The Wound Healing Index for Predicting Venous Leg Ulcer Outcome

Caroline E. Fife[1,*] and Susan D. Horn[2,3]

[1]U.S. Wound Registry, The Woodlands, Texas.
[2]International Severity Information Systems, Inc., Salt Lake City, Utah.
[3]School of Medicine, University of Utah, Salt Lake City, Utah.

Caroline E. Fife, MD

Submitted for publication May 31, 2019. Accepted in revised form July 5, 2019.

*Correspondence: U.S. Wound Registry, 2700 Technology Forest Boulevard, Suite 250, The Woodlands, TX 77381
(e-mail: cfife@uswoundregistry.com).

Objective: To develop a venous leg ulcer (VLU) risk stratification system for use in research and clinical practice.
Approach: U.S. Wound Registry data were examined retrospectively and assigned an outcome. Bivariate analysis identified significant variables ($p < 0.05$) that were used to create a multivariable logistic regression model. Ulcers with data for wound area at the first visit before debridement were included in regression analysis, which was based on a 90% development sample. The model was validated on a hold-out 10% data sample.
Results: The original dataset included 26,713 VLUs, of which 11,773 ulcers were eligible for preliminary analysis and 10,942 ulcers were eligible for regression analysis. The 90% development model included 9,898 ulcers, of which 7,498 healed (75.8%). The 10% validation sample included 1,044 ulcers, of which 809 healed (77.5%). The following variables significantly predicted healing: number of concurrent wounds of any etiology, wound size, wound age (in days), evidence of bioburden/infection, being nonambulatory, and hospitalization for any reason.
Innovation: The VLU Wound Healing Index (WHI) is a comprehensive, validated risk stratification model for predicting VLU healing that incorporates patient- and wound-specific variables.
Conclusions: The WHI can identify which VLUs most likely require adjunctive therapies to heal, prioritize referral to venous experts, risk-stratify ulcers to create more generalizable clinical trials and understand the impact of clinical interventions. The Centers for Medicare and Medicaid Services accepts this method for reporting VLU outcome under the Quality Payment Program.

Keywords: venous leg ulcers, wound healing index, risk stratification, predictive factors of healing, quality reporting

INTRODUCTION

With an annual incidence rate >2% and an annual cost of $14.9 billion,[1] a method is needed to stratify venous leg ulcers (VLUs) by severity to accurately report wound healing rates, create more generalizable trials, identify those in need of advanced therapeutics, and evaluate the relative benefits of different venous interventions. Absent a way to stratify VLUs by healing likelihood, randomized controlled trials (RCTs) evaluating efficacy of VLU treatments exclude patients with serious but common comorbid diseases.[2–5] Risk stratification could facilitate design of "real-world" trials, by including more representative (*i.e.*, "sicker") patients to better understand the

DOI: 10.1089/wound.2019.1038

value of advanced therapeutics and venous interventions for real-world patients with VLUs.[3–6]

A risk stratification system is also needed to allow fair comparisons of provider performance under new reimbursement systems, so that clinicians caring for sicker patients will not appear to have worse outcomes than their peers.[3,4,7] Without risk stratification, it is not possible to understand or justify the wide variations in cost associated with VLU treatments. The Centers for Medicare and Medicaid Services (CMS), the US Food and Drug Administration, and The Health and Medicine Division promote mining of real-world data from electronic health records (EHRs).[3,8–10] The validated Wound Healing Index (WHI™)[11] was developed from data collected in the usual course of treatment and submitted to the U.S. Wound Registry (USWR) by a national clinical data research network (CDRN) of wound care centers.[12]

Predictive models in venous ulcer disease are not new. Previous investigators used simple logistic regression models to identify predictive factors for VLU healing, including wound size,[13–22] wound duration,[13,16,19,22–25] wound location,[22] early healing rates,[18,21,24,25] presence of certain bacteria,[25] treatment response,[15] patient age,[19,20,22,23] body mass index (BMI),[13,19,20] previous ulceration,[13] wound debridement,[20] heavy exudate,[20] wound severity,[26] sex,[20,22] type of compression therapy,[27] living alone,[28] venous refill time (VRT),[22] wound protease level,[29] cellular senescence,[30] renal disease,[31] and lower extremity arterial disease.[21] Previously developed wound scoring systems combine predictive healing variables and allocate points to each factor to determine prognosis to create tools such as wound severity scales [including the Ulcerated Leg Severity Assessment (ULSA)],[23,32] a wound bed score,[33] and a risk assessment tool that uses Area Under the Receiver Operating Characteristic Curve (AUC) analysis.[34] These models can help clinicians identify VLUs that will be difficult to heal. However, because these tools are generally difficult to use, they are rarely used in clinical practice.[35] Mathematical models can also predict VLU healing likelihood,[36–39] but previously developed systems have not utilized clinically relevant data elements and, thus, lack practical utility.[40]

We describe the WHI for VLUs, a predictive model based on commonly documented patient and wound characteristics, which is the CMS-approved method for reporting real-world VLU healing rates under the Merit-Based Incentive Payment System (MIPS). By facilitating and standardizing VLU outcome reporting at a national level, the WHI harnesses real-world patient data to improve clinical care research.

