)	.585	21 (24)	18 (21)	.585
Rutherford category			.651			.858
5	110 (78.0)	74 (75)		67 (77)	66 (76)	
6	31 (22.0)	24 (24)		20 (23)	21 (24)	
Wound character			.067			.648
Ulcer	65 (46.1)	57 (58)		45 (52)	48 (55)	
Gangrene	76 (53.9)	41 (42)		42 (48)	39 (45)	
Wound location			.545			.505
Toes	111 (78.7)	73 (74)		70 (80)	68 (78)	
Dorsal	4 (2.8)	5 (5)		2 (2)	4 (5)	
Plantar	2 (1.4)	2 (2)		0 (0)	2 (2)	
Heel	13 (9.2)	5 (5)		8 (9)	4 (5)	
Above ankle	1 (0.7)	1 (1)		1 (1)	1 (1)	
Multiple	10 (7.1)	12 (12)		6 (7)	8 (9)	
Wound infection	46 (32.6)	22 (22)	.086	21 (24)	21 (24)	1
WIfI score	3.6 ± 1.4	3.5 ± 1.7	.629	3.6 ± 1.4	3.5 ± 1.6	.694
WIfI score ≥ 5	33 (23.4)	25 (25)	.709	21 (24)	22 (25)	.860
CRP > 3 mg/L	37 (26.2)	26 (26)	.960	23 (26)	24 (27)	.864
Medication at discharge						
Aspirin	121 (85.8)	77 (78)	.144	75 (86)	70 (80)	.309
Clopidogrel	116 (82.3)	81 (83)	.939	71 (82)	71 (82)	1
Aspirin + clopidogrel	99 (70.2)	67 (68)	.813	60 (69)	61 (70)	.869
Cilostazol	31 (22.0)	25 (25)	.527	23 (26)	21 (24)	.727
Statin	98 (69.5)	73 (74)	.401	65 (75)	64 (74)	.863

Data are n (%) or mean ± standard deviation. PAR = pedal artery revascularization; BMI = body mass index; CKD = chronic kidney disease; ESRD = end stage renal disease; CAD = coronary artery disease; WIfI = Wound, Ischaemia, and foot Infection; CRP = C reactive protein.

Univariable analyses using Cox proportional hazards regression, including baseline clinical and procedural data, were performed to determine factors associated with wound healing. Those variables achieving a p value < .15 in univariable analysis were entered into a multivariable model to determine the independent predictors for wound healing. P values < .05 were considered statistically significant. All analyses were performed using SPSS for Windows, version 23 (IBM, Armonk, NY, USA).

RESULTS

Baseline clinical and lesion data

The enrolled patients were mostly male (76.2%), with a mean age of 67.2 ± 10.3 years. Diabetes mellitus and dialysis dependent end stage renal disease were present in 86.2% and 32.3% of patients, respectively. The majority of patients (77.0%) had a Rutherford category of 5. The wounds were located primarily in the toes (77.0%). An infected wound was present in 28.5% of patients. Most infrapopliteal target lesions were total occlusions (72.4%) and longer than 20 cm (85.8%).

PAR was attempted in 141 patients during the infrapopliteal artery interventions. In the other 98 patients, the infrapopliteal angioplasty was limited to the above ankle level. The PAR patient group showed more multiple infrapopliteal target vessels than the non-PAR group (68.1% *vs.* 54.1; p = .028). In addition, there were trends toward a higher frequency of gangrenous wounds (53.9% *vs.* 41.8%; p = .067), wound infection (32.6% *vs.* 22.4%; p = .086), and anterior tibial artery (85.8% *vs.* 76.5%; p = .066) as a target vessel in the PAR group than in the non-PAR group. Other characteristics were similar between the two groups.

