**Factors associated with healing outcomes in primary care patients with diabetic foot ulcers: a retrospective study in a multi-ethnic sample**

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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**Abstract**

**Objective**

To identify and determine patient- and ulcer- related factors associated with healing outcomes within 3 months for patients with diabetic foot ulcer (DFU) in a multi-ethnic primary care sample.

**Methods**

Retrospective data were collected over 3 months from 520 primary care patients with a DFU between 1st April 2016 and 31st March 2017 in a multi-ethnic sample. Multivariable prevalence ratios (PR) were calculated using Poisson regression to find associations between patient and ulcer related factors and ulcer healing outcomes.

**Results**

The majority of patients were male (66%), of Chinese ethnicity (49.8%) and had a diabetes mellitus duration >5 years (81.8%). Toe ulcers (64%) were most common. Healing occurred for 33.9%, 19.1%(minor) and 1.5% (major) underwent amputation respectively. Wound sizes between 1-10cm2 (PR: 0.61, 95% confidence interval (CI): 0.46-0.76, P<.001) and >10cm2 (PR: 0.55, 95% CI: 0.33-0.76, P=.003), ulcer duration ≥6 months (PR: 0.36, 95% CI: 0.19-0.53, P<.001), ischemic (PR: 0.54, 95% CI: 0.22-0.86, P=.044), and neuroischaemic ulcers (PR: 0.73, 95% CI: 0.53-0.93, P=.027) were negatively associated with healing outcomes. Female patients had a favored ulcer healing (PR: 1.18, 95% CI: 0.91-1.45, P=.157).

**Conclusions**

DFU Healing was associated with gender and affected by larger wound size, longer wound duration and ischemic aetiology, regardless of ethnicity. Prompt attention to these risk factors may reduce healing time. Further studies are warranted to elucidate the mechanism underlying gender differences in association with DFU healing.

**Key words**

Diabetes, diabetic foot ulcer, healing outcomes, primary care, Singapore

**Introduction**

Diabetic foot ulcer is a severe complication of diabetes mellitus, that affects between 40 and 60 million people globally1. The global prevalence and annual incidence of diabetic foot ulcer has been estimated at 1.7% and 6.3% respectively in the diabetes population 2. It has been predicted that as much as 15% to 25% of patients with diabetes may develop a diabetic foot ulcer during their lifetime 3. Once a patient develops a diabetic foot ulcer the recurrence rate is up to 40% that they may develop a new one within 1 year 2. Diabetic foot ulcers are also common precursors to lower extremity amputation, with lower limb amputations affecting between 25% to 28% of patients with diabetic foot ulcer 4,5. Slow or delayed healing of diabetic foot ulcers are associated with a greater risk of diabetic lower limb amputation 6–8 which can be either minor (foot and toes) or major (above ankle) 9.

In Singapore, diabetes is a huge challenge for the healthcare system as the prevenlence has increased rapidly in the past two decades, and is likely to increase to 15% in year 2050 10. Due to the high prevalence of diabetes in Singapore, diabetes-related lower extremity amputations have increased from 11.0 per 100,000 population to 13.3 per 100,000 population between year 2008 and 2013 11. Compared to other chronic wound patients in Singapore, patients with diabetic foot ulcer are considered to be the frailest and they also often have more comorbidities 12. Diabetes is also associated with a lower quality of life and an increased risk of early death for affected patients 1. Patients with diabetes related amputation have also reported to experience physical, psychosocial and financial distress13.

Given the detrimental impact of diabetic foot ulcers on individuals, healthcare systems and society, it is crucial to identify factors associated with ulcer healing to improve healing outcomes and enable predictions of clinical outcome 14. This information could be used when developing prophylactic strategies to reduce complications and offer appropriate treatments for optimal timely healing of DFU. Factors affecting healing of diabetic foot ulcer and progression from diabetic foot ulcer to diabetic lower limb amputation are often associated with multiple individual aspects, such as disease (presence of end-stage renal failure, increasing age, heart failure, presence of peripheral arterial disease, loss of protective sensation and characteristics of diabetic foot ulcer (e.g. prior minor amputation, wound size, location and presence of infection) 15.

Having a deeper understanding about how those factors may impact healing outcomes is pertinent for efficient decision making about care to optimize treatment 16,17. Healing times for diabetic foot ulcer that exceeds 3 months is commonly used as the end point for delayed healing and has been extensively used as a benchmark by various studies to assess healing outcomes 18–20. Although there is a growing body of research in the area of diabetic foot ulcers from an international perspective, there is no evidence from the primary care setting in Singapore, where most of those wounds are treated. Therefore, the aim of this study was to identify and describe factors pertaining to patient and ulcer characteristics that may affect healing within 3 months in the primary health care setting.

**Methods**

***Study design and subjects***

The researchers performed a retrospective review of electronic medical record of all patients with diabetic foot ulcer who received wound care between 1st April 2016 and 31st March 2017 at nine different primary care settings operated by the National Healthcare Group Polyclinics in Singapore. National Healthcare Group Polyclinics serves a substantial proportion of the population in the central and northern parts of Singapore and provides a comprehensive range of primary healthcare services including wound care 21.

The study population were all patients with diabetic foot ulcer and/or post-amputation ulcers that attended the study sites consecutively within the study period. The patients were followed over 3 months and the electronic medical record data extraction started with their first contact with the polyclinic. The data extraction followed a standardized extraction form developed by the research team and wound care specialists. This form was based on research literature, clinical guidelines and expert opinions. Four nurses specialized in wound care extracted the data from the electronic medical record after receiving training to ensure the standard quality control of the data collection. Queries related to the data collection were solved by discussions with the wound nurse specialist that developed the study protocol. Ethical approval was granted from the local institute review board at National Healthcare Group (DSRB Refer No. 2017/00588) prior to data extraction.

