Title: Wound Healing and Healing Process in Patients with Diabetic Foot Ulcers: A Survival Analysis Study

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Authors' contributions

M.G.P. was responsible for the study design, data interpretation, writing-review, editing and project administration; M.V. was responsible for literature review, data acquisition, data interpretation and draft preparation; S. P. was involved in the literature review, data interpretation and critical revision of the paper; K.V., A.C., and M.J. D. were responsible for data interpretation and critical revision of the paper; L. M. was responsible for the statistical analysis and data interpretation. All authors read and agreed to the published version of the manuscript.

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Abstract

Aims: This study aimed to identify demographic, clinical, and psychological contributors to DFU healing and favorable healing process.

Methods: Patients with a chronic DFU were evaluated at baseline (T0; *n* = 153), two months later (T1; *n* = 108), and six months later (T2; *n* = 71). Patients were evaluated on health literacy, perceived stress, anxiety, depression, and illness perceptions. Cox proportional hazard models were built to analyze the predictors of DFU healing and favorable healing process (wound area reduction) including the assessment of time to achieve those outcomes.

Results: More than half of patients had their DFU healed (56.1%) or showed a favorable healing process (83.6%). Median time for healing was 112 days, while for favorable process was 30 days. Illness perceptions were the only predictor of wound healing. Female gender, adequate health literacy, and being the first DFU predicted a favorable healing process.

Conclusions: This is the first study showing that beliefs about DFU are significant predictors of DFU healing, and that health literacy is a significant predictor of a favorable healing process. Brief, comprehensive interventions should be implemented, at the treatment initial stage, in order to change misperceptions and to promote DFU literacy and better health outcomes.

Keywords: Diabetic foot ulcer; healing; favorable healing process; DFU perceptions; health literacy; survival analysis.

1. Introduction

Diabetic foot ulcers (DFUs) are a severe and common complication of diabetes mellitus (DM), with a lifetime incidence that ranges from 15 to 25% among individuals with diabetes [1]. As the prevalence of diabetes increases all over the world, the number of patients with a DFU is also growing [2], making it a global public health issue [3]. In fact, DFUs are a leading cause of hospitalization in patients with DM [4], often preceding infection, lower extremity amputation, or, ultimately, premature death [5-6].

A DFU is a multifactor condition, frequent in patients with poor long-term glycemic control, inadequate healthy lifestyle habits, and improper foot care. However, the most important risk factors for the occurrence of DFU are peripheral neuropathy (responsible for loss of protective sensation), peripheral arterial disease of the lower extremity vessels (causing poor blood circulation), and foot deformities [7-8].

Patients with DFU have an increased risk of morbidity and mortality globally, and most of them experience impaired health-related quality of life [9]. The regular hospital visits not only cause a high burden of patient-healthcare interaction, but also result in higher healthcare expenditures [10]. According to Hicks et al. [11], the treatment by a multidisciplinary care team for a single wound episode costs more than $20.000, an expense that can increase depending on the wound stage. Thus, considering that the DFU healing process is complex, long, involves substantial costs of care, and impacts patients' daily life, it is essential to better understand which demographic, clinical and psychological factors are associated with positive healing progress. In addition to DFU complete healing, analysis of the wound area reduction as a favorable healing process is often used, in clinical studies, with chronic conditions [12].

Healing of a DFU is a dynamic process that involves several dimensions, such as, diabetes complications, ulcer characteristics, and adherence to treatment [13]. Apart from diabetic neuropathy, peripheral vascular disease, and foot deformities, male sex, type 2 DM, older age, chronic hyperglycemia, previous history of foot ulceration, and longer duration of DM have also been identified as relevant risk factors for DFUs [4, 14-15]. Health literacy has also an important role in DFU healing since diabetic foot care routines require patients' adherence to a series of daily self-care procedures, often complex, such as glucose monitoring, medication and carbohydrate intake management. However, the contribution of inadequate health literacy to DFU occurrence and healing is not consistent [16].

Due to mobility limitations, impaired ability to perform daily life activities, dependency of others, fear of amputation, increased health care needs, chronic pain, and frustration, DFU has an adverse impact on patients' mental health [10, 17-18]. In addition, their poor prognosis and high rates of recurrence can contribute to psychological burden [17]. In fact, depression and anxiety symptoms are prevalent in patients with DFU compared with patients with diabetes without foot wounds [19]. Furthermore,

physiological and psychological stress, anxiety, and depression may influence the DFU prognosis and impair wound healing [16, 20-21].

The role of illness perception, i.e., patient's cognitive evaluation and individual understanding of his/her medical condition [22], has been emphasized in the literature as an important aspect in the management of chronic diseases such as DM [22-23], being positively associated with adherence to treatment and health behaviors (e.g., diet, foot care, taking medication) [24]. Knowledge about ulceration and control beliefs are predictors of foot care practices [25], thus having an important role in DM management and patients' survival [26].

Understanding the contribution of relevant demographic, clinical, and psychological variables to wound healing and favorable healing process, and knowing the expected time to heal, would help in both prevention and treatment of chronic DFUs. The main objective of this study was to identify demographic, clinical, and psychological contributors to DFU healing and favorable healing process, as well as to understand which is the most appropriate time (over a six-month period) for intervention in order to promote chronic DFU closure. Specifically, this study aimed to: i) analyze the differences between healed *versus* non-healed DFUs and favorable *versus* poor healing process, considering demographic, clinical, and psychological variables; ii) identify demographic, clinical, and psychological predictors to DFU healing and favorable healing process; and iii) examine the elapsed time between the baseline assessment and DFU healing and favorable healing process.

