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A Multi-Center Prospective Study on the Healing of Neuro-Ischemic Ulcers in Singapore: A Prospective Cohort Study

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ABSTRACT

Background and Aims: Neuro-ischemic ulcers (NIU) present a substantial clinical and economic burden on the healthcare systems. This study aims to evaluate their healing rate, associated healthcare resource utilization, and prognostic factors influencing healing.

Methods: Consecutive patients attended specialist clinics or admitted to wards in three tertiary hospitals for new or existing NIUs from November 2019 to November 2021 were eligible for this study. Each participant was followed up three times (1-month, 3-month and 6-month after enrollment), with ulcer healing as the primary outcome of interest. Cox regression analysis was performed to identify independent predictors of NIU healing.

Results: In total, 439 patients were recruited. Six months after they seek care in the tertiary healthcare setting, 36.0% of the participants had their ulcer fully healed. Male gender (adjusted HR: 0.71, 95% CI: 0.53–0.93), history of coronary intervention (adjusted HR: 0.62; 95% CI: 0.41–0.93), requirement of lower extremity revascularization (adjusted HR: 0.72; 95% CI: 0.54–0.98) and offloading (adjusted HR: 0.61; 95% CI: 0.46–0.81) were found to be associated with failure to heal. Ulcers located over the toes (adjusted HR: 1.64; 95% CI: 1.17–2.32) was associated with better healing. Dependent activity of daily living (adjusted HR: 0.74; 95% CI: 0.55–1.01) was also potentially a risk factor for slow healing with borderline significance.

Nonhealed group of patients incurred higher requirement of revascularization (42.3% vs. 25.3%, $p < 0.001$), negative pressure wound therapy (40.6% vs. 29.7%, $p = 0.03$), off-loading (57.3% vs. 46.8%, $p = 0.04$) and antibiotic treatment (45.2% vs. 26.6%, $p < 0.001$), compared to those in the healed group.

Conclusion: NIU imposes a significant burden on both patients and the healthcare system in Singapore, with low healing rates even after 6 months of tertiary-level care. Early identification and risk stratification of high-risk patients may help improve outcomes.

All authors have read and approved the final version of the manuscript. The corresponding author A/Prof Ho Pei had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Summary

- Neuro-ischemic ulcers (NIU) present a challenging clinical and economic burden to the healthcare systems, but the treatment outcomes from prospective studies are under-reported in the Asian population.
- The aim of this study is to evaluate: (i) the healing rate of NIU treated in the tertiary healthcare institutions; (ii) the key patients- and ulcer-related factors affecting healing, in an Asian population.
- Six months since first clinical review in the tertiary healthcare institution for participated patients' index NIU, 36.0% of these ulcers fully healed.
- Male gender, history of CAD with PCI, requirement of lower limb revascularization and offloading were found to be associated with poor or nonhealing ulcer. Patients with ulcers over the toes and who are ADL independent had better prognosis in ulcer healing.

1 | Introduction

Neuro-ischemic ulcers (NIU) are ulcers that develop on the lower extremities of diabetic patients who have either or both peripheral neuropathy and arterial ischemia of varying severity. It presents a substantial clinical [1] and economic burden [2, 3] to the healthcare systems. It can be further classified into three groups by their underlying etiology-predominantly neuropathic, predominantly ischemic or both (neuro-ischemic). The enduring nature of NIU places a significant demand on healthcare resource, leading to significant costs associated with wound care. Furthermore, NIU may worsen and lead to major limb amputation. Patients with NIU were reported to have poor clinical prognosis, their 3-year amputation-free survival rate were 68.5%, 44.6% and 41.5% in the subgroup of neuropathic, ischemic and neuro-ischemic respectively [1]. It is also associated with an estimated gross healthcare cost, on an average, of USD $16,920 per patient in Singapore [2].

Despite the magnitude of this health matter, studies focused on wound healing outcomes for NIU in the Asia population is scarce [4]. A retrospective study has found ulcer size and duration, presence of ischemia component and gender were significantly associated with the healing of NIU in the Singapore's primary care setting [5]. Data from prospective study in tertiary care settings was under-reported. This is a pioneer multi-center endeavor to prospectively study NIU wound healing in Asia. The study investigates (i) the healing rate of NIU treated in the tertiary hospitals; (ii) the key patients- and ulcer-related factors affecting healing.