***Variables***

Diabetic foot ulcers were defined as a full-thickness wounds located distal to the ankle (level of malleoli) 8. Post-amputation ulcers were defined as wounds located on any part of the foot after a recent minor amputation procedure 22 but excluded ulcers that healed by primary intention. The extracted data from electronic medical record comprised the following:

1. Patient-related variables: demographics (age, gender, body mass index, ethnicity), diabetes status (duration of diabetes, latest HbA1c value in the past one month, healthcare institutions for diabetes treatment), which were collected at the first clinical visit for foot ulcer treatment. The first clinical visit was the first date the patient attended the polyclinics for foot ulcer care between 1st April 2016 and 31st March 2017.
2. Diabetic foot ulcer variables were collected on the first clinical visit and included wound sizes (areas) (cm2), duration, locations, type of ulcer (neuropathic, ischemic and neuroischemic ulcer) based on definition of wound etiology 23. Wound sizes were calculated by multiplying the longest and widest perpendicular areas since this method is most commonly used and described as most reliable in the literature 24. Ischemic ulcers were recorded if peripheral artery disease was evident based on the diagnosis in the patient record or as either toe blood pressure < 50mmHg, ankle pressure < 90mmHg, ankle‐brachial index <0.90, toe-brachial index <0.70, and/or absence of two foot pulses.
3. Other healing-related variables were also collected on the first clinical visit and included history of previous diabetic foot ulcers, previous amputation, end stage renal failure, frequency of diabetic foot screening and referral to emergency department. “Referral to emergency department” was recorded if a patient with diabetic foot ulcer was referred to emergency department on the first clinical visit because the foot ulcer was severely infected or critically ischemic.
4. Diabetic foot ulcer healing outcomes were collected between the first clinical visit until their foot ulcer healed or not at the 3 months study period, and was recorded as: 1) healed, 2) healing in progress, 3) minor amputation, 4) major amputation, and 5) death/unhealed. A wound was considered healed if the skin was intact on the whole foot 8. Death/unhealed was defined as death without healing within 3 months from the first clinical visit 25.

***Statistical analysis***

Descriptive statistics was used to describe the overall baseline characteristics of patients. Continuous variables were reported as mean and standard deviation (SD), and categorical variables were reported as frequencies and percentages. The proportion (or prevalence) of healing within 3 months was calculated for each included factor. The numerator for prevalence was the number of individuals healed within 3 months’ time-period.

The researchers calculated prevalence ratios rather than odds ratios to prevent overestimation in measuring strength of association 26. Prevalence ratio indicates how large is the prevalence of an event/outcome in one group of individuals with characteristics relative to the group without the characteristics. A Poisson regression with robust variance based on Huber’s sandwich estimator 27 was performed to examine the association between healing within 3 months and patient demographic, ulcer status, and other clinical factors. The results of the Poisson regression are presented as prevalence ratios (PRs), 95% confidence intervals (CIs). Univariable and multivariable regression models were fitted to explore the strength of association. To ensure validity of the results, the researchers checked collinearity (where variance inflation factor >10) between covariates in the model. The researchers also checked the clinically meaningful interactions by including cross-product terms and were considered significant if p < 0.1. Variables selection was done via stepwise backward selection in hierarchical fashion. A conservative probability less than 0.2 (instead of 0.157 as suggested in literature) was used to include a variable in the final model 28. Additionally, full model was also fitted by including all predictors. To check overfitting between stepwise and full model, Akaike information criterion and Bayesian information criterion (BIC) were calculated to compare both models29,30. A model with lower AIC and BIC was selected as final model (i.e., stepwise backward selection model). A two-sided p-value of <0.05 was considered statistically significant. Statistical analysis was carried out using Stata software version 16.1 (StataCorp, College Station, TX, USA).

**Results**

***Background demographic and characteristics of patients and diabetic foot ulcers***

The researchers reviewed the electronic medical records of 520 eligible patients. The background and demographic of patients and the clinical characteristics of their diabetes foot ulcerations are reported in Table 1. Most of participants were male (66%), the majority were of Chinese ethnicity (49.8%), and 81.8% of the sample had a diabetes duration > 5 years (81.8%). In the sample, 16.2% of the patients had been referred to hospital emergency department on their first ulcer presentation at the primary care clinic. Approximately 80% of foot ulcers had a duration < 6 months. Toe ulcers were the most common diabetic foot ulcer and made up more than half of study population (64%). Approximately one third of the ulcers (33.9%) healed within 3 months, 19.1% required a minor amputation, and 1.5% of the study sample underwent major amputation. More neuropathic ulcers (41.1%) healed compared to neuroishaemic (26.7%) and ischemic (18.7%) ulcers within 3 months. Proportion of unhealed and healed ulcers within 3 months by type of diabetic foot ulcer is shown in Figure 1.

***Univariate prevalence ratios for factors associated with healing within 3 months***

Proportion of healed ulcers within 3 months and univariate associations between background factors and healing are presented in Table 2. The percentage of healing varied from 13.5% (ulcer duration) up to 50.9% (ulcer size <1cm2). The Poisson regression revealed the following factors as related to ulcer healing within 3 months in the univariate analysis: being female (PR: 1.25, 95% CI: 0.98-1.59, P=.072), having a wound size between 1-10cm2 (PR: 0.60, 95% CI: 0.47-0.77, P<.001) and >10cm2(PR: 0.49, 95% CI: 0.33-0.73, P<.001), diabetic foot ulcer duration ≥6 months (PR: 0.34, 95% CI: 0.21-0.56, P<.001), type of ulcer, ischemic (PR: 0.46, 95% CI: 0.25-0.84, P=.011) and neuroischaemic (PR: 0.65, 95% CI: 0.50-0.86, P=.002), if the wound required emergency department referral (PR: 0.67, 95% CI: 0.31-0.40, P<.001), a diabetic foot screening more than one year ago (PR: 0.67, 95% CI: 0.53-0.99, P=.040) and if there were never/no records of diabetic foot screening PR: 0.72, 95% CI: 0.53 - 0.99, P=.040), and a history of previous amputation (PR: 0.68, 95% CI: 0.49-0.95, P=.024). Unrelated factors for diabetic foot ulcer healing within 3 months in univariate analysis were: age, race, body mass index, wound depth, ulcer location, wound infection, duration of diabetes, institutions for treatment of diabetes, HbA1c value, history of previous diabetic foot ulcers, and history of end stage of renal failure.

