

ORIGINAL ARTICLE

Outcomes and prognosis of diabetic foot ulcers treated by an interdisciplinary team in Canada

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Abstract

The aim of this study was to determine the wound healing outcomes of patients with a plantar diabetic foot ulcer (DFU) treated with an interdisciplinary team approach, and to identify associated variables. A retrospective observational cohort study of 140 adult patients, with a plantar DFU, treated between 2012 and 2018 at a wound care clinic of a University affiliated hospital was conducted. Predictive and explicative analyses were conducted with logistic multivariate methods and with a Receiver Operating Characteristics curve. The best predictor of wound healing at 3 months was a 41.8% wound size reduction at 4 weeks (AUC: 0.86; sensitivity: 83.1%; specificity: 67.2%, positive predictive value: 72.8%; negative predictive value: 78.9%; positive and negative likelihood ratios: 2.53 and 0.25, respectively). Main baseline variables independently associated with this predictor were: a monophasic Doppler waveform (OR 7.52, 95% CI [2.64–21.39]), cigarette smoking (OR 4.7, 95% CI [1.44–15.29]), and male gender (OR 3.58, 95% CI [1.30–9.87]). The health care provider should be cautious and intensify its management of DFUs particularly with patients of male gender; smoking, having a monophasic waveform with a hand-held Doppler, and not achieving a minimal 41.8% wound area reduction at 4 weeks of treatment.

KEYWORDS

diabetic foot ulcer, interdisciplinary team, wound care, wound healing

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1 | INTRODUCTION

Diabetes mellitus (DM) has an increasing prevalence in the United States: an estimated 30.3 million Americans (9.4%) had the condition in 2015, representing 12.2% of the adult US population.¹ Diabetic foot ulcer (DFU) is a frequent complication of DM, as 15 to 25% of diabetic patients will end up with this condition.² DFU develop mainly secondary to loss of protective sensation (neuropathy), abnormally high foot plantar pressures and shear stress,^{3,4} diminished vascular perfusion and skin oxygenation.⁵ Wound healing of DFUs is however achievable with adequate offloading, and if needed, revascularization, in a timely manner.^{6,7}

Unfortunately, recurrences of DFUs are frequent: the 3-year cumulative incidence has been reported to be almost 60%.⁸ DFUs are also the leading cause of non-traumatic lower limb amputations.⁹ It is reported that up to 24% of neuropathic patients with a DFU will require an amputation.³ In 2017, it was estimated that 108 000 U.S. patients with diabetes were admitted for a non-traumatic lower extremity amputations (LEA).¹ In Canada, the frequency of hospitalisation for LEA of patients with diabetes is considered 20 times that of the general population.¹⁰ Thus, chronic wounds and related complications have major impacts for patients in terms of functional limitations, social participation, and quality of life.¹¹ Direct and indirect health care costs in terms of treating DFUs, amputations, hospitalizations, and rehabilitation represent a significant socioeconomic burden.^{12,13}

In DFUs, a 50% decrease of the wound area at 4 weeks has been found to be a strong predictor of wound healing at 12 weeks,¹⁴⁻¹⁸ while a 30% change in wound area at 4 weeks is considered a reliable predictor of subsequent wound healing in venous leg ulcers.¹⁹

The optimal management of DFUs is well established.²⁰⁻²⁴ The International Working Group on the Diabetic Foot,²² the National Institute for Health and Care Excellence,²³ and Wounds Canada²⁴ all recommend an interdisciplinary, integrated, specialized, and dedicated team approach. However, only few studies have evaluated the role of such an interdisciplinary team approach in the management of DFUs. In Canada, only four recent studies²⁵⁻²⁸ evaluated that approach, and all of them found positive outcomes in terms of wound healing and reduction of complications.

We thus conducted this observational retrospective study (1) to determine the 1-year wound healing outcomes of Canadian diabetic patients with a plantar DFU treated with an interdisciplinary team approach, (2) to assess the validity of wound size reduction at 4 weeks to predict healing at 3 months, and (3) to identify the

Key Messages

- wound size is a common variable used in clinical practice for monitoring wound healing, especially diabetic foot ulcers (DFU)
- the aim of this study was to determine the wound healing outcomes of patients with a plantar diabetic foot ulcer (DFU) treated with an interdisciplinary team approach, and to identify associated variables. A retrospective observational cohort study of 140 adult patients with a plantar DFU was conducted
- a 41.8% wound area reduction at 4 weeks was a strong predictor of diabetic foot ulcers healing at 3 months
- having a monophasic Doppler at baseline, cigarette smoking and male gender were negatively associated with healing

baseline variables independently associated with this important predictor.

