Received: 17 February 2019 | Revised: 30 July 2019 | Accepted: 31 July 2019

DOI: 10.1111/iwj.13194

ORIGINAL ARTICLE

IWJ WILEY

Outcome predictors for wound healing in patients with a diabetic foot ulcer

Maryam Mohammad Zadeh[1] | **Hester Lingsma**[2] | **Johan W. van Neck**[1] | **Dalibor Vasilic**[1] | **Anne-Margreet van Dishoeck**[1]

[1]Department of Plastic, Reconstructive, and Hand Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands

[2]Department of Public Health, Center for Clinical Decision Making, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Maryam Mohammad Zadeh, BSc, Department of Plastic & Reconstructive Surgery and Hand Surgery, Erasmus University Medical Center, Dr. Molewaterplein 40, Rotterdam 3015 GD, The Netherlands.
Email: maloes.m.z@gmail.com

Abstract

The aim of this study was to identify diabetic foot ulcer (DFU) patients at risk for the development of a hard-to-heal wound. This is a post-hoc analysis of a prospective cohort study including a total of 208 patients with a DFU. The primary endpoints were time to healing and the development of a hard-to-heal-wound. Univariable and multivariable logistic and Cox regression analysis were used to study the associations of patient characteristics with the primary endpoints. The number of previous DFUs [odds ratio (OR): 1.42, 95% confidence interval (CI): 1.01-1.99, $P = .04$], University of Texas (UT) classification grade 2 (OR: 2.93, 95% CI: 1.27-6.72, $P = .01$), UT classification grade 3 (OR: 2.80, 95% CI: 1.17-6.71, $P = .02$), and a diagnosis of foot stand deformation (OR: 1.54, 95% CI: 0.77-3.08, $P = .05$) were significantly associated with the development of a hard-to-heal wound. Only UT classification grade 3 (HR: 0.61, 95% CI: 0.41-0.90, $P = .01$) was associated with time to healing. The number of previous DFUs, UT classification grade, and a diagnosis of foot deformation are significantly associated with development of a hard-to-heal wound in patients with a DFU. The only predictor significantly associated with time to healing was UT classification grade 3. These patient characteristics can be used to identify patients at risk for the development of hard-to-heal wounds, who might need an early intervention to prevent wound problems.

KEYWORDS

diabetic foot ulcer, multidisciplinary team, prediction model, wound care, wound healing

1 | INTRODUCTION

Diabetes mellitus is a prevalent and costly disease[1] that affects health care and well-being with associated morbidity and high mortality.[2,3] Diabetes mellitus is associated with several comorbidities, such as retinopathy, nephropathy, peripheral artery disease, heart disease, neuropathy, and foot ulceration.[2,3] Moreover, it leads to a substantial health-care cost.[4] According to death certificate statistics of the United States, diabetes is the seventh leading cause of death in the Unites States.[5]

Diabetic foot ulcers (DFUs) are the most common and feared complication of diabetes with a lifetime risk of 25%.[6] DFU could lead to a non-healing wound and in extreme cases, to amputation among diabetes patients.[7] A DFU complication is defined as a non-healing or poorly healing full-thickness wound, through the dermis, below the ankle in an individual with diabetes.[8] It is known that foot ulceration affects quality of life among these patients.[9] Approximately 1% of diabetic patients per year require a foot amputation.[10]

The pathogenesis of diabetic foot ulceration is multifactorial and frequently complicated by hard-to-heal wounds. Although the pathophysiology of foot ulceration is not fully understood, several risk factors are involved, such as peripheral vascular disease, peripheral neuropathy, arterial insufficiency, foot deformities, and impaired resistance to infection.[11] Other patient factors that might maintain a diabetic ulcer include sex, age, size of the wound, and duration of the ulcer.[6] Because of the wide variety in the clinical presentation, management of a diabetic foot requires early expert assessment.[12] In health-care research and management, there has been a lack of focused attend on DFU, and there seems to be a lack of evidence-based medicine in clinical practice.[12] There are no standard guidelines to detect patients who are at high risk of developing hard-to-heal wounds. Identification of these high-risk patients might lead to better and earlier treatment and targeted secondary prevention strategies. A treatment strategy to improve clinical outcome of DFU patients might be the introduction of a multidisciplinary team.[13,14] It has been shown that the introduction of such a team to DFU care enables to reduce the frequency of major amputations.[14,15] In order to optimise patients' outcomes of these multidisciplinary teams, early prediction of outcome followed by assigning the patient to the right health care professionals would enhance the efficacy.

