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Further evidence that wound size and duration are strong prognostic markers of diabetic foot ulcer healing

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Abstract

Diabetic foot ulcers (DFU) are a critical problem for those with diabetes mellitus. Predicting the healing likelihood of a DFU is important to implementing appropriate care, allocating resources, having access to advanced therapies, having successful clinical trials, calibrating clinical trial results, and providing information to administrative entities on patient and provider outcomes. Prognostic modeling can also be important when attempting to compare results across trials or care centers. In a prospective cohort study, we demonstrate and replicate that simple wound characteristics like wound area and wound duration can be used to predict wound healing by the 16th week of care. The models were based on previous literature and replicated using a machine learning algorithm. The use of wound duration and wound area in a prognostic model continues to be important when comparing study results, center-based outcomes, as well as designing clinical trials.

Introduction

Diabetic foot ulcers (DFU) are and will continue to be a major problem for those with diabetes mellitus (DM). At least 10% of patients with DM will develop DFU in their lifetime and about 4 per thousand of Medicare beneficiaries with DM will require lower extremity amputation (LEA).(1, 2) Predicting the healing likelihood of a DFU is critical to implementing appropriate care, allocating resources, having access to advanced therapies,

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having successful clinical trials, calibrating clinical trial results and providing information to administrative entities on patient and provider outcomes.

Several DFU prognostic models have been described that predict whether an individual with a DFU will heal. More than 20 years ago, we developed prognostic models that used simple wound attributes obtained at the initial patient visit.(3) Wound area and the duration of the wound alone and in combination with additional prognostic variables have been shown to predict healing in multiple clinical, often based on data from electronic medical records, and clinical trial settings.(1–6) Wound area and wound duration have also been used to risk stratify healing outcomes between wound care centers. (1–6) Given the improvement in diabetes care in general and DFU treatments specifically, we sought to reevaluate the validity of these variables in predicting healing especially across diverse clinical sites and wound severity.

Methods

Cohort

A multicenter study, called the Diabetic Foot Ulcer Consortium (DFUC), was designed to evaluate genetic and circulating cellular markers as prognostic and causal factors associated with the healing of DFU. The DFUC also collected routine data on DFU.

The DFUC is composed of wound care centers at University of Miami, Icahn School of Medicine, University of Pennsylvania and MVS Wound Care in Maryland. The goal was to enroll 200 subjects. All subjects were examined by a collaborator, had adult-onset DM, a history, and a physical examination consistent with DFU, per the local investigator, had adequate arterial flow for healing, were at least 40 years of age at the time of original DFU diagnosis, and had a DFU on the plantar aspect of the foot that was eligible for standard care. Standard care was determined by the site but included, conduct a history and physical examination including evaluation of flow, assessment of sensory neuropathy (e.g., Semmes Weinstein monofilaments) sharp debridement, off-loading (e.g., total contact cast, removable walker, etc.), treatment of infection (if present), primary bandage, and recurrent evaluation over one-to-three-week time frame. Based on progress over the first few weeks, change in the treatment plan including surgery or other therapies could be considered. The study outcome was a healed wound by the 16^{th} week of care. Standard information was obtained and is listed in Table 1. All subjects signed a consent form approved by the Institutional Review Board.

Analysis

As previously described, wound area (measured as the product of longest and widest aspects of the wound)(7) and wound duration (by history) were transformed using natural logarithm. (2) Sensory neuropathy was often tested by Semmes-Weinstein monofilaments and standard approach.(8) Logistic regression was used to assess the strength of association between each potential prognostic factor and the 16 week healing outcome; statistically significant covariates were then included in a prognostic model. The prognostic model discrimination was measured using the area under the receiver operating curve (RUC). We compared our

models to those evaluated by previous studies that focused on wound area and wound duration. The calibration of the model was evaluated using Hosmer-Lemeshow goodness-of-fit statistics. Additionally, we used LASSO (**L**east **a**bsolute **s**hrinkage and **s**election **o**perator), a machine learning algorithm, to build a prediction model. LASSO is an adaptive regression-based approach for high-dimensional data that uses 10-fold cross validation.