2 | MATERIAL AND METHODS

2.1 | Study design, setting, and population

A retrospective observational cohort study was conducted that included patients with at least one plantar DFU treated at the Complex Wound Care Clinic (CWCC) of a university affiliated regional hospital of the Greater Québec City Area, Canada.²⁹ CWCC is an interdisciplinary wound care clinic that delivers care to patients with any wounds on an outpatient or inpatient basis. Referrals come mainly from physicians and nurses. The interdisciplinary team is composed of two wound care nurses, four wound care physicians (one holding a podiatry degree), a physiatrist, orthopaedic, plastic and vascular surgeons, interventional radiologists, dermatologists, infectious disease and internal medicine physicians. Community care nurses, occupational and physical therapists, nutritionists, orthotists, and podiatrists are also involved upon need.

The CWCC has a tailored interdisciplinary patient-centred approach. Patients with a DFU are treated according to the guidelines of the International Working Group on Diabetic Foot Ulcers,^{22,30} the Infectious Disease Society of America,³¹ the Society of Vascular

Surgery practice³²⁻³⁴ and the Canadian Diabetes Association.²⁴ The frequency of the visits of patients at the clinic depends on the clinical judgement of team members. Patients can therefore be seen up to two times a week (if status deteriorates and requires such visits), or only once per month (if status is favourable). Between visits at the clinic, the patient usually receives wound care from community nurses, based on the CWCC team recommendations. An advanced access system is also available to patients having a deteriorating condition; they can be seen promptly by one member of the team. Moreover, in order to be more efficient, since 2015, the registered nurses of the CWCC can order and prescribe diagnostic tests such as wound cultures, plain radiographs, and vascular laboratories, when necessary. When patients heal completely of their DFU, the clinic offers systematically follow-up visits in order to prevent reoccurrences, with proper transition from offloading modalities to proper orthotics and footwear. When proper orthotics and footwear are in place, patients are offered follow-up appointments to another clinic dedicated to diabetic foot care (the Diabetic Foot Prevention Clinic) located in the same hospital.

2.2 | Eligibility criteria, patient selection, and data collection

Patients eligible for this study were aged ≥ 18 years, diagnosed with type-1 or type-2 diabetes, who had been treated at the CWCC between January 1st 2012 and December 6th 2018 for a wound located on the plantar aspect of the foot. Patients were eligible only if they visited the CWCC twice during the study period. Patients were excluded if they were taking any drugs that could inhibit wound closure (such as chemotherapy and immunomodulatory biological agents). Patients with a DFU between toes or on the dorsal aspect of the foot were excluded because this study was intended to determine the outcomes related to plantar ulcers and offloading modalities. When there was more than one DFU present on the plantar aspect of the foot, only the larger one (in cm^2) was included in the study.

Potential subjects were identified based on the hospital electronic registry of consultations at the CWCC (*MediVisit* Registry). A first selection was performed based on the diagnosis term "diabetes" and a list of electronic chart numbers was obtained. Then, two independent assessors screened each electronic chart (*Purkinje* medical electronic system v.4.30, Montréal, [Canada]) to confirm eligibility. Overall, eligible charts were retrieved and reviewed; the first 30 charts were reviewed by both assessors to calculate an inter-rater agreement on the

main 13 variables measured (Appendix A). Extraction of data was performed on a pre-specified extraction sheet (*Microsoft Excel* 2016) with denormalized data kept on a secure server of the hospital research centre.

Characteristics extracted from charts can be retrieved in Table 1. Apparels used for vascular exams were: for ABI values and Doppler waveforms (*Hadeco Minidop ES-100VX*, *Koven Technology Inc.*, St. Louis; and *Huntleigh Dopplex D900*, *Huntleigh Healthcare Ltd.*, Cardiff, UK), manual toe pressures (*Hadeco Smartdop 45*, *Koven Technology Inc.*, St. Louis), transcutaneous oximetry (*PeriFlux System 5000*, *Perimed Inc.*, Ardmore). Neuropathy was assessed with the *Semmes-Weinstein* 5.07 (10 g) sensory testing monofilament technique (*Wounds Canada*, North York, Canada). When referring to an offloading shoe, the offloading modality used was either a *DARCO OrthoWedge* or *MedSurg* shoes (*DARCO International*, Huntington).

Wound healing was defined as a complete closure or complete epithelialization (wound size of 0 cm^2). The date of the first visit served as the reference time-point for determining an adverse outcome after up to 1 year of follow-up. Cumulative adverse outcomes were counted upon 1 year of follow-up completion (for instance, if an amputation occurred 11 months after the first visit, it was counted even if the initial DFU had healed at 3 months and had reoccurred at 6 months). Patients were judged non-compliant to their offloading modalities if it was specifically written in the medical chart that the offloading modality was not used as prescribed. Reoccurrences were defined and classified as either reoccurrence at the same anatomical site of a previously healed ulcer, or a reoccurrence at another anatomical site.

