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Dynamic Prediction of Time to Wound Healing at Routine Wound Care Visits

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Objective: Having a wound decreases patients' quality of life and brings uncertainty, especially if the wound does not show a healing tendency. The objective of this study was to develop and validate a model to dynamically predict time to wound healing at subsequent routine wound care visits.
Approach: A dynamic prediction model was developed in a cohort of wounds treated by nurse practitioners between 2017 and 2022. Potential predictors were selected based on literature, expert opinion, and availability in the routine care setting. To assess performance for future wound care visits, the model was validated in a new cohort of wounds visited in early 2023. Reporting followed TRIPOD guidelines.
Results: We analyzed data from 92,098 visits, corresponding to 14,248 wounds and 7,221 patients. At external validation, discriminative performance of our developed model was comparable with internal validation (concordance statistic = 0.70 [95% confidence interval 0.69, 0.71]), and the model remained well calibrated. Strong predictors were wound-level characteristics and indicators of the healing process so far (e.g., wound surface area).
Innovation: Going beyond previous prediction studies in the field, the developed model dynamically predicts the remaining time to wound healing for many wound types at subsequent wound care visits, in line with the dynamic nature of wound care. In addition, the model was externally validated and showed stable performance.
Conclusion: The developed model can potentially contribute to patient satisfaction and reduce uncertainty around wound healing times when implemented in practice. When the predicted time of wound healing remains high, practitioners can consider adapting their wound management.

Keywords: Chronic Wounds, Nursing, Wound Closure, Trauma

INTRODUCTION

Clinical problem addressed

Having a wound decreases patients' quality of life[1] and brings a lot of uncertainty, especially if the wound does not show a healing tendency. Most wounds heal without complications and go through four successive phases: hemostasis, inflammation, proliferation, and remodeling.[2] Numerous factors can interfere with this process, resulting in the formation of a hard-to-heal or chronic wound. A chronic wound is defined as a wound that

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does not follow an orderly and timely reparative process to produce anatomical and functional integrity within a period of 3 months.[3] As the population ages and the prevalence of chronic diseases increases in many regions of the world, the number of wounds requiring specialized, long-term care is growing. A reliable prognosis of the remaining time to wound healing could help reduce uncertainty for patients and help with planning and care management.[4]

Background

Within wound care research, the number of studies that investigate artificial intelligence methodologies for the prediction, diagnosis, and management of chronic wounds has strongly increased in recent years.[5] Various prediction models have been developed to differentiate between probable uncomplicated wound healing and complicated wound healing based on clinical characteristics. Most models were aimed at wounds of a specific etiology such as burns,[6] diabetes,[7–12] venous ulcers,[9,13,14] and wounds occurring after trauma or surgery.[15] Recently, a model was developed that incorporates genetic information in addition to clinical variables for the prediction of diabetic foot ulcer healing.[16]

Three models have been developed for a more general range of wound etiologies on large, multicenter datasets in the United States.[17–19] These included classification models such as (penalized) logistic regression and regression trees to predict the probability of a wound being healed within a certain time frame (e.g., 4, 12, or 15 weeks) after the initiation of treatment. The models showed a reasonable-to-good apparent discriminative performance (area under the curve ranging from 0.71 to 0.85), where wound-level characteristics such as area, depth, location, and etiology were found to contribute most to predictive performance.[17,18] None of these studies explicitly reported on model calibration, nor did they include an external validation, and they did not account for loss to follow-up or death before the outcome could be observed. Furthermore, two of the models did not consider the dynamic nature of wound care. A recent review of wound risk prediction models concluded that there is a lack of validated wound risk prediction models and implementation remains difficult.[20]

Recently, systems for electronic medical records (EMRs) have been developed and implemented specifically for use by wound care organizations,[21] including systems in the Netherlands.[22] In such systems, patient characteristics and wound observations are recorded during routine wound care visits by nurse practitioners. Many of these characteristics are important for wound risk prediction.[18] Besides their role in treatment planning and management, the use of such systems provides real-world data on healing wounds in large cohorts, enabling the development of high-quality dynamic wound risk prediction models for routine care.

Objective

The objective of this study was to develop and validate a dynamic prediction model for time to wound healing at routine wound care visits. We specified three model aims:

(1) The model should include characteristics that are currently recorded in the EMR at each care visit so that implementation of the model in routine practice is feasible.

(2) The model should be applicable to acute and chronic wounds from a diverse range of wound etiologies.

(3) The model should be able to dynamically predict remaining time to wound healing at the first visit and subsequent visits, based on updated characteristics at each visit.

Innovation

Previous wound healing prediction studies were mostly aimed at specific etiologies.[6–11,13–15] Classification models have been developed for general wounds at their first care visit, showing good apparent discrimination,[17,18] yet no external validation was reported. There is a lack of validated wound risk prediction models, and implementation remains difficult.[20] In this study, a model was developed that dynamically predicts the remaining time to wound healing for many wound etiologies at subsequent wound care visits. The model showed stable performance at external validation and implementation is feasible. This can contribute to reducing uncertainty around wound healing for patients and practitioners.

MATERIALS AND METHODS

Study design

Reporting on this prediction study was according to the TRIPOD statement.[23] In this study, we developed and validated a prediction model for the remaining duration of wound care treatment until wound closure, based on wound and patient characteristics observed during a routine wound care visit. For the development of the model, we used EMR data on wounds from any cause that were treated by nurse practitioners in a large part of The Netherlands between January 1, 2017, and September 14, 2022 (with follow-up until December 14, 2022). One-time consultations without

further treatment or follow-up were excluded from the study. The model was externally validated in a cohort of all wounds visited between December 15, 2022, and April 15, 2023, with follow-up until July 30, 2023. This validation set was chosen to ensure a minimum of 3 months' potential follow-up after each visit.