CLINICAL PROBLEM ADDRESSED

There was a need for a comprehensive and practical VLU predictive healing model, which could identify at the first visit the ulcers most at risk for nonhealing, to optimize the use of advanced therapeutics, assess the value of venous interventions, explain the increased cost of care associated with some VLUs, enable more generalizable RCTs, create matched cohorts for retrospective analysis of real-world datasets, and nationally standardize outcome reporting under a new reimbursement paradigm.[3,4,7]

MATERIALS AND METHODS

Settings and Database Description

We previously described the USWR aggregate database used to develop the WHI models, in which data were sourced from a specialty-specific EHR that met applicable standards for electronic data exchange.[11] Fifty-six clinics in 24 states participated at the time of project initiation, although there are now more than 130 clinics in 34 states and Puerto Rico, as well as large office-based practices participating in the USWR.[3] The Woodlands Institutional Review Board determined that the retrospective analysis of HIPAA-deidentified data in this study was exempt from patient consent requirements. This study adhered to the 1975 Declaration of Helsinki.

Identification of VLUs

We defined ulcerations as VLUs diagnosed by wound care practitioners using the following ICD-9 CM (International Classification of Diseases, 9th edition, Clinical Modification) codes within the EHR:

- 459.31: chronic venous hypertension with ulcer
- 454.0: varicose veins of lower extremities with ulcer
- 454.2: varicose veins of lower extremities with ulcers and inflammation
- 459.33: chronic venous hypertension with ulcer and inflammation
- a chronic ulcer of the lower limb (707.1X) related to venous insufficiency (459.81).

Providers performed point-of-care electronic charting in the examination room with patients; "free text" data entries identified the affected side and specific body location (*e.g.*, "left medial ankle").

Additional inclusion criteria were: each VLU had at least two clinical encounters; there were at least 5 days between first and last encounter; the gap between two clinic visits was not more than 90 days; VLU date of onset was included; body location of the VLU was specified on the lower leg (but not the plantar foot); at least one wound assessment with a wound area $\geq 0.25\,cm^2$ was captured; and at least one wound area measurement or a clinician statement of ulcer outcome was captured.

To reduce misdiagnoses, we excluded ulcers classified as "VLUs" among patients with autoimmune or connective tissue disease (*e.g.*, rheumatoid arthritis, scleroderma), sickle cell anemia, and ulcers covered with eschar or within which deep structures were exposed (such as tendon).

Model Development

Dependent variable analysis. Supplementary Table S1 details the WHI healing definition.[11] Using the time frame of "ever healed," we used a semihierarchical order for healing definitions, under which the clinician assigned healed/healing outcomes in the first level. If no outcome was assigned to the VLU at the final visit, we performed longitudinal data analyses to establish healing status by assessing change in ulcer size over time and change in tissue type exposed over the course of care. Cases of amputation and death before healing were considered not healed.

Statistical Analysis

The Institute for Clinical Outcomes Research team (now part of University of Utah School of Medicine) performed analyses described below using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

We utilized descriptive statistics to test frequencies of patient, wound, and outcomes. The mean, median, quartiles, standard deviation, and range were calculated for continuous measures.

Independent Variables Analysis

We selected patient and wound variables that were candidate predictors of healing of VLUs based on prior research or original to the WHI analysis,[11] and which were routinely documented in the EHR at the first visit. Therefore, we excluded factors that are not typically performed by wound care practitioners or obtained at the initial visit, such as venous anatomical assessment and factors that targeted a change after a specific treatment or after a period of time. We then performed bivariate analyses to examine associations between each candidate predictor and "healed" outcome using either contingency tables and chi-squared tests, Fisher's exact tests, or Wilcoxon tests (for ordered categories) to determine significance of bivariate associations for discrete predictors, or logistic regression to determine significance of bivariate associations for continuous variables. A two-sided p-value <0.05 was statistically significant.

Patient and wound variables significantly associated with predicting VLU healing in bivariate analyses included the following: infection/bioburden, patient admitted for acute hospital stay, first wound area, patient age at first treatment, patient has insulin-dependent diabetes, mobility of patient at arrival (*e.g.*, bed bound, wheelchair bound, walks with assistance, walks unaided), peripheral vascular disease (PVD), wound age at first encounter, number of previous or concurrent other wounds or ulcers, and malnutrition. Table 1 provides definitions of these predictive healing

Table 1. *Significant variables used in predicting venous leg ulcer healing*

Variable
Beginning wound area in cm^2
Caregiver encounter ending with patient sent to emergency department or hospital
Patient chronological age at first encounter
Mobility of patient at arrival; patient bed bound at arrival
Mobility of patient at arrival; patient in wheelchair
Mobility of patient at arrival; patient able to ambulate
Number of wounds or ulcers that started previous to or concurrent with the index wound, but existed on the patient during the timeframe the index wound was being treated
Patient was said to be malnourished if he/she had an ICD-9 code of the form 263.XX, 262.XX, or 995.84, Braden nutrition 1 or 2, or a BMI <18.5
Insulin-dependent diabetes was present if patient was said to be on any of the following medications: insulin, Humalog, Humulin, insulin pump, Lantus, Lente, Levimir, or Novolog; or patient had an ICD-code of the form 250.XX
The number of days from wound onset to the first encounter date
Signs of inflammation and/or infection in the wound as indicated by the words milky, purulent, green, or malodorous describing wound exudates or the words indurated, edematous, tender to palpation, warm to touch, or erythematous describing the periwound area.

Nonsignificant bivariate variables included: sex, patient is paralyzed, wound location, history of autoimmune disease, patient resides in nursing home or skilled nursing facility, patient has dementia or Alzheimer's, and patient has renal failure.

The variables are mutually exclusive and are positive for the worst condition during the wound episode (whole course of care model). A second set of variables was created for use in the first encounter model based on mobility at first encounter arrival.

