Risk factors associated with the venous leg ulcer that fails to heal after 1 year of treatment

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ABSTRACT

Background: Despite regular treatment of venous leg ulcers (VLUs), some fail to heal. Although several risk factors have previously been identified to be associated with the failure of VLUs to heal, the majority of studies are limited to <24-week follow-up.

Methods: A retrospective cohort study was performed at an academic vascular and wound center. A total of 65 patients with VLUs who were observed for a year or more were identified. These patients underwent a variety of treatments following the Society for Vascular Surgery and American Venous Forum VLU guidelines. Risk factors, which were based on previously defined elements for failure of VLUs to heal after a period of treatment, were examined. Both univariate (unadjusted) and multivariate (adjusted) logistic regression analyses were used to assess the magnitude of effect that a given risk factor had on healing.

Results: Of 65 patients treated for a minimum of 52 weeks, 19 (29%) remained unhealed. By univariate analysis, deep venous disease ($P = .01$; odds ratio [OR], 5.82; 95% confidence interval [CI], 1.49-22.72), history of deep venous thrombosis ($P < .001$; OR, 14.06; 95% CI, 3.77-52.39), and depression ($P = .04$; OR, 3.89; 95% CI, 1.10-13.80) were all shown to be significant risk factors for nonhealing. The patient's race (ie, being nonwhite; $P = .02$; OR, 103.45; 95% CI, 1.94-5.53 $\times 10^3$), deep venous disease ($P = .05$; OR, 37.0; 95% CI, 1.05-1.31 $\times 10^3$), and history of deep venous thrombosis ($P = .01$; OR, 122.4; 95% CI, 3.09-4.84 $\times 10^3$), however, were all shown to be significant for nonhealing under multivariate analysis. In addition, identification of an incompetent perforator ($P = .02$; OR, 0.006; 95% CI, 9.27 $\times 10^{-5}$-0.44) was conversely shown to be a good prognostic factor for healing.

Conclusions: This study confirmed that risk factors known to be associated with the failure of a VLU to heal—deep venous disease and post-thrombotic etiology—were significant at 52 weeks, whereas depression and race (nonwhite) are novel risk factors. An analysis of markers of access to care showed no difference between white and nonwhite, suggesting other factors as a cause. The predominance of deep venous disease in the unhealed vs healed cohort (84% vs 48%) highlights the need for a viable treatment option for deep venous disease due to reflux. Overall, this study emphasizes the need to consider all risk factors when evaluating a patient for VLU to coordinate an effective treatment plan and to identify gaps in our treatment. (J Vasc Surg: Venous and Lym Dis 2019;7:98-105.)

Keywords: Prolonged treatment; Venous ulcer; Recalcitrant ulcer; Risk factors

Venous leg ulcers (VLUs) are frequently associated with a high cost of care, loss of productivity, pain, and reduced quality of life. VLUs represent the largest proportion of chronic lower extremity wounds and affect approximately 1% of the total population.[1,2] The prevalence of venous disease is likely to increase with the aging population and the worsening epidemic of obesity, known risk factors for lower extremity venous disease. Furthermore, the economic burden of chronic venous insufficiency is impactful, representing 2.5% of the total health care budget in industrialized nations.[3,4]

VLUs may be treated by a variety of providers, including primary care physicians, dermatologists, infectious disease specialists, and vascular surgeons; they are the most common ulcer treated in wound centers. Despite treatment, some VLUs ultimately fail to heal. For example, the randomized controlled Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) trial[5] observed a 65% healing rate at 6 months (thus 35% nonhealed), and subsequently 21% unhealed at 12 months in 341 VLU patients treated either with both compression and wound care or with the addition of an intervention on the great saphenous vein (GSV). It is important to identify risk factors

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associated with delayed healing to construct an effective treatment strategy during the initial evaluation of a wound, to highlight gaps in available treatment modalities, or to initiate more aggressive interventions.

Previous studies have identified various risk factors associated with delayed ulcer healing, including the patient's age, body mass index, wound area, ulcer chronicity, impairment of calf muscle pump, deep venous reflux, and history of deep venous thrombosis (DVT).[6-9] For the majority of publications, however, the length of follow-up was limited to a 24-week period or less, in addition to using patients who underwent compression therapy only. Furthermore, there is a paucity of available literature on the subject, which is often contradictory.