***Multivariable regression analysis and factors associated with healing within 3 months***

In the multivariable regression, ischemic ulcers (PR: 0.54, 95% CI: 0.22-0.86, P=.044), neuroischemic ulcers (PR: 0.73, 95% CI: 0.53-0.93, P=.027), ulcer duration ≥6 months (PR: 0.36, 95% CI: 0.19-0.53, P<.001), wound size 1-10cm2(PR: 0.61, 95% CI: 0.46-0.76, P<.001) and >10cm2(PR: 0.55, 95% CI: 0.33-0.76, P=.003) all remained independently inversely associated with healing within 3 months. The stepwise backward selection model showed that being female (PR: 1.18, 95% CI: 0.91-1.45, P=.157) was the only factor that strongly favored diabetic foot ulcer healing within 3 months while type of ulcer, ulcer duration and size of the ulcer were weakly favored in regards to ulcer healing within 3 months. The final multivariable model can be seen in Figure 2.

***Sensitivity analysis***

In addition to the stepwise backward model, the researchers also fitted full model to check the model overfitting and direction of effect estimates. AIC and BIC values were higher in the full model indicating the main stepwise backward model was better fit and not overestimating effect estimates. Furthermore, the direction of the effect estimates was similar in both full and stepwise backward model). Results of full model are attached as supplementary materials (see supplementary Table S1).

Table 1: Background demographic and characteristics of participants and ulcerations

|  |  |  |  |
| --- | --- | --- | --- |
| **Background characteristics**  **(N=520)** | **N (%)/ mean (SD)** | **Background characteristics (N=520)** | **N (%)** |
| ***Demographic variables*** |  | ***Other clinical variables*** |  |
| Age (years) (mean (SD)) | 66.3 (11.3) | Duration of DM |  |
| BMI (kg/m2) (mean (SD)) | 26.7 (5.8) | <5 years | 95 (18.2) |
| Gender |  | ≥5 years | 425 (81.8) |
| Male | 343 (66.0) | Treatment of DM |  |
| Female | 177 (34.0) | Polyclinic | 229 (44.0) |
| Race |  | Hospital | 238 (45.8) |
| Chinese | 259 (49.8) | GP or self-manage | 53 (10.2) |
| Malay | 154 (29.6) | Management of DM |  |
| Indian | 97 (18.7) | Diet control | 36 (6.9) |
| Others | 10 (1.9) | Oral hypoglycemic agents | 228 (43.9) |
| ***DFU related variables*** |  | Insulin | 76 (14.6) |
| Wound size (cm2) (mean (SD)) | 7.0 (12.5) | Oral and insulin | 156 (30.0) |
| Wound depth (cm) | 0.5 (0.9) | No record | 24 (4.6) |
| Duration of DFU |  | HbA1c |  |
| <6 months | 409 (78.6) | <7% | 99 (19.0) |
| ≥6 months | 111 (21.4) | ≥7% | 340 (65.4) |
| DFU management before polyclinic |  | Not done or recorded | 81 (15.6) |
| Self-referral after ulcer debut | 244 (46.9) | Diabetic foot screening |  |
| Referred from hospitals | 198 (38.1) | Within one year | 83 (16.0) |
| Referred from GPs | 22 (4.2) | More than one year ago | 258 (49.6) |
| Self-referral after failed wound self-care | 56 (10.8) | Never/no record | 179 (34.4) |
| Ulcer on toe only | 333 (64.0) | History of previous ulcer | 232 (44.6) |
| Ulcer on toe and others (plantar/heel/dorsum) | 26 (5.0) | History of previous amputation | 124 (23.9) |
| Ulcer on plantar only | 123 (23.7) | History of ESRF | 71 (13.7) |
| Ulcer on heel only/ dorsum only/ more than two locations other than toe | 93 (17.9) |  |  |
| Type of DFU |  |  |  |
| Neuropathic | 285 (54.8) |  |  |
| Ischaemic | 48 (9.2) |  |  |
| Neuroischaemic | 187 (36.0) |  |  |
| Wound infected (on oral antibiotics) | 297 (57.1) |  |  |
| Emergency referral | 84 (16.2) |  |  |
| Healing outcomes |  |  |  |
| Healed within 3 months | 176 (33.9) |  |  |
| Require more than 3 months (healing in progress) | 181 (34.8) |  |  |
| Require minor amputation (below ankle) | 99 (19.1) |  |  |
| Require major amputation (above ankle) | 8 (1.5) |  |  |
| Lost to follow up | 49 (9.4) |  |  |
| Died | 7 (1.3) |  |  |

DFU: diabetes foot ulcer; DM: diabetes mellitus; GP: general practitioner; ESRF: end stage renal failure

Table 2: Univariate prevalence ratios with 95% confidence intervals for factors associated with healing within three months

