Negative determinants of diabetic foot ulcer healing: 6-month follow-up of a large multicentre cohort

P8.03

WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

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Background

Knowing the determinants that negatively influence diabetic foot ulcer (DFU) healing is crucial for improving DFU care. First, although many studies have identified such determinants, it is unclear to what extent they have an impact on prognosis, while the prognosis is important information both for patients and clinicians. Second, knowing the negative determinants allows for risk-adjustment of DFU healing probability in a scenario where healing probability between diabetic foot clinics (DFCs) is benchmarked. Periodical audits followed by benchmarking have been shown to lead to quality improvements (QI) in various care settings.

Aims of the study

We identified negative determinants of DFU healing in DFCs participating in a QI initiative with periodical audits and feedback (anonymous benchmarking). The aim was twofold:

1. To obtain an easy-to-use prognostic model that allows patients and clinicians to know the expected DFU healing probability as a function of follow-up time and disease severity.
2. To obtain a model and methods that allow intuitive benchmarking of risk-adjusted DFC-level DFU healing probabilities.

Study design

Belgian recognized DFCs treat and follow patients with diabetic foot ulcers (DFU). They participate in a nation-wide initiative for quality of care monitoring. Patient-level data with regard to medical history, diagnosis, treatment and outcome are routinely collected (1).

For this study, we used data of the 2011 audit, in which 32 DFCs followed 1,528 patients with a DFU of Wagner grade 2 or more. In case of multiple DFUs, only the DFU with the highest expected impact on prognosis was included ("index" DFU). The follow-up lasted six months or until DFU healing, major amputation or death, whichever occurred first.

Cumulative incidence functions were studied and Cox proportional hazards regression was used to identify determinants of DFU healing by using a forward selection method, taking into account competing risks (major amputation and death), missingness of covariates and clustering of outcomes in DFCs. Predictions and frailties (DFC-level random effects) of DFU healing probability were obtained.

Analyses were done in R statistical software (version 2.15.2) using the packages `survival`, `frailtypack` and `Amelia II`.