To the best of our knowledge, a predictive model based on baseline characteristics to identify patients at risk for the development of hard-to-heal wounds is currently lacking. To identify these high-risk patients, we investigated baseline patient characteristics in a cohort of patients with diabetic ulcers treated in a multidisciplinary setting. In this study, we aimed to develop a prediction model to identify patients who are at risk of developing hard-to-heal wounds. This might ultimately lead to enhance triage and treatment strategies.

Key Messages

- diabetic foot ulcers (DFUs) are the most common and feared complication of diabetes
- the aim of this study was to identify DFU patients at risk for the development of hard-to-heal wounds
- the number of ulcers in history, University of Texas classification grade, and a diagnose of foot stand deformation were significantly associated with the development of a hard-to-heal wound
- these patient characteristics can be used to identify patients at risk, who might need an early intervention to prevent wound problems

2 | METHODS

2.1 | Study design and population

We performed a post-hoc analysis using data of a prospective cohort study with a historical control group including a total of 304 patients. The original study investigated the effect of a multidisciplinary paramedic triage team on the wound healing among DFU patients, and was presented elsewhere.[15] The intervention group consisted of patients included from August 2012 until December 2014 who were screened and treated by a paramedic triage team in a specialised diabetic foot clinic at the University Erasmus Medical Center, Rotterdam, The Netherlands. The paramedic triage team involved a nurse practitioner, a wound consultant, a podiatrist, and a diabetic nurse. If needed, the patients were seen by the multidisciplinary team, which consisted of an orthopaedic surgeon, a vascular surgeon, a rehabilitation physician, and an internist specialising in diabetes care. Data of these patients were compared with an historical control group treated by a vascular surgeon. All patients who presented at the outpatient clinic with a new or preexistence DFUs were included in this study. Informed consent was obtained from all patients. The study was conducted according to the ethical guidelines of the declaration of Helsinki.

The aim of the current study was to develop prediction models based on baseline characteristics of DFU patients in order to identify patients at risk for the development of hard-to-heal wounds. For this purpose, we performed a post-hoc analysis on data from the primary study to investigate baseline characteristics that were significantly associated with healing time and the development of head-to-heal wounds. Only patients with a new DFU were included in the current study. DFUs were defined as full-thickness skin break at least to University of Texas (UT) DFU Classification System of A1 extends distal to the malleolus.[16] Patients were excluded if they did not have a diabetic ulcer at the first visit or had a UT Classification A0, B0, C0, D0, or unknown. Baseline characteristics (eg, age, comorbidity, UT Classification, and BMI) were collected from patient records.

We collected patient and wound characteristics at first visit. The ulcer location was determined by the vascular surgeon and wound consultant, respectively, at the first visit. The UT Classification categorises the ulcer by using, respectively, four grades and four stages with a scale from 0 through 3 including stages to clarify the presence of infection or ischemia (Supplementary Table 1, which demonstrates the UT Classification).[17]

2.2 | Outcome measures and predictive factors

Based on the primary objective of this study, we choose two dependent outcome measures, time to healing and the development of a hard-to-heal wound among diabetes mellitus patients with a DFU for our prediction models. Normal wound healing was defined as a wound that healed within 12 weeks, based on the median healing time in our population.[18] A hard-to-heal wound was defined as a wound that did not heal within a 12 weeks period. Time to healing was defined as the time from first visit to the clinic with a DFU until complete epithelialization of the ulcer.[19] A healed wound was defined by a UT classification A0-Do.

