The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers

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ABSTRACT

Objective: Previous studies have reported correlation between the Wound, Ischemia, and foot Infection (WIfI) classification system and wound healing time on unadjusted analyses. However, in the only multivariable analysis to date, WIfI stage was not predictive of wound healing. Our aim was to examine the association between WIfI classification and wound healing after risk adjustment in patients with diabetic foot ulcers (DFUs) treated in a multidisciplinary setting.

Methods: All patients presenting to our multidisciplinary DFU clinic from June 2012 to July 2017 were enrolled in a prospective database. A Cox proportional hazards model accounting for patients' sociodemographics, comorbidities, medication profiles, and wound characteristics was used to assess the association between WIfI classification and likelihood of wound healing at 1 year.

Results: There were 310 DFU patients enrolled (mean age, 59.0 ± 0.7 years; 60.3% male; 60.0% black) with 709 wounds, including 32.4% WIfI stage 1, 19.9% stage 2, 25.2% stage 3, and 22.4% stage 4. Mean wound healing time increased with increasing WIfI stage (stage 1, 96.9 ± 8.3 days; stage 4, 195.1 ± 10.6 days; $P < .001$). Likelihood of wound healing at 1 year was 94.1% ± 2.0% for stage 1 wounds vs 67.4% ± 4.4% for stage 4 ($P < .001$). After risk adjustment, increasing WIfI stage was independently associated with poor wound healing (stage 4 vs stage 1: hazard ratio, [HR] 0.44; 95% confidence interval, 0.33-0.59). Peripheral artery disease (HR, 0.73), increasing wound area (HR, 0.99 per square centimeter), and longer time from wound onset to first assessment (HR, 0.97 per month) also decreased the likelihood of wound healing, whereas use of clopidogrel was protective (HR, 1.39; all, $P \leq .04$). The top three predictors of poor wound healing were WIfI stage 4 (z score, −5.40), increasing wound area (z score, −3.14), and WIfI stage 3 (z score, −3.11), respectively.

Conclusions: Among patients with DFU, the WIfI classification system predicts wound healing at 1 year in both crude and risk-adjusted analyses. This is the first study to validate the WIfI score as an independent predictor of wound healing using multivariable analysis. (J Vasc Surg 2018;68:1096-103.)

Keywords: Diabetic foot ulcer; DFU; WIfI; Multidisciplinary care

The Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIfI) classification system was first described in 2014 by Mills et al[1] as a means of providing prognostic information and 1-year risk of major amputation for patients presenting with foot wounds. Since that time, multiple studies have also reported a correlation between the WIfI classification system and wound healing time (WHT) in a wide range of populations of patients based on univariable and Kaplan-Meier analyses. The WIfI score has been shown to be associated with wound healing in ischemic, diabetic, and nondiabetic foot wound[2-5]; in patients treated in a standard hospital setting or by specialized multidisciplinary limb preservation teams[5-7]; and after revascularization interventions.[8-10]

Importantly, in its original description, WIfI score was "not meant to function as a stand-alone clinical decision-making tool. Patient risk factors and comorbidities also play a major part."[1] As such, it is important to consider other patient risk factors in interpreting the meaning of the WIfI score. Certain studies have subsequently demonstrated an independent association between WIfI stage and risk of major amputation on multivariable analysis.[7,11] However, in the only multivariable analysis assessing the association between WIfI

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Author conflict of interest: none.

Presented as a podium presentation at the Thirty-ninth Annual Meeting of the Canadian Society for Vascular Surgery, Banff, Alberta, Canada, September 15-16, 2017.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2017.12.079

stage and WHT, WIfI stage was not significant after adjusting for potential confounding variables.[6] In a cohort of 91 limbs with neuroischemic foot wounds treated by a multidisciplinary amputation prevention service, Vartanian et al[6] reported that only wound location was independently associated with wound healing. In contrast, we have previously shown that WIfI stage is a strong predictor of wound healing based on univariable analysis.[5] Therefore, although the WIfI classification continues to be broadly applied in the recent literature, it is unclear whether the scoring system is truly predictive of wound healing once baseline patient and wound characteristics are accounted for.