The aim of this study was to identify influential risk factors associated with the failure of a VLU to heal despite maximal therapy under the clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum (SVS/AVF VLU guidelines)[10] for a minimum of 52 weeks at a vascular surgeon-staffed wound center within an academic medical center.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Take Home Message:** Sixty-five patients were treated for venous leg ulcers (VLUs) for a minimum of 52 weeks in a vascular surgeon-staffed wound center within an academic medical center; VLUs in 19 (29%) failed to heal. Nonwhite race, history of deep venous thrombosis, deep venous disease, and depression were risk factors for nonhealing. Ulcer size and obesity did not influence healing.
- **Recommendation:** In patients with VLUs, novel risk factors, such as depression and race, predicted nonhealing in addition to traditional risk factors, such as a history of deep venous thrombosis and deep venous disease.

METHODS

Patients. Fig 1 details an outline of the study design. A retrospective review was performed of patients treated at The Center for Vascular, Wound Healing, and Hyperbaric Medicine at Tufts Medical Center (Boston, Mass) between 2005 and 2015. A total of 121 patients who were diagnosed with and treated for Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) class C6 VLUs were identified. Patients underwent active treatment only until the ulcer healed; this included in-person wound care in addition to any necessary procedures and operations. Once a patient healed, the patient was no longer considered to be undergoing active treatment but was still followed up for a minimum of 1 year from the initial presentation date to manage chronic venous insufficiency and to monitor for any ulcer recurrence (Fig 2). To be included in the study, patients had to have met all of the following criteria: an ulcer of venous origin located from the ankle to the knee; a minimum of 52 weeks of follow-up; serial wound measurements taken at each visit; and a documented duplex ultrasound examination with imaging and valve closure times. Lastly, patients must have either never healed their ulcers or permanently healed their ulcers within the 12-month period. As the focus was on healing, patients whose ulcers healed and then recurred were excluded. Patients without wound measurements were excluded because of the inability to calculate ulcer size, and patients with no duplex ultrasound examination were excluded because valve closure times are necessary to assign the diagnosis of superficial vs deep venous reflux. With use of these inclusion criteria, 56 patients were excluded, leaving a total of 65 patients in this study of VLU healing. From this group of 65 patients, 19 patients never healed their VLUs by the end of the 1-year follow-up period (the nonhealed cohort). In regard to concomitant arterial disease in study patients, all patients in our center were evaluated by vascular surgeons for palpable pedal pulses. If palpable pulses were not present, patients received testing for ankle-brachial pressure indices by Doppler interrogation. If significant arterial disease was present, appropriate treatment addressing underlying arterial disease was carried out. Data collection and review were conducted after approval by the Tufts Medical Center Institutional Review Board, which granted a waiver in regard to obtaining individual patient informed consent because the data analysis would be performed on deidentified data.

Risk factors. Potential risk factors for a VLU not to heal were chosen on the basis of previously defined factors in the literature. Treatment disparity factors included age (years), sex, and race (white vs nonwhite). Disease-specific factors included ulcer size, superficial venous disease (reflux), deep venous disease (reflux and obstruction), presence of an incompetent perforator around the ulcer site, documented history of a superficial venous procedure in the affected limb, and duplex ultrasound-verified history of DVT in the affected limb. Last, potential systemic factors included hypertension, obesity, diabetes mellitus, congestive heart failure, depression, history of smoking (former and current), and presence of an inflammatory or autoimmune condition predisposing to chronic steroid use.

To establish the diagnosis of venous reflux, valve closure times >0.5 second in the superficial system and >1.0 second in the deep system were used. Initial screening for deep venous outflow obstruction of the external or common iliac veins (the outflow segments) involved duplex ultrasound assessment of the common femoral vein for normal respiratory variations in blood