This study was approved by both institutional and University Research Ethics Board.

2.3 | Statistical analyses

For descriptive analyses, continuous data were reported as means and standard deviation (SD), while categorical data were expressed as proportions.

To address the second objective, Receiver Operating Characteristics (ROC) curve analyses were performed. ROC curves allow identifying the best cut-off of a continuous predictor of a dichotomous outcome in terms of combined sensitivity and specificity, reflected by the area under the curve (AUC). The predictive validity and best cut-off of wound size reduction at 4 weeks were assessed on this basis. Comparisons with Youden's indexes were also performed.

From the results of ROC analyses, we performed bivariate and multivariate logistic regression analyses in

TABLE 1 Baseline characteristics of the study sample

Characteristics	n (%)	Mean (SD)	95% CI
<i>Population characteristics</i>			
	140		
Age (years)		67 (12.7)	
Sex			
Male	91 (65.0)		
Female	49 (35.0)		
Body Mass Index (BMI) (kg/m ²)		32.1 (8.2)	
Smokers	29 (20.7)		
Alcohol users (for 133, 7 missing)	46 (32.9)		
Diabetes			
Type 1	5 (3.6)		
Type 2	135 (96.4)		
HbA1c (%) (for 137, 3 missing)		8.1 (2.4)	
LDL values (for 128, 12 missing)		2.0 (0.8)	
Modified Charlson Index		6.3 (2.7)	
Peripheral Neuropathy (for 138, 2 missing)	112 (81.2)		
Ankle-Brachial Index			
Compressible vessels	115 (82.1)	0.89 (0.32)	
Non-compressible vessels	25 (17.9)		
Doppler waveform			
Biphasic/Triphasic	85 (60.7)		
Monophasic	55 (39.3)		
Toe pressure (mmHg) (99 performed, 41 missing)		71.4	
<30 mmHg	17 (17.2)		
30 to 59 mmHg	26 (26.3)		
≥60 mmHg	56 (56.6)		
Peripheral artery disease ^a	59 (42.1)		
Foot deformity	77 (55.0)		
Previous lower extremity amputation	15 (10.7)		
<i>Foot ulcer characteristics</i>			
Wound size (cm ²)		1.95 (3.69)	(1.33; 2.57)
Depth (cm) (for 58, missing 82)		0.85 (1.14)	(0.55; 1.15)
Location			
Toes	60 (42.9)		
Metatarsal heads	58 (41.4)		
Midfoot	6 (4.3)		
Rearfoot	16 (11.4)		
Infection			
Superficial	37 (26.4)		
Deep ^b	62 (44.3)		
Granulation tissue			
≥50% of ulcer area	63 (45.0)		
<50% of ulcer area	77 (55.0)		

(Continues)

TABLE 1 (Continued)

Characteristics	n (%)	Mean (SD)	95% CI	
<i>Offloading modalities</i>				
Offloading modalities prescribed at baseline				
Total contact cast	10 (7.1)			
Removable cam walker	3 (2.1)			
Offloading shoe	43 (30.7)			
Orthotics	20 (14.3)			
Orthopaedic or regular shoes	64 (45.7)			
Offloading modalities used during the follow-up period (cumulative: 247 modalities for 140 patients)				
Total contact cast	27			
Removable cam walker	19			
Offloading shoe	59			
Orthotics	73			
Orthopaedic or regular shoes	69			
Overall patients' compliance to their offloading modality				
Yes	64 (45.7)			
No	76 (54.3)			
Impossible to determine	5 (3.6)			
<i>Outcomes</i>	<i>All</i>		<i>Healable (%)</i>	<i>Non-healable (%)</i>
Wound healing at	140		112	28
4 weeks	26 (18.6)		24 (21.4)	2 (7.1)
3 months	71 (50.7)		65 (58.0)	6 (21.4)
12 months	109 (77.9)		96 (85.7)	13 (46.4)
Time to wound healing (days) (for 109 wounds)		116.8	(93.1; 140.5)	
One-year cumulative adverse outcomes				
Reoccurrence at same anatomical site	31/109 ^c (28.4)			
Time to reoccurrence (days)		66.9 (55)	(46.7; 87.1)	
Reoccurrence at new anatomical sites	63/118 ^d (53.4)			
Time to new ulceration (days)		115.6 (98.3)	(90.7; 140.6)	
Amputation	17/125 ^e (13.6)		9/112 (8.0)	8/28 (28.6)
Time to amputation (days)		144.8 (101.6)	(92.5; 197.0)	
Death (all causes)	13/125 ^e (10.4)			
Time to death (days)		244.7 (330.4)	(45.0; 444.3)	7/112 (6.3) 6/28 (21.4)

Abbreviations: HbA1c: glycated haemoglobin; LDL, low-density lipoprotein.