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Background factors** | **Total** | **% healed within**  **three months** | **PR** | **9%%CI** | **P-value** |
| ***Demographic variables*** |  |  |  |  |  |
| Age group |  |  |  |  |  |
| <60 years | 140 | 34.3 | 1 [Ref.] |  |  |
| 60-74 years | 262 | 35.9 | 1.05 | 0.79 - 1.39 | 0.752 |
| ≥75 years | 118 | 28.8 | 0.84 | 0.58 - 1.21 | 0.351 |
| Gender |  |  |  |  |  |
| Male | 343 | 31.2 | 1 [Ref.] |  |  |
| Female | 177 | 39.0 | 1.25 | 0.98 - 1.59 | 0.072 |
| Race |  |  |  |  |  |
| Chinese | 259 | 32.8 | 1 [Ref.] |  |  |
| Malay | 154 | 35.7 | 1.09 | 0.83 - 1.43 | 0.546 |
| Indian and others | 107 | 33.6 | 1.03 | 0.75 - 1.41 | 0.878 |
| BMI |  |  |  |  |  |
| Normal | 212 | 33.0 | 1 [Ref.] |  |  |
| Overweight | 198 | 31.3 | 0.95 | 0.72 - 1.26 | 0.712 |
| Obese | 110 | 40.0 | 1.21 | 0.90 - 1.63 | 0.208 |
| ***DFU variables*** |  |  |  |  |  |
| Woud size |  |  |  |  |  |
| < 1 (cm2) | 108 | 50.9 | 1 [Ref.] |  |  |
| 1-10 (cm2) | 316 | 30.7 | 0.60 | 0.47 - 0.77 | p<.001 |
| >10 (cm2) | 96 | 25.0 | 0.49 | 0.33 - 0.73 | p<.001 |
| Wound depth |  |  |  |  |  |
| <0.5 cm | 317 | 36.0 | 1 [Ref.] |  |  |
| ≥0.5 cm | 203 | 33.9 | 0.85 | 0.66 - 1.10 | 0.208 |
| DFU duration |  |  |  |  |  |
| <6 months | 409 | 39.4 | 1 [Ref.] |  |  |
| ≥6 months | 111 | 13.5 | 0.34 | 0.21 - 0.56 | p<.001 |
| Ulcer on toe only | 333 | 33.6 | 0.98 | 0.77 - 1.26 | 0.891 |
| Ulcer on toe and others (plantar/heel/dorsum) | 26 | 23.1 | 0.67 | 0.33 - 1.37 | 0.272 |
| Ulcer on plantar only | 123 | 30.9 | 0.89 | 0.66 - 1.20 | 0.436 |
| Ulcer on heel only/ dorsum only/ more than two locations other than toe | 93 | 35.5 | 1.06 | 0.78 - 1.44 | 0.710 |
| Type of DFU |  |  |  |  |  |
| Neuropathic | 285 | 41.1 | 1 [Ref.] |  |  |
| Ischaemic | 48 | 18.8 | 0.46 | 0.25 - 0.84 | 0.011 |
| Neuroischaemic | 187 | 26.7 | 0.65 | 0.50 - 0.86 | 0.002 |
| Wound infected (on oral antibiotics) | 297 | 34.7 | 1.06 | 0.83 - 1.35 | 0.644 |
| Emergency referral | 84 | 25.0 | 0.70 | 0.31 - 0.40 | p<.001 |
| ***Other clinical variables*** |  |  |  |  |  |
| Duration of DM |  |  |  |  |  |
| <5 years | 95 | 40.0 | 1 [Ref.] |  |  |
| ≥5 years | 425 | 32.5 | 0.81 | 0.61 - 1.08 | 0.147 |
| Treatment of DM |  |  |  |  |  |
| Polyclinic | 229 | 36.7 | 1.02 | 0.69 - 1.52 | 0.910 |
| Hospital | 238 | 30.7 | 0.86 | 0.57 - 1.29 | 0.454 |
| GP or self-manage | 53 | 35.9 | 1 [Ref.] |  |  |
| HbA1c |  |  |  |  |  |
| <7% | 99 | 34.3 | 1.03 | 0.68 - 1.56 | 0.887 |
| ≥7% | 340 | 33.8 | 1.02 | 0.72 - 1.43 | 0.933 |
| Not done or recorded | 81 | 33.3 | 1 [Ref.] |  |  |
| Diabetic foot screening |  |  |  |  |  |
| Within one year | 83 | 45.8 | 1 [Ref.] |  |  |
| More than one year ago | 258 | 30.6 | 0.67 | 0.50 - 0.90 | 0.008 |
| Never/no record | 179 | 33.0 | 0.72 | 0.53 - 0.99 | 0.040 |
| History of previous ulcer | 232 | 30.6 | 0.84 | 0.66 - 1.07 | 0.164 |
| History of previous amputation | 124 | 25.0 | 0.68 | 0.49 - 0.95 | 0.024 |
| History of ESRF | 71 | 25.4 | 0.72 | 0.48 - 1.10 | 0.125 |

PR: prevalence ratio; Ref.: reference category; CI: confidence interval; DFU: diabetes foot ulcer; DM: diabetes mellitus; GP: general practitioner; I: end stage renal failure

Figure 1: Proportion of unhealed and healed cases within three months by type of diabetes foot ulcer

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Figure 2: Multivariable regression analysis showing association between factors and healing within three monthsC:\Users\Julia\Desktop\Research\DFU population based study\Manuscript\Re-analysis\From Ram_Results 280920\251020 Correction\Figure 2.tif

**Discussion**

The present study did not find any associations between patient characteristics such as age, ethnicity, body mass index, duration of diabetes, healthcare institutions (hospitals, polyclinics or general practitioners) of diabetes treatment follow-up, HbA1c level, and 3 months ulcer healing outcomes. This is consistent with the findings in several other studies on diabetic foot ulcers that reported similar results 18,31–33. The present study also found that less ischemic ulcers (18.7%) healed within 3 months compared to neuropathic (41.1%) and neuroishaemic ulcers (26.7%). The univariate analysis in the present study showed that ischemic ulcers (PR: 0.46, 95% CI: 0.25-0.84, P=.011) and neuroischemic ulcers (OR: 0.65, 95% CI:0.50-0.86, P=.002) were negatively associated with healing within 3 months. Similar results have reported in other previous studies 31,34,35.