Data collection

For each wound care visit, information on patient and wound characteristics at the visit was extracted from the EMRs. The outcome of interest was the time from the visit until wound closure. Wound closure was defined as total epithelialization of the wound. For most patients, the wound closes completely during specialist wound nursing, though some patients are referred to other care providers or pass away. Moreover, some wounds may remain under treatment with no closure observed by the end of follow-up. Therefore, the time and status of each wound at the end of follow-up were recorded.

Data-quality checks were performed by examining distribution summaries of each variable and individually reviewing (and correcting where possible) extreme or impossible values. Assuming that some mistakes in filling out patient records were made completely at random, records with impossible values (e.g., negative time between wound occurrence and start of treatment) were excluded from our development cohort. For data on wound etiology, comorbidities, and medication use, two nurse practitioners checked individual EMRs for agreement with free text correspondence between practitioners. Corrections were made where needed.

The data had a multilevel structure because there could be multiple wound care visits associated with the same wound, and a single patient could have more than one wound.

Prediction target

We aimed to predict the remaining time to wound closure in a situation where treatment would not be terminated before wound closure (e.g., because of referral or death). The prediction model was intended to be applicable at the first as well as subsequent wound care visits. We hereto updated the prediction at each visit with actual characteristics of the wound, which changed during treatment. The predictions were intended to inform patients about their wound's expected healing time under current treatment practices.[24]

Selection of potential predictors

Potential predictors were selected based on literature,[25–28] previously published wound risk prediction models,[15,17,18] expert opinion of a nurse practitioner, and availability of predictors in the routine care setting. Patient-level candidate predictors were age, sex, comorbidities (diabetes, hypertension, peripheral vascular disease, kidney failure, heart failure, varices, rheumatoid arthritis, and post-thrombotic syndrome), medication use (carbasalate calcium, clopidogrel, vitamin K antagonists, direct-acting anti-thrombotics, and corticosteroids), and primary/secondary care setting. Wound characteristics considered were treatment delay (i.e., time between occurrence of the wound and treatment initiation by a specialized wound care professional), wound location, wound depth, wound surface area, periwound skin state, stage of wound healing, wound etiology, wound recurrence, infection, edema, undermining, exudate, the number of concurrent wounds in the same patient, and the treatment duration up to this visit.

Some candidate predictors were included because of their supposed biological relation to wound healing (e.g., infection, medication use, and comorbidities). Care setting and treatment delay were considered indicators of the wound's care environment. Other variables describe the dynamic healing process so far or the current state of the wound (e.g., wound surface area, treatment duration up to this visit, and stage of wound healing) and might therefore be predictive of the remaining time to wound healing.[17–19]

Statistical analysis

Statistical analyses were performed using R version 4.2.2.[29] Categorical variables were summarized with frequencies and percentages, while numerical variables were described using medians and interquartile ranges (IQRs). The median wound healing time was estimated using Kaplan–Meier curves with adjustment of the corresponding standard errors for the clustered nature of the data.

Since all potential predictors were based on mandatory fields in the electronic patient files, there were no missing data. The remaining time to wound healing at each visit was the outcome of interest. The natural logarithm of the remaining time to wound healing was assumed to be normally distributed conditional on the model predictors. A linear regression model was fitted with the log transformed time as dependent variable. The assumption of a normal distribution was assessed

using a quantile–quantile (QQ) plot of the regression residuals. Model coefficients can be interpreted as factors by which to multiply the expected wound healing time. For example, if the coefficient for male versus female gender were 0.7, then the predicted wound healing time for a man would be twice [exp(0.7) = 2] the predicted wound healing time for a woman with the same values for all other predictors.

Wound healing times were censored for patients in whom complete wound healing was not (yet) observed at the end of follow-up or at the time of another event that would preclude observing wound healing, such as death or relocation. This was in line with our targeted prediction of healing times in the situation where treatment would not be terminated before wound closure. Such a model can also be viewed as a parametric survival model with a log-Gaussian distribution of survival times. We used the "rsm"[30] and "survival"[31,32] packages in R for estimation.

All numerical predictor variables were Winsorized[33] at their 2nd and 98th percentile and modeled with restricted cubic splines.[34] This means that we allowed for flexible, nonlinear relationships between continuous predictors and the outcome in the model. We performed backward selection of predictors based on Akaike's Information Criterion (AIC), using 40 bootstrap resamples. The AIC is a measure of model fit penalized for model complexity. Robust standard errors were calculated for the predictor effects to account for clustering in the data. The estimated residual variance was used to calculate prediction intervals, which provide patients with a time range in which their wound is expected to be healed.

Internal validation was performed using bootstrap resampling with clustering by patient to correct for optimism in performance.[35] The discriminative performance of the model was assessed using the concordance statistic (c-statistic). Values of the c-statistic range from 0.5 to 1, where 0.5 indicates that the model can distinguish longer versus shorter healing times no better than a coin flip and 1 indicates perfect discrimination. Model calibration was evaluated using the calibration intercept and slope and visually examined in plots of observed versus predicted outcomes.[36] The calibration intercept assesses mean calibration and is ideally =0. The calibration slope is ideally =1, where values <1 (>1) indicate that predictor effects are too strong (weak) overall. The amount of variance in the data explained by the model was quantified using R-squared.[37]

The same performance measures were used in the external validation of the developed model. Robust standard errors of performance measures were calculated to account for the multilevel structure of the validation data. In a sensitivity analysis, we limited the validation dataset to new wounds that had no previous visits in the development dataset and assessed model performance within this restricted set of visits.

Sample size

At model development, all wound care visits that were available from electronic records at the time were included. It was known that >100,000 visits from roughly 15,000 wounds and 7,000 patients would be available and that the time of wound closure was observed for most (about 80%) wounds. When all numerical predictor variables were modeled with restricted cubic splines with four knots, there were just below 60 candidate parameters in our model. Assuming an R-squared of 0.25, we calculated that an independent sample of 1,805 visits with the outcome observed would be sufficient to satisfy each of the criteria for prediction model development.[38] Therefore, the available visits would be more than sufficient for reliable model development in this study.