After one to one propensity score matching, a total of 87 patient pairs who showed no significant differences in baseline clinical and lesion characteristics were obtained. The baseline clinical and lesion characteristics of the PAR

Table 2. Lesion and procedural data

	Before matching			After matching		
	PAR (n = 141)	Non-PAR (n = 98)	p value	PAR (n = 87)	Non-PAR (n = 87)	p value
Number of runoff vessels			.359			.641
0	55 (39.0)	57 (58)		55 (63)	51 (59)	
1 or 2	54 (38.3)	41 (42)		32 (37)	36 (41)	
Total occlusion	103 (73.0)	70 (71)	.783	62 (71)	61 (70)	.868
Lesion length, cm	30.2 ± 12.5	28.8 ± 12.7	.403	30.0 ± 13.0	28.9 ± 12.7	.541
Lesion length > 20 cm	123 (87.2)	82 (84)	.438	76 (87)	73 (84)	.517
TASC lesion type D	128 (90.8)	90 (92)	.777	78 (90)	0 (92)	.600
Infrapopliteal target vessel						
Anterior tibial artery	121 (85.8)	75 (76)	.066	73 (84)	87 (79)	.434
Posterior tibial artery	90 (63.8)	53 (54)	.131	50 (57)	46 (53)	.542
Peroneal artery	33 (23.4)	26 (26)	.581	19 (22)	22 (25)	.592
Multiple infrapopliteal target vessels	96 (68.1)	53 (54)	.028	52 (60)	48 (55)	.540
Combined proximal procedure	44 (31.2)	40 (41)	.126	30 (35)	36 (41)	.349
Subintimal approach	62 (44.0)	29 (29)	.024	41 (47)	26 (30)	.019
Pedal–plantar loop technique	26 (18.4)	0 (0)	.001	16 (18)	0 (0)	<.001
Transpedal approach	0 (0)	1 (1)	.410	0 (0)	0 (0)	–
Transcollateral approach	0 (0)	2 (2)	.167	0 (0)	2 (2)	.497
Tibial bailout stenting	19 (13.5)	5 (5)	.034	12 (14)	5 (6)	.074
Successful PAR	89 (63)	–	–	53 (61)		
Direct angiosome direct	116 (82.3)	32 (33)	<.001	71 (82)	29 (33)	<.001
Pre-pedal arch type			.722			.534
2	86 (61.0)	62 (63)		51 (59)	55 (63)	
3	55 (39.0)	36 (37)		36 (41)	32 (37)	
Post-pedal arch type			<.001			<.001
1	58 (41.1)	0 (0)		34 (39)	0 (0)	
2	66 (46.8)	62 (63)		41 (47)	55 (63)	
3	17 (12.1)	36 (37)		12 (14)	32 (37)	
Pre-ABI	0.74 ± 0.31	0.62 ± 0.25	.014	0.66 ± 0.27	0.63 ± 0.24	.576
Post-ABI	0.90 ± 0.22	0.85 ± 0.22	.184	0.88 ± 0.22	0.86 ± 0.22	.611
Complications						
Puncture site haematoma	6 (4.3)	5 (5)	.995	3 (3)	4 (5)	1
Vascular rupture	5 (3.5)	6 (6)	.353	2 (2)	6 (7)	.152
Flow limiting distal embolisation or dissection	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Complications requiring surgery	1 (0.7)	1 (1)	1	0 (0)	1 (1)	1

Data are n (%) or mean ± standard deviation. PAR = pedal artery revascularization; TASC = The Inter-Society Consensus for the Management of Peripheral Arterial Disease; ABI = ankle brachial index.

and the non-PAR groups before and after propensity score matching (PSM) are summarised in Table 1.