Results

DFUC enrolled 207 subjects. One subject was enrolled but lost to follow-up prior to sample collection and survey completion and two subjects have yet to reach the 16-week outcome. The mean age at enrollment was 57.8 years (median 57 years) and 73.0% (N=149) were male (Table 1). The mean age of onset of DM was 39.4 years (median 40) and the mean time with DM was 18.3 years (median 19). 58.3% (119) of the subjects identified as Black, 36.8% (75) as White, and 11.3% Hispanic (23 overall: 5 Black and 10 White). The mean BMI was 33.1 (median 32). Chronic kidney disease was reported in 29.5% with 11.5% having a history of requiring dialysis. Neuropathy was noted in 88.8% by clinic examination and 71.1% after Semes-Weinstein filament testing. Any history of peripheral arterial disease (PAD) was noted in 22.2%, but 99.5% of those with PAD were also neuropathic and 99.9% of subjects were felt by an investigator to have arterial flow consistent with healing (Table 1).

The mean wound area at the initial visit was 14.50 cm^2 (median 2.8 cm^2). The mean duration of the wound was 34.85 weeks (median 48.6) (Table 1). 27.4% had a primary wound that did not extend deeper than the dermis (e.g., Wagner Grade 1) and 39.1% were Wagner 3 or greater. Thirteen (6.3%) individuals had a LEA by week 4 and an additional 12 had a primary amputation (3) or revision of the earlier amputation (9) between week 4 and by week 16. Two of the LEA were major amputations. Overall, 35.1% (N=72) healed by week 16. Individuals at the MD site were almost twice as likely to heal (51.52% versus 28.76% combined average at the other sites) as the other sites (Table 1).

Based on the first visit, the natural log (*ln*) of wound duration was associated with healing by week 16 (OR: 0. 0.71(95% CI: 0.54,0.93); p=0.012) as was *ln* wound area (OR: 0.70 (95% CI: 0.59,0.83); p<0.0001) (Table 1). A history of dialysis was associated with not healing (0.19(0.04, 0.78, p=0.034) and the MD site was more likely to heal (OR: 2.64(1.34,5.20). Unlike previous studies, wound depth (deeper than the dermis) was not significantly associated with a healed wound (OR: 0.60 (95% CI: 0.31,1.19) p=0.144). The effect estimates changed minimally when all five covariates were in the model together, with the exception of site. The OR for the MD site changed to 1.65(0.75,3.61), p=0.211 and was significantly confounded by wound area and wound duration. The RUC for the remaining four covariates modeled together was 0.7250 (Table 2). Notably, the parsimonious model including only wound area and wound duration (RUC=0.7051) had a similar RUC to the larger models (Table 2). The parsimonious model was well calibrated (Hosmer-Lemeshow p=0.4451).The modeled healing rate using *ln* wound duration and *ln* wound area was 34.4% (as noted above the actual healing rate was 35.1%). The site healing rate difference was alleviated by these two parameters (MD effective rate 37.8% as compared to the other sites 33.7%).

Using LASSO regression that included all Table 1 variables revealed four variables that were the most highly associated with healing by week 16. These variables were wound duration, wound area, BMI, and adequate arterial flow. This group of variables yields an RUC of 0.7212. BMI and adequate arterial flow add little overall to the RUC as compared to wound duration and wound area alone.

As compared to previous publications and modeling done by our group this group of subjects is more severe.(2, 3) Similar variation was noted between the MD site and the other sites. Overall, only 12.8% of our cohort is in the best prognostic group; in the past it was 21.8%. 45.6% are in the worst prognostic group and in the past, it was about 10% (supplement Table).