ICD-9, International Classification of Diseases, 9th edition; BMI, body mass index.

variables. Nonsignificant bivariate variables in this large dataset included the following: sex; paralysis; wound location (left vs. right); autoimmune disease; residence in nursing home or skilled nursing facility; dementia or Alzheimer's; and renal failure.

Multivariate Logistic Regression Analyses and Model Validation

When analyzing large datasets to create a prediction model, a small proportion of that sample, typically called a validation sample, is commonly set aside to determine how the model works for objects not used in model creation. After defining the dichotomous outcome of healed and healing, 10% of the VLUs were randomly selected for model validation, with ulcer as the unit of analysis. We conducted multivariable logistic regression for the dichotomous outcome of healed on the remaining 90% of VLUs. For regression analysis, the variable "area at first visit prior to any debridement" was included as a predictor of healing. We, therefore, excluded from regression analyses VLUs from the 10% validation and 90% development ulcer samples that did not have this area recorded. The VLU WHI predicts healing probability of a specified VLU, independent of a time constraint, using multiplication of logistic regression parameter estimates by values of significant VLU variables and is verified by the 10% validation sample. We developed two healing likelihood models using: (1) data available at the "first encounter" (suitcase model) or (2) data available from the "whole course of care" (whole course).

We allowed variables to enter models using stepwise selection but only retained significant variables (Table 1). Pairwise Spearman correlations confirmed that no independent variables were collinear in final models. All correlations between independent variables were less than 0.75. Using the 90% sample, the AUC (c-statistic) measured model discrimination on both models to determine how well the model distinguished VLUs that did not heal from those that did heal.

We additionally examined the 10% validation sample for degree of correspondence between probabilities estimated by the WHI of achieving the "healed" outcome and the actual outcome proportion over groups spanning the entire range of probabilities (calibration), by using the Hosmer–Lemeshow goodness-of-fit test, which is a standard statistical method to examine how well a prediction model predicts the actual outcome, and it serves to further demonstrate the validity of the WHI for VLU healing.

Finally, individual physician outcome data were analyzed according to the number of VLUs treated, dividing practitioners into two groups using 30 VLUs as the cut-point. Physicians treating fewer than 30 total VLUs over the time frame of their available data were defined as clinically inexperienced, a definition based on expert opinion and the minimum number of VLUs needed to create three valid risk categories. This enabled us to examine complete wound healing in relationship to the WHI breakpoints currently used in quality reporting (probability breakpoints ≤33%, > 33–67%, and >67%).

RESULTS

From July 2003 to July 2011, there were 26,713 VLUs included in the original dataset. There were 11,773 VLUs included for bivariate analysis (44.1% of the original VLU dataset, Table 2). Excluded ulcers did not meet inclusion criteria (reasons and frequency provided in Table 2).

Table 3 indicates variables examined in bivariate analyses and significantly associated with a VLU being healed and which remained significant in the final regression model predicting healing likelihood.

For the first encounter model, the 10% model validation sample initially comprised 1,177 VLUs, 133 of which were removed for not having first visit wound area recorded, leaving 1,044 VLUs for validation. Remaining VLUs ($n = 10{,}596$) were used for the 90% development sample, but 698 of them did not have first wound area recorded, so 9,898 were ultimately analyzed. Table 4 shows significantly predictive variables of VLU healing in

Table 2. *Reasons and number of venous leg ulcers excluded from venous leg ulcer wound healing index model development*

Reason for Exclusion	*No. of VLUs*
Starting number of ulcers/wounds	26,713
Wound location not specified adequately for analysis	–8,640
No data available at the first encounter	–858
Delete when encounter date is after resolved date	–1,496
Require more than one wound encounter	–6
Require that first encounter date is not resolved date	–1,725
Keep wounds where longest gap between encounters is <90 days	–256
Require days between first and last encounter>=5	–201
Wound outcome group "Throw out" (lost to follow up)	–212
Require wound age	–607
No areas, no evidence of outcome	–939
EvidenceStatus = None and MeasureStat2 = Depth or No	–0
Max wound area <0.25 cm^2	–0
Encounter date duplicates with nonidentical data—keep worst	–0
Encounters after resolved date	–0
End number of VLUs	11,773

VLU, venous leg ulcer.

Table 3. *Variables allowed in regression models and p-values in bivariate analyses of healed versus not healed (n= 11,773 venous leg ulcers)*

Variable[a]	*In Final Regression Models*	p-*value*
Infection/Bioburden	Yes	(–)<0.001
Patient admitted for acute hospital stay	Yes	(–)<0.001
First Wound Area (–: healed wound associated with smaller area)	Yes	(–)<0.001
Patient age at first treatment (–: healed wound associated with younger age, +: nonhealed wound associated with older age)	No	(+)0.030
Patient has insulin dependent diabetes	Yes	(+)<0.001
Mobility of patients at arrival–bed bound vs. wheelchair or able to ambulate	Yes	(–)<0.001
Peripheral vascular disease-severe[b]	No	(–)0.039
Wound Age at first encounter	Yes	(–)<0.001
Previous or concurrent other wounds or ulcers (–: healed wound associated with fewer other wounds)	Yes	(–)<0.001
Worst Braden Score (+: healed wounds associated with higher score)	No	(+)0.006
Braden Malnutrition (+: healed wounds associated with higher score)	No	(+)0.010

[a]Nonsignificant bivariate variables included: sex, patient is paralyzed, wound location, history of autoimmune disease, patient resides in nursing home or skilled nursing facility, patient has dementia or Alzheimer's, and patient has renal failure.