^aAs per chart complete evaluation.

^bIncluding wound deep tissue infection, cellulitis, osteomyelitis.

^c31 patients had not healed at 1 year of follow-up.

^d22 patients were excluded from the denominator because in the combined group of deceased/lost to follow-up patients (n = 30) 8 had at least one new ulceration during the period.

^e15 patients were lost to follow-up.

order to identify major baseline determinants of the best cut-off of wound size reduction at 4 weeks, using the odds ratio (OR) and its 95% confidence interval (95% CI) as measure of association. Only variables with a *P* value <0.15 in bivariate analyses were included in a backward multiple logistic regression analysis. Then, each variable

was taken off the full model one by one, and only those identified as potential confounders in the literature, that brought about a 15% change in the OR were kept in the final model. Statistical significance was set at 0.05. Statistical analyses were performed with the SAS[®] software, Version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Cohort characteristics

The sample included 140 patients with at least one DFU on the plantar aspect of their foot. Fifteen patients (10.7%) were lost before the end of the follow-up period of 1 year. Extraction agreement between the two independent reviewers was very good (Appendix A) either for continuous variables (intraclass correlations ranging from 0.950 to 0.997) and categorical variables (inter-rater agreement from 83.3% to 100%, corresponding Kappa from 0.65 to 1.00). Selected baseline characteristics of study participants are presented in Table 1. The majority were males (65.0%) with a mean age of 67 years (SD 12.7), with type-2 diabetes (96.4%), and a mean BMI of 32.1 (SD 8.2). The mean Charlson Comorbidity Index was 6.3 (SD 2.7) and 20.7% were current cigarette smokers.

Based on pre-specified criteria, peripheral artery disease (PAD) was present for 42.1% of patients included. Neuropathy was found in the majority (81.2%) of patients, as foot deformities (55.0%); a few patients had a prior history of amputation of the foot (10.7%). Plantar ulcers were predominantly located at the forefoot (84.3%). Plantar DFU had a mean area of 1.95 cm² (SD 3.69) at baseline. Granulation tissue at baseline was seen predominantly in 63 patients (45.0%). Superficial infection and deep tissue infections of wounds at onset affected, respectively, 26.4% and 44.3% of patients.

3.2 | Offloading modalities

A total of 247 offloading modalities were used to treat 140 patients with a plantar DFU: TCC (for 27 patients), RCW (for 19 patients), offloading shoes (for 59 patients), orthotics (for 73 patients), orthopaedic or regular shoes (for 69 patients). Patients' compliance to their offloading modality was generally low, representing 45.7%. At baseline, patients chose regular and orthopaedic shoes as their preferred offloading modalities (64/140), followed by offloading shoes (43/140), orthotics (20/140), TCC (10/140), and RCW (3/140).

3.3 | Wound healing outcomes

Figure 1 describes the outcomes of participants at different follow-up points. At 4 weeks of follow-up, 18.6% of DFUs had healed; at the 3-month follow-up, 50.7% of DFUs had healed; this proportion reached 77.9% at 1-year. Figure 1 details specifically reasons related to

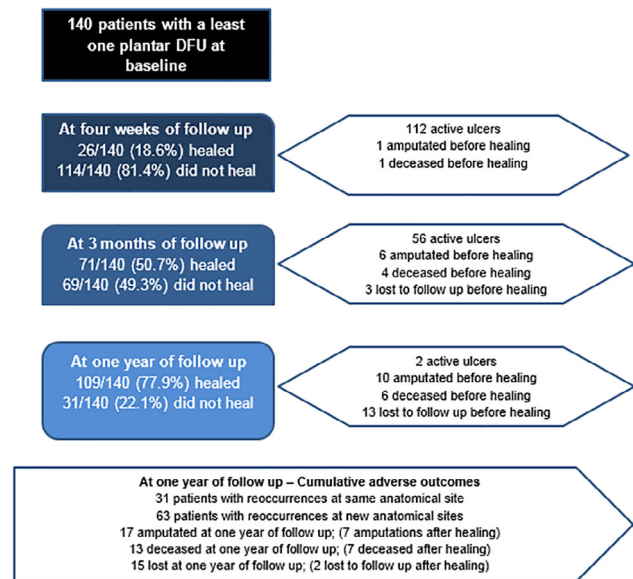


FIGURE 1 Flowchart of the cohort

non-healing cases. Mean time to achieve wound healing during the 1-year follow-up period (for 109 wounds) was 116.8 days.

Adverse outcomes at 1 year were: reoccurrence at the same anatomical site counted for 31/109 (28.4%) and at other anatomical sites 63/118 (53.4%), amputation 17/125 (13.6%) and death 13/125 (10.4%). A total of 94 hospitalizations occurred at 1-year. Of those, DFU-related hospitalizations counted for 63 (for 42 patients). Specifically, 15 occurred at baseline while 48 occurred during the year of follow-up.