The aim of this study was to examine the association between WIfI classification and wound healing after risk adjustment in patients with diabetic foot ulcers (DFUs) treated in a multidisciplinary setting.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective study of prospectively collected data
- **Take Home Message:** This study of 709 diabetic foot ulcers revealed that the Society for Vascular Surgery Wound, Ischemia, and foot Infection classification system predicts wound healing at 1 year in both crude and risk-adjusted analyses.
- **Recommendation:** The authors suggest using the Society for Vascular Surgery Wound, Ischemia, and foot Infection classification to predict healing of diabetic foot ulcers treated in a multidisciplinary setting.

METHODS

Cohort of patients. All patients presenting to our multidisciplinary diabetic limb preservation service between June 2012 and July 2017 were enrolled in a prospective database designed to track wound characteristics, interventions, and healing. Patients are referred through both inpatient consultation and outpatient referral to our service. We are responsible for the assessment and management of all DFUs in our hospital system, and thus the scope of our practice includes a wide range of minor to extensive wounds. Only patients with medication-dependent diabetes are enrolled in our database. The Johns Hopkins Institutional Review Board approved the study. All patients signed informed consent to be part of the longitudinal database before enrollment.

The patients' demographics, socioeconomic status, comorbidity, medication profile, and wound characteristics were collected at initial presentation and updated prospectively at each subsequent clinic visit. Each wound was assigned a WIfI stage at the time of first assessment based on the WIfI classification system. WIfI stages were calculated according to SVS definitions[1] based on provider consensus as previously described.[5] Patients with WIfI stage 5 wounds were excluded from the analysis as affected limbs are considered unsalvageable (n = 7).[1]

Multidisciplinary diabetic limb preservation service. Our multidisciplinary diabetic limb preservation service has been previously described in detail.[5] Briefly, our team consists of a vascular surgeon, surgical podiatrist, endocrinologist, physician assistant, wound care nurse, and prosthetist. Infectious disease, plastic surgery, and orthopedic foot and ankle consultations are obtained on a case-by-case basis as needed. All patients are assessed by all primary team members at each visit in an integrated fashion. All patients are observed closely on an outpatient basis to assess wound healing, medication compliance, and glycemic control.

At their initial visit, all patients undergo noninvasive vascular laboratory testing. Patients with evidence of peripheral artery disease (PAD) are subsequently scheduled for angiography with an intent to perform early lower extremity revascularization. The method of revascularization, open or endovascular, is left to the primary vascular surgeon. Of note, PAD was defined as ischemia on vascular laboratory noninvasive testing or documented stenoses or occlusions on angiography. The presence or absence of PAD was recorded as a separate variable from the WIfI ischemia grade. WIfI ischemia was defined per the hemodynamic parameters outlined in the original classification system[1]; any ischemia grade >0 would be considered chronic limb-threatening ischemia (CLTI). However, PAD exists in patients without CLTI and was thus included as a separate variable in our analysis.

All wounds undergo assessment with X-ray imaging, followed by magnetic resonance imaging when indicated. After revascularization, wounds are débrided to clean margins in all cases. Any radiographic evidence of osteomyelitis is surgically excised. All patients are treated with culture-targeted antibiotics after débridement; wounds limited to the toes are treated with 2 weeks of oral antibiotics, whereas wounds involving the metatarsophalangeal joint or more proximally are treated with 6 weeks of intravenous antibiotics with guidance of the infectious diseases service.