Based on the performance of the prediction model at development, it was estimated that an independent sample of 865 visits with observed wound closure times would be sufficient to externally validate our model.[39] All new data available at the time of validation were used, which we expected to exceed the minimum required sample size for validation.

Ethical approval and patient consent

The dataset used in this study was recorded as part of routine care; hence, no patients were subject to any intervention as part of the study. The study was reviewed by the ethical review board at the Isala Hospital (Zwolle, The Netherlands) under ID 221202, where the study was found to be exempt from the Medical Research Involving Human Subjects Act.

RESULTS

Descriptive summaries

Our development dataset included 92,098 visits, corresponding to 14,248 wounds and 7,221 patients. Wound and patient characteristics at the first recorded wound care visit are summarized in Table 1. Complete wound closure was

Table 1. *Patient and wound characteristics at the first included visit of each wound in development and validation data*

	Development (n *Wounds = 14,248)*	*Validation* (n *Wounds = 2,051)*
Age (years, median [IQR])	76 [63, 85]	74 [64, 83]
Sex		
Male	7,823 (54.9%)	1,135 (55.3%)
Comorbidities		
Median number [IQR]	1 [0, 2]	1 [0, 2]
Diabetes mellitus	4,997 (35.1%)	731 (35.6%)
Kidney failure	479 (3.4%)	172 (8.4%)
Heart failure	2,686 (18.9%)	457 (22.3%)
Hypertension	3,787 (26.6%)	611 (29.8%)
Peripheral vascular disease	2,771 (19.4%)	412 (20.1%)
Varices	802 (5.6%)	82 (4.0%)
Rheumatoid arthritis	598 (4.2%)	90 (4.4%)
Post-thrombotic syndrome	187 (1.3%)	15 (0.7%)
Wound etiology		
Arterial ulcer	1,185 (8.3%)	114 (5.6%)
Burn	525 (3.7%)	50 (2.4%)
Decubitus ulcer	1,657 (11.6%)	324 (15.8%)
Diabetic ulcer	1,627 (11.4%)	277 (13.5%)
Erysipelas	169 (1.2%)	23 (1.1%)
Mixed arterial-venous ulcer	574 (4.0%)	92 (4.5%)
Edema	164 (1.2%)	19 (0.9%)
Surgical wound	2,358 (16.5%)	278 (13.6%)
Oncological ulcer	222 (1.6%)	24 (1.2%)
Other	1,290 (9.1%)	245 (11.9%)
Sinus pilonidalis	95 (0.7%)	19 (0.9%)
Trauma ulcer	2,953 (20.7%)	367 (17.9%)
Vasculitis ulcer	137 (1.0%)	11 (0.5%)
Venous ulcer	1,292 (9.1%)	208 (10.1%)
Number of concurrent wounds [IQR]	2 [1, 2]	1 [1, 2]
Recurring wound	1,632 (11.5%)	295 (14.4%)
Phase of wound healing		
Debridement	9,821 (68.9%)	1339 (65.3%)
Granulation	3,744 (26.3%)	576 (28.1%)
Epithelialization	683 (4.8%)	136 (6.6%)
Care setting		
Primary care	3,767 (26.4%)	787 (38.4%)
Secondary care	10,481 (73.6%)	1,264 (61.6%)
Treatment delay (days, median [IQR])	11 [2, 36]	14 [2, 45]
Wound location		
Arm	439 (3.1%)	34 (1.7%)
Hand	243 (1.7%)	27 (1.3%)
Head/Neck	211 (1.5%)	25 (1.2%)
Sacrum	375 (2.6%)	63 (3.1%)
Torso	966 (6.8%)	131 (6.4%)
Upper leg	873 (6.1%)	111 (5.4%)
Lower leg	5,720 (40.1%)	798 (38.9%)
Foot	5,421 (38.0%)	862 (42.0%
Wound surface area (cm^2, median [IQR])	2.21 [0.50, 9.30]	1.96 [0.40, 8.40]
Wound depth (cm, median [IQR])	0.20 [0.10, 0.30]	0.20 [0.10, 0.30]
Infection	5,554 (39.0%)	755 (36.8%)
Oedema	7,752 (54.4%)	1,136 (55.4%)
Exudate		
Dry	1,602 (11.2%)	242 (11.8%)
Moist	11,052 (77.6%)	1,580 (77.0%)
Wet	1,390 (9.8%)	198 (9.7%)
Very wet	204 (1.4%)	31 (1.5%)
Undermining	1,220 (8.6%)	124 (6.0%)
Normal periwound skin state	7,021 (49.3%)	838 (40.9%)
Medication use		
Antibiotics	2,551 (17.9%)	313 (15.3%)
Carbasalate calcium	2,914 (20.5%)	335 (16.3%)
Clopidogrel	306 (2.1%)	191 (9.3%)
Vitamin K antagonists	40 (0.3%)	25 (1.2%)
Direct-acting oral anti-coagulants	917 (6.4%)	244 (11.9%)
Corticosteroids	1,050 (7.4%)	97 (4.7%)

IQR, interquartile range.

observed in 10,635 (75%) of wounds. For 631 (4.4%) wounds, the patient died before wound closure. At the end of follow-up, 909 (6.4%) wounds were still in care. In the remaining wounds, closure was not observed because the patient and nurse had decided to end the treatment (1,263; 8.9%), because the patient moved to a different care organization (403, 2.8%), was referred to hospital (404, 2.8%), or had emergency admission into a care home (3, 0.0%). The total follow-up time in the development data was 31,667 wound months. The median number of recorded visits per wound was 4 (IQR 2, 8). The median time from treatment start to wound healing was 1.6 (95% confidence interval [CI] 1.5, 1.6) months.