In line with previous literature, it is expected that female, younger patients, with adequate health literacy, shorter duration of DM and DFU, shorter DFU area, less psychological morbidity, and less threatening illness representations will predict DFU healing and favorable healing process, at a specific time point from baseline to six months later.

2. Subjects, materials and methods

2.1. Design and settings

This is a longitudinal study conducted with patients diagnosed with a chronic DFU who attended the first consultation of the multidisciplinary diabetic foot clinic of three major central hospitals, in northern Portugal. Patients were consecutively enrolled in the study. The inclusion criteria were: i) being 18 years or older; ii) having one or two

active(s) chronic DFU(s) (wounds with more than six weeks but less than 14 weeks [27]; in case of having two DFUs, the largest was chosen as the study ulcer); and iii) providing written informed consent. Exclusion criteria included: i) having more than two active DFUs; ii) the active DFU being a recurrence i.e. the time between the DFU healing and recurrence was less than six months; iii) having undergone a solid organ transplant; iv) undergoing hemodialysis; v) having an active oncology disease, psychosis, or dementia (recorded in the patient's medical records); and vi) receiving psychological support. Patients' diabetic foot was classified as neuropathic or neuroischemic. A neuropathic diabetic foot was defined as the loss of sensitivity to detect the monofilament in at least an examination location, and a neuroischemic foot was defined by the absence of distal pulses or through the transcutaneous oxygen pressure exam.

After providing written informed consent, assessment interviews were conducted face-to-face at baseline (T0; n = 153), two months later (T1; n = 108), and six months later (T2; n = 71). Assessment interviews were always scheduled for the same day of the patient's diabetic foot consultation and were conducted in a separate room reserved, in each hospital, for this study. All assessment measures were administered at T0, T1 and T2, except for the self-report measure of illness representations that was not included in the assessment interview at T1 or T2 if the patients' DFU was healed at that stage.

Regarding the study outcomes, wound healing was defined as the complete wound epithelization, while a favorable healing process was defined as a reduction of the wound area from baseline. A more detailed description of the study design, methodology, and ethical procedures is included in the protocol study publication [28].

2.2. Measures

2.2.1. Sociodemographic and Clinical Questionnaire. Sociodemographic information (e.g., age, gender, education) was collected directly from patients at the baseline assessment. Clinical data were collected by the patient's physician or nurse during the medical consultation at all the three assessment moments. This questionnaire addresses issues regarding the duration of diabetes mellitus, diabetic foot type, and DFU duration (number of weeks), among others. The wound size (extent) was calculated in squared centimeters, multiplying width and length measurements.

2.2.2. Medical Term Recognition Test (METER) [29-30]. This is a widely used measure to assess general health literacy levels in patients, consisting of a list of 40 medical words and 30 made-up words phonetically similar to medical terms. Patients

were asked to mark only those words that they recognized as real. The score is calculated as the sum of all marked correct words. Cronbach's alpha for the original total scale was .94. The Portuguese METER version includes two subscales, words and non-words, with a Cronbach's alpha of .92 and .83 respectively. In the present study, internal consistency coefficients were .89 for words and .84 for non-words showing good reliability [31]. Health literacy is considered adequate when scores for words and non-words are $\geq$ 35/40 and $\geq$ 18/30, respectively.

2.2.3. Perceived Stress Scale (PSS) [32-33]. This instrument is a brief scale that assesses the global level of perceived stress during the last month. The instrument contains 10 items answered on a five-point Likert scale, ranging from 0 ("Never") to 4 ("Very often"). Higher scores indicate higher levels of perceived stress. Cronbach's alpha for the original version was adequate (α = .78), and high in the Portuguese version (α = .87). In this study, PSS Cronbach's alpha was also high (α = .88).

2.2.4. Hospital Anxiety and Depression Scale (HADS) [34-35]. The scale consists of 14 items to assess depression (7 items) and anxiety (7 items) in the general medical population of patients during the last week. Each item is answered on a four-point Likert scale (0-3) using different answer possibilities. Higher scores indicate higher levels of anxiety and depression symptoms. In the original scale, Cronbach's alphas for the depression and anxiety subscales were .80 and .90 respectively. The Portuguese version presented high internal consistency for depression (α = .81) and adequate internal consistency for anxiety (α =. 76). In this study, Cronbach's alpha for depression was adequate (α = .77) and high (α = .81) for anxiety.

2.2.5. Illness Perception Questionnaire - Brief (IPQ-B) [36-37]. IPQ-B includes eight single item-subscales that assess three main dimensions of illness representations: cognitive dimension that includes identity, duration, personal control, treatment control, and consequences emotional dimension comprise concern and emotional responses; and comprehensibility dimension that consists of a single item/ subscale. In this study, patients were asked to answer questions regarding DFU representations [26]. Items are rated on a 0-10 visual analogue scale, and higher scores represent more threatening DFU representations. Given that each item represents a subscale, both the original and the Portuguese versions do not report internal consistency coefficients. However, Broadbent et al. [22] have suggested a global coefficient for the total scale (i.e., the sum of all

items). Thus, in this study, Cronbach's alpha for the total scale was .65, which is considered acceptable given the small number of items.