All wounds are offloaded to maximize wound healing after revascularization and débridement, and patients are educated on foot care, lifestyle habits, and medication compliance to ensure close adherence to our treatment paradigm. Once wound healing is achieved, patients continue to follow up on an outpatient basis at regular intervals for regular noninvasive testing and for assessment of new ulcer development, in accordance with the comprehensive foot examination and risk assessment guidelines.[12]

Primary outcome. The primary outcome of our study was wound healing at 1 year. The 1-year time period was chosen on the basis of the original intention of the

WIfI classification system.[1] WHT included any time after an index wound was healed or converted to a surgical incision. Wounds were considered healed only if they maintained complete epithelialization with the restoration of sustained functional and anatomic continuity for 6 weeks after complete healing, meaning that the wound has sustainable healing even after the patient begins to walk on it.[13,14]

Statistical analysis. All baseline characteristics were described for each patient using mean ± standard error of the mean or count (percentage) as appropriate. Wound characteristics and outcomes were reported for each wound overall and stratified by WIfI stage. Univariable analyses were performed to assess the association of WIfI stage with various wound characteristics and healing using Student *t*-tests (continuous variables) and analysis of variance (categorical variables). A multivariable Cox proportional hazards model including the patients' sociodemographic, comorbidity, and wound characteristics was then created to assess whether WIfI stage was an independent predictor of wound healing after adjusting for potential disease confounders and mediators. Wounds that did not achieve healing and those that underwent major amputation were censored at the date of death, loss to follow-up, major amputation, or end of follow-up. All wound healing covariates were analyzed with clustering by patient to account for the fact that some patients had multiple wounds. The covariates included in the multivariable model were chosen on the basis of our initial work describing baseline characteristics of DFU patients stratified by WIfI stage.[5] We did not include wound location in our initial multivariable model because the WIfI classification system accounts for wound location in its grading scheme.[1] However, we did construct a second multivariable model including all covariates from the initial model as well as wound location (leg/ankle, heel, midfoot, forefoot, toe), similar to the model created by Vartanian et al,[6] to confirm our findings. We also constructed a third multivariable model analyzing wound outcomes by limb (rather than by wound) to reduce the likelihood of confounding by patient-level factors despite patient clustering.

All analyses were performed using Stata version 14.0 (StataCorp LP, College Station, Tex). A significance level of $P < .05$ was used for all comparisons.

RESULTS

Cohort of patients. There were 310 DFU patients enrolled during the study period. Mean age was 59.0 ± 0.7 years; 60.3% (n = 187) were male, and 60.0% (n = 186) were black. The majority of patients had Medicare or Medicaid insurance (73.6%; n = 228); the median household income was $56,067 ± $1668, and area deprivation index was 3 (ie, severe deprivation) in 21.1% (n = 63). Nearly all patients (82.9%; n = 257) had hypertension, 53.6% (n = 166) had dyslipidemia, and 40.7% (n = 126) had PAD. At the time of their initiation presentation, 62.3% (n = 193) of patients were taking aspirin, 11.9% (n = 37) were taking clopidogrel, and 61.6% (n = 191) were taking statins. Nearly two-thirds of patients (67.4%; n = 209) were insulin dependent, and half (49.0%; n = 152) were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for blood pressure control. A complete summary of the patients' baseline characteristics is provided in Table I.

Wound characteristics. Among the 310 patients, there were 709 wounds treated, including 32.4% (n = 230) WIfI stage 1, 19.9% (n = 141) WIfI stage 2, 25.2% (N = 179) WIfI stage 3, and 22.4% (n = 159) WIfI stage 4 (Table II). The majority of wounds were located on the toes (47.7%; n = 329), followed by the forefoot (25.5%; n = 176), heel (19.0%; n = 131), midfoot (5.5%; n = 38), and leg/ankle (2.3%; n = 16). Sixty (8.5%) were recurrent wounds. Mean wound area was 6.7 ± 0.6 cm^2, which increased with increasing WIfI stage (stage 1, 3.1 ± 0.9 cm^2; stage 4, 14.9 ± 2.0 cm^2; $P < .001$). Wound depth also increased with increasing WIfI stage (stage 1, 0.20 ± 0.01 cm; stage 4, 0.99 ± 0.09 cm; $P < .001$). The mean time from wound onset to initial assessment by our team was 2.1 ± 0.1 months, including 1.7 ± 0.2 months for stage 1 wounds and 2.7 ± 0.3 months for stage 4 wounds ($P = .08$; Table II).