[b]Peripheral vascular disease and its severity were defined by scanning eight different database tables containing initial and follow-up examination information, medical history, surgery summaries, nursing assessments, and comorbid conditions for the following words or word segments: claudication, gangrene, rest pain, and the association of the words "peripheral" and "ischemia" or "leg." Patients were also considered to have peripheral arterial disease, as indicated by any ICD-9 CM diagnosis (codes 440.23, 440.24, 443, or 444.2), or it was indicated in the structured field of "secondary diagnosis" in the EHR.

multivariable logistic regressions, which are ordered from strongest significant predictor to weakest significant predictor for both the whole course and first encounter models. All regression coefficients were negative, which means that they were associated with less likelihood of healing. Table 4 excludes PVD, because after we added "method of arrival" to the model, it was strongly correlated with PVD and acted as a surrogate for PVD.

Table 5 displays the performance of each VLU model in the validation dataset. Both the whole course and first encounter models validated well. Because the WHI was developed using structured data commonly available at the initial visit, the WHI can be calculated as soon as the initial visit documentation is completed by embedding the programmatic specifications of the WHI within an EHR. Absent an automated system within an EHR, the significant variables required for the VLU WHI can be obtained by answering the seven specific questions depicted in Table 6. Question data can be transmitted to the USWR, which can compute the likelihood of VLU healing based on VLU regression coefficients multiplied by the specified variable values.

For physicians who each treated ≤30 VLUs over the time frame of the dataset ($n = 1{,}412$ VLUs), there were only four VLUs in the WHI likelihood category of ≤33%; this sample size was too small to assess the actual rate of healing with accuracy, and so, it was not possible to compare the predicted healing rate with the observed rate of healing in the very unlikely to heal category. For the WHI categories that roughly represent VLUs highly likely to heal and for which healing may or may not

Table 4. *Models of whole course of care and first encounter healing likelihood for venous leg ulcers*

	No. of VLUs= 9,898;[a] *No. Healed (%)= 7,498 (75.8%)*			
	90% Whole-Course Model c-statistic[b] *= 0.636*		*90% First Encounter Model c-statistic*[b] *= 0.603*	
Variable	*Wald Order*[c]	p-*value*	*Wald Order*[c]	p-*value*
Wound age at first encounter	1	<0.0001	1	<0.0001
Infection/bioburden	2	<0.0001		
Number of previous or concurrent other wounds or ulcers	3	<0.0001		
First wound area	4	<0.0001	2	<0.0001
Mobility of patients at arrival—wheelchair	5	<0.0001	3	<0.0001
Mobility of patients at arrival—bed bound	6	<0.0001		
Patient admitted for acute hospital stay or emergency department visit	7	<0.0001		

All estimates are negative.

[a]A 90% development sample was used for model building analysis. First, 10% of VLUs were randomly selected from the study sample to be used for model validation. The remaining 90% (10,596 VLUs) were used in the development sample. However, 698 of these were missing a wound area at first visit before debridement and were excluded from regression analysis. Therefore, 9,898 VLUs were ultimately used in the development sample.

[b]c-statistic = performance metric of model discrimination equivalent to the area under the receiver operating characteristic curve.

[c]Most significant = 1 to least significant.

Table 5. *Validation statistics for models of whole course of care and first encounter healing likelihood*

	Number of VLUs = 1,044;[a] *Number Healed (%) = 809 (77.5%)*					
	90% Whole-course model			*90% First Encounter Model*		
	p-*value*	*Hosmer–Lemeshow* p-*value*	*C-statistic*[b]	p-*value*	*Hosmer–Lemeshow* p-*value*	*C-statistic*[b]
Wound Healing Index	<0.0001	0.3319	0.619	<0.0001	0.4741	0.594

[a]A 10% validation sample ($n = 1,177$) was randomly selected from the study sample. However, 133 of these VLUs did not have a wound area recorded at first visit before debridement and were therefore excluded from the model validation analysis. Thus, the final sample used to validate the regression analysis was 1,044.
[b]c-statistic = performance metric of model discrimination equivalent to the area under the receiver operating characteristic curve.

occur (>67% and >33–67%, respectively), the percentages of wounds actually healed were 75.8% and 50.1%, respectively, demonstrating model validity. In contrast, for physicians each treating ≥31 VLUs, there were 25 discrete VLUs in the low-healing likelihood (≤33%) category, and corresponding observed healing rates for experienced practitioners were 32.0%, 60.0%, and 79.1% within the same three categories.

DISCUSSION

There are many risk stratification models for predicting VLU healing,[13–40] but they are all based on significantly smaller datasets (*e.g.*, <300 VLUs analyzed) than the VLU WHI ($n = 11,773$). For example, a prospective, single-center study included 189 patients with VLUs, of which 24 wounds failed to heal after multilayer compression therapy.[13] Simple logistic regression models demonstrated that small wound area, shorter VLU duration, >3 cm decrease in calf circumference, and new skin islets on >10% of wound surface during the first 50 days of treatment were predictive of healing. A high BMI, short walking distance during the day, history of wound debridement, deep ulcers, and impaired calf muscle pump were predictive of impaired healing. However, this model is overspecified, because there are nine variables used to predict healing but only 24 wounds that failed to heal, which do not meet the threshold of 10 wounds in the least frequent category (in this case 24 unhealed wounds) for each predictor variable included in logistic regression analysis. To not be overspecified, this model would require at least 90 wounds in the least frequent category. From a practical standpoint, clinical use of this model requires an observation period of >7 weeks to make a prediction.