2.3. Data analysis

Descriptive statistics were used to characterize the sample, using means and standard deviations (M±SD) for the continuous variables, and frequencies and percentages (%) for the categorical variables. Comparisons between patients (dropouts *versus* those who completed the study; healed *versus* non-healed DFUs; and favorable *versus* poor healing process) were performed considering demographic, clinical, and psychological variables at baseline (T0). Comparisons between groups were conducted using independent sample *t*-tests and Mann-Whitney U tests for continuous variables (e.g., DFU duration, psychological variables), and chi-square tests (χ^2) for categorical variables (e.g., sex, health literacy). The complete DFU healing and favorable healing process rates were calculated for the three assessment moments.

Survival analysis was used to analyze the associations between demographic, clinical, and psychological variables, and the elapsed time since the baseline assessment (T0) until DFU healing. To this end, single-variable and multivariable Cox proportional hazard regression models [38] were built. Cox proportional hazard models were also tested to study the associations between the same variables and time until favorable healing process. The univariate and multivariate Cox's Proportional Hazards Models were used to estimate the Hazard Ratios and 95% CIs or probability values of some important demographic (gender, age, health literacy), clinical (DM duration, type of diabetic foot, DFU duration, first DFU, DFU area, HbA1c), and psychological variables (stress, psychological morbidity, DFU representations). Nevertheless, only covariables that were statistically significant ($p < .05$) in the univariate model were included in the multivariable model. Since DFU representations significantly predicted healing, a univariate Cox model was further conducted with the IPQ-B dimensions (cognitive, emotional, and comprehensibility). Finally, the Kaplan-Meier method was used to plot survival curves.

When analyzing the elapsed time since the baseline assessment until DFU healing, 63 patients did not show a complete wound epithelization before the end of the study. Those patients contributed with right-censored observations. In addition, to right censoring, interval censoring was also found in the analyses of the outcome variable "time to favorable healing process". This type of censorship occurs when it is not known

the exact time that an event occurs, but only the interval in which it occurred. Therefore, for the analyses, a proportional hazards model was used for interval-censored data, proposed by Pan [39], which is implemented in the R package icenReg.

All analyses employed the SPSS statistics, v. 26.0 (IBM Corp., Armonk, New York) and the RStudio, R version 4.1.2 (R Core Team, Vienna, Austria).

3. Results

3.1. Sample characteristics

The demographic, clinical, and psychological characteristics of the 153 patients diagnosed with DFUs, assessed at baseline (T0), are presented in Table 1. Most participants were men (n = 124, 81%), with a mean age of 64 years old (SD = 10.52). Comparing patients with healed *versus* non-healed DFU(s) over the follow-up period, at the baseline, those with a healed DFU showed a higher level of education (χ^2 = 6.91, p = .032, phi = .24), and reported less threatening DFU representations globally (t = 4.60, p < .001), as well as cognitive (t = 4.23, p < .001) and emotional (t = 3.22, p = .002) representations. Patients with a good healing process were younger (t = 2.41, p = .017), and also expressed less threatening DFU representations globally (t = 3.76 p < .001), as well as cognitive (t = 2.81, p = .008) and emotional (t = 3.30, p = .002) DFU representations, but reported more anxiety (t = - 2.39, p = .022) than those with a poor healing process (Table 1).

Insert Table 1

After the baseline assessment (T0), 108 patients were followed for two months (T1) and 71 patients were followed for more six months (T2). The patients' dropout rate from T0 to T1 was 5% (eight patients), and from T0 to T2 was 7% (11 patients). Patients that dropout between T0 and T1 did not differ in terms of demographic, clinical and psychological characteristics, while those that dropped out during the six months follow-up only differed in terms of the duration of DM, with those that completed the study presenting shorter duration of DM compared with those that withdraw their participation (U = 1109.00, p = .013) (Figure 1).

Insert Figure 1

3.2. DFU healing and healing process

Overall rates were calculated based on the cumulative incidence of DFU healing and the healing process over the follow-up period. Over the course of the study, 69 patients (56.1%) had their DFU healed, and 102 patients (83.6%) obtained a favorable healing process. The results indicated higher rates of DFU healing (43.5%) and of favorable healing process (84.0%) between T0 and T1 assessment moments (Table 2).

Insert Table 2

Based on the Kaplan-Meier estimates, the median healing time was 112 days with a 95% CI (91, 172) (Figure 2), while the median time for a favorable healing process was 30 days (Figure 3).

Insert Figure 2 and Figure 3

3.3. Predictors of DFU healing

In the univariate Cox model, the duration of the DFU (p = .02), i.e., number of weeks after the wound emergence, the area of the DFU at T1 (p = .03) and T2 (p = .01), and illness representations at baseline (p < .005) were statistically significant. Only illness representations at T0 (p = .03) remained statistically significant in the multivariate Cox model (Table 3). In order to understand which illness representations dimension better predicted the DFU healing, a univariate Cox model was conducted considering the IPQ-B dimensions, showing that cognitive representations at T0 (p = .001) and emotional representations at T1 (p = .009), independently, predicted wound healing (Table 4).