Discussion

Understanding the likelihood that a DFU might heal is critical and prediction models based on first visit assessment of the size and the duration of the wound have been used in the design of experiments, risk stratification, clinical prediction, as tools for patient care, and outcomes analysis in large administrative datasets, cohort studies and randomized clinical trial data.(2, 3, 5, 6, 9, 10) In this study we demonstrate that a 25-year-old prognostic model is still valid and reproducible in our recent prospective dataset of subjects with wounds that are more severe than those frequently seen in administrative and clinical data. We demonstrate that more complex models do not appear to discriminate better. We also demonstrate that a machine learning approach that is more optimal for small datasets and large numbers of predictors, identified the same basic predictors. Finally, we show that the models can be used to compensate for the heterogeneity in patient characteristics often seen between centers. Importantly, these easy to obtain variables are generalizable and help to explain the heterogeneity seen between study (or clinical) sites.(1–6, 9)

Our study has limitations as it was designed to replicate previous studies regarding genetic and circulating cell associations and a healed wound and might not fully generalize to all patients seen in a wound care environment.(11, 12) It is also important to remember that the goal of this study was prognostic model and not understanding causation. It is highly probable that many of the variables in Table 1 are helpful in explaining wound repair or failure. It is also likely that parameters that we did measure like advanced treatments and osteomyelitis could have influenced our prognostic modeling. In our setting, however, we focused on information obtained at the first visit, without knowledge of future treatment options, so it is unlikely that these parameters would or could be available and substantially add to our ability to prognosticate.

In conclusion, wound area and wound duration are strong predictors of healing. We have shown that these factors replicate in different clinical centers and over decades. We also show the importance of using them to understand the likelihood that a wound will heal when comparing centers and likely studies. While the prognostic model's predictions based on our previous work is surprisingly consistent, we may need to be careful when considering our analysis and how the factors that we study interact with wounds that are highly unlikely to heal. Future studies should evaluate causal variables associated with these factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Patient and wound characteristics are the first study visit. Means or percentages with 95% CI and logistic regression based on healed by week 16 outcome.