Procedural data

Procedural data before and after PSM are presented in Table 2. Angiosome based direct flow was obtained more frequently in the PAR group than in the non-PAR group (81.6% *vs.* 33.3%; $p < .001$ between the matched groups). Successful PAR was achieved in 60.9% of the matched PAR group. Subintimal angioplasty (47.1% *vs.* 29.9%; $p = .019$) and pedal plantar loop technique (18.4% *vs.* 0%; $p < .001$) were more frequently adopted in the PAR group. The PAR group also showed a trend towards a higher rate of tibial bailout stenting (13.8 *vs.* 5.7; $p = .074$). As a result of successful PAR, there were more type 2 pedal arches (39.1% *vs.* 0%) and fewer type 3 pedal arches (13.8% *vs.* 36.8%) in the PAR group than in the non-PAR group ($p < .001$). However, post-procedural ABI was similar between the two groups. Procedural complications also did not differ between the PAR and the non-PAR groups.

Late outcomes

Patients were followed for a median of 644 days. The one year clinical outcomes of PAR and non-PAR groups are shown in Table 3. Overall survival did not differ significantly before or after PSM. Freedom from major amputation was significantly higher in the PAR group than in the non-PAR group before PSM (96.1% *vs.* 84.0%; $p = .001$), as well as after PSM (96.3% *vs.* 84.2%; $p = .009$) (Table 3, Fig. 3). Freedom from MALE was significantly higher in the PAR group before PSM (80.5% *vs.* 70.3%; $p = .042$). However, after PSM, there was no significant difference between the two groups (75.7% *vs.* 72.6%; $p = .418$). Freedom from re-intervention did not differ significantly before or after PSM. However, there was a trend towards lower freedom from re-intervention in the PAR group after PSM (79.2% *vs.* 88.0%; $p = .174$). In the matched groups, there were three and 13 major amputations in the PAR and the non-PAR group, respectively. All major amputations occurred within one year, none of which was planned prior to the index procedure. The time to major amputations was 77.7 ± 73.1

Table 3. Comparison of clinical outcomes at one year between the pedal artery revascularisation (PAR) and the non-PAR groups before and after propensity score matching

	Before matching (%)			After matching (%)		
	PAR (n = 141)	Non-PAR (n = 98)	p value	PAR (n = 87)	Non-PAR (n = 87)	p value
Overall survival	91	90	.793	90	90	.739
Freedom from major amputation	96	84	.001	96	84	.009
Freedom from MALE	81	70	.042	76	73	.418
Freedom from re-intervention	83	86	.617	79	88	.174
Wound healing	74	70	.088	70	67	.130

MALE = major adverse limb event.