Mean times to the occurrence of adverse outcomes were: for reoccurrence at the same anatomical site (31 values) 66.9 days (SD: 55) and at another anatomical site (63 values) 115.6 days (SD: 98.3), for amputation (17 values) 144.8 days (SD: 101.6), and for death (13 values) 244.7 days (SD: 330.4).

3.4 | Wound area reduction at 4 weeks as a predictor of wound healing at 3 months

During the first 4 weeks of follow-up, 34 patients had their wound increased in size (including amputation and death), while 106 had either a wound size reduction or achieved wound healing. From the ROC analyses (Figure 2), a 41.8% wound size reduction at 4 weeks was identified as the best cut-off value, and was associated with an AUC of 0.86 (sensitivity: 83.1%, specificity: 67.2%, positive (PPV) and negative (NPV) predictive values: 72.8% and 78.9% respectively, and positive (LR+) and

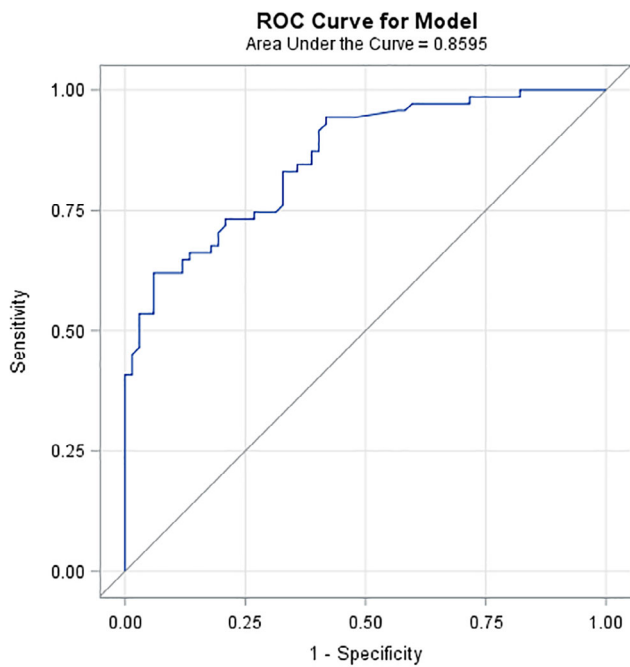


FIGURE 2 ROC curve analysis for wound area reduction at 4 weeks and wound healing at 3 months

negative (LR-) likelihood ratios: 2.53 and 0.25. This threshold was judged (after consensus by MPM and JP) as being the most reliable clinically (maximising a greater number of patients, while optimising both sensitivity and specificity), when compared with the Youden's index performed, and compared with the literature reference of 50%.¹⁴⁻¹⁸ In our population, a 50.08% change (AUC of 0.74) was associated with a sensitivity of 76.1%, a specificity of 67.2%, PPV and NPV values of 71.1% and 72.6%, LR + of 2.32 and LR- of 0.36.

3.5 | Baseline characteristics associated with wound area reduction at 4 weeks

Table 2 presents the results of bivariate and multivariate logistic regression analyses conducted to identify independent determinants of wound size reduction at 4 weeks, dichotomized at 41.8%. Nine independent baseline variables were retained in the final model, of which six were statistically significant. Variables associated with having not attained a minimal 41.8% wound size improvement at 4 weeks from the adjusted multivariate analysis were: type-1 diabetes (OR 21.37, 95% CI [1.41–324.15]), a monophasic Doppler waveform (OR 7.52, 95% CI [2.64–21.39]), a wound requiring an antimicrobial dressing (OR 6.39, 95% CI [1.96–20.81]), cigarette smoking (OR 4.7, 95% CI [1.44–15.29]), being a male (OR 3.58, 95% CI [1.30–9.87]), and using systemic

antibiotic for deep tissue infection (OR 0.36, 95% CI [0.14–0.95]).

4 | DISCUSSION

One of the main findings of this study is that a 41.8% wound area reduction at 4 weeks of treatment is a strong predictor of wound healing at 3 months. The 41.8% cut-off point was determined, primarily based on its sensitivity, specificity, and negative likelihood ratio and compared with Youden's index and literature reference of 50% area reduction. On clinical grounds, this means that among patients who have not achieved a 41.8% wound size reduction at 4 weeks, 78.9% will not achieve healing within 3 months; while among patients who have achieved a 41.8% wound size reduction at 4 weeks, 72.8% will achieve healing within 3 months. Moreover, the LR+ and LR- obtained suggest its use as a moderate to an important diagnostic value.