Duration of ulcer before first visit is the time in weeks that the patient was aware of the DFU until the first visit to the specialised diabetic foot clinic. Peripheral arterial disease (PAD) was confirmed by ankle-brachial index examination and defined as ankle-brachial index <0.9.[20] A diagnosis of foot deformation includes any form of foot deformities (eg, Charcot foot, hammertoes).

The following characteristics were included in our analyses: special footwear at first visit, comorbidity claudication, history of DFU, the number of previous DFUs, history of amputation, UT classification grade, UT classification stage, glycosylated haemoglobin A (HbA1c), and a diagnosis of foot stand deformation.[4,6,16,19,21-23]

2.3 | Regression analysis

Univariable and multivariable logistic regression were used to develop a prediction model to identify patients who are at high risk of the development of hard-to-heal wounds. Univariable and multivariable Cox regression were used to determine which characteristics were associated with time to healing. Baseline characteristics were described using descriptive statistics. Normal distributed continuous variables were presented using mean and SD. In the case of non-normal distribution, values were presented as median and interquartile range. Results were reported by odds ratio (OR) with 95% confidence intervals (CIs) for the logistic-regression model and hazard ratio (HR) with 95% CIs for the Cox-regression model.

Univariable logistic regression analyses were conducted for all potential characteristics associated with outcome. Values from univariable analysis were presented as odds with 95% CI. According to the Akaike information criterion, all characteristics with $P < .157$ in univariable analysis were taken into multivariable analysis.[24] When comparing UT classification grade and stage, only the most significant parameter was taken into multivariable analysis because of their dependent character. A multivariable logistic regression model was constructed using stepwise elimination at the 5% level. In the multivariable model, statistical significance was defined as a two-sided P-value of <.05. The primary endpoint of the model was the development of a hard-to-heal wound. In addition, Cox multivariable regression analysis was performed predicting time to healing as a continuous variable.

TABLE 1 Patient baseline characteristics (n = 208)

Variables	Overall N (%)/mean ± SD
Age (years)	64 ± 13.4
Sex (man)	145 (69.7)
BMI (kg/m^2)	29 ± 6.5
Instability to stand or walk without help	57 (27.4)
Currently smoking (yes)	47 (22.6)
Special foot wear at first visit (no)	80 (38.5)
Comorbidity claudication	29 (13.9)
Comorbidity cardio vascular disease	107 (51.4)
HbA1C (mM/mol)	64.5 ± 19.7
Diagnose neuropathy	28 (13.5)
Diagnose foot stand deformation	55 (26.4)
Diagnose PAD	44 (21.2)

Abbreviations: BMI, body mass index; PAD, peripheral artery disease.

TABLE 2 Wound characteristics

Variables	Overall N (%)/mean ± SD
History of DFU	106 (51.0)
Number of previous DFUs	0.82 ± 1.0
History of amputation	70 (33.7)
Duration of ulcer before first visit (weeks)	8.7 ± 15.1
Number of DFUs at first visit (n)	1.33 ± 0.64
UT classification	
- A1	104 (50.0)
- A2	23 (11.1)
- A3	8 (3.8)
- B1	15 (7.2)
- B2	13 (6.3)
- B3	24 (11.5)
- C1	3 (1.4)
- C2	4 (1.9)
- C3	7 (3.4)
- D3	7 (3.4)

Abbreviations: DFU, diabetic foot ulcer; UT, University of Texas.

All analyses were carried using the IBM SPSS software package version 23.2 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.2. Armonk, NY: IBM Corp.)

2.4 | Multiple imputation of missing values

In classic regression, all the cases in which any of the inputs are missing are automatically excluded from the analysis, and this can limit the amount of information available. Therefore, we used multiple data imputation to deal with missing values. Using multiple imputation, the imputation of a single variable uses all other variables as predictors by the appropriate regression model.[25] Linear regression was used for continuous variables and logistic regression for categorical variables to fit the model that predicts the missing value.