Insert Table 3 and Table 4

3.4. Predictors of a favorable DFU healing process

In the univariate Cox analysis, gender (p = .005), health literacy (p < .001), and being the first DFU in the patient's clinical history (p < .001) were associated with a

favorable healing process. The multivariate regression analysis indicated that all the previous variables remained statistically significant ($p < .001$) (Table 3).

4. Discussion

This study analyzed the role of demographic, clinical, and psychological variables in predicting DFU healing and favorable healing process, and analyzed time to positive healing outcomes in patients with chronic DFUs, using survival analysis.

Approximately half of the sample achieved the "healing status" (56.1%), and more than half (84.0%) had a favorable healing process during the study period. However, the majority of those improvements occurred within the first two months (between T0 and T1). Moreover, this study found a median of 112 days (~3 months) to achieve healing, and 30 days for a favorable healing process. Similarly, in a study conducted with 31 patients [40], the authors found that the average time of healing in patients with neuropathic DFUs was 77.7 days, while in patients with neurosichemic DFUs was 123.4 days. However, compared with previous research showing that, with adequate therapy - surgical debridement, off-loading pressure, attention to infection, and (if necessary), vascular reconstruction - approximately 77% of DFUs heals within 1 year [3,41], our results are better than expected. Recently, in a study conducted with 140 patients, the authors found that only 18.6% of DFUs had healed at the four weeks of follow-up; 50.7% at the 3-month follow-up; and 77.9% at 1-year [41]. Although Patry´s et al. [42] study sample characteristics are similar to the sample analyzed in this study, it is difficult to compare healing rates between studies due to the wide variation in ulcer measurements, definitions, and characteristics.

Furthermore, it is important to highlight that the first two months were the key period to reach clinical results (43.5% for healing and 84.1% for obtaining a favorable healing process). This result emphasizes the importance of including an educational and psychological intervention in this key period, as a complement to the medical standard treatment, to boost better clinical outcomes.

Of the 153 patients evaluated at the baseline, 54 did not reach the healing state within six months, and 20 showed a poor healing process. Overall, these were male patients, less educated, with inadequate general health literacy, but also with more threatening wound representations than those who have a healed DFU or a favorable healing process. The identification of patients' characteristics may be useful in identifying patients at higher

risk of developing hard-to-heal wounds, who may need early intervention to prevent long lasting ulcers.

Although, initially, the DFU duration, DFU area (over six months) and the DFU representations (at baseline) were significant predictors of healing, in the multivariate model only DFU representations remained a healing predictor, specifically cognitive representations at baseline and emotional representations two months later. This finding is very important for the development of future studies focusing on the role of psychological factors during the DFU healing process and for clinical practice as well. In fact, the results of the present study inform healthcare professionals of the importance to assess patients' representations about their DFU when they begin treatment since they were found to be the best predictor of wound healing compared to other relevant demographic or clinical factors. Furthermore, illness (e.g. DFU) beliefs are potentially modifiable psychological factors that may be changed and influence illness-related outcomes [43]. Although there are few studies focusing on changing illness perceptions, research has shown its efficacy regarding the increase of health-related behaviors in patients diagnosed with diabetes, promoting a sense of empowerment to manage their condition and its treatment [44], as well as decreasing threatening illness perceptions [45].

In this study, favorable healing process predictors included being female, with adequate health literacy, and a first DFU. Therefore, health professionals should be cautious and intensify the management of DFUs, especially with male patients, with lower levels of health literacy, and with recurrent ulcers. Discussions about the role of gender in the DFU prevention, development, and healing are extensive, but not consistent. Yet, being a male has been identified as a risk factor for subsequent foot complications in patients with type 2 DM [46]. Also, given that health literacy plays a significant role as a predictor of diabetes knowledge, self-care behaviors, self-efficacy, glycemic control, medication adherence, and communication with doctors [47-48], it makes sense that it significantly predicts a favorable process for DFU healing. Even though the prognosis for all possible DFU outcomes is better in early ulcers than in recurrent ulcers, 65% of DFU patients may have recurrent ulcers within five years of healing [3], which suggests that most DFU patients that health professionals care present a long history of re-ulceration.

4.1. Limitations and Future Studies

This study has some limitations that must be acknowledged, such as the large imbalance between male and female participants, shorter follow-up period, and the high dropout rate at follow-up, over time. Future research should replicate the predictive model resulting from this study, using a more sex-balanced sample, larger follow-up time periods and employing strategies to prevent patients' dropouts. This study was carried out in three major hospitals in Northern Portugal, which also may limit the generalizability of findings.

Analysis of health literacy should also be included in future studies with samples of patients with diabetes and DFU, as it is essential to understand whether patients can access, comprehend, and apply information about their health. Increasing general health literacy, promoting patient empowerment and co-responsibility for their health care are priority intervention targets to increase patients' quality of life and well-being, reduce health costs, increase efficiency in the use of health care services and reduce disparities [49]. Finally, there is an urgent need for studies to assess the role of health literacy on clinical outcomes in order to tailor interventions to the patient's health literacy levels and needs. Intervention should also address the individual's DFU representations, at the beginning of treatment, in order to address inaccurate perceptions and include both the patient and family caregiver since health beliefs, in chronic disease, are often shared by the family or the dyad [50].