Both the univariate and multiple regression analysis in the present study found positive associations between being female and ulcer healing within 3 months (PR: 1.25, 95% CI: 0.98-1.59, P=.072, respectively PR: 1.18, 95% CI: 0.91-1.45, P=.157). These findings align with the results of a previous study 32 that diabetic foot ulcers in women were twice as likely to heal compared to those in men (P= 0.009). In addition to this, other studies have found that being male was a predictor for non-healing ulcers (OR: 1.50, 95% CI: 1.07-1.97, P=.017) 8, with males having negatively affected time to healing (HR: 0.83, 95% CI: 0.72-0.96, P=.001)6. However, some studies report to not have found any association between male patients and effects on ulcer healing 35,36. However, there have been reports suggesting that males are at higher risk of having to undergo diabetic lower limb amputation 11,37 as well as a higher risk of developing recurrent or new foot ulcers (OR: 1.26, 95% CI: 1.01–1.56)38, (OR: 1.71; 95 % CI 1.2–3.7) 37. This could potentially be related to differences in male and female health seeking behavior and their self-care adherence. Another possible explanation could be the gender norms in the Singaporean society where men more often have passive health-related behavior to DFU as compared to women. Previous studies have shown that male patients presented poorer self-care behaviors and lower treatment adherence to diabetes and diabetic foot care compared to female patients 39,40.

The multivariate analysis in this study showed an association between larger ulcer size (>1-10cm2) and delayed ulcer healing within 3 months. This finding aligns with several previous studies that found that wound size is significantly correlated with wound healing (HR: 1.014, 95% CI: 1.002-1.027, P=.027)41, and that a larger ulcer size was a predictor for non-healing or delayed ulcer healing 8,20,31,42. In the present study, the results showed that ulcers <1cm2 had the highest healing proportion (50.9%) compared to ulcers 1-10cm2 (30.7%) and ulcers >10cm2(25.0%). The univariate analyses revealed that ulcer sizes 1-10cm2 (PR: 0.60, 95% CI: 0.47-0.77, P<.001) and >10cm2 (PR: 0.49, 95% CI: 0.33-0.73, P<.001) were negatively associated with healing within 3 months. These findings are in line with the results reported by a recent study 36 that healing time was significantly longer for patients with a ulcer size >10cm2 compared to those with an ulcer size between 2–10cm2, or ulcer size of <2cm2.

The univariate analysis in the present study also found that ulcer duration ≥ 6 months was negatively associated with healing (PR: 0.34, 95% CI: 0.21-0.56, P<.001), however, this was not significant in the multivariable analysis (PR: 0.35, 95% CI: 0.18-0.52, P<.001). A previous study reported that a longer duration of ulcers showed decreased healing process (B= -0.038, HR: 0.963, 95% CI: 0.918-1.010, P=.121)6,8,33,41 and the range of ulcer duration was from 1 month (PR: 0.187, 95% CI: 0.111–0.313 0.479, P<.001) 33 up to 3 months (OR: 2.61, 95% CI: 1.60-4.27, P<.001) 8, (HR: 0.69, 95% CI: 0.52-0.91, P=.001)6. To avoid diabetic foot ulcers to become chronic more vigilant care and early interventions must be considered to treat and enable favorable healing outcomes. Preventing diabetic foot ulcers from evolving into chronic and complicated ulcers, which have an overall higher risk of amputation, could possibly have positive effects on patients quality of life as well as reduce healthcare costs if amputations were to be avoided43.

In the present study the univariate analysis showed that prior amputation history was associated with ulcer healing (PR:0.68, 95% CI: 0.49-0.95, P=.024), however, this was not significant in the multivariable analysis (PR:0.77, 95% CI: 0.52-1.02, P=.116). One previous study found that the healing time for patients with a history of amputation was longer compared to patients with no history of amputation (P=0.004)36. This could possibly be related to patients’ suboptimal functional status and that post-amputation patients are at higher risk of delayed healing, re-ulceration, as well as re-amputation, since they require more care and support related to rehabilitation needs after the procedure 13.

In relation to healing outcomes of diabetic foot ulcer, the healing rate in the present study (33.9%) is similar to healing rates reported in the United States of America’s wound registry (30.5%) 19, but the healing rate in the present cohort is relatively low compared to the findings from a Canadian (52%)42 and an Australian (47%) study 18. This could be explained by the fact that patients in the two mentioned studies 18,42 were cared for in multidisciplinary specialist clinics and they also had smaller wound sizes (median 0.55cm2, 0.05 to 22.50)42 (mean wound area of 1.92cm2, SD: 2.97)18 compared to the patients in the present study (7.0cm2 SD: 12.5). This further emphasizes the urgency to treat diabetic foot ulcers at an early stage by a multidisciplinary team when they are smaller in size and less complex. Additionally, co-morbidities and personal adherence may play a greater role than the place of treatment as well as using nursing as the primary wound practitioner.