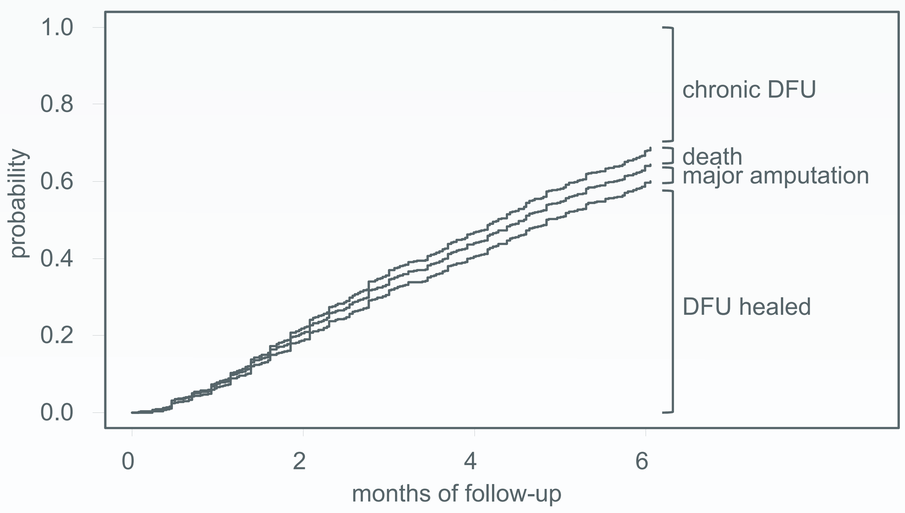
Results

Patient and DFU characteristics at presentation

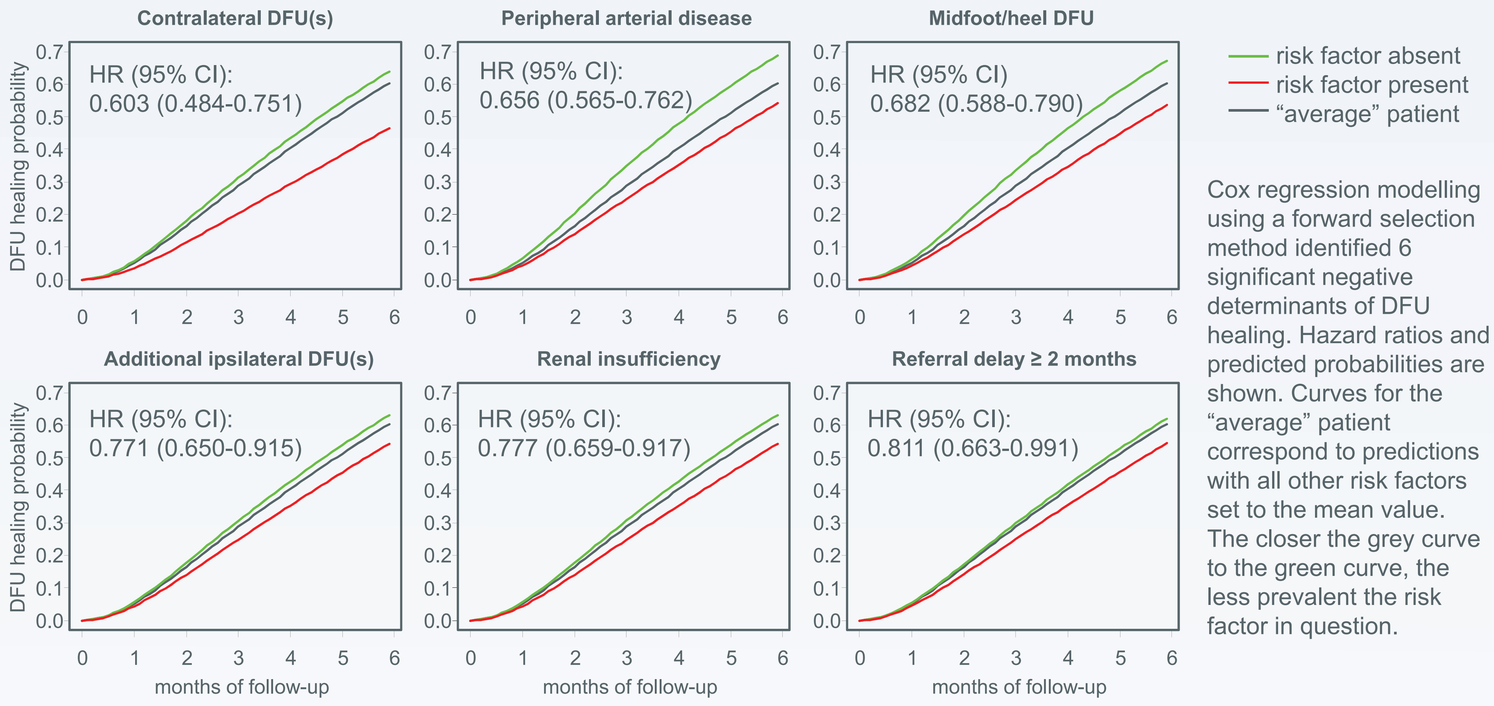
Age, years (N = 1,528)	68.5 ± 11.9
Diabetes duration, years (N = 1,202)	16.2 ± 11.7
Men (N = 1,528)	1042 (68.2)
Diabetes type, T1/T2/other (N = 1,501)	133/1,346/22 (8.9/89.7/1.5)
Smoking, never/quit/current (N = 1,443)	729/452/262 (50.5/31.3/18.2)
Cardiovascular history[a] (N = 1,522)	558 (36.7)
Renal insufficiency[b] (N = 1,524)	470 (30.8)
End-stage renal disease[c] (N = 1,508)	128 (8.5)
History of lower-limb revascularization (N = 1,515)	467 (30.8)
History of DFU (N = 1,515)	952 (62.8)
History of minor amputation[d] (N = 1,516)	401 (26.5)
History of major amputation[d] (N = 1,492)	59 (4.0)
Foot/DFU characteristics	
Wagner grade, 2/3/4-5 (N = 1,528)	836/476/216 (54.7/31.2/14.1)
Location: plantar (N = 1,514)	801 (52.9)
Location: midfoot or heel (N = 1,514)	757 (50.0)
Surface area ≥ 3 cm² (N = 1,476)	347 (23.5)
Depth: probing to bone (N = 1,511)	479 (31.7)
Loss of protective sensation (N = 1,499)	1,286 (85.8)
Peripheral arterial disease[e] (N = 1,499)	860 (57.4)
Deep or systemic infection (N = 1,513)	639 (42.2)
Not referred by healthcare professional (N = 1,489)	327 (22.0)
Referral/treatment delay ≥ 2 months (N = 1,381)	292 (21.1)
Additional ipsilateral DFU(s) (N = 1,477)	440 (29.8)
Contralateral DFU(s) (N = 1,461)	277 (19.0)