Wound outcomes. The mean WHT for all wounds was 127.9 ± 4.8 days and increased with increasing WIfI stage (stage 1, 96.9 ± 8.3 days; stage 4, 195.1 ± 10.6 days; $P < .001$; Table III). The likelihood of wound healing at 1 year was 94.1% ± 2.0% for stage 1 wounds vs 67.4% ± 4.4% for stage 4 wounds ($P < .001$; Fig). The overall incidence of major amputation at 1 year was 9.2% ± 2.5% and did not significantly differ across WIfI stages ($P = .96$).

Wound healing was achieved most commonly with podiatry surgery interventions alone (38.3%), followed by wound care alone (38.0%), vascular surgery interventions alone (12.5%), and combined vascular surgery and podiatric interventions (11.2%). Combined vascular and podiatric surgery interventions were more common in WIfI stage 4 wounds (38.0%; $P < .001$; Table IV). Overall, 101 limbs underwent revascularization procedures during the study period, including 64.4% endovascular, 24.8% open, and 10.9% hybrid revascularizations.

There were 47 wounds that did not achieve healing by 1 year. Of these, 15 (31.9%) had a podiatric intervention and eventually achieved wound healing, 9 (19.2%) had a combination of vascular surgery and podiatric interventions and eventually achieved healing, 4 (8.5%) had vascular surgery interventions and achieved healing with continued wound care, and 4 (8.5%) achieved healing with wound care only. The mean time to wound

Table I. Demographics and baseline characteristics of diabetic foot ulcer (DFU) patients treated by the multidisciplinary limb preservation team

Variable	Overall (N = 310)
Age, years	59.0 ± 0.7
Male sex	187 (60.3)
Race	
White	114 (36.8)
Black	186 (60.0)
Other/unknown	10 (3.2)
Insurance status	
Medicare/Medicaid	228 (73.6)
Private	75 (24.2)
Other	5 (1.6)
None	2 (0.7)
Area deprivation index (quartile)	
0	182 (61.1)
1	16 (5.4)
2	37 (12.4)
3	63 (21.1)
Median household income	$56,067 ± $1668
Type of diabetes	
Type 1	19 (6.1)
Type 2	291 (93.9)
Baseline hemoglobin A_{1c}, %	8.65 ± 0.16
Comorbidities	
HTN	257 (82.9)
Dyslipidemia	166 (53.6)
CAD	82 (26.5)
CHF	49 (15.8)
CVD	28 (9.0)
PAD	126 (40.7)
CKD	61 (19.7)
Dialysis	37 (11.9)
Retinopathy	78 (25.2)
LOPS	289 (93.2)
Gastroparesis	8 (2.6)
COPD	26 (8.4)
Smoking status	
Current	72 (23.2)
Former	97 (31.3)
Never	141 (45.5)
Baseline medications	
Aspirin	193 (62.3)
Clopidogrel	37 (11.9)
Anticoagulation	
Warfarin	32 (10.3)
Other anticoagulant	11 (3.6)
Statin	191 (61.6)
ACE inhibitor or ARB	152 (49.0)
Diabetes medications	
Oral medications only	72 (23.2)
Insulin dependent	209 (67.4)
Insulin dose, units	64.4 ± 3.5

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *COPD,* chronic obstructive pulmonary disease; *CVD,* cerebrovascular disease; *HTN,* hypertension; *LOPS,* loss of protective sensation; *PAD,* peripheral artery disease.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard error of the mean.

healing in this group was 475 ± 21 days. There were 15 wounds that never achieved wound healing; of these, 6 underwent major amputation and 9 continue to be observed or have been lost to follow-up.

Multivariable analysis of wound healing. After risk adjustment, WIfI stage was independently associated with wound healing (Table V). Compared with WIfI stage 1 wounds, the likelihood of wound healing by 1 year was significantly lower for WIfI stage 3 (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.54-0.87) and stage 4 (HR, 0.44; 95% CI, 0.33-0.59) wounds. Concomitant PAD (HR, 0.73; 95% CI, 0.58-0.92), increasing wound area (HR, 0.99 per increase in square centimeter; 95% CI, 0.98-0.99), and longer time from wound onset to initial assessment (HR, 0.97 per month; 95% CI, 0.94-0.99) were also independently associated with lower rates of wound healing. The three strongest predictors of poor wound healing were WIfI stage 4 (absolute *z* score, 5.40), increasing wound area (absolute *z* score, 3.14), and WIfI stage 3 (absolute *z* score, 3.11), respectively (Table VI).