2 | Methods

2.1 | Study Design

This is a prospective cohort study on patients with NIU as part of the Chronic Wound Registry (Approved by the Domain Specific Review Board Ref No: 2019/00971). Patients were recruited from three tertiary hospitals of the three healthcare clusters of Singapore - National University Health System, National Healthcare Group and SingHealth. Written consent was obtained from all the participants.

Consecutive patients who attended hospital specialist clinics or being admitted to the ward for a new or existing NIU from November 2019 to November 2021 were eligible for this study. Inclusion criteria were: (i) patients with diabetes and/or peripheral artery disease; (ii) presence of foot ulcers or gangrene; and (iii) willingness to provide written consent. Exclusion criteria were patients who were age < 21, had ulcers with mixed arterial and venous etiology or did not consent to participate. All participants were followed up for 6 months. The flow of cohort study was illustrated in Figure 1. The study was reported based on the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

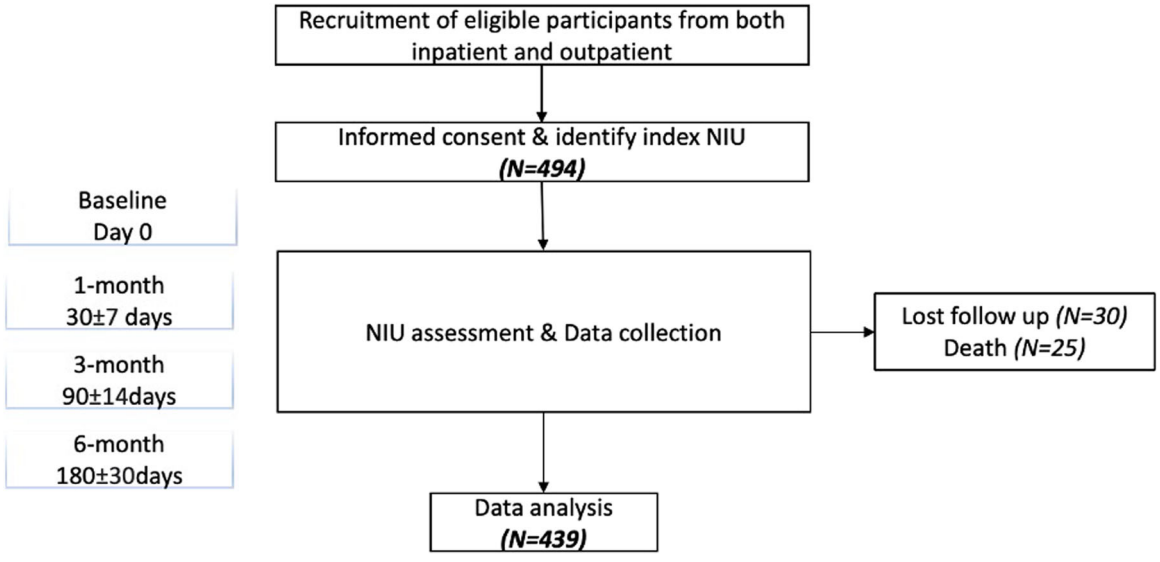

FIGURE 1 | Study flow diagram.

2.2 | Management of NIU

All patients received due multidisciplinary care. All NIU patients were under the care of one or more of the following specialists - orthopedic surgeon, vascular surgeon or endocrinologist. Furthermore, patients also received wound care by the podiatrists and nurse specialists. The scope of care included wound management, the treatment of any infections (if any), optimization of medical therapy (especially diabetes control), offloading if necessary, revascularization if required, and performing amputation/debridement if needed.

In the out-patient setting, patients' ulcer was reviewed by specialists and podiatrists every 1–3 weeks. Debridement of the ulcer and appropriate dressing were regularly carried out. Negative pressure wound therapy (NPWT) was applied and changed twice weekly for deep ulcers. Off-loading was provided by podiatrists as required.