4.2. Conclusion

This is the first study showing that beliefs about DFU are significant predictors of DFU healing, and that health literacy is a significant predictor of a favorable healing process. According to our results, the most appropriate period to intervene is at the beginning of the DFU management when patients arrive at the diabetic foot clinic and during the first two months. Therefore, brief holistic and comprehensive interventions should be planned and implemented through the treatment initial stage in order to change misperceptions and promote DFU literacy and better outcomes.

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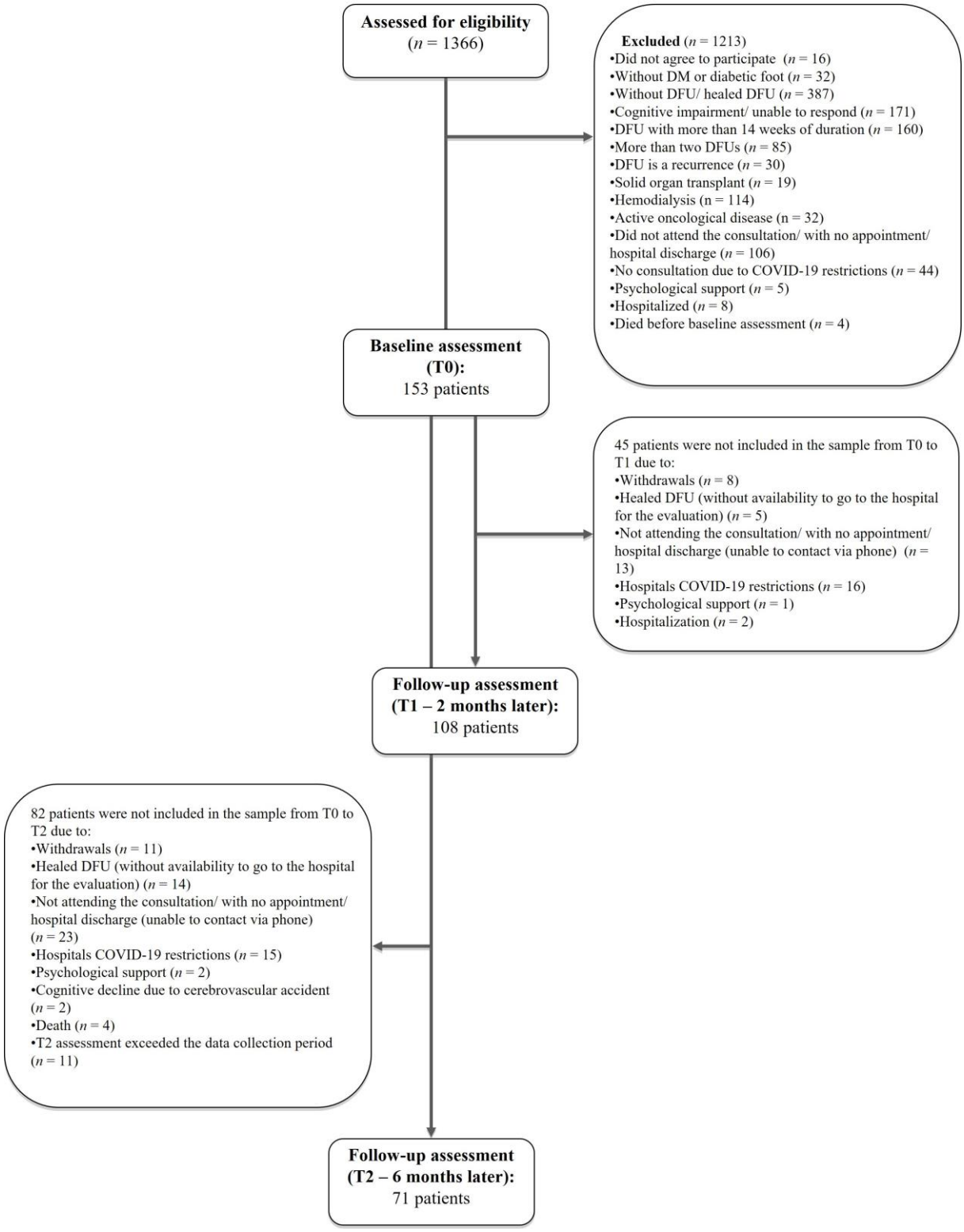

Figure 1. Flowchart of data collection.