		Means or Percentages (%)			Odds ratio	
Covariate	**N**	**Full cohort**	**Unhealed**	**Healed**	**OR 96% CI**	**p-value**
Site	97	PA 47.55(40.53,54.64)	52.27(43.41,61.03)	38.89(27.62,51.10)	Ref	
	58	MD 28.43 (22.3,35.15)	21.21(14.58,29.18)	41.67(30.15,53.89)	2.64(1.34,5.20)	0.005
	16	FL 7.84(4.55,12.43)	9.09(4.78,15.34)	5.56(1.53,13.62)	0.82(0.24,2.76)	0.751
	33	NY 16.18(11.40,22.00)	17.42(11.38,24.99)	13.89(6.87,24.06)	1.07(0.45,2.54)	0.875
Sex (male)%	204	73.04 (66.90,79.18)	74.24 (66.68,81.80)	70.83 (60.08,81.59)	1.26 (0.67,2.40)	0.473
Ethnicity (not Hispanic)%	204	88.67 (84.27,93.07)	85.50 (79.39,91.61)	94.44 (89.02,99.86)	2.48 (0.88,6.96)	0.085
Age at enrollment	202	57.80 (56.46,59.14)	57.51 (55.85,59.17)	58.32 (55.99,60.65)	1.01 (0.98,1.04)	0.698
Black%	204	58.33 (51.51,65.16)	57.58 (49.03,66.12)	59.72 (48.12,71.33)	1.08 (0.60,1.93)	0.807
White%	204	36.76 (30.09,43.44)	35.61 (27.33,43.88)	38.89 (27.35,50.42)	1.13 (0.62,2.04)	0.689
Body mass index	193	33.10 (31.42,34.77)	31.91 (30.62,33.21)	35.27 (31.14,39.40)	1.02 (0.99,1.06)	0.160
Age of diabetes onset	180	39.44 (37.54,41.34)	39.55 (37.06,42.03)	39.28 (36.28,42.28)	1.00 (0.98,1.02)	0.958
Duration of Diabetes	178	18.32 (16.73,19.91)	17.56 (15.48,19.63)	19.49 (17.00,21.98)	1.02 (0.99,1.05)	0.272
ho Congestive Heart Disease %	200	23.50 (17.57,29.43)	21.71 (14.50,28.92)	26.76 (16.21,37.31)	1.30 (0.66,2.55)	0.447
ho Peripheral Arterial Disease %	198	22.22 (16.38,28.06)	24.03 (16.56,31.50)	18.84 (9.38,28.30)	0.64 (0.31,1.33)	0.231
ho Adequate Arterial Flow %	197	95.94 (93.16,98.72)	94.53 (90.54,98.52)	98.55 (95.66,101.44)	3.93(0.47,32.65)	0.205
ho Chronic Kidney Disease %	166	29.52 (22.51,36.53)	30.09 (21.50,38.68)	28.30 (15.77,40.84)	0.76 (0.37,1.57)	0.462
ho Dialysis %	200	11.52 (6.59,16.44)	15.04 (8.35,21.74)	3.85 (−1.56,9.25)	0.19 (0.04,0.87)	0.034
HemoA1c	157	7.97 (7.57,8.37)	7.92 (7.38,8.47)	8.04 (7.48,8.61)	1.05 (0.92,1.20)	0.450
Glucose	182	158.01 (149.10,166.92)	162.36 (150.02,174.69)	150.55 (138.62,162.49)	1.00 (0.99,1.00)	0.105
eGFR	133	47.89 (42.61,53.18)	44.42 (38.38,50.46)	55.43 (44.97,65.88)	1.01 (1.00,1.02)	0.152
Serum Creatine	165	3.68 (1.49,5.86)	4.04 (0.98,7.11)	2.91 (0.71,5.10)	0.99 (0.96,1.02)	0.598
# of Wounds	202	1.35 (1.25,1.44)	1.39 (1.27,1.52)	1.26 (1.11,1.42)	0.79 (0.51,1.22)	0.282
Wound Duration	196	34.85 (28.00,41.70)	40.10 (30.59,49.60)	25.41 (16.88,33.95)	0.99 (0.98,1.00)	0.050
ln Wound Duration	193	2.91 (2.74,3.07)	3.08 (2.89,3.27)	2.59 (2.29,2.89)	0.71 (0.54,0.93)	0.012
Wound area	200	14.50 (8.44,20.55)	18.60 (10.09,27.11)	6.87 (−0.12,13.86)	0.99 (0.97,1.00)	0.111
ln Wound Area	200	0.92 (0.65,1.19)	1.39 (1.07,1.71)	0.05 (−0.40,0.50)	0.70 (0.59,0.83)	<0.0001
Wagner grade	192	3.28 (3.12,3.44)	3.28 (3.07,3.48)	3.27 (3.01,3.53)	1.00 (0.76,1.30)	0.976
Abnormal Semes Weinstein testing	194	71.13 (64.70,77.57)	70.77 (62.85,78.69)	71.88 (60.56,83.19)	1.25 (0.64,2.47)	0.514
ho Neuropathy %	196	88.78 (84.32,93.23)	86.51 (80.46,92.56)	92.86 (86.67,99.04)	2.31 (0.81,6.60)	0.118
ho Amputation %	202	48.01 (40.95,55.14)	47.69 (38.86,56.63)	48.61 (37.65,60.69)	1.24 (0.70,2.21)	0.466
Wound Depth Dermis only %	204	27.45 (21.28,33.63)	30.30 (22.36,38.25)	22.22 (12.38,32.06)	0.60 (0.31,1.19)	0.144

Table 2 :

The area under the receiver operating curve (RUC) for individual variables of potential interest as well as potential prognostic models.

Variables	**RUC**
ln Area	0.6974
ln Wound duration	0.6109
Site(categories)	0.6093
Wound depth-dermis	0.5404
ho Dialysis	0.5560
BMI	0.5654
Adequate Arterial Flow	0.5201
Area, Wound Duration, Dialysis, Site	0.7250
Area, Wound Duration, Depth-dermis	0.7217
Area, Wound Duration, BMI, Adequate Arterial Flow	0.7212
Area, Wound Duration	0.7211
Wound Area and Wound Duration (supplement table categories)	0.7051