Data are presented as mean (standard deviation) or as frequency (percentage).
[a] Defined as history of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, stroke or transient ischemic attack
[b] Defined as serum creatinine >1.5 mg/dL or MDRD eGFR <50 mL/min/1.73 m²
[c] Defined as renal transplantation or peritoneal or hemodialysis
[d] Minor amputation was defined as amputation below the ankle. Any amputation above that level was a major amputation.
[e] Defined as absence of pedal pulses and/or signs of critical limb ischemia

Patient and DFU outcomes during 6-month follow-up



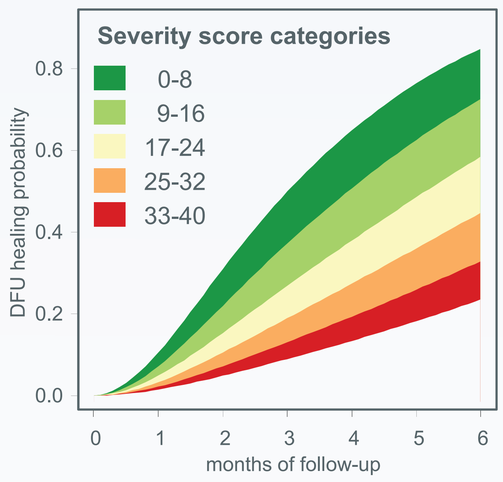
Determinants of DFU healing: results of the multivariate Cox regression model

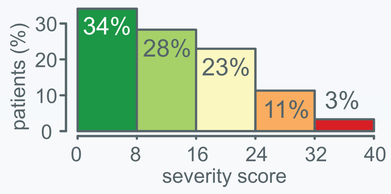


Cox regression modelling using a forward selection method identified 6 significant negative determinants of DFU healing. Hazard ratios and predicted probabilities are shown. Curves for the "average" patient correspond to predictions with all other risk factors set to the mean value. The closer the grey curve to the green curve, the less prevalent the risk factor in question.

Application 1: prognostic model of DFU healing as a function of disease severity

	Model coefficients	Proposed severity score
Contralateral DFU(s)	-0.506	10
Peripheral arterial disease	-0.421	8
Midfoot/heel DFU	-0.383	8
Additional ipsilateral DFU(s)	-0.260	5
Renal insufficiency	-0.252	5
Referral/treatment delay ≥ 2 months	-0.210	4