2.3 | Study Variables

At baseline, data on participants' demographics, comorbidities, NIU-related histories, characteristics of the wound (appearance, signs of infection, exudate, size) and procedures (revascularization, minor amputation or wound debridement in the operating theater) done on the index lower limb were collected. The university of Texas wound classification system [6] was used to classify the NIU from three grades (wound depth: I–II) and four stages: non-ischemic clean ulcer (A), infection only (B), ischemic only (C) and infected ischemic ulcer (D).

During the three follow up visits (1-month, 3-month and 6-month), dates and nature of procedures, dressing regime, bed days in hospital, bill incurred and ulcer outcome were collected. Ulcer healing was the primary outcome of interest, which was defined by complete epithelization of the index NIU as assessed by doctors or podiatrists. Ulcer area (cm^2) of the lesion, which was estimated by length(cm) × width (cm), were also collected. Amputations at or above the ankle joint were defined as major, whereas amputations below the level of the ankle were classified as minor. Patients who had major amputation were classified as ulcer not healed. The time required for ulcer to heal was calculated as the interval between the date of first consultation with doctors in the tertiary hospitals for the index NIU and the date of ulcer healing.

2.4 | Statistical Analysis

All statistical analyses were performed with R software (R-4.2.1). Patients were divided into two groups–those whose NIU healed within the 6 months' study period and those who failed to heal. The demographics, comorbidities, ulcer characteristics and ulcer treatment were compared between the two groups. Categorical variables were expressed as *n* (%), and chi-square test was used for comparison. Normally distributed continuous variables were described as mean accompanied by standard deviation (SD), and skewed continuous variables were summarized as median (first quartile–third quartile). Two sample *t*-test and Mann Whitney U test were used for comparison respectively. Local regression smoothing technique (LOESS) curves was used to identify cut points for numeric variables.

Cox regression analysis was performed to identify independent predictors of NIU healing. Hazard ratio (HR) was estimated. Candidate variables were selected based on expert opinions. All variables with $p < 0.1$ in univariable analysis were included in the multivariable analysis. Variance inflation factor (VIF) is used to detect the severity of multicollinearity (VIF < 5). Statistical significance was defined as two-tailed $p < 0.05$.

3 | Results

3.1 | Study Participants

In total, 494 eligible participants were recruited in the study with written consent obtained. Thirty participants lost follow up and 25 of them deceased (not NIU-related mortality) during the study. As a result, 439 participants' data was included in the analysis (Figure 1). Six months after the first clinical review in the tertiary healthcare institution for their index NIU, 36.0% of the participants had their ulcer fully healed. Twenty-two (4.5%) of the nonhealed ulcers resulted in major amputation. There is no significant difference in the ulcer healing rate or major amputation rate across the three institutions.

The participants' demographics, comorbidities, ulcer characteristics and treatment received were presented in Table 1. The demographics between the two groups (healed vs. nonhealed) were comparable except gender and their activity of daily living (ADL) status. More males were seen in the nonhealed group, compared to the healed group (73.3% vs. 63.9%, $p = 0.05$). There were more ADL assisted or dependent participants in the nonhealed group, compared to healed group (42.0% vs. 24.1%, $p < 0.001$).

In terms of comorbidities, majority of the participants had diabetes, hypertension and dyslipidaemia in both groups. Approximately half of them had chronic renal impairment and one-third of them had coronary artery disease (CAD). The percentage of participants had history of percutaneous coronary intervention (PCI) in nonhealed group was twice of that in the healed group (16.0% vs. 8.2%, $p = 0.03$). There were more participants with history of peripheral arterial disease (PAD) in the nonhealed group, compared to the healed group (69.8% vs. 57.6%, $p = 0.01$).

3.2 | Ulcer Characteristics and Treatment

A small proportion of the participants had prior history of healed NIU other than the index ulcer. 16.0% (nonhealed group) and 20.3% (healed group) in the two groups were recurrent ulcers, with a prior ulcer over the same lower extremity that had healed before the index lesion occurred. About one-third of the participants had existing neuropathy and about one fifth had foot deformity. At baseline assessment, the ulcer size was smaller in the healed group than the nonhealed group (median size: 1.0 cm^2 vs. 2.5 cm^2, $p < 0.01$).

TABLE 1 | Participants' demographics, comorbidities, ulcer characteristics and treatment between nonhealed and healed groups.