Based on that cut-off point of 41.8%, we were able to differentiate patients having an early healing response compared with those who did not, or have had a delayed healing response. Based on the adjusted multivariate analysis of wound healing, type-1 diabetes was the leading factor associated with delayed healing. Caution should be used with interpretation of this result, as our study sample only had 5 patients (3.6%) with type-1 diabetes.

The detection of a monophasic Doppler waveform was another determinant of delayed healing. While the ABI was statistically significant in the bivariate analysis, it was not in the multivariate analysis. Also, toe pressure could not be used due to missing data (representing 30% of the population). This occurred because toe pressure measurement is not routinely performed for patients with excellent underlying blood supply.

The use of topical antimicrobial dressings at baseline for either deep tissue and superficial infection or either based on clinical judgement was also associated with not achieving a 41.8% wound size reduction at 4 weeks of follow-up. Again, caution should be used while interpreting this result, as the occurrence of an underlying infection (without use of antibiotics) is probably the underlying factor. At the opposite, the use of systemic antibiotics at baseline for a deep tissue infection (either deep infection at the wound site, cellulitis, or osteomyelitis) was positively associated with achieving at least a 41.8% wound size reduction at 4 weeks. Once again, this should be interpreted as a wound requiring systemic antibiotics, and not as the use of antibiotics for any wounds at large (including those without infection and those with a superficial infection).

TABLE 2 Results of multivariate logistic regression analyses conducted to identify baseline variables associated with wound size reduction <41.8% at 4 weeks

Baseline characteristics	Bi-variate analysis			Backward multivariate analysis ^b			Adjusted multivariate analysis ^c		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	1.01	(0.98-1.03)	0.64	-	-	-	1.00	(0.96-1.05)	0.91
Sex	Woman vs Man	0.49 (0.24-1.03)	0.06	0.33	(0.13-0.84)	0.02	0.28	(0.10-0.77)	0.01
BMI		1.02 (0.97-1.08)	0.41	-	-	-	-	-	-
Modified Charlson Index		1.15 (1.01-1.32)	0.03	-	-	-	-	-	-
HbA1C		0.91 (0.76-1.08)	0.26	-	-	-	0.95	(0.75-1.20)	0.66
LDL		0.97 (0.63-1.47)	0.88	-	-	-	-	-	-
Diabetes	Type 1 vs Type 2	6.04 (0.66-55.52)	0.11	14.10	(1.10-179.92)	0.04	21.37	(1.41-324.15)	0.03
Smoker	Yes vs No	2.44 (1.06-5.63)	0.04	4.53	(1.51-13.66)	<0.01	4.7	(1.44-15.29)	0.01
Alcohol	Yes vs No	0.60 (0.28-1.26)	0.17	-	-	-	-	-	-
ABI categories	< 0.9 vs Normal	7.01 (2.95-16.66)	<0.01	-	-	-	-	-	-
	> 1.3 or NC vs Normal	3.38 (1.34-8.53)	0.58	-	-	-	-	-	-
Neuropathy	Yes vs No	0.67 (0.28-1.57)	0.35	-	-	-	0.54	(0.18-1.64)	0.27
Deformity	Yes vs No	0.49 (0.25-0.98)	0.04	-	-	-	-	-	-
Prior history of amputation	Yes vs No	2.34 (0.78-7.00)	0.13	-	-	-	-	-	-
Abnormal Doppler	Yes vs No	5.57 (2.64-11.76)	<0.01	8.76	(3.42-22.46)	<0.01	7.52	(2.64-21.39)	<0.01
Topical antimicrobial	Yes vs No	4.00 (1.68-9.55)	<0.01	3.8	(1.39-10.40)	<0.01	6.39	(1.96-20.81)	<0.01
Superficial infection	Yes vs No	0.70 (0.32-1.53)	0.37	-	-	-	-	-	-
Infection with antibiotics	Yes vs No	0.64 (0.32-1.28)	0.21	-	-	-	0.36	(0.14-0.95)	0.04
Location	Forefoot vs Rearfoot	0.34 (0.13-0.87)	0.02	-	-	-	-	-	-
Wound size at baseline		1.04 (0.95-1.14)	0.42	-	-	-	-	-	-
Depth at baseline ^a		1.59 (0.93-2.71)	0.09	-	-	-	-	-	-
Time between onset and 1st CWCC consultation		1.00 (0.99-1.00)	0.76	-	-	-	-	-	-
Total contact cast	Yes vs No	0.53 (0.22-1.32)	0.17	-	-	-	-	-	-
Removable cam walker	Yes vs No	2.18 (0.82-5.83)	0.12	-	-	-	-	-	-
Offloading show	Yes vs No	1.08 (0.55-2.14)	0.83	-	-	-	-	-	-
Orthotics	Yes vs No	0.48 (0.24-0.95)	0.03	-	-	-	-	-	-
Shoes	Yes vs No	2.44 (1.22-4.88)	0.01	-	-	-	-	-	-
Compliance	Yes vs No	0.75 (0.37-1.52)	0.43	-	-	-	-	-	-
Toe Pressure ^a		0.99 (0.98-1.00)	0.01	-	-	-	-	-	-

Abbreviations: CWCC, Complex Wound Care Clinic; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; NC, non-compressible vessels; OR, Odds ratio.