3 | RESULTS

3.1 | Baseline characteristics

From a total of 304 patients included in the primary study, 96 were excluded, because they did not have a diabetic ulcer at the first visit or had an UT classification A0, B0, C0, D0, or unknown. A total of 208 patients with a DFU were included in the current study. The baseline characteristics of the patients are reported in Table 1. The wound characteristics are reported in Table 2. Approximately 70% of patients were male. The vast majority of the patients were Caucasian (73%) and had type 2 diabetes (71%). Comorbidity was seen in almost all patients, with cardiovascular disease being the most frequent (51%). In this study, the incidence of a hard-to-heal wound was 45%. Of all patients with DFU, 84% of wounds healed with a median healing time of 14 weeks. A Kaplan-Meier curve is shown in Supplemental Figure 1.

3.2 | Univariable and multivariable logistic regression model for predicting hard-to-heal wounds

Using stepwise logistic regression, the following predictors were related to the development of a hard-to-heal wound in univariable analysis: special footwear at first visit (OR: 1.80, 95% CI: 0.91-3.53, $P = .09$), the number of previous DFUs (OR: 1.35, 95% CI: 0.97-1.88, $P = .08$), UT classification grade 2 (OR: 2.58, 95% CI: 1.17-5.69, $P = .02$), UT classification grade 3 (OR: 2.27, 95% CI: 1.02-5.07, $P = .05$), and a diagnosis of foot stand deformation (OR: 2.18, 95% CI: 1.11-4.29, $P = .02$) (Table 3). Unrelated to the development of a hard-to-heal wound in univariable analysis were: comorbidity claudication, history of amputation, duration of ulcer before first visit, UT classification stage, and HbA1C. In multivariable logistic regression, the

TABLE 3 Logistic regression analysis univariable and multivariable with dependent predictors of hard-to-heal wound (n = 208)

	Univariable model		Multivariable model	
Predictors	**OR (CI)**	***P*-value**	**OR (CI)**	***P*-value**
Special foot wear at first visit	1.80 (0.91-3.53)	**.09**	1.79 (0.84-3.82)	.13
Comorbidity claudication	0.52 (0.20-1.35)	.18		
Number of previous DFUs	1.35 (0.97-1.88)	**.08**	1.42 (1.01-1.99)	**.04**
History of amputation	1.14 (0.60-2.17)	.70		
Duration of ulcer before first visit (weeks)	1.00 (0.98-1.01)	.96		
Texas classification (stage)				
UT (ref: A)				
B	1.59 (0.77-3.28)	0.21		
C	1.53 (0.41-5.69)	0.53		
D	2.03 (0.36-11.54)	0.42		
Texas classification (grade)				
UT (ref: 1)				
2	2.58 (1.17-5.69)	**0.02**	2.93 (1.27-6.72)	**.01**
3	2.27 (1.02-5.07)	**0.05**	2.80 (1.17-6.71)	**.02**
HbA1C (mM/mol)	1.01 (1.00-1.02)	0.50		
A diagnosis of foot stand deformation	2.18 (1.11-4.29)	**0.02**	1.54 (0.77-3.08)	**.05**

Abbreviations: CI, confidence interval; DFU, diabetic foot ulcer; OR, odds ratio; UT, University of Texas.

TABLE 4 Cox regression analysis univariable and multivariable with dependent predictors for time to healing (n = 208)

	Univariable model		Multivariable model	
Predictors	**HR (CI)**	***P*-value**	**HR (CI)**	***P*-value**
Special foot wear at first visit	0.82 (0.60-1.12)	.21		
Comorbidity Claudication	1.12 (0.71-1.76)	.62		
History of diabetic foot ulcer	0.78 (0.58-1.05)	.10	0.79 (0.58-1.07)	.13
Number of previous DFUs	0.91 (0.77-1.07)	.25		
History of amputation	0.90 (0.65-1.25)	.52		
Duration of ulcer before first visit (weeks)	1.00 (0.99-1.01)	.67		
Texas classification (stage)				
UT (ref: A)				
B	0.72 (0.59-0.86)	.07		
C	0.90 (0.65-1.25)	.75		
D	0.92 (0.60-1.39)	.83		
Texas classification (grade)				
UT (ref: 1)				
2	0.80 (0.66-0.97)	.24	0.81 (0.56-1.19)	.29
3	0.62 (0.51-0.76)	.02	0.61 (0.41-0.90)	.01
HbA1C (mM/mol)	0.99 (0.98-1.01)	.29		
A diagnosis of foot stand deformation	0.75 (0.54-1.05)	.10	0.75 (0.54-1.05)	.09