Variables	Levels[a]	Nonhealed in 6-month ($n = 281$)	Healed in 6-month ($n = 158$)	p
Demographics				
Age	Mean (SD)	61.7 (10.6)	61.8 (10.3)	0.92
Ethnicity	Chinese	163 (58.0)	84 (53.2)	0.63
	Indian	51 (18.1)	37 (23.4)	
	Malay	56 (19.9)	33 (20.9)	
	Others	11 (4.0)	4 (2.5)	
Gender	Male	206 (73.3)	101 (63.9)	0.05
ADL	Assisted/Dependent	118 (42.0)	38 (24.1)	< 0.001
Smoking	Current	48 (17.1)	25 (15.8)	0.22
	Ex-smoker for at least 6 months	26 (9.3)	11 (7.0)	
	No	207 (73.7)	122 (77.2)	
BMI[b]	Normal	116 (41.3)	59 (37.3)	0.34
	Overweight or obese	165 (58.7)	99 (62.7)	
Comorbidities				
DM	Yes	273 (97.2)	155(98.1)	0.77
HbA1c	Median (first–third quartile)	7.8 (6.8–9.6)	7.7 (6.8–9.3)	0.68
Year of DM	Median (first–third quartile)	12.1 (5.8–16.2)	12.6 (5.1–17.0)	0.71
DM treatment	On Insulin	169 (60.1)	87 (55.1)	0.29
Hypertension	Yes	246 (87.5)	136 (86.1)	0.77
Dyslipidemia	Yes	261 (92.9)	141 (89.2)	0.26
History of CAD	Yes	102 (36.3)	49 (31.0)	0.31
History of CAD requiring PCI	Yes	45 (16.0)	13 (8.2)	0.03
History of CAD requiring CABG	Yes	35 (12.5)	13 (8.2)	0.23
Chronic heart failure	Yes	44 (15.7)	23 (14.6)	0.87
Renal impairment[c]	Yes	161 (57.3)	88 (55.7)	0.19
History of PAD	Yes	196 (69.8)	91 (57.6)	0.01
Ulcer characteristics				
Prior History of healed NIU	Yes	49 (17.4)	36 (22.8)	0.22
Index Ulcer is a recurrent ulcer	Yes	45 (16.0)	32 (20.3)	0.32
Existing neuropathy	Yes	109 (38.8)	56 (35.4)	0.74
Foot deformity	Yes	62 (22.1)	28 (17.7)	0.34
Baseline ulcer size (cm^2)	Median (first–third quartile)	2.5 (0.5–12.2)	1.0 (0.2–5.0)	< 0.001
Baseline ulcer size (cm^2) > 2 cm^2	Yes	151 (53.7%)	55 (34.8%)	< 0.001
Ulcer site	Dorsum/lateral/ Medial	70 (24.9)	26 (16.5)	0.04
	Heel	26 (9.3)	9 (5.7)	

(Continues)

TABLE 1 | (Continued)

Variables	Levels[a]	Nonhealed in 6-month ($n = 281$)	Healed in 6-month ($n = 158$)	p
	Sole	65 (23.1)	35 (22.2)	
	Toes	120 (42.7)	88 (55.7)	
Texas score[d]	1A	103 (36.7)	83 (52.5)	0.001
	1B	43 (15.3)	18 (11.4)	
	1C	33 (11.7)	18 (11.4)	
	1D	57 (20.3)	11 (7.0)	
	2A/3A	9 (3.2)	11 (7.0)	
	2B/3B	7 (2.5)	6 (3.8)	
	2C/3C	9 (3.2)	4 (2.5)	
	2D/3D	20 (7.1)	7 (4.4)	
Toe pressure index[e]	Median (IQR)	0.5 (0.3–0.7)	0.5 (0.3–0.6)	0.82
Treatment and healthcare cost				
Revascularization	Yes	119 (42.3)	40 (25.3)	0.001
Minor amputation	Yes	94 (33.5%)	39 (24.7%)	0.07
NPWT	Yes	114 (40.6)	47 (29.7)	0.03
Off-loading	Yes	161 (57.3)	74 (46.8)	0.04
Antibiotic therapy	Yes	127 (45.2)	42 (26.6)	< 0.001
Total surgery cost[f]	Median (first–third quartile)	S$5782.7 (2824.0–11,498.4)	S$5314.8 (2312.6–8276.7)	0.16
Require inpatient admission	Yes	115 (40.9)	37 (23.4)	< 0.001
Total inpatient cost[g]	Median (first–third quartile)	S$27,754.1 (12,799.6–56,559.5)	S$25,028.7 (15,841.6–32672.3)	0.52
Total outpatient cost	Median (first–third quartile)	S$794.8 (348.0–1261.0)	S$486.4 (188.0–884.8)	< 0.001