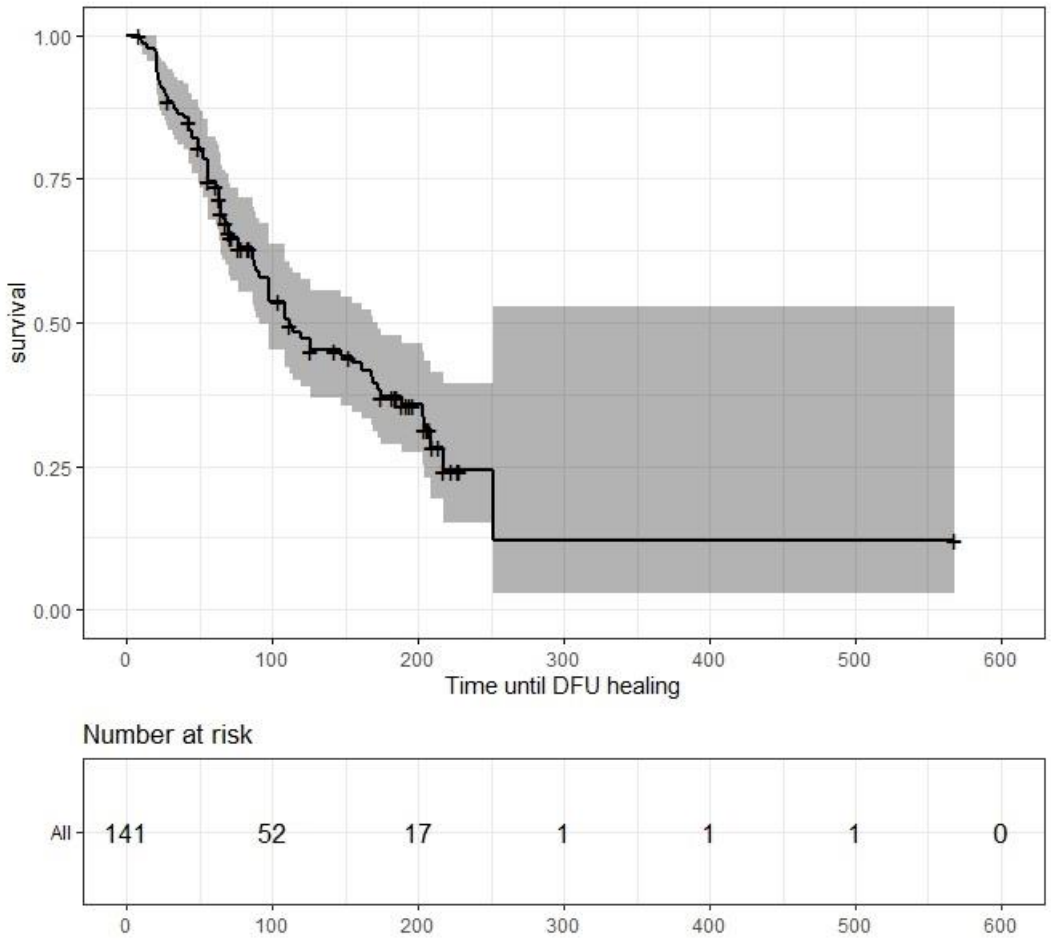

Figure 2. Kaplan-Meier estimate of survival for time since baseline assessment until DFU healing.

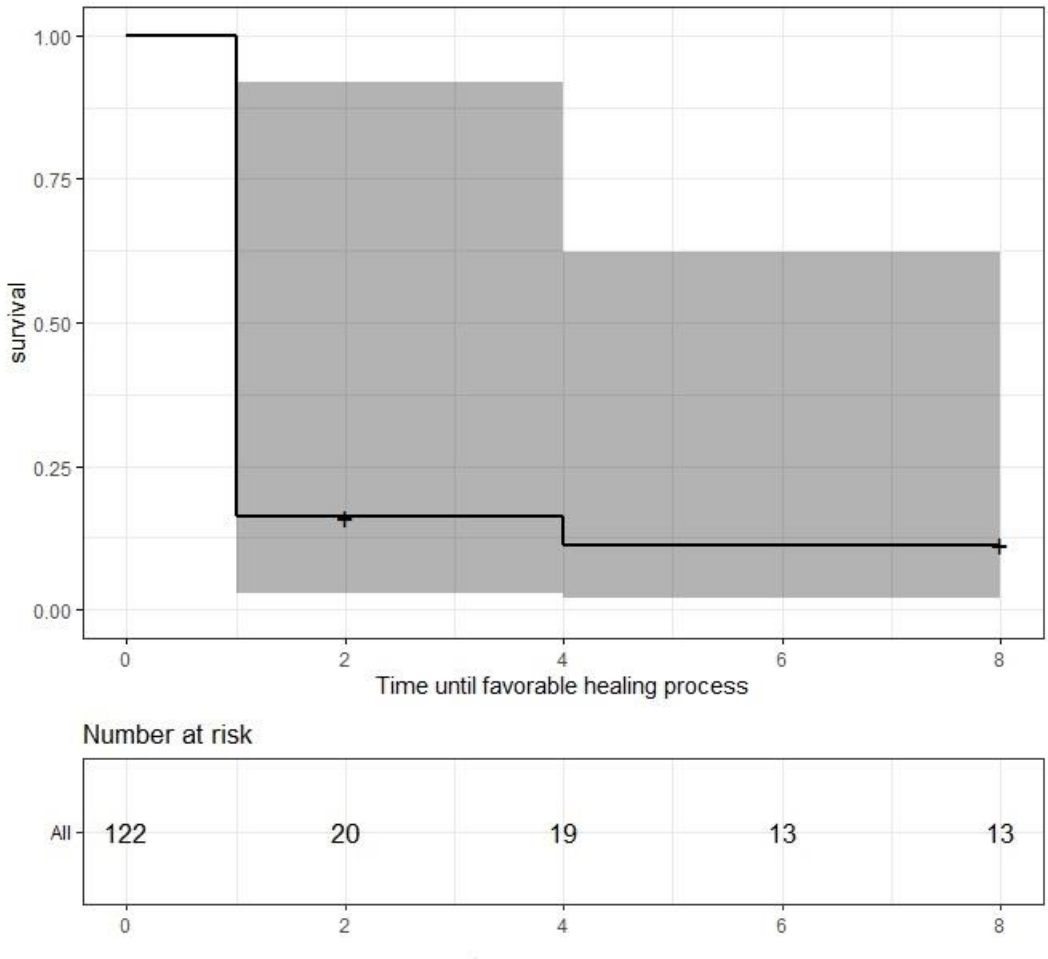

Figure 3. Estimate of survival for time since baseline assessment until favorable DFU healing process.