A second multivariable model including wound location was run as a sensitivity analysis based on previously published work on this topic.[6] Even after accounting for wound location, WIfI stage 4 was still the single strongest predictor of poor wound healing in the model (HR, 0.49; 95% CI, 0.36-0.66; *z* score, −4.61; $P < .001$).

To ensure that our results were not subject to confounding because of repeated counts of patient-level factors for those patients with multiple wounds, we repeated our analysis by limb. Even with this more conservative analysis approach, WIfI stage 4 remained an independent predictor of poor wound healing (HR, 0.43; 95% CI, 0.29-0.65; *z* score, −4.12; $P < .001$).

DISCUSSION

Previous studies have reported a correlation between the WIfI classification system and WHT on unadjusted analyses.[2-10] However, in the only multivariable analysis to date, WIfI stage was not predictive of wound healing.[6] In this study, we examined the association of WIfI

Table II. Wound characteristics for diabetic foot ulcer (DFU) patients overall and by Wound, Ischemia, and foot Infection (WIfI) stage

Variable	Overall (N = 709)	Stage 1 (n = 230)	Stage 2 (n = 141)	Stage 3 (n = 179)	Stage 4 (n = 159)	*P* value
Area, cm^2	6.7 ± 0.6	3.1 ± 0.9	2.9 ± 0.4	7.0 ± 1.2	14.9 ± 2.0	<.001
Depth, cm	0.5 ± 0.03	0.20 ± 0.01	0.38 ± 0.03	0.70 ± 0.06	0.99 ± 0.09	<.001
Wound location						<.001
Leg/ankle	16 (2.3)	8 (3.6)	2 (1.5)	4 (2.3)	2 (1.3)	
Heel	131 (19.0)	32 (14.2)	14 (10.3)	38 (21.6)	47 (30.7)	
Midfoot	38 (5.5)	4 (1.8)	9 (6.6)	12 (6.8)	13 (8.5)	
Forefoot	176 (25.5)	39 (17.3)	49 (36.0)	51 (29.0)	37 (24.2)	
Toe	329 (47.7)	142 (63.1)	62 (45.6)	71 (40.3)	54 (35.3)	
Recurrent wound	60 (8.5)	24 (10.4)	20 (14.2)	7 (3.9)	9 (5.7)	.004
Time from onset to assessment, months	2.1 ± 0.1	1.7 ± 0.2	2.0 ± 0.4	2.0 ± 0.3	2.7 ± 0.3	.08

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard error of the mean.

Table III. One-year outcomes for diabetic foot ulcer (DFU) patients overall and by Wound, Ischemia, and foot Infection (WIfI) stage

Variable	Overall (N = 709)	Stage 1 (n = 230)	Stage 2 (n = 141)	Stage 3 (n = 179)	Stage 4 (n = 159)	*P* value
WHT, days	127.9 ± 4.8	96.9 ± 8.3	78.5 ± 6.4	146.9 ± 9.6	195.1 ± 10.6	<.001
12-month wound healed, %	84.9 ± 1.7	94.1 ± 2.0	96.3 ± 2.3	83.1 ± 3.4	67.4 ± 4.4	<.001

WHT, Wound healing time.
Values are reported as mean ± standard error of the mean.

classification with wound healing in 709 DFUs treated in a multidisciplinary setting. We found that increasing WIfI stage was independently predictive of poor wound healing after risk adjustment. Furthermore, the presence of an advanced-stage wound (WIfI stage 3 and 4) was the strongest predictor for poor wound healing, even above wound size, PAD, and other patient risk factors. Our study is the first that we know of to validate the WIfI score as an independent predictor of wound healing using multivariable analysis.