For external validation, 10,186 wound care visits were included. This comprised data from 2,051 wounds and 1,288 patients, where 253 (12%) wounds also had visits before September 15, 2022, that were included in the development data. Complete wound closure was observed in 1,120 (55%) of wounds, which was less than in the development data because of the shorter follow-up time. At the end of follow-up, 620 (30%) wounds were still in care. Other reasons why wound closure was not observed were similar to the development cohort (Table 2). The total follow-up time in the development data was 7,600 wound-months. The median number of recorded visits per wound was 3 (IQR 2, 7). The median time from treatment start to wound healing in wounds that started treatment after December 14, 2022, was 2.2 (95% CI 2.0, 2.5) months. This was longer than in the development cohort.

Compared with the development cohort, more wounds in the validation dataset were in primary care (38% versus 26%, Table 1). More often, clopidogrel (9.3% vs. 2.1%) and direct-acting oral anticoagulants (12% versus 6.4%) were used, whereas carbasalate calcium was less frequently used in the validation cohort (16% vs. 21%). Fewer wounds had a normal periwound skin state (41% vs. 49%). We did not observe large differences in the distribution of other wound characteristics between the validation and development cohorts.

Development of prediction model

When fitting a prediction model with all candidate predictors, all but the use of clopidogrel (p = 0.56) and the use of corticosteroids (p = 0.07) had contributed significantly ($p < 0.05$, Fig. 1). Some comorbidities were so rare that effect estimates were highly uncertain. We therefore included the total number of comorbidities as a predictor in the model instead of individual comorbidities, without negative impact on model fit.

Bootstrapping of the backward selection based on AIC showed that all predictors were retained in at least half of the iterations. We therefore did not further exclude candidate predictors from the model. Visual inspection of the QQ plot indicated

Table 2. *Wound status at the last observed wound care visit for each wound in the development and validation data*

*Wound Status at Last Visit (*N *[%])*	*Development (n = 14,248)*	*Validation (n = 2,051)*
Full wound closure	10,635 (75%)	1,120 (55%)
Wound still in care	909 (6.4%)	620 (30%)
Patient died before wound closure	631 (4.4%)	96 (4.7%)
Patient and nurse had decided to stop treatment	1,263 (8.9%)	61 (2.5%)
Patient moved to a different care organization	403 (2.8%)	110 (5.4%)
Referral to hospital	404 (2.8%)	44 (2.1%)
Emergency admission into a care home	3 (0.0%)	0 (0.0%)

that the lognormal distribution fitted the data very well (Supplementary Fig. S1). The strongest predictors were wound location, treatment delay, phase of wound healing, wound etiology, wound depth, wound surface area, and the time since start of treatment (Fig. 1). The complete model formula is provided in the supplementary information, as well as example predictions at two visits for a fictional wound (Supplementary Data). We also created a freely available online tool to calculate predictions, which can be found at https://www.evidencio.com/models/show/10370 under the same title as this article.

Validation

At internal bootstrap validation, we found an optimism-corrected c-statistic of 0.70, which was identical to the apparent c-statistic 0.70 (95% CI 0.69, 0.71), indicating fairly good discriminative ability of the model. The size of predictor effects was appropriate on average as indicated by a calibration slope of 0.98 (0.97–0.99). On the level of individual wound care visits, the model explained $R^2 = 25\%$ of the variation in healing times (Fig. 2).

At external validation, in newly recorded wound care visits, the discriminative performance of the model was very similar to the internal validation (c-statistic = 0.72 [0.70, 0.73]). The calibration slope was very close to 1 at 1.05 (1.01, 1.09), indicating that predictor effects were appropriate overall (Fig. 3). The calibration intercept was close to 0 at 0.060 (–0.10, 0.22) indicating that on average, the observed remaining wound healing time was close to the predicted wound healing time.

In our sensitivity analysis, we observed a different distribution of treatment times compared with our development and validation data, as it only included new wounds with a relatively short follow-up. In this restricted dataset, the model underpredicted the average remaining wound healing time by 25% (10 – 38%). The discriminative performance of the model remained stable in the restricted dataset (c-statistic 0.69 [0.67,0.71]) and so did the predictor effects (calibration slope: 0.99 [0.94, 1.04]).

DISCUSSION

In this study, we developed and internally validated a model that dynamically predicts time to wound healing based on routinely collected data at wound care visits. The model showed reasonable and robust discriminative performance (c-statistic = 0.70) both in internal and external validation. Predictor effects were appropriate on average at internal and external validation.

The most important predictors were wound location, treatment delay, phase of wound healing, wound etiology, wound depth, wound surface area, and time since the start of treatment. These are mostly wound-level characteristics that indicate the status of the wound itself or the healing process so far. These findings are in line with previous wound healing prediction studies that reported wound-level indicators of the healing process (e.g., size and wound age) among their most powerful predictors.[7,9,10,13–15,17,18] Most studies were conducted in the United States, whereas our study was conducted in The Netherlands, indicating that the prognostic value of these variables generalizes to other populations.

The discriminative performance of our model at validation was similar to the discrimination of both models developed by Cho et al.[18] (logistic regression and classification tree). A model by Jung et al.[17] showed a higher c-statistic than our model indicating better discrimination. The models by Berezo et al.[19] also showed better discriminative performance, although these models predicted the chance of healing at 4, 8, and 12 weeks from baseline using visits after baseline.