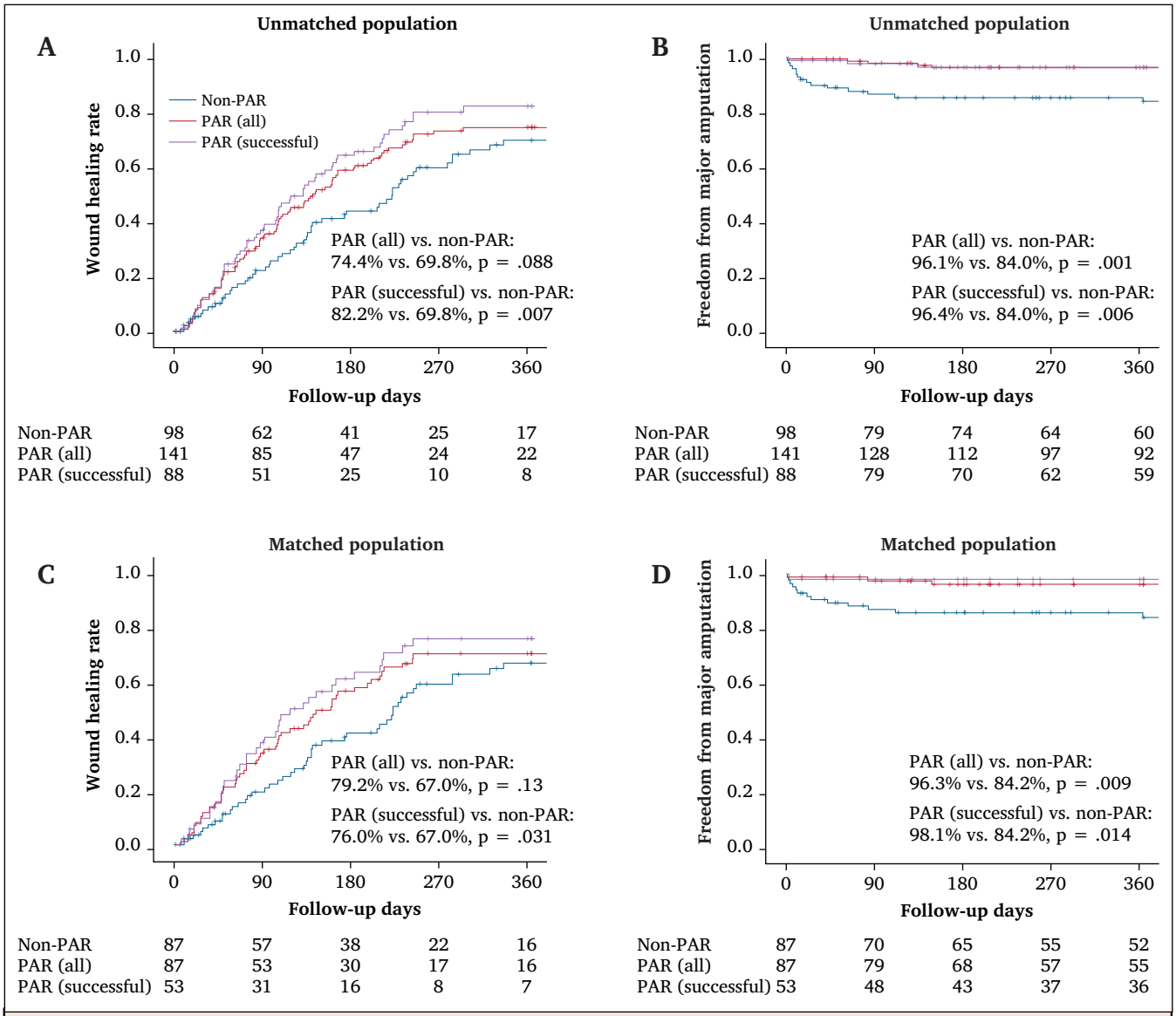
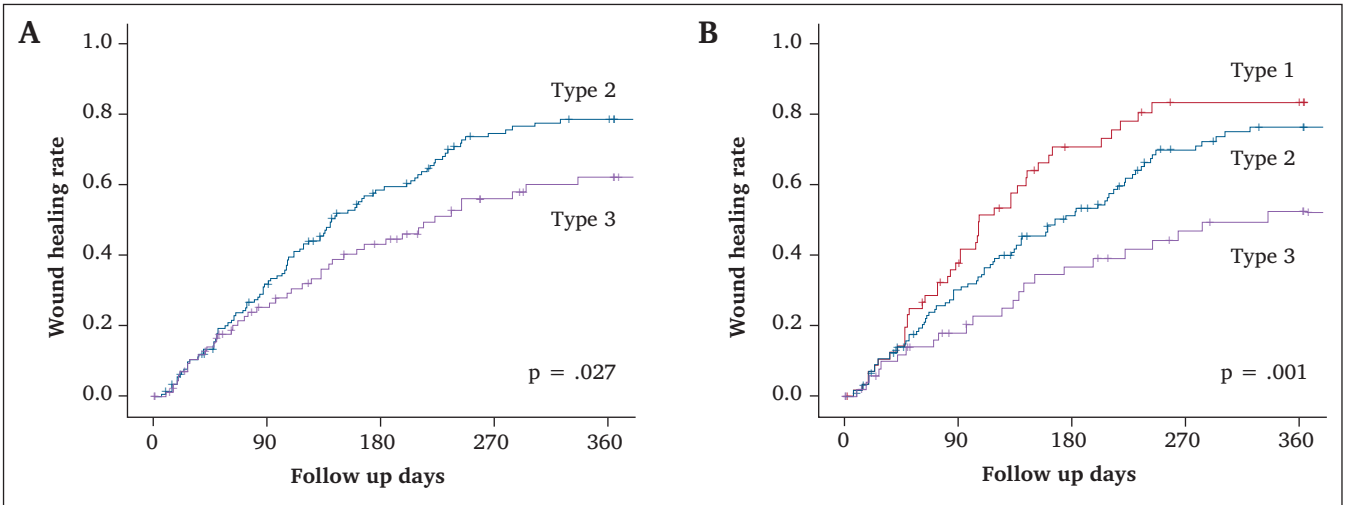