Vartanian et al[6] first assessed the association between WIfI stage and wound healing in a multivariable analysis accounting for the patient's sex, ambulatory status, renal function, immunosuppression, presence of diabetes, and wound chronicity and location. In that study, the likelihood of wound healing was not significantly affected by WIfI stage (stage 4: odds ratio, 0.97; 95% CI, 0.34-2.81). Instead, only wound location was independently associated with wound healing. However, WIfI stage was not associated with wound healing on univariable analysis either, which was different from most other published work on the topic. In early validation studies of the WIfI classification system, both Cull et al[2] and Zhan et al[3] demonstrated that the SVS WIfI classification system correlates with important clinical outcomes for both limb salvage and wound healing. Similarly, our group published data showing a strong correlation between

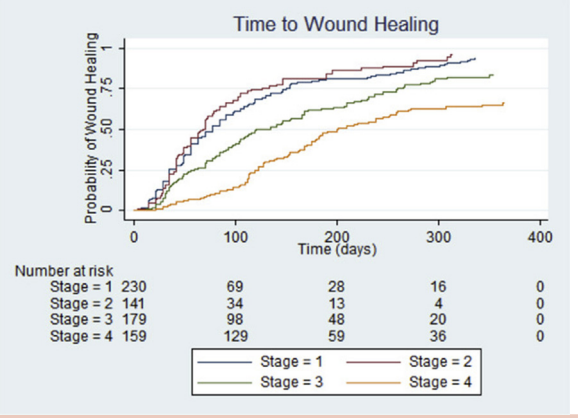

Fig. Kaplan-Meier plot demonstrating probability of wound healing over time stratified by Wound, Ischemia, and foot Infection (WIfI) stage. The mean wound healing time (WHT) increased significantly with increasing WIfI stage ($P < .001$).

WIfI stage and wound healing among patients with DFU.[5] In this updated, expanded analysis of our cohort of DFU patients, WIfI stage was again negatively associated with wound healing on univariable analysis, and the relationship persisted on multivariable analysis. Even in a secondary multivariable model adjusting for wound location, which is inherently captured by the WIfI wound

Table IV. Breakdown of interventions for healed diabetic foot ulcers (DFUs) overall and by Wound, Ischemia, and foot Infection (WIfI) stage

	Overall (N = 527)	Stage 1 (n = 174)	Stage 2 (n = 110)	Stage 3 (n = 135)	Stage 4 (n = 108)	*P* value
Intervention						<.001
Wound care only	200 (38.0)	130 (74.7)	42 (38.2)	22 (16.3)	6 (5.6)	
Podiatric surgery only	202 (38.3)	28 (16.1)	49 (44.5)	90 (66.7)	35 (32.4)	
Vascular surgery only	66 (12.5)	10 (5.7)	14 (12.7)	16 (11.9)	26 (24.1)	
Vascular surgery + podiatric surgery	59 (11.2)	6 (3.4)	5 (4.5)	7 (5.2)	41 (38.0)	

Values are reported as number (%).

grade, WIfI stage was still significantly associated with wound healing. This finding is an important contribution to the WIfI literature as it validates the use of the classification system for providing wound healing prognoses regardless of patient risk factors, comorbidities, and wound location.

In addition to WIfI stage, wound area, presence of PAD, and longer time from wound onset to assessment were also independently associated with wound healing. Both wound area and presence of PAD are characteristics that overlap with portions of the WIfI scoring system, and their significance in our multivariable analysis likely represents the importance of the role they play in affecting wound healing. While the WIfI system accounts for wound area, we demonstrate that every square centimeter increase in wound area confers a 1% decrease in likelihood of wound healing. This finding allows us to provide an objective measure of wound healing risk (or lack thereof) based simply on the area of a patient's wound at presentation.