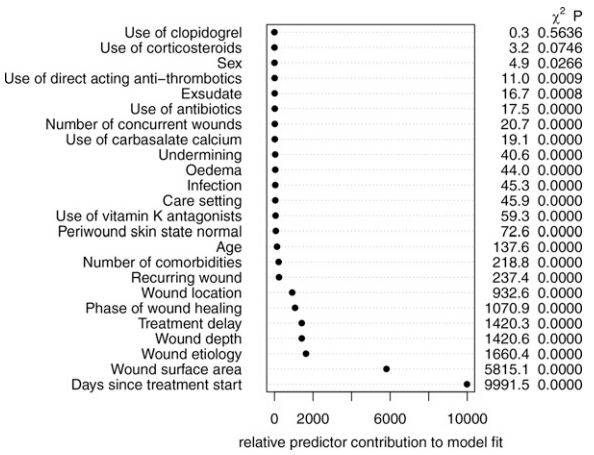

Figure 1. Relative contributions of the predictors to model fit, expressed through their AIC contribution (*x*-axis). AIC, Akaike's Information Criterion.

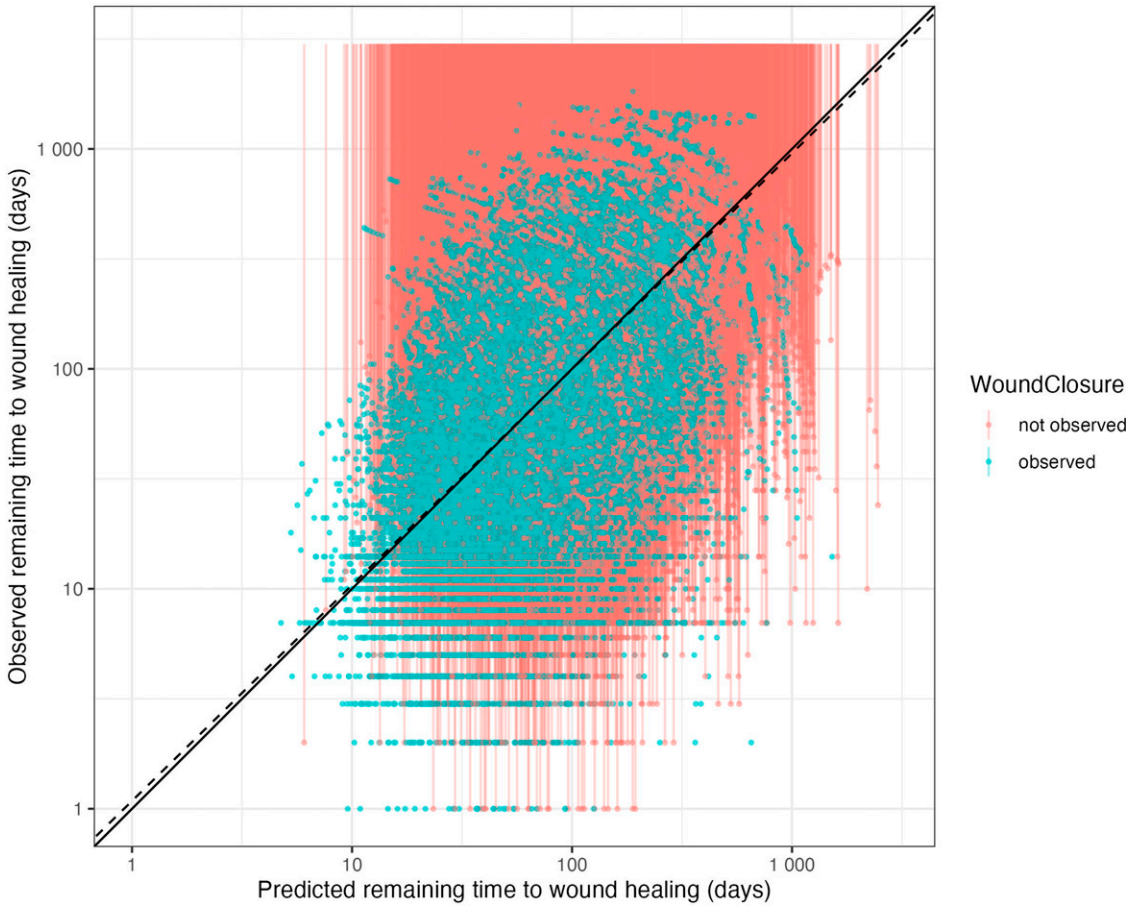

Figure 2. Observed (*y*-axis) versus predicted (*x*-axis) remaining healing time for each wound care visit in our development data. This shows the internal calibration of our model. Points on the solid black reference line have perfect agreement between the observed and predicted healing time. The dashed black line summarizes the optimism-corrected calibration of the model and is ideally equal to the solid black reference line. The axes have a logarithmic scale. Censored observations (where wound closure was not observed during follow-up) are depicted by a dot at the censoring time (last available visit) and a line for the time after the last visit during which the wound may have closed.

Therefore, a part of the models' good performance may be because of "predicting the past": at a visit 7 weeks from baseline, it is already known that the wound has not healed within 7 weeks, which is informative for the probability of being healed within 8 weeks from baseline. For this reason, we opted to predict the *remaining* time to healing at each visit instead of the total healing time from baseline in our study. None of the publications mentioned reported calibration measures. No external validations of either of the models have been published to our knowledge. This limits further comparison of the performance of our model with existing models for wound healing for diverse wound etiologies.

A strength of our model is that it provides continuous predictions of time to healing, in contrast to previous studies that predicted whether healing time would be shorter or longer than a certain number of weeks. And although the previous models were intended to be used at the first encounter with a wound, our model is applicable to the first as well as subsequent wound care visits, reflecting the dynamic nature of wound care. Finally, patients who were lost to follow-up before the time point of interest were excluded from the analyses by Jung et al. and classified as not healed by Cho et al., potentially leading to biased estimates. Our analyses explicitly took loss to follow-up into account in the form of censoring in the dynamic statistical modeling.