Abbreviations: ADL, activity of daily living; BMI, Body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DM, Diabetes Mellitus; eGFR, estimated glomerular filtration rate; NPWT, Negative pressure wound therapy; PCI, percutaneous coronary intervention; S$, Singapore dollar; SD, standard deviation.
[a]Variables were reported as *N* (%) unless otherwise specified.
[b]BMI: If BMI < 25 kg/m^2, it falls within the normal weight range; If BMI ≥ 25 kg/m^2, it falls within the overweight or obese range.
[c]Renal impairment: Creatinine> 75 μmol/L for females and Creatinine > 105 μmol/L for males.
[d]The University of Texas grading system classifies wounds as grades 1–3 for depth, ranging from a healed lesion to wound penetrating to bone or joint; then stage A to D indicating if there is the presence of: none (A), infection (B), ischemia (C) or both (D).
[e]Toe pressure index subject to 59.0% missing data: 58.3%; in the not healed group; 60.1% in the healed group.
[f]The total surgery cost was calculated from 117 patients (85 in the not-healed group and 32 in the healed group) who had endovascular or open surgery.
[g]The total inpatient cost was calculated from 152 patients who had inpatient admission.

The location of ulcer varied between the two groups ($p = 0.04$). Compare to the nonhealed group, NIUs in the healed group more frequently located over the toes and less frequently over the heel or dorsum/lateral/medial foot (Table 1). The healed group had higher proportion of NIU with baseline Texas score of 1A, 2A or 3A (ulcers without infection and ischemia), compared to the nonhealed group. Whereas the nonhealed group had high proportion of Texas score stage 1D, 2D or 3D (ischemic ulcers with infection), compared to the healed group ($p = 0.001$).

More participants required revascularization to optimize their blood flow to the foot ulcer in the nonhealed group, compared to the healed group (42.3% vs. 25.3%, $p < 0.001$). Similarly, more participants in the nonhealed group required negative pressure wound therapy (40.6% vs. 29.7%, $p = 0.03$), off-loading (57.3% vs. 46.8%, $p = 0.04$) and antibiotic treatment (45.2% vs. 26.6%, $p < 0.001$).

Significantly more patients required NIU-related inpatient admission in the nonhealed group, compared to the healed group (40.9% vs. 23.4%, $p < 0.001$). For those with ulcer related in-patient admission, the median of 6-months total surgery cost (S$5782.7 vs. S$5314.8, $p = 0.16$) and inpatient cost (S$27,754.1 vs. S$25,028.7, $p = 0.52$) were comparable between the nonhealed group and healed group, respectively. Compared to the healed group, higher 6-months outpatient cost was incurred in the nonhealed group (Median: S$794.8 vs. S$486.4, $p < 0.001$).

3.3 | Predictors for Ulcer Healing

The results of the multivariable cox regression was presented in Figure 2. Males gender (adjusted HR: 0.71, 95% CI: 0. 53–0.93, $p = 0.01$), those with history of CAD required PCI (adjusted HR: 0.62; 95% CI: 0.41–0.93, $p = 0.02$) were less likely to have their ulcer healed. Participants who required revascularization (adjusted HR: 0.72; 95% CI: 0.54–0.98; $p = 0.04$) and required offloading (adjusted HR: 0.61; 95% CI: 0.46–0.81; $p < 0.001$) were found to be associated with lower likelihood of ulcer healing.

Compared to ulcers on dorsum, lateral or medial foot regions, those on toe(s) were found to be more likely to heal (adjusted HR: 1.64; 95% CI: 1.17–2.32; $p < 0.01$). ADL assisted or dependent (adjusted HR: 0.74; 95% CI: 0.55–1.01; $p = 0.06$) showed borderline significance as a risk factor for poor ulcer healing.