Figure 3. Kaplan–Meier curves for wound healing (A, unmatched population; C, matched population) and freedom from major amputation (B, unmatched population; D, matched population). PAR = pedal artery revascularisation.



Number at risk
Pre-pedal arch

Type 2:	148	91	49	26	21
Type 3:	91	56	39	23	18

Number at risk
Post-pedal arch

Type 1:	58	33	12	5	5
Type 2:	148	91	49	26	21
Type 3:	91	56	39	23	18

Figure 4. Kaplan–Meier curves for wound healing according to (A) pre-procedural and (B) post-procedural pedal arch types.

days in the PAR group and 57.2 ± 98.5 days in the non-PAR group. None of the patients who underwent major amputations required re-interventions.

The PAR group showed a trend towards higher wound healing rate than the non-PAR group before the PSM (74.4% *vs.* 69.8%; $p = .088$) and after the PSM (70.3% *vs.* 67.0%; $p = .130$) (Table 3, Fig. 3). In the patient subgroup with successful PAR, the wound healing rate was significantly higher than in the non-PAR group (76.0% *vs.* 67.0%; $p = .031$).

The wound healing rate was significantly lower in patients with pre-procedural type 3 pedal arch than in patients with pre-procedural type 2 ($p = .027$; Fig. 4A) and lower in patients with post-procedural type 3 pedal arch than in patients with post-procedural type 1 or type 2 ($p = .001$; Fig. 4B).

In a multivariable Cox proportional hazards regression model, successful PAR (hazard ratio [HR] 1.564, 95% confidence interval [CI] 1.068–2.29; $p = .022$) was identified as an independent factor associated with improved wound healing, whereas gangrene (HR 0.659, 95% CI 0.471–0.923; $p = .015$), C reactive protein (CRP) > 3 mg/dL (HR 0.591, 95% CI 0.386–0.904; $p = .015$), and pre-procedural type 3 pedal arch (HR 0.628, 95% CI 0.431–0.916; $p = .016$) were associated with impaired wound healing (Table 4).

DISCUSSION

Successful endovascular revascularisation of the pedal arteries achieved higher rates of wound healing and major amputation free survival. Absence of a patent pedal arch before, and especially after, endovascular therapy was associated with poor wound healing. Gangrene, high CRP (>3 mg/L), type 3 pedal arch before the procedure, and successful PAR were independent factors associated with wound healing.

In patients with CLI, the majority of vascular lesions are located below the knee.[17,18] In the last decade, endovascular therapy has evolved considerably as a result of advances in procedural techniques and devices, and has demonstrated favourable clinical outcomes in patients with CLI. In general, endovascular therapy has been associated with lower primary patency but similar wound healing and freedom from major amputation, when compared with bypass surgery.[19,20] Because of its lower morbidity, endovascular therapy has become the preferred first line treatment in many centres.