Another strength of our study is that the data were routinely collected in clinical practice. Results are therefore well applicable in real world data, even though we recognize the limitation that data quality may be less than in a dedicated scientific study. There were no missing data because of mandatory fields in the EMR system. We acknowledge, however, that, for example, filling in a "no" for "antibiotics use" could mean "this did not come up during the appointment" rather than "I checked that the patient is not on antibiotics," leading to potential measurement error. Despite our efforts

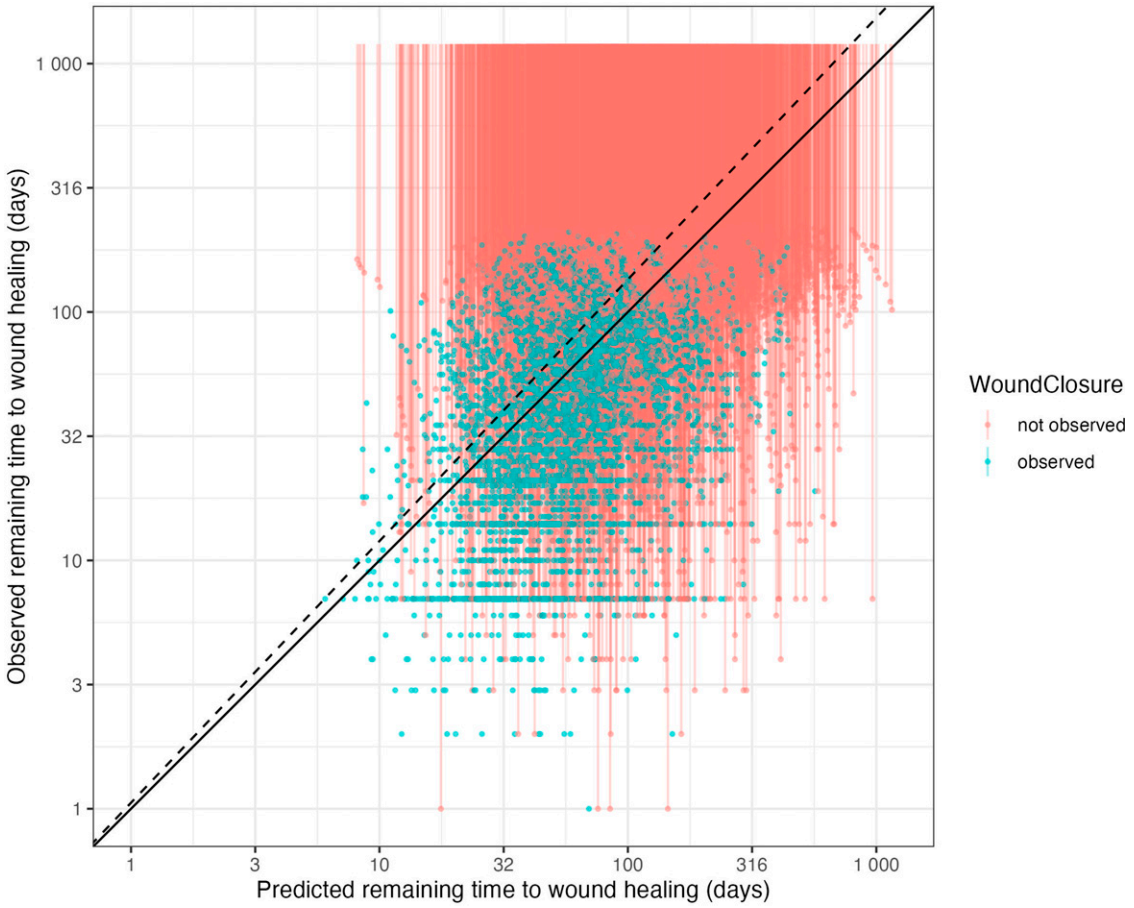

Figure 3. Observed (*y*-axis) versus predicted (*x*-axis) remaining healing time for each wound care visit in our validation data. This shows the external calibration of our model. Points on the solid black reference line have perfect agreement between the observed and predicted healing time. The dashed black line summarizes the calibration of the model and is ideally equal to the solid black reference line. The axes have a logarithmic scale. Censored observations (where wound closure was not observed during follow-up) are depicted by a dot at the censoring time (last available visit) and a line for the time after the last visit during which the wound may have closed.

to detect and correct improbable values, mistakes in recording characteristics during routine care were likely made, also resulting in measurement error. If the model is implemented in practice, and it becomes known which characteristics are important for prediction, these characteristics may be more carefully reported in the future.

Our dynamic modeling approach assumed that the effect of the predictors was not dependent on time. Indeed, we verified that extensions of our model that allow for time-varying predictor effects had limited improvement in predictive ability. Even so, there was still substantial residual variation in the data that was not explained by the model. Future studies should assess additional predictors to improve the model. There are indicators of the general health state of a patient (*e.g.,* ankle-arm index, polypharmacy) that could be relevant for predicting wound healing that were not part of the EMR and therefore not included.

To be suitable for use in clinical practice, the model's performance should remain reasonably stable when applied to new wound care visits. We showed consistent performance at external validation. When the average wound healing time changes over calendar time because of factors not included in the model (i.e., reduced access to care during the covid pandemic, changing patient population because of changing referral protocols), this may lead to average over- or underprediction of healing times. In a sensitivity analysis, we observed some underprediction of the healing times in the newest wounds. The overall calibration of the model on new data may be improved by periodically updating the model intercept based on a recent cohort of wound visits.[40–42] If implemented, it is generally useful to monitor the model's performance over time in new visits and update when appropriate.[43]

Our external validation shows stability over time in the target population, and predictor

importance findings are in line with previous studies in other regions of the world. Still, fine-tuning may be needed when the prediction model is applied to another population, for example, in regions of the world where different types of patients are eligible for specialized wound care. If the populations differ in a way that is not sufficiently explained by the variables in the model, the model's applicability may be affected. In addition, the model is developed to predict outcomes under treatment as usual, but what constitutes treatment as usual might vary between regions. When possible, it is recommended to validate and update a clinical prediction model in the population where it is intended to be used.[43,44]

KEY FINDINGS

- A model to dynamically predict time to wound healing at subsequent wound care visits was developed.
- The developed prediction model and shows stable performance (discrimination and calibration) at external validation.
- Strong predictors were wound-level characteristics and indicators of the healing process so far (e.g., wound surface area, wound location, and phase of wound healing).
- As the model is based on characteristics recorded during routine care, it can feasibly be implemented in clinical practice, where it may help reduce uncertainty for wound care patients and practitioners.