The independent association of PAD with wound healing that we describe highlights the importance of adequate perfusion for achieving wound healing.[15] The Ischemia portion of the WIfI system addresses this; patients are assigned an ischemia grade on the basis of ankle-brachial index or toe pressure (for diabetics) that is meant to assist in determining which patients should be considered candidates for revascularization to improve wound healing potential.[1] Although we did not analyze the associations of the individual WIfI components with wound healing in our study, the presence of any level of PAD decreased the likelihood of wound healing by 27%, even after accounting for WIfI stage. This finding is consistent with that reported by Ramanan et al,[16] who showed that severe (grade 3) ischemia was the only factor to be independently associated with time to wound healing among a group of patients presenting with CLTI. Importantly, the association between PAD and wound healing is notable because not all patients in our study had PAD. Our cohort was composed of all patients presenting with DFU, of which only 40% had a diagnosis of PAD. The majority of previous WIfI publications have focused on patients with CLTI of atherosclerotic origin,[6,8,16] which by definition assumes the presence of inadequate lower extremity perfusion. Our validation of the WIfI score in a population that is not exclusively atherosclerotic in nature demonstrates the breadth of applicability of this classification system.

An increased time from onset to assessment was independently associated with poor wound healing in our study. This finding suggests that chronic wounds may take longer to heal than acute wounds. Consistent with this notion, a delay of >1 month between wound onset and assessment has been shown to dramatically increases the risk of diabetic foot complications.[17] Furthermore, limbs with chronic wounds (>6 weeks) have been shown to achieve full healing by 1 year in only 57% of cases.[6] In our experience, chronic wounds tend to have an underlying cause that contributes to their nonhealing, which is usually infectious or ischemic in origin. Our wound treatment paradigm focuses on addressing these issues, including early revascularization and aggressive wound débridement to clean margins with complete excision of infected bone. The fact that wound chronicity independently predicts prolonged WHT also suggests that diabetic foot screening initiatives focused on identifying patients with wounds earlier in their disease course could potentially reduce WHT.[18] This is particularly true because there was a trend between longer time from onset to assessment and higher WIfI stage; by focusing public health efforts on reducing time to diagnosis, we may be able to downstage wounds at presentation and thereby improve overall outcomes.

The final independent predictor of wound healing in our study was use of clopidogrel at baseline. Although it is possible that clopidogrel may confer a wound healing advantage in chronic wounds,[19] we suspect that clopidogrel use is more than likely a surrogate marker for a previous revascularization. The precise associations between medication profiles and wound healing deserve closer attention in future studies.

There are some reports in the literature demonstrating an independent association between WIfI stage and risk of major amputation. In a study of 98 threatened limbs presenting to an urban safety net hospital with rest pain or tissue loss, Ward et al[11] reported than an increasing WIfI score was associated with an 84% increased risk in

Table V. Multivariable analysis of factors associated with wound healing at 1 year among diabetic foot ulcer (DFU) patients treated by the multidisciplinary limb preservation team

Variable	Wound healed at 1 year, HR (95% CI)	*P* value
WIfI stage		
1	Reference	
2	1.16 (0.91-1.50)	.22
3	0.68 (0.54-0.87)	.002
4	0.44 (0.33-0.59)	<.001
Age (per year)	1.00 (0.99-1.00)	.70
Male sex	1.01 (0.83-1.23)	.91
Race		
White	Ref	
Black	1.06 (0.84-1.34)	.62
Other	0.50 (0.25-1.03)	.06
Area deprivation index (quartile)		
0	Reference	
1	0.80 (0.52-1.22)	.30
2	1.12 (0.81-1.55)	.50
3	1.06 (0.83-1.36)	.63
PAD	0.73 (0.58-0.92)	.007
Chronic obstructive pulmonary disease	1.25 (0.86-1.82)	.25
Clopidogrel	1.39 (1.01-1.90)	.04
ACE inhibitor or ARB	1.19 (0.97-1.45)	.09
Wound area (per cm^2)	0.99 (0.98-0.99)	.002
Time from wound onset to assessment (per month)	0.97 (0.94-0.99)	.04

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *CI*, confidence interval; *HR*, hazard ratio; *PAD*, peripheral artery disease; *WIfI*, Wound, Ischemia, and foot Infection.