The angiosome concept was proposed as a strategy for the revascularisation of infrapopliteal arteries.[21] An angiosome is a block of tissue supplied by a specific artery, which consists of the skin, subcutaneous tissue, fascia, muscle, and bone.[22] According to wound location, the arteries supplying the corresponding angiosome are considered the primary targets for revascularisation. Several studies have demonstrated that direct revascularisation of the ischaemic area based on the angiosome concept produced superior outcomes during endovascular therapy, when compared with indirect revascularisation.[2–4] However, the usefulness of the angiosome concept remains controversial. Correlations between angiosome based direct revascularisation and lower limb outcomes were not consistently observed in other studies, similar to the current study.[11,23–25] Furthermore, definitions of foot angiosomes vary.[26] Owing to dual arterial supply of the heel and digits, it is difficult to define the direct revascularisation.[26] Interestingly Rother *et al.*[27] investigated pedal tissue perfusion after tibial artery

Table 4. Univariable and multivariable Cox proportional hazards regression analyses of factors associated with wound healing

Factor	Univariable analysis – HR (95% CI)	*p* value	Multivariable analysis – HR (95% CI)	*p* value
Age	1.010 (0.993–1.027)	.237		
Male	0.876 (0.591–1.299)	.511		
BMI	1.984 (0.879–1.102)	.785		
DM	0.725 (0.452–1.164)	.183		
Hypertension	0.757 (0.524–1.093)	.137	0.772 (0.530–1.125)	.177
Dyslipidaemia	0.971 (0.699–1.349)	.863		
ESRD	0.822 (0.575–1.175)	.282		
Smoking	0.868 (0.627–1.203)	.396		
Previous angioplasty	0.855 (0.580–1.261)	.617		
Previous amputation	0.935 (0.651–1.343)	.715		
Rutherford category 6	1.096 (0.740–1.624)	.648		
Gangrene	0.642 (0.461–0.893)	.008	0.659 (0.471–0.923)	.015
WIfI score $\geq$ 5	0.757 (0.495–1.158)	.199		
Wound location other than toes	0.863 (0.568–1.311)	.490		
Infected wound	1.100 (0.766–1.579)	.608		
CRP > 3 mg/dL	0.996 (0.990–1.001)	.123	0.591 (0.386–0.904)	.015
Total occlusion	0.804 (0.566–1.141)	.222		
Lesion length > 200 mm	1.173 (0.738–1.864)	.499		
Multiple infrapopliteal target vessels	0.980 (0.696–1.382)	.910		
Inflow target lesions	0.962 (0.682–1.357)	.827		
No runoff vessel	0.575 (0.142–2.321)	.437		
Pre-ABI	1.471 (0.777–2.784)	.236		
Post-ABI	1.022 (0.394–2.649)	.964		
Pre-type 3 pedal arch	0.668 (0.470–0.950)	.025	0.628 (0.431–0.916)	.016
Pedal artery revascularisation				
Attempted	1.356 (0.912–2.015)	.133	–	
Successful	1.499 (1.078–2.084)	.016	1.564 (1.068–2.290)	.022
Direct flow	1.363 (0.958–1.939)	.085	1.127 (0.747–1.699)	.570
Dual antiplatelet therapy	1.129 (0.792–1.610)	.501		
Cilostazol	1.003 (0.686–1.468)	.986		
Statin	1.018 (0.709–1.461)	.925		

HR = hazard ratio; CI = confidence interval; BMI = body mass index; DM = diabetes mellitus; ESRD = end stage renal disease; WIfI = Wound, Ischaemia, and foot Infection; CRP = C reactive protein; ABI = ankle brachial index.

angioplasty and found that improvement of tissue perfusion was global and not restricted to certain borders, such as those defined by angiosomes. This result suggests that chronic ischaemia of the foot leads to significant collateralisation between angiosomes, which may result in reorganisation of the angiosome borders. The Global Vascular Guidelines on the Management of Chronic Limb Threatening Ischaemia[28] recommends angiosome guided revascularisation in patients with significant wounds, particularly those involving the mid- or hindfoot. However, the guidelines consider angiosome guided revascularisation irrelevant for toe lesions. In accordance with this, in the present study, where the majority (77%) of the ischaemic wounds were toe lesions, angiosome based direct revascularisation was not associated with improved wound healing.