Table 1

Sample characteristics.

	Total (n = 153)	Healed (n = 69)	Non-healed (n = 54)	Favorable healing process (n = 102)	Poor healing process (n = 20)
Demographic variables					
Sex					
Female	29.00 (19.00)	10.00 (14.5)	8.00 (14.80)	16.00 (15.70)	2.00 (10.00)
Male	124.00 (81.00)	59.00 (85.5)	46.00 (85.20)	86.00 (84.30)	18.00 (90.00)
Age (years)	64.42 ± 10.52	63.84 ± 9.66	64.22 ± 11.42	62.85 ± 10.04	68.80 ± 10.29
(min. – max.)	41.00 – 87.00	45.00 – 82.00	41.00 – 87.00	41.00 – 84.00	53.00 – 87.00
≤ 60	59.00 (38.60)	28.00 (40.60)	22.00 (40.70)	45.00 (44.10)	5.00 (25.00)
> 60	94.00 (61.40)	41.00 (59.40)	32.00 (59.30)	57.00 (55.90)	15.00 (75.00)
Residence					
Rural	92.00 (60.10)	38.00 (55.10)	34.00 (63.00)	59.00 (57.80)	12.00 (60.00)
Urban	61.00 (39.90)	31.00 (44.90)	20.00 (37.00)	43.00 (42.20)	8.00 (40.00)
Marital status					
Single	13.00 (8.50)	5.00 (7.20)	5.00 (9.30)	9.00 (8.80)	1.00 (5.00)
Married	112.00 (73.20)	51.00 (73.90)	42.00 (77.70)	74.00 (72.50)	18.00 (90.00)
Divorced/ widowed	28.00 (18.30)	13.00 (18.80)	7.00 (13.00)	19.00 (18.60)	1.00 (5.00)
Education					
≤ Primary	92.00 (60.10)	34.00 (49.30)	36.00 (66.70)	53.00 (52.00)	16.00 (80.00)
≤ Secondary	54.00 (35.30)	29.00 (42.00)	18.00 (33.30)	43.00 (42.20)	4.00 (20.00)
≤ University	7.00 (4.60)	6.00 (8.70)	0.00 (0.00)	6.00 (5.90)	0.00 (0.00)
Adequate health literacy					
Yes	32.00 (20.90)	18.00 (26.10)	13.00 (24.10)	24.00 (23.50)	7.00 (35.00)
No	120.00 (78.40)	51.00 (73.90)	41.00 (75.90)	78.00 (76.50)	13.00 (65.00)
Clinical variables (T0)					
Diabetes duration (years)	18.40 (10.49)	17.36 (10.80)	19.94 (11.00)	17.78 (10.51)	22.50 (12.39)
(min. – max.)	0.00 – 51.00	0.00 – 51.00	3.00 – 51.00	0.00 – 51.00	3.00 – 51.00
HbA1c	8.15 (1.81)	8.38 (1.93)	8.12 (1.77)	8.28 (1.96)	8.24 (1.28)
(min. – max.)	5.00 – 14.00	5.40 – 13.50	5.30 – 14.00	5.30 – 14.00	5.80 – 10.20
Type of diabetic foot					
Neuropathic	84.00 (54.90)	43.00 (62.30)	29.00 (53.70)	63.00 (61.80)	9.00 (45.00)
Neuroischemic	69.00 (45.10)	26.00 (37.70)	25.00 (46.30)	39.00 (38.20)	11.00 (55.00)
DFU duration (weeks)	8.60 (2.62)	8.41 (2.44)	8.65 (2.66)	8.46 (2.51)	8.60 (2.62)
(min. – max.)	6.00 – 14.00	6.00 – 14.00	6.00 – 14.00	6.00 – 14.00	6.00 – 14.00
DFU area	4.21 (11.48)	2.71 (5.84)	6.65 (17.28)	4.02 (10.17)	6.68 (20.57)
(min. – max.)	0.01 – 90.00	0.01 – 42.00	0.04 – 90.00	0.01 – 84.00	0.04 – 90.00