Table 6. *Questions to produce venous leg ulcer wound healing index*

Question
Patient age in years (calculated from date of birth) at first treatment
VLU age (duration) in days (calculated from VLU onset) at first encounter
VLU area in cm^2 (calculated from length × width) at first encounter
What is the patient's primary ambulatory method? (walks unaided, cane, crutches, walker, roll about, scooter, wheelchair bound, bed bound)
Was the patient admitted to the hospital or the emergency department on the date of service?
How many total wounds or ulcers of any type does the patient have?
Does this VLU have evidence of infection or bioburden? (evidenced by: purulent, green, malodorous drainage, periwound induration, tenderness to palpation, warmth)

See Table 1 for more detail.

The ULSA scoring system is a simple, validated system that predicts VLU healing based on 24-week healing rates among patients treated with compression, using only three healing parameters[22] (compared to seven WHI variables). Patient age, ulcer duration, and VRT of ≤20 s were predictive factors in this prospective baseline study of 229 patients with VLUs. Based on these factors and hazard ratios from Cox regression analysis, the ULSA score was equal to age+chronicity-50 (when VRT is >20 s). A score of ≤50 had higher 24-week ulcer healing rates than those with higher scores in both the baseline study ($p < 0.001$) and validation study performed with 86 patients ($p = 0.007$).[22]

Another validated wound bed score was tested on 177 patients with VLUs treated either with compression therapy alone or a living bilayered cellular product.[33] Wound bed parameters included healing edges, presence of eschar, greatest wound depth/granulation tissue, amount of exudate, edema, periwound dermatitis, periwound callus and/or fibrosis, and a pink/red wound bed. Each factor was scored from 0 (worst) to 2 (best) and added to the total score, which could range from 0 to 16 for each VLU. The scoring system was validated by evaluating serial photographs at baseline to determine whether scores could predict complete wound closure among patients receiving these specific treatments. Healed VLUs had statistically significant higher scores than nonhealing ulcers ($p = 0.0012$), which was also true for each treatment. A 1-unit increase in total wound bed score resulted on average in 22.8% increase in odds of healing (odds ratio = 1.228).[33] Although this wound bed score is easy to calculate, it targets patients undergoing specific treatments and excludes patient factors, limiting its clinical

utility. The WHI was created by analyzing the entire EHR of all patients (and all wounds) from all participating clinics, thus avoiding selection bias. All clinics performed point-of-care charting using the same purpose-built EHR with structured data fields designed specifically for wound care documentation; thus, data were captured uniformly in a manner designed to facilitate subsequent analysis of their predictive value. Data represent the patient's actual medical record. Because there is end-to-end transmission of EHR data directly to the registry, there can be no *post hoc* vetting of outcome information to artificially inflate a facility's reported "healing rate" for marketing or other purposes.[3,4] This model was designed to identify inherent patient and wound characteristics that are prognostic of healing. It is agnostic with regard to VLU treatment, which is why it was not necessary to control for variations in care among facilities. Indeed, the goal of the WHI is to identify whether specific treatments change actual outcome in comparison to predicted outcome.

Predictive models such as the WHI have multiple uses for patient care and clinical research. The WHI is currently embedded within one EHR, and it can be calculated immediately upon completion of an initial patient assessment using health care information obtained during the first encounter. Despite its use in quality reporting since 2014, the WHI has not been revealed to practitioners at the point of care, absent a national discussion about the unintended consequences of informing clinicians that a given wound may be unlikely to heal. Its current use is limited to quality measure reporting and clinical research. However, the first encounter model could be used on the initial visit to identify VLUs unlikely to heal with compression therapy alone, allowing the earlier implementation of advanced therapeutics and improving care efficiency, which is highly desirable as the CMS implements episode-based payment models. As a symptom of venous disease, VLUs should undergo assessment by a venous expert. Given the large number of VLU patients, the WHI could be used to identify patients most urgently in need of expert venous assessment or likely to require treatment with a cellular and/or tissue-based product (*e.g.*, "skin substitute"), although further research is needed to determine the clinical and economic benefit of identifying patients in this way.

For research, the model can be used to stratify patients enrolled in trials to ensure appropriate allocation of study and control groups.[3,4,7] It may allow individuals with common comorbid diseases to be enrolled in RCTs, permitting a study population that more closely resembles real-world patients and thus improving the generalizability of wound care trials.[2] We have shown that the clinical trials of cellular and/or tissue-based products in VLUs are not generalizable to real-world patients with VLUs, since VLUs in the real world are five times larger than those enrolled in prospective trials (performed in the same centers), and the trials exclude commonly present comorbid diseases.[5] Although the WHI model with its complex calculations is more challenging to utilize in clinical practice than simple scoring tools, clinicians and researchers can pay a small fee to obtain WHI predictions through the USWR, if answers to questions in Table 6 are available. The USWR is a nonprofit organization, although it receives no funding from industry or government, nor is it supported by society dues, since wound care is not a specialty. Thus, the nominal fees associated with accessing the WHI defray a small portion of registry overhead and the considerable cost of developing and maintaining VLU quality measures, enabling wound care practitioners to participate in MIPS in a clinically relevant way, despite the absence of funding typically available to Qualified Clinical Data Registry (QCDRs).