The quality of the pedal arch is also regarded as an important factor for foot circulation because the pedal arch connects the anterior and posterior circulations and is the main blood supply for the entire distal forefoot. Kawarada *et al*.[10] reported that post-procedural pedal arch classification was an independent predictor of wound healing, whereas angiosome based direct revascularisation had no impact on wound healing. Similarly, in patients treated by infrapopliteal bypass, Rashid *et al*.[11] found that the rates of wound healing and time to healing were directly influenced by the quality of the pedal arch rather than the angiosome chosen for revascularisation. In addition, Higashimori *et al*.[28] demonstrated that direct flow into a patent pedal arch is essential for improving amputation free survival and limb salvage rates, especially when only one runoff vessel can be established to the foot. Recently, Nakama *et al*.[24] reported the benefit of pedal artery angioplasty for improving wound healing in the Rendezvous prospective registry. However, the benefit was noted only in a moderate risk population, not in low or high risk patients. They defined high risk as the presence of three risk factors: (i) delayed wound healing, including non-ambulatory status; (ii) treatment by haemodialysis; and (iii) University of Texas grade $\geq$ 2 wound. This finding could not be confirmed in the present study population because other factors were identified as being independently associated with wound healing (gangrene, CRP > 3 mg/L, baseline pedal arch type 3, and partial or complete PAR). In previous studies, factors such as diabetes mellitus, wound infection, low serum albumin, Rutherford category 6, indirect angiosome

revascularisation, and wound depth had been independently associated with wound healing.[10,29,30]

There may be concerns about potential damage causing loss of target vessels for bypass with interventions on pedal arteries. However, in the present study, only one patient with a failed PAR procedure required bypass surgery. The major amputation rate in the PAR group was very low (3.9% at one year). In the present study population, the PAR success rate was relatively low (approximately 60%). However, direct angiosome flow was obtained in 81.6% of the PAR group. In the Rendezvous registry, direct revascularisation was also achieved in only 74.3% of the patients undergoing pedal artery intervention.[24] This may reflect the technical difficulty of the PAR in the patient with CLI due to lesion complexities. Currently, there is no guideline recommendation regarding endovascular revascularisation for inframalleolar lesions.[28] The present study showed the benefit of pedal artery revascularisation for wound healing and may serve as clinical data supporting endovascular inframalleolar revascularisation in patients with CLI.

Other studies have advocated the benefit of the multiple vessel revascularisation instead of single angiosome related artery revascularisation for better wound healing and limb salvage.[7–9] However, there has been only one small prospective study.[7] It was also thought that multivessel recanalisation would be more advantageous for wound healing than single vessel revascularisation. In particular, in patients with ischaemic wounds, an attempt was made to revascularise as many tibial and pedal arteries as possible, whenever feasible. However, the current study has shown that multivessel revascularisation was not associated with improved wound healing. Similarly, in the Rendezvous registry, multivessel infrapopliteal revascularisation had no significant impact on wound healing. Depending on various clinical and anatomical factors, such as wound extent, presence of infection, and existing perfusion status, there may be need for multivessel revascularisation. Which patient subgroups would benefit from multivessel revascularisation remains to be defined.

This study has several limitations. Firstly, it was a single centre retrospective study, with the intrinsic limitations of this study design. Secondly, owing to the significant difference in baseline characteristics between the patient groups, only 72.8% of the study subjects could be paired for comparison. Thirdly, tissue perfusion was not evaluated before or after the procedure. Thus, the real impact of the revascularisation procedure on the perfusion of the wound area was not validated. Fourth, the treated vessels were not followed with imaging studies to directly assess the durability of the achieved patency. To validate the present findings, larger scale prospective clinical trials using objective tissue perfusion assessments are required.

CONCLUSION

Successful PAR achieved better wound healing and a higher rate of freedom from major amputation. Gangrene, high CRP, absence of a pedal arch, and successful PAR were factors independently associated with wound healing in patients undergoing endovascular therapy for CLI. Thus, efforts should be made to revascularise the pedal arteries, especially when the pedal arch is completely absent.

CONFLICTS OF INTEREST

None.

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