As our model is based on characteristics that are routinely collected in an EMR, implementation of the model in clinical practice is well feasible. The model could run in the background of the EMR system, as the calculation of a prediction only requires basic mathematical operations. At each wound care visit, the practitioner could complete the usual fields in the EMR and a prediction of the remaining time to wound healing could be shown, without any additional effort by the practitioner or the patient. The patient could then receive updated prognostic information at each visit. To communicate uncertainty around the predicted healing time, a prediction interval could be provided as a reasonable range of expected healing times.

Interpretation of the model output is reasonably straightforward as it comprises an expected number of days, limiting the need for training of staff and patient education. The model is intended for use by wound care professionals, and its use does require specific knowledge of the wound-healing process, for example, to determine the stage of wound healing or classify the wound exudate as input for the model. Differences in EMR systems may form a technical barrier to wider implementation. To integrate predictions in the clinical workflow, some EMR systems may have to add characteristics to their files and/or unify their definitions. It is also important that the EMR is designed such that predictors are recorded as accurately as possible, for example, by not allowing impossible values to be filled in.

Our dynamic prediction model based on routinely collected characteristics shows stable performance and can feasibly be implemented in daily practice. An increase in the predicted wound healing time could be a sign to the practitioner that the wound is not developing as expected. Practitioners may then reconsider their wound management. Most importantly, a prediction of remaining time to wound healing from our model could reduce the uncertainty that patients experience and thereby contribute to their satisfaction and health-related quality of life.

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AUTHORS' CONTRIBUTIONS

The study was conceptualized by N.P.S., D.T., and S.F.A., in consultation with S.L.C. and E.W.S. The data were curated by N.P.S. with support from S.F.A. and D.T. Formal analyses were performed by D.T., with supervision of S.L.C. and E.W.S. Visualization was conducted by D.T. The original draft of the article was prepared by D.T. and S.F.A. All authors reviewed and edited the article.

AUTHOR DISCLOSURE AND GHOSTWRITING

The authors have no competing financial interest with respect to the content of the article. The article was written only by the authors listed.

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SUPPLEMENTARY MATERIAL

Supplementary Figure S1
Supplementary Data

REFERENCES

1. 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
2. Mathieu D, Linke J-C, Wattel F. Non-Healing Wounds. In: Handbook on Hyperbaric Medicine. (Mathieu D .ed) Springer-Verlag.: Berlin/Heidelberg; 2006; pp. 401–428; doi: 10.1007/1-4020-4448-8_20
3. Järbrink K, Ni G, Sönnergren H, et al. Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. Syst Rev 2016;5(1):152; doi: 10.1186/s13643-016-0329-y
4. Kurd SK, Hoffstad OJ, Bilker WB, et al. Evaluation of the use of prognostic information for the care of individuals with venous leg ulcers or diabetic neuropathic foot ulcers. Wound Repair Regen 2009;17(3):318–325; doi: 10.1111/j.1524-475X.2009.00487.x
5. Dabas M, Schwartz D, Beeckman D, et al. Application of artificial intelligence methodologies to chronic wound care and management: A scoping review. Adv Wound Care (New Rochelle) 2023;12(4):205–240; doi: 10.1089/wound.2021.0144
6. Rittenhouse BA, Rizzo JA, Shields BA, et al. Predicting wound healing rates and survival with the use of automated serial evaluations of burn wounds. Burns 2019;45(1):48–53; doi: 10.1016/j.burns.2018.10.018
7. Fife CE, Horn SD, Smout RJ, et al. A predictive model for diabetic foot ulcer outcome: The wound healing index. Adv Wound Care (New Rochelle) 2016;5(7):279–287; doi: 10.1089/wound.2015.0668
8. Sheehan P. Early change in wound area as a predictor of healing in diabetic foot ulcers: "Knowing; when to say when." Plast Reconstr Surg 2006; 117(7 Suppl):245S–247S; doi: 10.1097/01.prs.0000222566.56432.22
9. Cardinal M, Eisenbud DE, Phillips T, et al. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008;16(1):19–22; doi: 10.1111/j.1524-475X.2007.00328.x
10. Margolis DJ, Allen-Taylor L, Hoffstad O, et al. Diabetic neuropathic foot ulcers: Predicting which ones will not heal. Am J Med 2003; 115(8):627–631; doi: 10.1016/j.amjmed.2003.06.006
11. Hicks CW, Canner JK, Mathioudakis N, et al. The society for vascular surgery wound, ischemia, and foot infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. J Vasc Surg 2018;68(4):1096–1103; doi: 10.1016/j.jvs.2017.12.079
12. 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 2021;15(5): 1161–1167; doi: 10.1177/1932296820942307
13. Fife CE, Horn SD. The wound healing index for predicting venous leg ulcer outcome. Adv Wound Care (New Rochelle) 2020;9(2):68–77; doi: 10.1089/wound.2019.1038
14. Margolis DJ, Allen-Taylor L, Hoffstad O, et al. The accuracy of venous leg ulcer prognostic models in a wound care system. Wound Repair Regen 2004; 12(2):163–168; doi: 10.1111/j.1067-1927.2004.012207.x
15. Ubbink DT, Lindeboom R, Eskes AM, et al. Predicting complex acute wound healing in patients from a wound expertise centre registry: A prognostic study. Int Wound J 2015;12(5):531–536; doi: 10.1111/iwj.12149
16. Hettinger G, Mitra N, Thom SR, et al. An improved clinical and genetics-based prediction model for diabetic foot ulcer healing. Adv Wound Care (New Rochelle) 2024; doi: 10.1089/wound.2023.0194
17. Jung K, Covington S, Sen CK, et al. Rapid identification of slow healing wounds. Wound Repair Regen 2016;24(1):181–188; doi: 10.1111/wrr.12384
18. Cho SK, Mattke S, Gordon H, et al. Development of a model to predict healing of chronic wounds within 12 weeks. Adv Wound Care (New Rochelle) 2020;9(9):516–524; doi: 10.1089/wound.2019.1091
19. Berezo M, Budman J, Deutscher D, et al. Predicting chronic wound healing time using machine learning. Adv Wound Care 2022;11(6):281–296; doi: 10.1089/wound.2021.0073
20. Veličković VM, Spelman T, Clark M, et al. Individualized risk prediction for improved chronic wound management. Adv Wound Care (New Rochelle) 2023;12(7):387–398; doi: 10.1089/wound.2022.0017
21. Shi C, Dumville JC, Juwale H, et al. Evidence assessing the development, evaluation and implementation of digital health technologies in wound care: A rapid scoping review. J Tissue Viability 2022;31(4):567–574; doi: 10.1016/j.jtv.2022.09.006
22. Excen. EPD PatDoc. n.d. Available from: https://www.excen.nl/home/epd-patdoc/ [Last accessed: February 27, 2024].
23. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med 2015;162(1):W1–73; doi: 10.7326/M14-0698
24. Van Geloven N, Swanson SA, Ramspek CL, et al. Prediction meets causal inference: The role of treatment in clinical prediction models. Eur J Epidemiol 2020;35(7):619–630; doi: 10.1007/s10654-020-00636-1
25. Guo S, DiPietro LA. Factors affecting wound healing. J Dent Res 2010;89(3):219–229; doi: 10.1177/0022034509359125
26. Godbout JP, Glaser R. Stress-Induced immune dysregulation: Implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol 2006;1(4):421–427; doi: 10.1007/s11481-006-9036-0