First DFU in clinical history					
Yes	57.00 (37.30)	26.00 (37.70)	20.00 (37.00)	42.00 (41.20)	4.00 (20.00)
No	96.00 (62.70)	43.00 (62.30)	34.00 (63.00)	60.00 (58.80)	16.00 (80.00)
Psychological variables (T0)					
Anxiety	5.49 ± 4.75	5.93 ± 4.92	5.13 ± 4.88	5.99 ± 5.05	3.75 ± 3.55
Depression	4.85 ± 4.19	4.94 ± 4.67	5.07 ± 4.00	5.21 ± 4.62	4.20 ± 2.69
Stress	12.67 ± 8.92	13.13 ± 9.56	12.57 ± 8.28	13.20 ± 9.22	11.50 ± 7.98
Illness represent.	33.97 ± 13.01	29.39 ± 14.52	39.48 ± 9.76	32.26 ± 13.95	40.70 ± 7.91
Cognitive rep.	18.94 ± 8.15	16.17 ± 8.82	22.20 ± 6.26	18.02 ± 8.56	22.35 ± 5.76
Emotional rep.	12.36 ± 6.09	10.74 ± 6.94	14.15 ± 4.78	11.62 ± 6.56	15.00 ± 3.54
Comprehensibility	2.67 ± 2.95	2.48 + 3.12	3.13 ± 2.88	2.63 ± 3.11	3.35 ± 2.58
			T0	**T1**	**T2**
			(*n* = 153)	**(*n* = 108)**	**(*n* = 70)**
Psychological variables during the study (total sample)					
Anxiety			5.49 ± 4.75	4.08 ± 4.13	4.82 ± 4.32
Depression			4.85 ± 4.19	3.83 ± 3.75	5.00 ± 3.70
Stress			12.67 ± 8.92	10.82 ± 8.05	11.06 ± 7.42
DFU representations			33.97 ± 13.01	31.89 ± 14.40	36.88 ± 11.73
Cognitive rep.			18.94 ± 8.15	17.25 ± 8.81	19.33 ± 7.63
Emotional rep.			12.36 ± 6.09	11.77 ± 6.52	14.71 ± 5.61
Comprehensibility			2.67 ± 2.95	2.88 ± 3.17	2.83 ± 3.44

Table 2

Rates for DFU complete healing and for favorable healing process between T0, T1, and T2 assessment moments.

Outcome variables	Between T0 and T1	Between T1 and T2	During the study
DFU complete healing[a]	47 (43.52%)	24 (33.80%)	69 (56.10%)
Favorable healing process[b]	89 (83.96%)	21 (39.62%)	102 (83.61%)

Note. [a]108 patients were evaluated in both T0 and T1; 71 patients were evaluated at T0, T1 and T2; 123 patients were evaluated at T0 and T1, T0, T1 and T2, or T1 and T2; [b]108 patients were evaluated in both T0 and T1; 53 patients were evaluated at T0, T1 and T2; 122 patients were evaluated at T0 and T1, T0, T1 and T2, or T1 and T2.

Table 3

Univariate and multivariate analysis of Cox Models for DFU healing and favorable healing process.

	Healing			Favorable Healing Process		
	n	Univariate *HR* (95% CI)	Multivariate *HR* (95% CI)	*n*	Univariate *HR*	Multivariate *HR*
Age (years)	140	0.99 (0.97-1.01)		108	1.01	
Sex	140			108		
Male		1			1	1
Female		1.36 (0.76-2.43)			6.00 **	7.48 **
Health literacy	139			108		
No		1			1	1
Yes		0.89 (0.53-1.49)			6.38 **	7.42 **
DM duration (years)	137	0.99 (0.97-1.01)		105	0.99	
Diabetic foot type	140			108		
Neuroischemic		1			1	
Neuropathic		1.42 (0.90-2.24)			1.03	
DFU duration (weeks)	140	0.90 (0.82-0.99)*		108	1.10	
First DFU	140			108		
No		1			1	1
Yes		1.15 (0.73-1.83)			6.82 **	7.71 **
DFU area						
T0	140	0.97 (0.93-1.01)		108	1.03	
T1	102	0.63 (0.42-0.96)*	0.71 (0.47-1.05)	93	0.94	
T2	65	0.00 (0.00-0.21)*		60	0.91	
HbA1c (at baseline)	138	1.04 (0.92-1.17)		106	0.99	
Perceived Stress						
T0	140	1.01 (0.99-1.04)		108	0.98	
T1	106	0.99 (0.96-1.03)		96	0.99	
T2	70	1.01 (0.97-1.05)		65	0.99	
Psychological morbidity						
T0	140	1.01 (0.99-1.04)		108	0.97	
T1	106	1.00 (0.96-1.04)		96	0.99	
T2	70	1.00 (0.94-1.07)		65	0.97	
Illness representations						
T0	139	0.98 (0.96-1.00)*	0.98 (0.96-0.99)*	108	.99	
T1	57	0.98 (0.95-1.00)		55	0.98	
T2	24	0.87 (0.71-1.07)		20	0.98	

Note. HR = Hazard ratio; CI = Confidence intervals; *$p < .05$; **$p < .001$.

Table 4

Univariate analysis of Cox Model for DFU healing with illness representations dimensions.

		Healing
	n	Univariate *HR* (95% CI)
Illness cognitive representations		
T0	139	0.95 (0.93-0.98) **
T1	57	0.96 (0.92-1.01)
T2	24	0.79 (0.53-1.19)
Illness emotional representations		
T0	139	0.97 (0.94-1.00)
T1	57	0.92 (0.86-0.98) *
T2	24	0.88 (0.66-1.19)
Illness comprehensibility		
T0	139	0.96 (0.88-1.04)
T1	57	1.07 (0.93-1.22)
T2	24	0.39 (0.02-7.95)

Note. HR = Hazard ratio; CI = Confidence intervals; *p < .05; **p < .005.