Abbreviations: CI, confidence interval; DFU, diabetic foot ulcer; HR, hazard ratio for the risk of wound healing; UT, University of Texas.

number of previous DFUs (OR: 1.42, 95% CI: 1.01-1.99, $P = .04$), UT classification grade 2 (OR: 2.93, 95% CI: 1.27-6.72, $P = .01$), UT classification grade 3 (OR: 2.80, 95% CI: 1.17-6.71, $P = .02$), and a diagnosis of foot stand deformation (OR: 1.54, 95% CI: 0.77-3.08, $P = .05$) all remained independently associated with the development of a hard-to-heal wound. The final multivariable model is shown in Table 3.

3.3 | Univariable and multivariable Cox regression model for predicting time to healing

Univariable Cox regression analysis showed that the following predictors were associated with time to healing: history of DFU (HR for the risk of wound healing: 0.78, 95% CI: 0.58-1.05, $P = .10$), UT classification grade 3 (HR: 0.62, 95% CI: 0.51-0.76, $P = .02$), and a diagnosis of foot stand deformation (HR: 0.75, 95% CI: 0.54-1.05, $P = .10$) (Table 4). The following baseline characteristics showed no association with time to healing in univariable analysis: special footwear at the first visit, comorbidity of claudication, the number of previous DFUs, history of amputation, duration of ulcer before first visit, and HbA1C. In multivariable Cox regression, UT classification grade 3 (HR: 0.61, 95% CI: 0.41-0.90, $P = .01$) remained the only factor that was independently associated with time to healing. The final Cox-regression model is shown in Table 4.

4 | DISCUSSION

In this study, we found that the number of previous DFUs, the depth of an ulcer defined by the UT classification grade, and a previous diagnosis of foot deformation were all significantly associated with the development of hard-to-heal wounds. In addition, UT classification grade was the only factor significantly associated with time to healing.

We report these predictors from a patient population treated in a multidisciplinary setting. Our findings are concordant with a previous multidisciplinary study by Hicks et al who demonstrated that The Society for Vascular Surgery Wound, Ischemia, and foot Infection classification independently predicted wound healing in patients with a DFU.[26] The identification of these high-risk patients in our study defined by previous DFU and the UT classification can be applied in the clinic to enhance triage and treatment strategies. By recognising a patient at high risk of a poorly healing wound and long-term recovery period, an early treatment intervention might ultimately lead to a better treatment outcome. In addition, such high-risk patients might benefit from a more stringent follow-up to monitor wound healing

in order to facilitate timely treatment interventions to avoid the development of a hard-to-heal wound.

Our results relating the number of previous DFUs to the development of hard-to-heal wounds are consistent with findings previously reported by Boyko et al[21] and Jeon et al.[16] Boyko et al showed that a history of ulcers is related to the risk of developing a new DFU (RR 1.63, 95% CI: 1.17-2.26, $P = .004$). Jeon et al showed an association between history of previous DFU and lower extremity amputations (LEAs), (OR: 3.38, 95% CI: 1.43-8.72, $P = .008$). In addition, we found that the number of previous DFUs predicted hard-to-heal wounds.

Likewise, Soewondo et al[27] reported that a history of a previous wound decreased the healing process, although this was not significant in multivariable analysis (HR: 0.56, 95% CI: 0.19-1.68, $P = .30$). The population in this study was younger than in our study (56 years versus 64 years). And the mean BMI was lower (22 kg/m^2 versus 29 kg/m^2 in our study) indicating a better performance status of the patients in this study compared with our population.