4 | Discussion

NIU presents a major clinical and economic burden to the healthcare system. The substantial major amputation rate [7–9] and mortality rate of NIU [7, 10, 11] were widely recognized. During the 6-month follow-up period in this study, approximately 5% of the recruited participants demised, highlighting the overall high-risk profile of the patients with NIU. Nonetheless, the impact of NIU towards the population health extends beyond major amputation and mortality. Data from NIU studies conducted in Western countries revealed that population with various underlying conditions of NIU, including ischemia, structural abnormality and infection, generally exhibit poor wound healing [12–15]. There is a paucity of data regarding the healing of NIUs in Asian countries. Furthermore, the majority of the studies conducted were retrospective in nature. The current study is the first prospective study in Asia aimed at evaluating the characteristics, treatment and healing outcome of NIU. Its prospective nature allowed for the reliable capture of data, proving crucial in wound research studies where a large number of data fields are required. It enables the accurate recording of ulcer characteristics and healing status during the study duration. In contrast, retrospective studies often subject to missing wound healing information due to patients' default follow-up or incomplete documentation in the hospital electronic medical record.

This study revealed that only about one-third of the NIUs healed by 6 months after patients received care in the tertiary healthcare institutions. Due to high heterogeneity of the study design (including inclusion criteria, follow up period and definition of healed ulcer), direct comparison of the results of current study with prior studies is difficult. The ulcer healing rates from two retrospective studies conducted by Guest et al. [13] (UK) and Sorensen et al. [14] (Denmark) were about one-third by 1 year. A prospective study conducted by Ndosi et al. [12] (UK) reported a healing rate of 45.4%, but with a 9.6% recurrence rate by 1 year. The EURODIALE prospective study [16], on the other hand, reported a more favorable ulcer healing rate of 77% by 1 year.