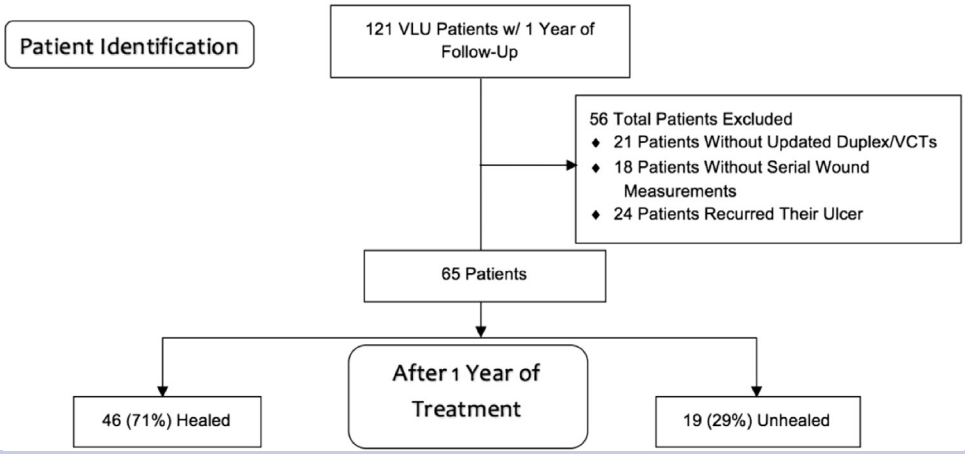

Fig 1. Study design. *VCTs,* Valve closure times; *VLU,* venous leg ulcer.

flow and, if body habitus allowed, direct imaging of the iliac veins. When duplex ultrasound screening was suggestive of outflow obstruction, patients underwent subsequent testing including magnetic resonance venography, ascending phlebography, and intravascular ultrasound. If initial findings on duplex ultrasound screening were normal but a patient's ulcer remained unhealed after 6 months of active treatment, deep venous obstruction was assessed by using the modalities of magnetic resonance venography and intravascular ultrasound.

Treatment. Under the leadership of vascular surgeons, patients were seen and treated by a multidisciplinary team, which included plastic surgeons, infectious disease physicians, and wound care nurses. Patients received a variety of treatments for their ulcers based on the SVS/AVF VLU guidelines.[10] Treatment modalities included appropriate compression therapy; surgical wound debridement; split-thickness skin grafting; ligation and stripping of the GSV or small saphenous vein (SSV); ligation of an incompetent perforator by an open or subfascial endoscopic technique; endovenous ablation of the GSV, SSV, or incompetent perforator; and iliac vein balloon angioplasty and stenting. We categorized a patient's initial type of compression therapy as follows: high-pressure therapy as recommended by SVS/AVF VLU guidelines[10]; elastic stockings; and low-pressure compression. Detailed subtypes of therapy can be seen in Table I.

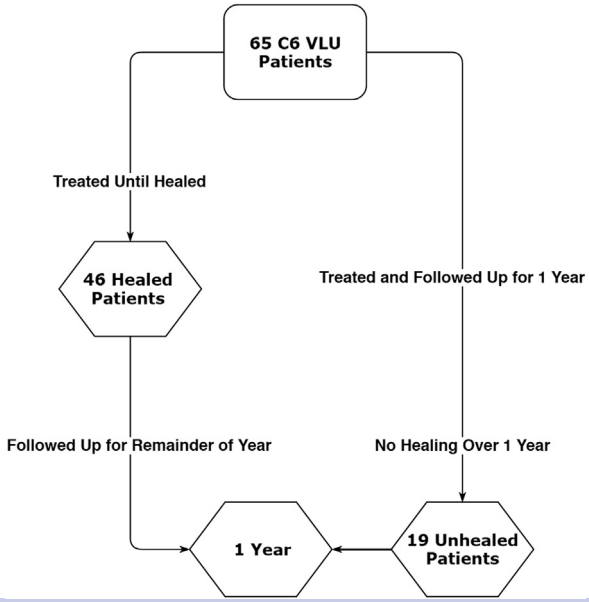

Fig 2. Treatment and follow-up. *VLU,* Venous leg ulcer.

Statistical analysis. Specific risk factors were assessed using both univariate (unadjusted) and multivariate (adjusted) logistic regression, producing an estimated odds ratio and 95% confidence interval. Age and ulcer size were analyzed as continuous variables, whereas all others were categorical. To compare means between two groups, a two-sample *t*-test was conducted. Statistical significance was established at $P = .05$. Data were compiled in Excel 2016 (Microsoft, Redmond, Wash), and all statistical analyses were performed using Stata 14 (StataCorp LP, College Station, Tex).