^aNot considered in the multivariate analysis due to missing data (59% for Depth at baseline and 30% for Toe pressure).

^bInitial variables included in the backward regression had a bi-variate *P* value <0.15 (15 variables in bold).

^cThe adjusted multivariate analysis included nine variables, of which six were statistically significant.

Other variables may have been included in the final multivariate model if the study sample had been larger. There was no significant statistical association with the use of a TCC, a RCW, or an offloading shoe due to the

paucity of patients that had chosen these offloading modalities during the very first 4 weeks of treatment. Even though the compliance to wearing an offloading modality properly was low, it was not a variable

associated with wound size reduction at 4 weeks. This is probably due to the fact that patients could have worn different modalities over the course of their follow-up, especially during the first 3-month period. Moreover, the majority of patients chose solely shoes as their therapeutic footwear, while they were instructed to wear an offloading device for better outcomes. This may be explained by the fact that when proposing and choosing an offloading modality, the practitioner has to consider different factors such as: the healing potential (e.g. maintenance or non-healing wounds due to critical limb ischemia that cannot be revascularized), quality of life and patients' preferences and contraindication of having a specific offloading modality such as the presence of an active infection, and the potential risk of fall injuries. Patients' motives were difficult to retrieve from medical charts. The cost of offloading devices might be one reason, as they are not reimbursed by the Canadian Public Health Care Insurance.

While literature suggests that a 50% change in wound size at 4 weeks is a strong predictor of wound healing at 3 months, a 41.8% wound size reduction at 4 weeks gave a better prediction in our study sample with individuals with plantar DFU. Due to its stronger negative predictive value (78.9%) than its positive predictive value (72.8%), the 41.8% wound size reduction threshold has to be interpreted adequately. Therefore, not achieving a 41.8% wound size reduction at 4 weeks has a better prognosis utility for determining failure to heal by 3 months. Its corollary appears to be of utility, but it cannot predict perfectly healing at 3 months. A potential hypothesis is that some individuals with a DFU may have early positive healing process, but with a slower healing rate thereafter. This observation has been previously documented, as wound healing trajectories were analysed in individuals that achieved at least a 50% wound size reduction at 4 weeks.³⁵ In those individuals, it was highlighted that ulcers that failed to progress or worsen for 2 weeks or more (between weeks 5 and 12) resulted in lower healing rates at 12 weeks.³⁵ Moreover, not achieving a 90% wound size reduction at 8 weeks provided a strong negative predictive value (82%) for DFU healing at 12 weeks.³⁵ In those cases, authors recommended re-evaluation of the wound and its treatment, regardless of early positive healing process.

Also, our results are comparable with previous literature findings as cigarette smoking and peripheral artery disease are DFU risk factors.³⁶ The female gender has been previously reported to be a characteristic associated with improved wound healing.³⁷ Contrary to previous studies that evaluated factors associated with DFU healing, this study examined the factors associated with wound size reduction at 4 weeks of treatment. The

rationale of this approach was to improve early recognition of factors associated with delayed healing based on a strong predictor of wound healing at 3 months: the wound area reduction at 4 weeks of treatment.

Peripheral artery disease (PAD) is a known factor impacting wound healing. Thus, the prevalence of PAD in our population (42.1%) should be taken into account. This can therefore have major impacts on the outcomes of this study. Other retrospective studies have reported the occurrence of PAD of 55.2%,³⁸ 51.8%,²⁶ 34.7%,²⁵ and 29.1%.³⁹ Those previous studies used the diagnosis of PAD as a variable, but did not use specifically vascular studies values individually (such as from the ABI, the occurrence of a monophasic Doppler waveform or an angiogram, toe pressure measurements and transcutaneous oximetry). Therefore, the sensitivity of the diagnosis of PAD may differ, according to the vascular assessment modality used.^{7,40}

Accordingly, we decided not to use a wound classification system for determining predictors of wound healing because wound classification systems do not define precisely the extent of the spectrum of PAD, and especially critical limb ischemia.⁴¹ However, the *Wound, Ischemia, and foot Infection (WIFI) Classification* of the *Society for Vascular Surgery* would have been of interest to integrate in the analyses as it defines ischemia and PAD based on ABI, ankle systolic pressure, toe pressure, and transcutaneous oximetry. However, the classification was initially published in 2014⁴¹ and recently validated and our study period was from 2012 to 2018. Nevertheless, we considered individual wound characteristics in order to identify variables that can predict healing.