In our study, UT classification grade showed a significant positive association with the development of a hard-to-heal wound among diabetic patients. This indicates that high UT classification grade increases the risk for stagnation of DFUs. In order to investigate whether UT classification is related to a poor wound healing of DFU, Oyibo et al[23] showed that UT grade is positively associated with increased number of amputations. These findings confirm our results showing that high UT grade is related to a poor DFU outcome.

Although we did find an association between UT classification grade and the development of hard-to-heal wounds, we did not show any association for UT classification stage. These findings are in contrast with Jeon et al[16] who showed that UT classification stages C and D are related to LEAs. In this study, the majority of the patients were in UT classification stage D (42%) (especially UT stage D3, 27%) and UT classification stage A1 (10%). This might be explained by less diversity in our population where approximately 50% of the patients had an UT classification stage A1 at first visit which was not significantly associated with the development of a hard-to-heal wound. This implies that the overall wound condition of the patient population in the study by Jeon et al was worse than ours explaining the different results.

In contrast to our univariable model, Boyko et al[21] showed a positive association between HbA1c and ulcer occurrence increasing DFU risk (RR): (1.26, 95% CI: 1.11-1.43, $P < .001$). We found no association of HbA1c with the development of a hard-to-heal wound in our univariable and multivariable models. The mean HbA1c in our population was 64.5 mM/mol as compared with 97 mM/mol in study by Boyko et al. This might imply a poor diabetic control in their population, which led to a stronger association for HbA1c.

In our study, a diagnosis of foot deformation was independently predicting the development of a hard-to-heal wound. Previous studies showed an association between hammer toes and Charcot deformity with foot ulcer risk.[28] Our study showed that every form of foot deformity can be associated with the development of a hard-to-heal wound. With this finding, we would recommend to emphasise on orthopaedic footwear for patients with foot deformities in the daily care of diabetic patients.

Our study is limited by its post-hoc design, which led to missing data for some patients. However, to correct for this limitation, we used multiple data imputation to accurately correct for the missing data in order to develop the regression models. Other limitations of this study were the relatively small sample size and the single-centre setting. In addition, we did not collect neutrophil and lymphocyte counts in this study, which has been suggested to be a predictive factor for wound healing.[29] A recent study also suggested a predictive role for previous percutaneous transluminal angioplasty or retinopathy for treatment failure in patients with a DFU. However, this was only shown in univariable analysis.[30]

Our study suggests that the chance to heal a wound is depended on whether the wound is deep or superficial. In our study, we have shown that a deeper wound, known as UT classification grade 2 and UT classification grade 3, is related to hard-to-heal wounds and that time to healing is negatively influenced by these two predictors. The number of previous DFUs is a solid predictor, which can be used in the clinic to recognise the patient who is at risk for a hard-to-heal wound. A diagnosis of foot deformation is also related to the development of a hard-to-heal wound.

The findings from our study can be applied in clinical practice to enhance the quality of diabetic ulcer care. By recognising a patient at high risk of a poor wound healing and long-term recovery period, a multidisciplinary triage team can refer these patients earlier to the specialist for a more intensive treatment. In addition, general practitioners can use these findings as a guideline in order to refer such patients to specialist health care for an earlier treatment intervention. For future studies, we would recommend a prospective design including variables based on meta-analysis, to investigate which wound-related factors play a major role in DFU in order to develop a solid clinical guideline. This way every clinician can recognise the patients at risk of a poor wound healing to be treated more efficiently.

In conclusion, this study confirms important associations between specific patient and wound characteristics and identifies patients at risk for the development of a hard-to-heal wound. We showed that the number of previous DFUs, UT

classification grade, and a diagnosis of foot deformation are associated with development of a hard-to-heal wound in diabetic patients. These patient characteristics can be used to identify patients at risk for the development of hard-to-heal wounds who might need an early intervention to prevent wound problems.

ACKNOWLEDGEMENTS

The authors have no conflicts of interest to disclose.