The present study found that only 16% of the patients had attended their recommended diabetic foot screening within 1 year, which includes a foot examination and patient education for ulcer prevention. The descriptive results in the present study showed that more ulcers healed for those patients who attended their recommended foot screening within 1 year (45.8%) compared to those who attended their foot screening longer than a year ago (30.6%). The univariate analysis in this study also revealed that attending foot screening more than a year ago (PR: 0.67, 95%CI 0.50-0.90, P=.008) and never attend/no records of foot screening (PR: 0.72, 95% CI: 0.53 - 0.99, P=.040) were negatively associated with healing outcomes. This finding is supported by a previous study which reported that non-adherence to recommended treatment plans may lead to delayed ulcer healing 7, and even lower limb amputation 44.

Recommendations from International Working Group on the Diabetic Foot guidelines from year 2019, suggests that diabetic foot screening should be frequent, ideally as often as once a month up to once a year based on the level of ulcer risk 45. The guidelines emphasize to screen patients with diabetes at-risk for diabetic foot ulcer to identify risk factors early and prevent first or recurrent ulcers 45. The researchers therefore argue that healthcare professionals in primary care should focus on identifying and addressing those factors associated with non-adherence to recommended treatment in order to maximize primary and secondary prevention of diabetic foot ulcer, and increase chances for early treatment and fast healing.

A recent study from year 2017 suggested that diabetic foot ulcers and ulcer infections constitute a risk factor for emergency department visits and hospital admission 46. In the present study, the researchers found that 16.2% of patients were referred to hospitals for emergency care on their first presentation at the primary care clinics. Referrals to emergency department were associated with delayed ulcer healing within 3 months (PR 0.70, 95% CI: 0.31 - 0.40, P<.001) and this effect was also seen in the multivariate analysis (PR: 73, 95% CI: 0.45-1.02, P=.116) of the present study. The association between referrals for emergency care and non-healing within 3 months could possibly be explained by that those ulcers were considered more complicated with deep/extensive infection or severe ischemia therefore required more urgent and invasive treatments and even hospitalization to save patients lower limbs47. Diabetic foot ulcers that required emergency care when first presented to primary care were more severe and complicated which may be related to delays in seeking professional medical help after identified a foot problem, or delays in identifying foot ulcers due to a lack of foot self-care knowledge. Further research is recommended to explore diabetic foot ulcer patients’ health seeking behavior and their knowledge of self-care related to treatment adherence.

The descriptive analysis of the present study revealed that more than half of the patients (65.4%) in the present study had abnormal HbA1c >7% and most of patients had diabetes >5 years. Patients with previous history of diabetic foot ulcer and diabetic lower limb amputation made up 68.5% of study population. These findings corroborated the two preceding factors (low adherence rates to recommended foot screening and high rates of emergency department referral due to late presentation of diabetic foot ulcer in primary care) and further elucidated the complexity of diabetes/diabetic foot ulcer care, including both management and prevention in primary care. A previous study has reported that up to 98% of diabetes management is self-care 48. The International Working Group on the Diabetic Foot guidelines, recommend patients with diabetic foot ulcer to perform daily foot self-care and seek professional help in a timely manner for any foot problem 45. Knowledge regarding warning signs for ulcer deterioration relates to patients healthcare seeking behavior 49 and it is therefore important to enhance patient’s self-management knowledge in order to improve treatment adherence (i.e. self-care and health seeking behaviors) 47. Both knowledge and behavioral change should be the priority in foot self-care and self-management to achieve optimal healing. Further studies are required in order to develop educational and behavioral interventions to improve clinical outcomes for healing of diabetic foot ulcers.

The present study is the first study in Singapore from primary care perspective which identified factors associated diabetic foot ulcer healing outcomes within 3 months. In Singapore and the global context, most follow-ups in wound care, including care for diabetic foot ulcers, is performed by healthcare professionals, in particular, nurses, in primary care settings 50. The researchers believe that the findings of this study will add valuable information for clinical decision making by healthcare providers in primary care for better DFU care.

Limitations includes that the data collection was based on retrospective electronic medical records data, hence some desired variables that were not recorded, such as if patient was a former or current smoker, previously ulcer classifications, other clinical indications and biomarkers, i.e. congestive heart failure, types of diabetes, C-Reactive Protein value, wound infection markers, ulcer staging and psychosocial status, could not be retrieved.

**Conclusions**

This study focused on a study sample with diabetic foot ulcer from primary care settings in Singapore and described factors, such as, patient and ulcer characteristics associated with ulcer healing outcomes within 3 months. The findings revealed that male patients, larger sized diabetic foot ulcers, longer duration of the ulcer and ischemic etiology were related to poor healing within 3 months. Prompt attention to these risk factors may reduce healing time. Further prospective studies are warranted to understand factors associated with wound healing, particularly, elucidate the mechanism underlying gender differences in association with DFU healing. Understanding factors associated with poor healing may assist clinicians to improve risk profiling of diabetic foot ulcer treatment and inform future interventions, to improve knowledge and treatment adherence in this patient group.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

**Author contributions**

Study design, data analysis and manuscript preparation: ZX; study design and data analysis: GLJ; data analysis: RP; manuscript preparation: MO; study design, data collection: LVH; approval of the final manuscript: all authors

**References**

1. Karuranga S, Malanda B, Saeedi P, Salpea P, eds. *International Diabetes Federation Diabetes Atlas 2019*. 9th editio.; 2019. www.diabetesatlas.org. Accessed May 20, 2020.

2. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med*. 2017;376:2367-2375. doi:10.1056/NEJMra1615439

3. Amin N, Doupis J. Diabetic foot disease: From the evaluation of the &quot;foot at risk&quot; to the novel diabetic ulcer treatment modalities. *World J Diabetes*. 2016;7(7):153-164. doi:10.4239/wjd.v7.i7.153

4. Zubair M, Malik A, Ahmad J. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a North Indian tertiary care hospital. *Foot*. 2012;22(1):24-30. doi:10.1016/j.foot.2011.09.003

5. Bakheit HE, Mohamed MF, Mahadi SEDI, et al. Diabetic Heel Ulcer in the Sudan: Determinants of Outcome. *J Foot Ankle Surg*. 2012;51(2):152-155. doi:10.1053/j.jfas.2011.10.032

6. Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC, Eurodiale consortium. Diabetic foot disease: impact of ulcer location on ulcer healing. *Diabetes Metab Res Rev*. 2013;29(5):377-383. doi:10.1002/dmrr.2400

7. Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers. *Diabetes Care*. 2018;41(4):645-652. doi:10.2337/dc17-1836

8. 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(5):747-755. doi:10.1007/s00125-008-0940-0

9. Chan AS, Montbriand J, Eisenberg N, Roche-Nagle G. Outcomes of minor amputations in patients with peripheral vascular disease over a 10-year period at a tertiary care institution. *Vascular*. 2019;27(1):8-18. doi:10.1177/1708538118797544

10. Phan TP, Alkema L, Tai S, et al. Forecasting the burden of type 2 diabetes in Singapore using a demographic epidemiological model of Singapore. *Care*. 2014;2:12. doi:10.1136/bmjdrc-2013

11. Ang Y, Yap CW, Saxena N, Lin LK, Heng BH. Diabetes-related lower extremity amputations in Singapore. *Proc Singapore Healthc*. 2017;26(2):76-80. doi:10.1177/2010105816663521

12. Lo ZJ, Lim X, Eng D, et al. Clinical and economic burden of wound care in the tropics: a 5-year institutional population health review. *Int Wound J*. 2020;17(3):790-803. doi:10.1111/iwj.13333

13. Zhu X, Goh LJ, Chew E, Lee M, Bartlam B, Dong L. Struggling for normality: experiences of patients with diabetic lower extremity amputations and post-amputation wounds in primary care. *Prim Health Care Res Dev*. 2020;21:e63. doi:10.1017/S146342362000064X

14. Monteiro‐Soares M, Boyko EJ, Jeffcoate W, et al. Diabetic foot ulcer classifications: A critical review. *Diabetes Metab Res Rev*. 2020;36(S1). doi:10.1002/dmrr.3272

15. Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol*. 2016;4(9):781-788. doi:10.1016/S2213-8587(16)30012-2

16. Apelqvist J. The foot in perspective. *Diabetes Metab Res Rev*. 2008;24(S1):S110-S115. doi:10.1002/dmrr.834

17. Bender C, Cichosz SL, Pape-Haugaard L, et al. Assessment of Simple Bedside Wound Characteristics for a Prediction Model for Diabetic Foot Ulcer Outcomes. *J Diabetes Sci Technol*. July 2020:193229682094230. doi:10.1177/1932296820942307

18. Rhou YJJ, Henshaw FR, McGill MJ, Twigg SM. Congestive heart failure presence predicts delayed healing of foot ulcers in diabetes: An audit from a multidisciplinary high-risk foot clinic. *J Diabetes Complications*. 2015;29(4):556-562. doi:10.1016/J.JDIACOMP.2015.02.009

19. Fife CE, Eckert KA, Carter MJ. COMPREHENSIVE INVITED REVIEW Publicly Reported Wound Healing Rates: The Fantasy and the Reality. *Adv WOUND CARE*. 2017;7(3):77-94. doi:10.1089/wound.2017.0743

20. Ince P, Game FL, Jeffcoate WJ. Rate of Healing of Neuropathic Ulcers of the Foot in Diabetes and Its Relationship to Ulcer Duration and Ulcer Area. *Diabetes Care*. 2007;30:660-663. doi:10.2337/dc06-2043

21. National Healthcare Group Polyclinics. https://www.nhgp.com.sg/About\_Us/. Accessed April 30, 2020.

22. Jia L, Parker CN, Parker TJ, et al. Incidence and risk factors for developing infection in patients presenting with uninfected diabetic foot ulcers. *PLoS One*. 2017;12(5):e0177916. doi:10.1371/journal.pone.0177916

23. Bus SA, Van Netten JJ, Lavery LA, et al. IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes on the Diabetic Foot. *Int Work Gr Diabet Foot*. 2015. http://www.iwgdf.org/files/2015/website\_prevention.pdf. Accessed April 18, 2018.

24. Sussman C, Bates-Jensen BM. *Wound Care: A Collaborative Practice Manual*. Third Edit. Lippincott Williams & Wilkins, Philadelphia; 2007. https://books.google.com/books?id=LaNuvQTjYeEC&pgis=1. Accessed May 18, 2020.

25. Apelqvist J, Elgzyri T, Larsson J, Lndahl M, Nyberg P, Thrne J. Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. *J Vasc Surg*. 2011;53(6). doi:10.1016/j.jvs.2011.02.006

26. Tamhane AR, Westfall AO, Burkholder GA, Cutter GR. Prevalence odds ratio versus prevalence ratio: choice comes with consequences. *Stat Med*. 2016;35(30):5730-5735. doi:10.1002/sim.7059

27. Hardin JW. THE SANDWICH ESTIMATE OF VARIANCE. *Adv Econom*. 2003;17:45-73. doi:10.1016/S0731-9053(03)17003-X

28. Heinze G, Wallisch C, Dunkler D. Variable selection – A review and recommendations for the practicing statistician. *Biometrical J*. 2018;60(3):431-449. doi:10.1002/bimj.201700067

29. Akaike H. *Information Theory and an Extension of the Maximum Likelihood Principle. In Second International Symposium on Information Theory*. (B. N. Petrov and F. Csaki, ed.). Budapest: Akailseoniai–Kiudo; 1973.