RESULTS

A total of 65 patients with open VLUs (C6) were treated and followed up for an average of 378 days in the study. The average age of the patients was 60 years, with an average ulcer size of 14.3 cm^2 (area) at the initial visit. By the end of this 12-month study, 19 patients (29%) had never healed the ulcer, whereas 46 (71%) patients healed and remained permanently healed during the entire follow-up period (Fig 3).

Table II represents ulcer characteristics in the two groups. The proportion of secondary and post-thrombotic

Table I. Compression therapy

	Healed (n = 46), % (No.)	Unhealed (n = 19), % (No.)	*P*
SVS/AVF guideline recommended	63 (29)	53 (10)	.44
4-Layer compression	48 (22)	32 (6)	.24
CircAid	2 (1)	10.5 (2)	.14
Unna boot	13 (6)	10.5 (2)	.78
Elastic stockings	20 (9)	26 (5)	.55
Prescription stockings	13 (6)	21 (4)	.42
Elastic compression	7 (3)	5 (1)	.85
Low-pressure compression	17 (8)	21 (4)	.73
ACE bandage	11 (5)	10.5 (2)	.97
Tubigrip	4 (2)	10.5 (2)	.35
Kerlix wrap	2 (1)	0 (0)	.52

AVF, American Venous Forum; *SVS*, Society for Vascular Surgery.

Table II. Patients' ulcer characteristics

	Healed cohort (n = 46), % (No.)	Unhealed cohort (n = 19), % (No.)	*P*
Primary etiology	78 (36)	32 (6)	**<.001**
Secondary etiology	22 (10)	63 (12)	**.001**
Congenital etiology	0 (0)	5 (1)	.13
Duplex ultrasound-documented post-thrombotic	11 (5)	63 (12)	**<.0001**
Superficial venous reflux	83 (38)	63 (12)	.09
Overall deep venous disease	48 (22)	84 (16)	**.006**
Deep venous reflux	48 (22)	79 (15)	**.02**
Deep venous obstruction	15 (7)	42 (8)	**.02**
Incompetent perforator around ulcer	24 (11)	5 (1)	.08

Boldface values indicate statistical significance.

ulcers (validated by characteristic changes on duplex ultrasound imaging) was significantly higher in the unhealed cohort, as was the presence of deep venous reflux and obstruction.

The types of initial compression therapy were similar between the two groups (Table I). Low-pressure compression, however, was employed by those 12 patients who could not tolerate high-compression garments. The healed cohort received significantly more interventions to the GSV and SSV ($P = .03$) and, when combined with perforator interventions, outweighed the unhealed group 85% (39/46) to 63% (12/19; $P = .06$). The unhealed cohort received more interventions to the deep venous system (ie, iliac stenting) during the study ($P = .01$; Table III).

On univariate logistic regression, three risk factors were identified as being significant for not healing: deep venous disease, history of DVT in the affected limb, and history of depression (Table IV). The same risk factors were analyzed using multivariable logistic regression. This analysis showed that depression was no longer a significant risk factor, but being nonwhite achieved significance as an independent factor for a VLU not to heal (Table IV). In addition, under multivariate analysis, the presence of an incompetent perforator around the ulcer site was conversely shown to be a favorable prognostic factor for healing. Given the multifactorial nature of VLUs, there is an expected discrepancy between univariate and multivariate analysis. With multivariable analysis, the potential for confounding is removed. Thus, the factors that were identified represent true independent risk factors for nonhealing; that is, if all other factors are kept constant, the addition of this factor by itself will produce the presented effect.

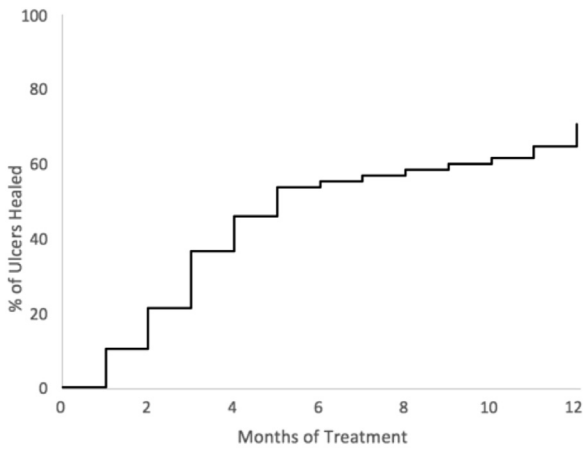

Fig 3. Kaplan-Meier analysis of ulcer healing for all patients.