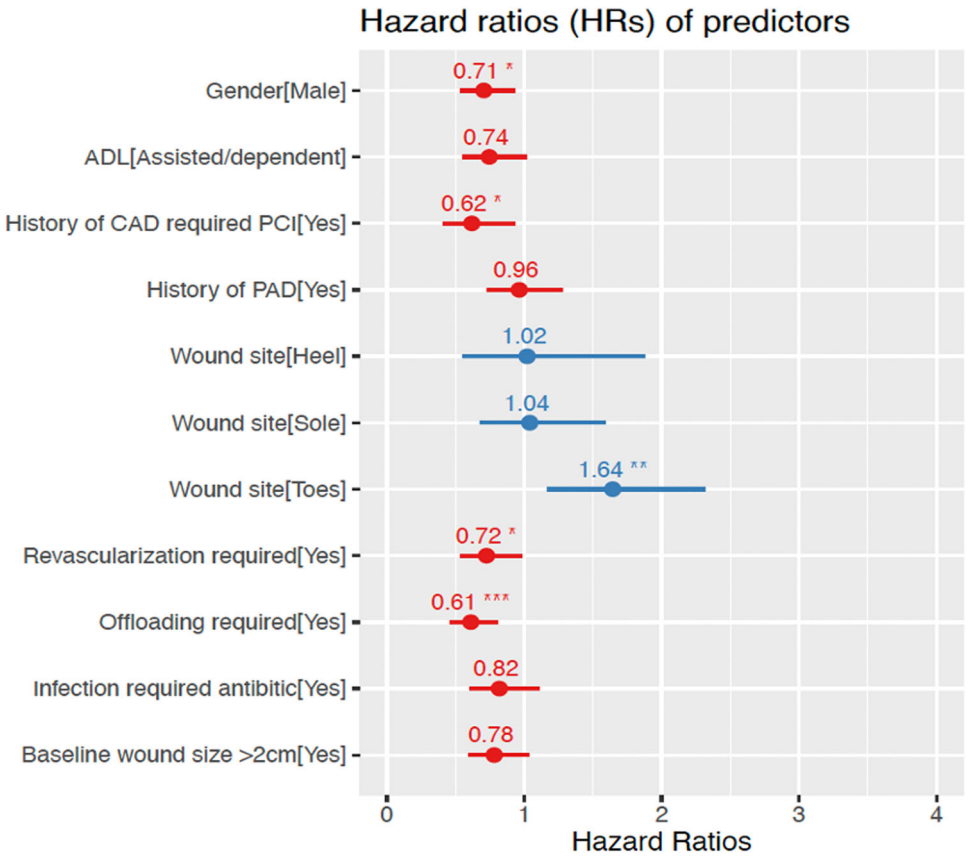

FIGURE 2 | Coefficients of Predictors of ulcer healing in the Cox regression analysis. The figure only showed hazard ratios (HR) of variables selected in the multivariable analysis ($p < 0.1$ in the univariable analysis). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Similarly, Jeffcoate et al. [15] (UK) reported an ulcer healing rate (without amputation done) of 55.0% at the same end-point we used (6-months) [15], which is much higher than the finding from our setting. Biz et al. (2024) reported favorable wound healing rate for predominantly neuropathic NIU patients after underwent minimally invasive distal metatarsal diaphyseal osteotomy (MIS-DMDO) [17] Although this may reflect more effective treatment, it could also be due to different severity of cases being referred from primary setting and patients' characteristics across settings. For instance, in the cohort studied by Jeffcoate et al, [15] 60.6% of the patients had the initial ulcer size $< 1\,cm^2$. Whereas in our cohort, more than half of the participants had an index ulcer bigger than $1\,cm^2$ (median size: 2.5 and $1.0\,cm^2$ in nonhealed and healed group respectively).

The potential gaps of NIU management within the Singapore context could be: (i) a lack of rapid access for referring patients from primary to tertiary care, (ii) an absence of a reliable imaging system to capture wound progress for continuity of care, (iii) a high clinic default rate, and iv) a deficiency in care coordination [18]. An ineffective referral system between primary and tertiary care might delay the necessary treatment of NIU. In an anonymized poll conducted among primary care providers, only about half of the respondents held a positive or very positive attitude on the item 'ease to refer a DFU patient from primary care to hospital' (56%) [18]. To address these challenges, there is a need to intensify efforts in streamlining the referral process, including the implementation of effective risk stratification in primary care and the establishment of a fast-track pathway [19].

Documenting the healing progress of NIU proves challenging when relying solely on textual entries in medical records. The adoption of a reliable wound imaging system, accessible across different settings, is believed to be valuable for ensuring continuity of care. Such a system could facilitate accurate assessment of wound, enable tracking of progress over time, detect changes, and allow informed decision making regarding the effectiveness of the treatment and further treatment strategies. Various modalities of wound imaging systems are available in the market, incorporating optical imaging or artificial intelligence technologies [20].

However, their efficacy requires further evaluation. Additionally, concerns about the safety of personal data create challenges in sharing patients' information across different healthcare institutions.

Due to the chronic nature of NIU, the progress of healing is substantially influenced by patients' compliance with treatment. In the current study, 6.1% of the recruited patients defaulted follow-up, despite the active tracking as outlined in the study protocol. A review has identified a positive correlation between patients' compliance and favorable foot ulcer outcomes [21]. It is important to understand the reason for noncompliance and find solutions to address nonadherence issues. This may involve incorporating counseling and financial support into the overall management process for NIU.

Lastly, there is a strong evidence that multi-disciplinary team (MDT) approach [22–24] improves the outcomes of NIU [22, 24, 25]. Despite this, challenges persist, as the MDT is a broad concept that requires intricate adaption to the resources and cultural nuances of each healthcare system. MDT care can be hindered by poor coordination, ineffective inter-discipline communication, and various other factors. Understanding and addressing these challenges requires a comprehensive approach, which may involve incorporating the establishment of standardized communication protocols and the cultivation of a collaborative working culture as some of the potential solutions.

In terms of factors associated with poor healing in NIU, the male gender was identified as a risk factor. It could be partially explained by the hypothesis that men tend to have a more passive attitude towards self-care compared to their female counterparts. A cross-sectional study reported that men were less likely to practice good self-care, including regular checking of feet, drying between toes and proper footwear [26]. When conducting foot care education to patients at risk, the health care professionals should take into account of potential gender variation in self-care behaviors.