REFERENCES

1. Huber CA, Diem P, Schwenkglenks M, Rapold R, Reich O. Estimating the prevalence of comorbid conditions and their effect on health care costs in patients with diabetes mellitus in Switzerland. *Diabetes Metab Syndr Obes*. 2014;7:455-465.
2. World Health Organization. Global report on diabetes. 2016.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl 1):S81-S90.
4. Crawford F, Inkster M, Kleijnen J, Fahey T. Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. *QJM*. 2007;100:65-86.
5. Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: evidence on health outcomes and antidiabetic treatment in United States adults. *World J Diabetes*. 2016;7:449-461.
6. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. *Diabetologia*. 2008;51:747-755.
7. Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review. *Acta Biomater*. 2013;9:7093-7114.
8. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev*. 2004;20(Suppl 1): S90-S95.
9. Ragnarson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabetes Complications*. 2000;14:235-241.
10. Rice JB, Desai U, Cummings AK, et al. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014;37: 651-658.
11. Noor S, Zubair M, Ahmad J. Diabetic foot ulcer—a review on pathophysiology, classification and microbial etiology. *Diabetes Metab Syndr*. 2015;9:192-199.
12. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet*. 2003;361: 1545-1551.
13. Apelqvist J, Bakker K, van Houtum WH, Schaper NC, on behalf of the International Working Group on the Diabetic Foot (IWGDF) Editorial Board. Practical guidelines on the management and prevention of the diabetic foot: based upon the international consensus on the diabetic foot (2007) prepared by the international working group on the diabetic foot. *Diabetes Metab Res Rev*. 2008;24(Suppl 1):S181-S187.
14. Wang C, Mai L, Yang C, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. *BMC Endocr Disord*. 2016;16:38.
15. van Dishoeck AM, Mohammad Zadeh M, Weststrate K et al. A specialized paramedical triage team contributes to efficient care for diabetic foot ulcer patients. Paper presented at: BMJ International Forum on Quality and Safety in Healthcare; April 21-24, 2015; London, England.
16. Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. *Int Wound J*. 2017;14:537-545.
17. Santema TB, Lenselink EA, Balm R, Ubbink DT. Comparing the Meggitt-Wagner and the University of Texas wound classification systems for diabetic foot ulcers: inter-observer analyses. *Int Wound J*. 2016;13:1137-1141.
18. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care*. 2003;26:1879-1882.
19. Smith-Strom H, Iversen MM, Igland J, et al. Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: a retrospective cohort study. *PLoS One*. 2017;12: e0177176.
20. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of international working group on diabetic foot (IWGDF). *Pak J Med Sci*. 2013;29:730-734.
21. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle diabetic foot study. *Diabetes Care*. 1999;22:1036-1042.
22. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle diabetic foot study. *Diabetes Care*. 2006;29:1202-1207.
23. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJM. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care*. 2001;24:84-88.
24. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. *J Clin Epidemiol*. 1999;52:935-942.
25. Royston P. Multiple imputation of missing values: update. *Stata Journal*. 2005;5:188-201.
26. Hicks CW, Canner JK, Mathioudakis N, et al. The Society for Vascular Surgery Wound, ischemia, and foot infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. *J Vasc Surg*. 2018;68:1096-1103.
27. Soewondo P, Suyono S, Sastrosuwignyo MK, et al. Prediction of wound healing in diabetic foot ulcers: an observational study in tertiary hospital in Indonesia. *Acta Med Indones*. 2017;49:41-51.
28. Abbott CA, Carrington AL, Ashe H, et al. The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med*. 2002;19:377-384.
29. Vatankhah N, Jahangiri Y, Landry GJ, et al. Predictive value of neutrophil-to-lymphocyte ratio in diabetic wound healing. *J Vasc Surg*. 2017;65:478-483.
30. Su CL, Chang CC, Peng YS, Chen MY. The predictive factors associated with comorbidities for treatment response in outpatients

with king classification III diabetes foot ulcers. *Ann Plast Surg*. 2018;81:S39-S43.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Mohammad Zadeh M, Lingsma H, van Neck JW, Vasilic D, van Dishoeck A-M. Outcome predictors for wound healing in patients with a diabetic foot ulcer. *Int Wound J*. 2019;16:1339–1346. https://doi.org/10.1111/iwj.13194