30. Raftery AE. Bayesian Model Selection in Social Research. *Sociol Methodol*. 1995;25:111. doi:10.2307/271063

31. Mahon AM, MacGilchrist C, McIntosh C, O’Brien T. Characterization of patients with diabetic foot disease presenting to an Irish Podiatry Centre: profiling suitability for entry to a clinical trial of advanced wound therapeutics. *Ir J Med Sci*. 2017;186(3):659-669. doi:10.1007/s11845-016-1511-x

32. Marston WA, Dermagraft Diabetic Foot Ulcer Study Group. Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia. *Ostomy Wound Manage*. 2006;52(3):26-28, 30, 32 passim. http://www.ncbi.nlm.nih.gov/pubmed/16567857. Accessed September 24, 2017.

33. Ezeani IU, Ugwu ET, Adeleye FO, Gezawa ID, Okpe IO, Enamino MI. Determinants of wound healing in patients hospitalized for diabetic foot ulcer: Results from the MEDFUN study. *Endocr Regul*. 2020;54(3):207-216. doi:10.2478/enr-2020-0023

34. Pemayun TGD, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-control study. *Diabet Foot Ankle*. 2015;6:29629. doi:10.3402/dfa.v6.29629

35. Gubara Musa H, Ahmed ME, Musa G, Ahmed ME. Associated risk factors and management of chronic diabetic foot ulcers exceeding 6 months’ duration Associated risk factors and management of chronic diabetic foot ulcers exceeding 6 months’ duration. *Diabet Foot Ankle*. 2012;3(1). doi:10.3402/dfa.v3i0.18980

36. Kee KK, Nair HKR, Yuen NP. Risk factor analysis on the healing time and infection rate of diabetic foot ulcers in a referral wound care clinic. *J Wound Care*. 2019;28(Sup1):S4-S13. doi:10.12968/jowc.2019.28.Sup1.S4

37. Parisi MCR, Moura Neto A, Menezes FH, et al. Baseline characteristics and risk factors for ulcer, amputation and severe neuropathy in diabetic foot at risk: the BRAZUPA study. *Diabetol Metab Syndr*. 2016;8:25. doi:10.1186/s13098-016-0126-8

38. Engberg S, Kirketerp‐Møller K, Ullits Andersen H, Rasmussen A. Incidence and predictors of recurrent and other new diabetic foot ulcers: a retrospective cohort study. *Diabet Med*. 2019;36(11):1417-1423. doi:10.1111/dme.13964

39. Rossaneis MA, Haddad M do CFL, Mathias TA de F, Marcon SS. Differences in foot self-care and lifestyle between men and women with diabetes mellitus. *Rev Lat Am Enfermagem*. 2016;24. doi:10.1590/1518-8345.1203.2761

40. Mutyambizi C, Pavlova M, Hongoro C, Groot W. Inequalities and factors associated with adherence to diabetes self-care practices amongst patients at two public hospitals in Gauteng, South Africa. *BMC Endocr Disord*. 2020;20(1):1-10. doi:10.1186/s12902-020-0492-y

41. Soewondo P, Suyono S, Kanoko Sastrosuwignyo M, Harahap AR, Sutrisna B, Makmun LH. *Prediction of Wound Healing in Diabetic Foot Ulcers: An Observational Study in Tertiary Hospital in Indonesia*. Vol 49.; 2017. http://www.actamedindones.org/index.php/ijim/article/viewFile/348/pdf. Accessed August 19, 2019.

42. Roth-Albin CCRA I, Mai SH, Ahmed Z, et al. Outcomes Following Advanced Wound Care for Diabetic Foot Ulcers: A Canadian Study. *Can J Diabetes*. 2016;41:26-32. doi:10.1016/j.jcjd.2016.06.007

43. Olsson M, Järbrink K, Divakar U, et al. The humanistic and economic burden of chronic wounds: A systematic review. *Wound Repair Regen*. 2019;27(1):114-125. doi:10.1111/wrr.12683

44. Ang GY, Wei Yap C, Saxena N, Ang Yee G. *Effectiveness of Diabetes Foot Screening in Primary Care in Preventing Lower Extremity Amputations*. Vol 46.; 2017. http://www.annals.edu.sg/pdf/46VolNo11Nov2017/MemberOnly/V46N11p417.pdf. Accessed August 23, 2019.

45. Bus; SA, Lavery LA, Monteiro-Soares M, et al. *IWGDF Guideline on the Prevention of Foot Ulcers in Persons with Diabetes*.; 2019. www.iwgdfguidelines.org. Accessed October 24, 2019.

46. Skrepnek G, Mills Sr JL, Lavery LA, Armstrong DG. Health Care Service and Outcomes Among an Estimated 6.7 Million Ambulatory Care Diabetic Foot Cases in the U.S. *Diabetes Care*. 2017;40. doi:10.2337/dc16-2189

47. Schaper C, Van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA. *IWGDF Practical Guidelines on the Prevention and Management of Diabetic Foot Disease*.; 2019. www.iwgdfguidelines.org. Accessed October 25, 2020.

48. Bullen B, Young M, McArdle C, Ellis M. Overcoming barriers to self-management: The person-centred diabetes foot behavioural agreement. *Foot*. 2019;38:65-69. doi:10.1016/j.foot.2019.01.004

49. Chin Y-F, Liang J, Wang W-S, Hsu BR-S, Huang T-T. The role of foot self-care behavior on developing foot ulcers in diabetic patients with peripheral neuropathy: a prospective study. *Int J Nurs Stud*. 2014;51(12):1568-1574. doi:10.1016/j.ijnurstu.2014.05.001

50. Sánchez-Ríos JP, García-Klepzig JL, Manu C, et al. Referral of patients with diabetic foot ulcers in four European countries: Patient follow-up after first GP visit. *J Wound Care*. 2019;28:S4-S14. doi:10.12968/jowc.2019.28.Sup8.S4