27. Beyene RT, Derryberry SL, Barbul A. The effect of comorbidities on wound healing. Surg Clin North Am 2020;100(4):695–705; doi: 10.1016/j.suc.2020.05.002

28. Maroz N, Simman R. Wound healing in patients with impaired kidney function. J Am Coll Clin Wound Spec 2013;5(1):2–7; doi: 10.1016/j.jccw.2014.05.002

29. R Core Team. R: A language and environment for statistical computing. 2022.

30. Harrell FE. Rms: Regression modeling strategies. 2022.

31. Therneau TM, Grambsch PM. Modeling survival data: extending the cox model. Statistics for Biology and Health. Springer: New York; 2000.

32. Therneau TM. Survival: A package for survival analysis in R. 2022.

33. Steyerberg EW. Restrictions on candidate predictors. In: Clinical Prediction Models: Statistics for Biology and Health. Springer International Publishing: Cham; 2019; pp. 191–206; doi: 10.1007/978-3-030-16399-0_10

34. Harrell FE. Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis. Springer Series in Statistics. Springer International Publishing: Cham; 2015; doi: 10.1007/978-3-319-19425-7

35. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal–external, and external validation. J Clin Epidemiol 2016;69:245–247; doi: 10.1016/j.jclinepi.2015.04.005

36. Van Calster B, McLernon DJ, van Smeden M, et al. Calibration: The Achilles heel of predictive analytics. BMC Med 2019;17(1):230; doi: 10.1186/s12916-019-1466-7

37. Nagelkerke NJD. A note on a general definition of the coefficient of determination. Biometrika 1991;78(3):691–692; doi: 10.1093/biomet/78.3.691

38. Riley RD, Snell KIE, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: Part I – Continuous outcomes. Stat Med 2019;38(7):1262–1275; doi: 10.1002/sim.7993

39. Archer L, Snell KIE, Ensor J, et al. Minimum sample size for external validation of a clinical prediction model with a continuous outcome. Stat Med 2021;40(1):133–146; doi: 10.1002/sim.8766

40. Binuya MAE, Engelhardt EG, Schats W, et al. Methodological guidance for the evaluation and updating of clinical prediction models: A systematic review. BMC Med Res Methodol 2022;22(1):316; doi: 10.1186/s12874-022-01801-8

41. Strobl AN, Vickers AJ, Van Calster B, et al. Improving patient prostate cancer risk assessment: Moving from static, globally-applied to dynamic, practice-specific risk calculators. J Biomed Inform 2015;56:87–93; doi: 10.1016/j.jbi.2015.05.001

42. Su T-L, Jaki T, Hickey GL, et al. A review of statistical updating methods for clinical prediction models. Stat Methods Med Res 2018;27(1):185–197; doi: 10.1177/0962280215626466

43. Van Calster B, Steyerberg EW, Wynants L, et al. There is no such thing as a validated prediction model. BMC Med 2023;21(1):70; doi: 10.1186/s12916-023-02779-w

44. Sperrin M, Riley RD, Collins GS, et al. Targeted validation: Validating clinical prediction models in their intended population and setting. Diagn Progn Res 2022;6(1):24; doi: 10.1186/s41512-022-00136-8

Abbreviations and Acronyms

AIC = Akaike's Information Criterion
c-statistic = concordance statistic
CI = confidence interval
EMR = electronic medical records
IQR = interquartile range
QQ = quantile–quantile