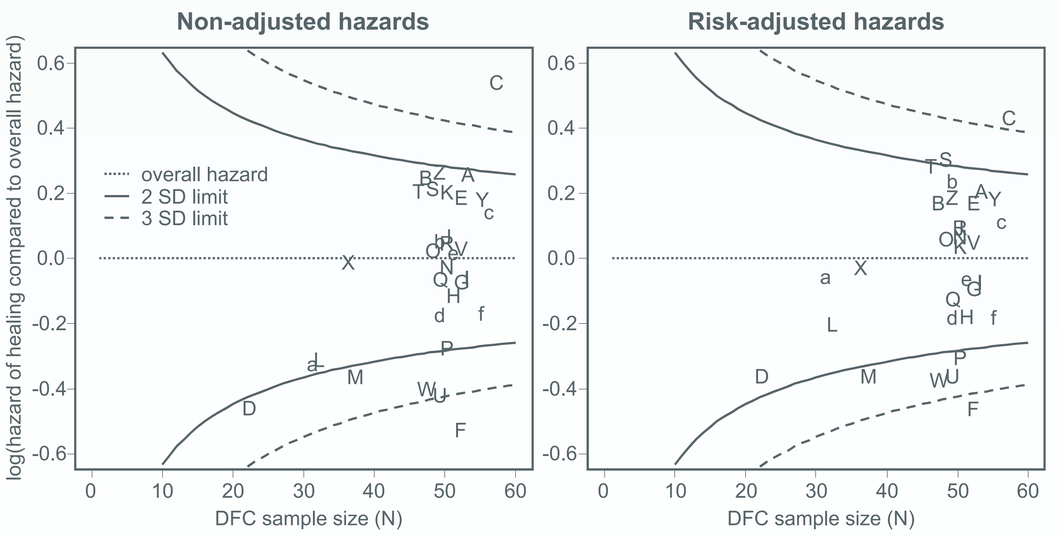


Expected % of DFUs healed

Severity score \ Months of follow-up	1	2	3	4	5	6
0	11	31	49	65	76	85
8	7	22	37	51	63	73
16	5	15	27	38	49	59
24	3	11	19	27	36	45
32	2	7	13	19	26	33
40	1	5	9	13	18	24

Left: model coefficients and the derived severity score (SS), which is an approximation of the weight of each parameter in the model (coefficient multiplied by -20). At presentation, each patient can easily be scored for the presence of these 6 risk factors. The obtained SS can range from 0 (no risk factors present) to 40 (all risk factors present). **Middle:** predicted cumulative incidence functions of DFU healing probability according to 5 categories of the SS. **Right top:** higher SS were increasingly less prevalent in the 2011 dataset. **Right bottom:** matrix showing the expected DFU healing probability at 1-6 months as a function of SS. Color codes show situations in which less than 25% (red), between 25 and 50% (orange) and more than 50% (green) of DFUs are expected to have healed.

Application 2: benchmarking of risk-adjusted DFC-level DFU healing probabilities



These funnel plots show the log(hazard) of each of the 32 DFCs, compared to the overall log(hazard), arbitrarily set at 0. Each DFC was awarded an upper or lowercase letter. The impact of risk-adjustment is large for some DFCs (e.g. DFC "a"). The log(hazard) is expressed as a function of DFC sample size (most DFCs sampled ~50 patients), which correlates with the precision with which the hazard was determined. The confidence limits corresponding to 2 and 3 standard deviations (SD) are shown. DFCs "M", "W", "U", "P" and "F" have a log(hazard) below the 2 SD limit, indicating higher than normal variation. An investigation into the possible causes is warranted.

Conclusions

We obtained a model of the 6-month healing probability of DFUs of Wagner grade 2 or more. The model includes 6 risk factors whose presence can be scored relatively easily by clinicians. After further validation (see Limitations), the model can be made available for nation-wide use in the evaluation of care of severe DFUs.

As a prognostic model, DFCs can benchmark the evolution of individual DFUs to the expected healing probability of DFUs of similar severity. This decision-support tool can aid DFCs in exploring alternative treatment strategies for individual patients.

As a risk-adjustment model, it allows valid benchmarking of DFC-level healing probabilities. After identifying outliers with low healing probability, the DFCs in question should be encouraged to evaluate their care and propose/implement QI measures. Regular meetings of DFCs and exchange of best-practices are important prerequisites to facilitate this QI process.

Limitations and avenues for future research

- The model awaits formal validation by applying it to new data.
- This specific model will likely only be valid or well-calibrated for DFUs of Wagner grade 2 or more and for DFUs treated within the context of the Belgian recognized DFCs. Nevertheless, many of the risk factors have also been identified in the Eurodiale study (2), thus supporting the external validity of the current model.

Key references

(1) Doggen K, Van Acker K, Beele H, Dumont I, Félix P, Lauwers P, Lavens A, Matricali GA, Randon C, Weber E, Van Casteren V, Nobels F; Initiative for Quality Improvement and Epidemiology in Diabetic Foot Clinics (IQED-Foot) Study Group. Implementation of a quality improvement initiative in Belgian diabetic foot clinics: feasibility and initial results. Diabetes Metab Res Rev 30 (2014): 435-43.
(2) 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. 29 (2013): 377-83.

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