Of pressing importance is the need to risk stratify patients for outcome reporting under MIPS.[7] The CMS requires that QCDRs risk adjust outcome data to ensure that publicly reported physician performance scores can be compared fairly.[3,4,7] Risk adjustment takes factors into account that might influence patient outcomes so that clinicians caring for sicker patients, whose outcomes may be less successful or who require greater health care resource utilization, do not experience financial penalties under current health care reform initiatives. In 2014, the CMS approved the USWR VLU healing rate quality measure, risk stratified by the WHI, and the USWR has since set a national benchmark rate for VLU healing. This quality measure can be reported by any wound care practitioner from any EHR that has incorporated the electronic clinical quality measure specifications, available free of charge on the USWR website.[41] In the Quality Payment Program, the CMS has committed to ensuring that reimbursement is closely tied to outcome, which is why the reporting of outcomes must be transparent and fair.[7] Absent risk stratification, practitioners have felt pressure to report impossibly high healing rates using methodologies that rely on the exclusion of the ulcers unlikely to heal.[4] The result is that practitioners and payers cannot justify the high cost associated with the most difficult-to-treat ulcers, the outcomes of which are simply not reported. This approach

jeopardizes future coverage of wound care services for the sickest patients. Reporting VLU healing in relationship to predicted likelihood of healing represents a significant change in the way wound outcomes are reported in the United States. However, doing so via the WHI stratification makes it possible to justify costs, quantify the impact of VLU treatments (*e.g.*, adequate compression at each visit, annual arterial screening), and understand the value of VLU interventions. Importantly, the venous community can use the WHI to show that VLUs otherwise predicted *not* to heal, in fact, may heal, if the patient undergoes appropriate intervention, thus validating such interventions. Likewise, because it incorporates patient specific factors, venous experts can use the WHI to explain why some VLUs fail to heal despite the correction of anatomical venous disease.

There are several study limitations. The WHI predicts likelihood of ever healing over any time frame and may therefore overestimate healing likelihood within the time frame typically used of 12–16 weeks; it does not predict likelihood of ulcer recurrence, an important concern. We believe limiting the model to variables available at the initial encounter is advantageous, because the WHI does not rely on the result of tests that may not always be performed or changes in wound characteristics over some time frame. Since the model is based on data available at the initial visit, we excluded VLUs that were missing key data points for that visit, even if they were collected at a subsequent encounter, because they might have impacted model validity. We also excluded both routine and advanced therapeutic interventions from the model, so that it could be used to assess the benefit of any intervention likely to influence healing. Wound care practitioners do not routinely use venous diagnostic assessment to diagnose VLUs. Instead, they use widely accepted, wound-specific clinical criteria. In fact, the entire field of wound care is predicated on the ability of a wound expert to make a reasonably accurate diagnosis based on well-established clinical criteria, without which it is not possible to make appropriate specialty referrals for arterial or venous intervention, serious infection, or the management of other ulcer types (*e.g.*, inflammatory ulcers). The mere presence of documented venous reflux cannot be used *a priori* to diagnose an ulcer as venous; patients with venous disease can have other ulcer types.

It is indeed possible that some nonvenous ulcers may have been included in this dataset due to intentional or unintentional misdiagnosis. (For example, clinicians may "code to coverage," because payers generally limit coverage of compression garments to active VLUs even though ulcers of many types require edema management.) We anticipate misallocation to represent a small portion of our large dataset and to be similar across centers.

Although only 44.1% of the original VLU dataset ($n = 11{,}773$) were analyzed, previous risk assessment tools were developed with fewer than 300 ulcers and suffered from significant selection bias.

The quality and consistency of clinical documentation vary across many practitioners and centers and may affect results. Because the specific EHR utilized internally audits the chart to determine both facility and physician billed level of service, charting completeness is incentivized without regard to individual physician or facility motivation for research. Direct transmission of data to the registry from the EHR eliminates selection bias and obviates the need for secondary data entry that erodes reliability. For over a decade, USWR data have demonstrated that the average patient with VLUs has three ulcers in contrast to other datasets reporting an average of one ulcer per patient, a difference likely attributable to selection bias.[4]

Another study limitation is that we computed a healing status for ulcers that had no outcome assigned at the final encounter. In the real world, many patients with ulcers that are "nearly" closed do not return to have their healing confirmed. On the contrary, many patients whose ulcers are not improving stop returning and are lost to follow-up. Including only ulcers with known outcomes would result in significant selection bias. In addition, we chose not to create an artificial time frame for healing assessment (*e.g.*, 12 or 16 weeks), because, in the real world, the much larger size of VLUs and the fact that patients have several VLUs at a time necessitates far longer periods of treatment than those used in RCTs. In addition, an artificial time cutoff might have prevented us from identifying all the factors that impact outcome.

Previous patient and wound risk stratification systems have strong limitations as practical tools and were created from relatively small datasets. The VLU WHI is a validated instrument derived from a large real-world dataset via direct-from-EHR to registry data transmission, which can predict likelihood of VLU healing using the following variables: wound size, wound age, number of concurrent wounds of any etiology, evidence of bioburden/infection, being nonambulatory, and patient hospitalization for any reason. The WHI can be used in clinical practice to identify patients likely to need advanced therapeutics, assess the value of treatments, strengthen the referral process to venous experts, to improve the gener-

alizability of RCTs, and to risk stratify patients whose outcomes are reported under MIPS.

KEY FINDINGS

- The VLU WHI predicts likelihood of VLU healing using the following patient- and wound-specific variables: number of concurrent wounds, wound size, wound age, evidence of bioburden/infection, being nonambulatory, and patient hospitalization for any reason.
- The VLU WHI can identify ulcers most likely to require advanced therapies to heal.
- The VLU WHI can prioritize referral to a venous expert and make it possible to understand the clinical impact of venous intervention.
- This risk stratification system can create more generalizable clinical trials involving VLUs.