Table VI. Rank of covariates associated with diabetic foot ulcer (DFU) healing by *z* score on multivariable analysis

Rank	Variable	Absolute *z* score value
1	WIfI stage 4	5.40
2	Wound area (per cm^2)	3.14
3	WIfI stage 3	3.11
4	PAD	2.72
5	Time from wound onset to assessment (per month)	2.11
6	Clopidogrel	2.04

PAD, Peripheral artery disease; *WIfI*, Wound, Ischemia, and foot Infection.

major amputation at 1 year after risk adjustment. In a study of 280 limbs presenting with either CLTI or DFU, WIfI stage 4 wounds were associated with a 12-fold increase in risk of 1-year major amputation after risk adjustment.[7] We did not assess whether there was an independent association between WIfI stage and 1-year major amputation in our study because there was no difference in major amputation rates across WIfI stages on univariable analysis and because the number of major amputation events in our study was too low to allow assessment with a valid multivariable model. The major amputation rate in both of the above-mentioned studies (27% and 15%, respectively)[7,11] was somewhat higher than the 9% rate that we report. In addition, the patients of the cohort that we evaluated were quite different from those of the previous studies. Our study focuses strictly on patients with DFU, whereas most previously published work on this topic evaluates wound healing and major amputation in patients presenting with CLTI.[2-10]

Importantly, our application of the WIfI classification system was somewhat different from its original design.[1] The WIfI clinical stages were originally intended to stratify the risk of major amputation for a threatened limb. In this study, we assigned WIfI clinical stages to individual wounds rather than to limbs. Because our primary outcome was wound healing, we hypothesized that the WIfI clinical stages could be applied to predict individual wound outcomes rather than just limb outcomes. This is particularly important in the diabetic population, which tends to suffer from multiple and recurrent wounds. Our finding that WIfI stage independently predicts wound healing for individual wounds demonstrates that the WIfI classification system has broader applications than just predicting amputation risk for a threatened limb. It can also be applied to provide prognostic information about healing potential and timing for individual wounds. Notably, we did perform a sensitivity analysis limiting our analysis by limb to ensure than our findings were applicable to the original intention of the WIfI system.

The limitations of our study deserve discussion. First, we describe outcomes for 709 wounds occurring in 310 patients, meaning that most patients were treated for multiple wounds. We accounted for potential confounding by clustering by patient in our multivariable analysis; nonetheless, not all of the wounds we described are independent from one another. Second, we chose the variables to include in our multivariable model on the basis of our original work describing the association between WIfI stage and wound healing in a DFU population.[5] The present work is a greatly expanded version of that cohort; we have accrued 93 new patients and 270 new wounds since our original publication. It is possible that other variables that we did not account for may also significantly affect WHT, resulting in residual confounding. Finally, the generalizability of our findings remains to be determined. Our cohort of patients was entirely composed of diabetic patients with foot ulcers rather than vasculopaths with classic CLTI. In addition, our multidisciplinary diabetic limb preservation service

is a resource-intense model[20] that incorporates care from a vascular surgeon, surgical podiatrist, endocrinologist, wound care nurse, physician assistant, and prosthetist in an integrated fashion.[5] The associations between WIfI stage and wound healing that we report are therefore applicable to DFU patients treated in a multidisciplinary setting; whether they extend to other populations remains to be determined.

CONCLUSIONS

Among patients with DFUs, the WIfI classification system predicts wound healing at 1 year in both crude and risk-adjusted analyses. This is the first study that we know of to validate the WIfI score as an independent predictor of wound healing using multivariable analysis accounting for patient risk factors and comorbidities.

AUTHOR CONTRIBUTIONS

Conception and design: CH, JC, CA
Analysis and interpretation: CH, JC, NM, RS, MM, JB, CA
Data collection: CH, JC, NM, RS, CA
Writing the article: CH, CA
Critical revision of the article: CH, JC, NM, RS, MM, JB, CA
Final approval of the article: CH, JC, NM, RS, MM, JB, CA
Statistical analysis: CH, JC, CA
Obtained funding: Not applicable
Overall responsibility: CA

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Submitted Sep 12, 2017; accepted Dec 29, 2017.