The presence of assisted or dependent ADL was found to be potentially associated with poor NIU healing. This association does not imply causation. One plausible explanation of the association is that patients facing limitation in performing ADL may encounter challenges in managing wound care in home, making them more susceptible to experiencing poor/nonhealing ulcers. The ADL- assisted or -dependent status could also serve as a proxy for the overall poor health condition of the patients. Another possible explanation is that the dressing or pain related to NIUs might limit patients' ability to perform their ADLs [27]. In the actual clinical care for NIU patients, understanding the intricate relationship between a patient's ADL capability and the impact of NIU, and how these factors mutually influence each other, is essential. Specialized support and resources may be necessary to facilitate wound care and healing for ADL-assisted or -dependent patients.

CAD with PCI to restore blood supply to the ischemic heart tissue was strongly associated with poor or nonhealing NIUs. In the existing evidence, the presence of NIU was strongly associated with CAD [28, 29] as both CAD and ischemic foot ulcer share similar atherosclerosis risk factor profiles [30]. Our data further suggested that poor healing NIU is associated with severe form of CAD, represented by the requirement of PCI. Similarly, the presence of a significant ischemic component in the lower extremities requiring revascularization was also found to be a unfavorable factor for NIU healing. The need for revascularization serves as a proxy for more severe PAD with significant foot ischemia. In our prior study, a significantly higher major amputation rate, together with healthcare cost, was associated with NIU bearing a significant PAD component [1]. This observation is also noted in the EURODIALE study [16].

Compared to the ulcers in other lower extremity locations, ulcers over the toes were found to be more favorable in healing, which is in alignment with other studies [31, 32]. NIUs over the sides, sole and heel regions of the foot are more associated with excessive pressure. In this study, use of off-loading was associated with poor healing. Off-loading devices was often used to redirect pressure away from pressure-bearing ulcer areas of

patients with neuropathy, structural abnormalities or deformities. It was applied at the podiatrists' discretion based on their assessment of the biomechanical structure of the foot and the location of the ulcers, presence of foot deformities and other specific factors (e.g. amputations) [33]. Use of off-loading device is a proxy for patients' poor biomechanics of the foot.

NIU imposes a tremendous economic burden on both the patients and the healthcare system. The nonhealing group of NIU patients had substantially higher percentage of hospital admission. Among those patients requiring inpatient admission, their median total inpatient cost within 6 months was S $27,754.1 for the nonhealed and S$25,028.7 for the healed group. In alignment with the findings of the United Kingdom's National Health Service data, patients' healthcare resource utilization (revascularization, NPWT, off-loading, antibiotic and inpatient admission) associated with the management of an unhealed ulcer was substantially higher than that of a swiftly healed ulcer [34].

The current study has its own limitations. Only healing outcomes and its risk factors within 6 months have been investigated. Longer follow-up data is not available due to limited resources. The longer term information will reveal ulcer-free period which is of value since NIU has a high tendency to recur. Also, this study was conducted only in the tertiary hospitals, whereas the patients' ulcer management often initiated in the primary care settings. Future research should focus on the risk stratification and referral pathway for the management of NIU across various sectors.

5 | Conclusion

NIU constitutes heavy burden to the patients and the healthcare system in Singapore, with only approximately one-third of the ulcer healed after 6 months tertiary level care. Male gender, history of CAD with PCI, requirement of lower limb revascularization and offloading were found to be associated with poor or nonhealing ulcer. Patients with ulcers over the toes and who are ADL independent had better prognosis in ulcer healing. Early identification and risk stratification of high-risk patients may help improve outcomes.

Author Contributions

Lingyan Meng: formal analysis, writing–original draft. **Priya Bishnoi:** data curation, project administration, validation, writing–review and editing. **Zhiwen Joseph Lo:** conceptualization, methodology, supervision. **Enming Yong:** methodology, supervision. **Tze Tec Chong:** conceptualization, methodology, supervision. **David Carmody:** conceptualization, methodology, supervision. **Rajesh Babu Dharmarah:** project administration, resources. **Yi Zhen Ng:** conceptualization, funding acquisition, methodology, supervision. **Keith Harding:** conceptualization, methodology, supervision. **Pei Ho:** conceptualization, methodology, supervision; writing–review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author for researchers who meet the criteia for access to the data. The data are not publicly available due to privacy or ethical restrictions.

Transparency Statement

The lead author Pei Ho affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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