INNOVATION

Previous wound scoring systems combine predictive healing variables and allocate points to each factor to identify VLUs that are likely to require advanced therapeutics, but they are not user-friendly and are rarely used. The VLU WHI is a comprehensive, validated risk stratification model for predicting VLU healing available through the USWR that incorporates the following predictive healing variables: number of concurrent wounds of any etiology, wound size, wound age, evidence of bioburden/infection, being nonambulatory, and hospitalization. The WHI is the CMS-accepted method for reporting VLU healing rates under the Quality Payment Program.

ACKNOWLEDGMENTS AND FUNDING SOURCES

Kinetic Concepts, Inc., partially funded this study. Strategic Solutions, Inc., funded this article.

AUTHOR DISCLOSURE AND GHOSTWRITING

C.E.F.: Baylor College of Medicine, Professor of Geriatrics, Houston, TX, Chief Medical Officer of Intellicure and Executive Director of the USWR, which is a 501 (c)(3) organization; S.D.H.: Adjunct Professor, University of Utah School of Medicine and formerly Senior Scientist, International Severity Information Systems, Inc., Salt Lake City, UT; no conflicts of interest.

The authors thank Kristen Eckert (Strategic Solutions, Inc., Cody, WY), who assisted with preparation of the article.

ABOUT THE AUTHORS

Caroline E. Fife, MD, did her residency in Family Medicine at the University of Texas, Southwestern in Dallas, followed by a Fellowship in Undersea and Hyperbaric Medicine (UHM) at Duke University, where she was subspecialty board-certified in UHM. She was Professor of Medicine in the Division of Cardiology at the University of Texas Health Science Center in Houston (1990–2013). A Certified Wound Specialist since 1998, she is now the Medical Director of the St. Luke's Wound Care Clinic in The Woodlands, Texas and a Professor of Geriatrics at Baylor College of Medicine in Houston. Dr. Fife is also the Chief Medical Officer of Intellicure, a Texas-based software company, and is the Executive Director of the USWR, a nonprofit organization which develops and reports wound care quality measures to facilitate physician participation in the MIPS. The USWR also provides data for comparative effectiveness studies in wound care.

Susan D. Horn, PhD, received her doctorate degree in statistics from Stanford University, Stanford, California. She was Professor at The Johns Hopkins University for 24 years before going to Utah to develop a new observational study design (called Practice-Based Evidence [PBE], controlling for severity of illness [using the Comprehensive Severity Index]).

SUPPLEMENTARY MATERIAL

Supplementary Table S1

REFERENCES

1. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ 2014;17:347–356.
2. Carter MJ, Fife, CE, Walker D, Thomson B. Estimating the applicability of wound-care randomized controlled trials to general wound care populations by estimating the percentage of individuals excluded from a typical wound care population in such trials. Adv Skin Wound Care 2009;22:316–324.
3. Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. Adv Wound Care (New Rochelle) 2018;7:77–94.
4. Fife CE, Eckert KA. Harnessing electronic healthcare data for wound care research: standards for reporting observational registry data obtained directly from electronic health records. Wound Repair Regen 2017;25:192–209.
5. Serena TE, Fife CE, Eckert KA, Yaakov RA, Carter MJ. A new approach to clinical research: integrating

clinical care, quality reporting, and research using a wound care network-based learning healthcare system. Wound Repair Regen 2017;25:354–365.