Among the strengths of this study are the use of electronic database and charts, the systematic extraction approach used by two independent assessors, and the fact that there were only a few patients lost to follow-up. Also, agreement between assessors was very good as depicted by intraclass correlations obtained (Appendix A). Kappa coefficients obtained were lower with values ranging from 0.65 to 1.00 with large confidence intervals, but their inter-rater agreement coefficients were higher ranging from 83.3% to 100%. These results can be explained by having used only of a subset sample of the population (30 charts) and possibly the difficulty retrieving information in medical charts.

Moreover, only wounds on the plantar aspect of feet were included, in respect of their specific pathophysiology and treatment. This is an important point, as plantar foot ulcers are associated with a worst outcome in terms of reoccurrence than non-plantar foot ulcers.⁸ All patients benefitted from an interdisciplinary team approach for the management of their DFU, based on national and international guidelines. Every patient also

had a complete vascular examination at baseline and compliance to the offloading modality was also assessed for every patient.

Our study also had some limitations. Patients lost to follow-up counted for 10.7% and this may have underestimated the number of adverse outcomes. However, a worst-case scenario was performed when interpreting the data. Other factors may have had impact on the results of this study. While potential confounders have been identified from prior literature search and efforts have been made to report independent associations, there may still be unmeasured confounders, resulting in residual confounding. Due to the retrospective nature of the study, we were not able to extract from medical charts every types of wound dressings used during the course of the follow-up. However, all CWCC members based their recommendations of DFU treatment and wound bed preparation on international recognised guidelines.^{22,24,30-34} The number of visits per patient at the clinic was variable and this is also a potential confounder. Consistent with the nature of an observational retrospective study design, associations can be identified between variables, but causality cannot be ascertained.

Data from this study support the use of a 41.8% wound size reduction at 4 weeks in order to predict plantar DFU healing at 3 months. To our knowledge, it is the first study with Canadian patients to determine a percentage of area reduction of plantar DFU, as an indicator of healing. Moreover, an abnormal monophasic Doppler waveform, either for the dorsalis pedis or posterior tibialis artery, detected with a hand-held Doppler was associated with delayed wound healing. Therefore, its occurrence at baseline should be considered by a red flag when treating patients. Before implementation to clinical practice and due to the observational retrospective nature of the study, clinicians should keep in mind that results could have been different with a prospective cohort study. Moreover, transcutaneous oximetry values could not be used in this study because of the lack of standardisation of sensors' location, and because it was not performed solely at baseline. Therefore, we recommend future prospective studies with an adequate standardisation regarding the use of transcutaneous oximetry. Finally, our study examined patients with a DFU located only on the plantar aspect of the foot. Therefore, results cannot be generalised to patients with interdigital or dorsal DFU.

Altogether data from this study add to the knowledge on prognosis of DFUs, especially those located on the plantar aspect of the foot. Non-achieving a 41.8% wound area reduction at 4 weeks suggests high probability of non-healing of plantar DFUs at a 3-month period. The occurrence of a monophasic waveform at baseline,

cigarette smoking, and male gender are also strongly associated with not achieving sufficient wound size reduction at 4 weeks and healing at 3 months. Our results corroborate previous studies as smoking, the absence of offloading modality, the presence of an infection requiring antimicrobial dressing, and the occurrence of PAD, especially a monophasic waveform found with a hand-held Doppler, are the main characteristics associated with delayed healing and should be considered red flags. Accordingly, in order to achieve healing at 3 months of follow-up, if there is no 41.8% wound area reduction at 4 weeks of treatment, or in the presence of a monophasic waveform with a hand-held Doppler, the health care provider should have a prompt response and intensify its management of DFUs.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX A

List of variables used for the inter-rater agreement analysis

Categorical variables

Variables	Inter-rater agreement (%)	Kappa (95% CI)
Abnormal Doppler	100.0	1.00
Infection status at baseline	83.3	0.65 (0.37; 0.93)
Smoking status	100.0	1.00
Amputation status during the 1-year follow-up	96.2	0.78 (0.37; 1.00)
Hospitalisation status during the 1-year follow-up	92.3	0.85 (0.64; 1.00)
Reoccurrence status during the 1-year follow-up	84.6	0.67 (0.39; 0.95)
Death status during the 1-year follow-up	100.0	1.00

Continuous variables

Variables	Intra-class correlations	(95% CI)
Ankle brachial index	0.968	(0.931, 0.985)
Glycated haemoglobin	0.997	(0.993, 0.998)
Modified Charlson Index	0.950	(0.897, 0.976)
Wound area at baseline	0.988	(0.975, 0.994)
Wound area at 4 weeks of treatment	0.992	(0.981, 0.996)
Number of days until wound healing or until occurrence of amputation or death	0.981	(0.956, 0.992)