6. Kent D, Hayward R. Limitations of applying summary results of clinical trials to individual patients, the need for risk stratification. JAMA 2007;298:1209–1212.
7. Fife CE, Walker D, Eckert KA. Qualified Clinical Data Registries: how wound care practitioners can make the most out of MIPS. Adv Wound Care 2018;7:11.
8. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood) 2005;24:180–184.
9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff. 2016. www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf?source5govdelivery&utm_medium5email&utm_source5govdelivery (last accessed February 12, 2019).
10. Institute of Medicine. Key capabilities of an Electronic Health Record system (Electric Health Record Functional Model: Letter Report). Washington, DC: Institute of Medicine National Academies Press, 2003. www.nap.edu/catalog.php?record_id=10781. (last accessed November 6, 2018).
11. Horn SD, Fife CE, Smout RJ, Barrett RS, Thomson B. Development of a wound healing index for patients with chronic wounds. Wound Rep Regen 2013;21:823–832.
12. Patient-Centered Outcomes Research Institute (PCORI). Cooperative agreement funding announcement: improving infrastructure for conducting patient-centered outcomes research. The National Patient-Centered Clinical Research Network. Clinical Data Research Networks (CDRN)—Phase One. April 23, 2013. http://pcori.org/assets/PCORI-CDRN-Funding-Announcement-042313.pdf. (last accessed November 6, 2018).
13. Milic DJ, Zivic SS, Bogdanovic DC, Karanovic ND, Golubovic ZV. Risk factors related to the failure of venous leg ulcers to heal with compression treatment. J Vasc Surg 2009;49:1242–1247.
14. Kiguchi MM, Hager ES, Winger DG, Hirsch SA, Chaer RA, Dillavou ED. Factors that influence perforator thrombosis and predict healing with perforator sclerotherapy for venous ulceration without axial reflux. J Vasc Surg 2014;59:1368–1376.
15. Prince S, Dodds SR. Use of ulcer size and initial responses to treatment to predict the healing time of leg ulcers. J Wound Care 2006;15:299–303.
16. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. The accuracy of venous leg ulcer prognostic models in a wound care system. Wound Repair Regen 2004;12:163–168.
17. Flanagan M. Improving accuracy of wound measurement in clinical practice. Ostomy Wound Manage 2003;49:28–40.
18. Gelfand JM, Hoffstad O, Margolis DJ. Surrogate endpoints for the treatment of venous leg ulcers. J Invest Dermatol 2002;119:1420–1425.
19. Meaume S, Couilliet D, Vin F. Prognostic factors for venous ulcer healing in a non-selected population of ambulatory patients. J Wound Care 2005; 14:31–34.
20. Taylor RJ, Taylor AD, Smyth JV. Using an artificial neural network to predict healing times and risk factors for venous leg ulcers. J Wound Care 2002; 11:101–105.
21. Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008;16:19–22.
22. Marston WA, Ennis WJ, Lantis JC 2nd, et al. HP802-247 Study Group. Baseline factors affecting closure of venous leg ulcers. J Vasc Surg Venous Lymphat Disord 2017;5:829–835.e1.
23. Kulkarni SR, Gohel MS, Wakely C, Minor J, Poskitt KR, Whyman MR. The Ulcerated Leg Severity Assessment score for prediction of venous leg ulcer healing. Br J Surg 2007;94:189–193.
24. Gohel MS, Taylor M, Earnshaw JJ, Heather BP, Poskitt KR, Whyman MR. Risk factors for delayed healing and recurrence of chronic venous leg ulcers—an analysis of 1324 legs. Eur J Vasc Endovasc Surg 2005;29:74–77.
25. Lantis JC 2nd, Marston WA, Farber A, et al. The influence of patient and wound variables on healing of venous leg ulcers in a randomized controlled trial of growth-arrested allogeneic keratinocytes and fibroblasts. J Vasc Surg 2013;58:433–439.
26. Kecelj Leskovec N, Perme MP, Jezersek M, Mozina J, Pavlović MD, Lunder T. Initial healing rates as predictive factors of venous ulcer healing: the use of a laser-based three-dimensional ulcer measurement. Wound Repair Regen 2008;16:507–512.
27. Margolis DJ, Gross EA, Wood CR, Lazarus GS. Planimetric rate of healing in venous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. J Am Acad Dermatol 1993; 28:418–421.
28. Parker CN, Finlayson KJ, Edwards HE. Ulcer area reduction at 2 weeks predicts failure to heal by 24 weeks in the venous leg ulcers of patients living alone. J Wound Care 2016;25:626–634.
29. Hoffman R, Noble J, Eagle M. The use of proteases as prognostic markers for the healing of venous leg ulcers. J Wound Care 1999;8:273–276.
30. Stanley A, Osler T. Senescence and the healing rates of venous ulcers. J Vasc Surg 2001;33: 1206–1211.
31. Treiman GS, Oderich GS, Ashrafi A, Schneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. J Vasc Surg 2000;31: 1110–1118.
32. Kerstein MD, Brem H, Giovino KB, Sabolinski M. Development of a severity scale for evaluating the need for Graftskin in nonhealing venous ulcers. Adv Skin Wound Care 2002;15:66–71.
33. Falanga V, Saap LJ, Ozonoff A. Wound bed score and its correlation with healing of chronic wounds. Dermatol Ther 2006;19:383–390.
34. Edwards HE, Parker CN, Miller C, et al. Predicting delayed healing: the diagnostic accuracy of a venous leg ulcer risk assessment tool. Int Wound J 2018;15:258–265.
35. Parker CN, Finlayson KJ, Edwards HE. Predicting the likelihood of delayed venous leg ulcer healing and recurrence: development and reliability testing of risk assessment tools. Ostomy Wound Manage 2017;63:16–33.
36. Renner R, Simon JC. Mathematical modeling of venous ulcer healing rates after implantation of keratinocytes: new ways to predict the efficacy of wound healing after regenerative methods. Wound Repair Regen 2010;18:624–628.
37. Cardinal M, Phillips T, Eisenbud DE, Harding K, Mansbridge J, Armstrong DG. Nonlinear modeling of venous leg ulcer healing rates. BMC Dermatol 2009;9:2.
38. Jessup RL. What is the best method for assessing the rate of wound healing? A comparison of 3 mathematical formulas. Adv Skin Wound Care 2006;19:138–147.
39. Cardinal M, Eisenbud DE, Armstrong DG. Wound shape geometry measurements correlate to eventual wound healing. Wound Repair Regen 2009;17:173–178.
40. Geris L, Gerish A, Schugar RC. Mathematical modeling in wound healing, bone regeneration, and tissue engineering. Acta Biotheor 2010;58: 355–367.
41. U.S. Wound Registry. Quality Measures Provided by the US Wound & Podiatry Registries. https://uswoundregistry.com/quality-measures/(last accessed May 30, 2019).

Abbreviations and Acronyms

AUC = area under the receiver operating characteristic curve
BMI = body mass index
CDRN = clinical data research network
CMS = The Centers for Medicare and Medicaid Services
EHR = electronic health record
ICD-9 CM = International Classification of Diseases, 9th edition, Clinical Modification
MIPS = the merit-based incentive payment system
PVD = peripheral vascular disease
QCDR = qualified clinical data registry
RCT = randomized controlled trial
ULSA = ulcerated leg severity assessment
USWR = U.S. Wound Registry
VLU = venous leg ulcer
VRT = venous refill time
WHI = the wound healing index