An additional analysis of VLUs restricted to the healed cohort addressed ulcer healing time. The influence of the same risk factors on length of time (in days) until an ulcer healed was assessed. All risk factors were nonsignificant in both univariate and multivariate linear regression, except that the presence of congestive heart failure was significant for delayed healing in only univariate analysis ($P = .02$).

Table V highlights crude factors that might affect access to health care between whites and nonwhites. Whereas the proportion of Medicaid coverage was significantly higher in nonwhites, there was no significant difference in the number of visits during the 1-year study period or in the number of procedures (iliac stenting and superficial surgery or ablation) performed. Patients in both groups were seen, at the minimum, on a monthly basis in clinic; in addition, the majority had home wound care by visiting nurses.

Table III. Treatment

	Healed (n = 46), % (No.)	Unhealed (n = 19), % (No.)	*P*
Compression only	37 (17)	42 (8)	.70
Intervention to GSV or SSV during study	50 (23)	21 (4)	**.03**
Intervention to GSV or SSV before study	22 (10)	37 (7)	.21
Total with history of GSV or SSV intervention	65 (30)	58 (11)	.58
Perforator surgery during study	15 (7)	5 (1)	.27
Perforator surgery before study	4 (2)	0 (0)	.36
Total with history of perforator surgery	20 (9)	5 (1)	.15
Iliac stenting during study	11 (5)	37 (7)	**.01**
Iliac stenting before study	0 (0)	5 (1)	.12
Total with history of iliac stenting	11 (5)	37 (7)	**.01**

GSV, Great saphenous vein; *SSV*, small saphenous vein.
Boldface values indicate statistical significance.

DISCUSSION

Identifying risk factors associated with an ulcer that fails to heal, despite 1 year of VLU guidelines-directed treatment, has important implications for both patients and providers. Patients can be informed of the difficult path they may face, and providers will be given the opportunity to alter treatment protocols accordingly.

Multiple previous studies have demonstrated that the patient's age and ulcer size are prognostic factors for poor ulcer healing; however, in this study, these were shown not to be significant in either univariate or multivariate analysis.[6,8,11-17] All but one of these previous studies had a time frame of 24 weeks or less to be considered nonhealing, whereas this study extended the definition of nonhealing to 52 weeks. The extra 28 weeks of treatment is the likely explanation for these risk factors for nonhealing becoming insignificant, as it provides a greater length of time for the VLU to heal. An additional analysis of ulcer size was conducted; rather than considering size as a continuous variable, we assigned ulcers into one of three categories, <5 cm^2, 5-20 cm^2, and >20 cm^2, similar to the study conducted by Marston et al.[18] Ulcers >20 cm^2 were shown to be significant for nonhealing in univariate analysis, but when corrected for other factors in multivariate analysis, the effect of size on VLU healing was again negligible. Previous studies have also consistently shown that ulcer duration before initiation of treatment is associated with delayed healing.[6,11,15-17,19,20] One limitation of our study is that duration of ulcer before treatment was not consistently available because of lack of this specific information on a retrospective chart review.

Both groups of patients received the recommended time-honored treatment of VLU care—compression and wound care. Nearly 80% of the patients in both groups were provided a variety of high-compression garments, with a smaller fraction of patients who were unable to tolerate these garments long term (Table I). As has been noted in other studies, it is difficult to ensure and objectively to document compliance with wearing of these garments. In this study, deep venous disease (ie, reflux and obstruction) was shown to be a significant

Table IV. Demographics and unadjusted (single variable) and adjusted (multivariable) odds ratios (*ORs*) for risk factors

Risk factor	Healed (n = 46)	Unhealed (n = 19)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age, years	60.3	60.42	1.00 (0.97-1.04)	.97	0.99 (0.92-1.06)	.76
Male	63 (29)	58 (11)	0.81 (0.27-2.40)	.70	0.87 (0.10-7.67)	.90
Nonwhite	**33 (15)**	**42 (8)**	**1.50 (0.50-4.51)**	**.47**	**103.45 (1.94-5.53 × 10^3)**	**.022**
Size of ulcer, cm^2	11.5	20.9	1.02 (0.99-1.04)	.15	1.02 (0.98-1.07)	.34
Superficial venous disease	83 (38)	63 (12)	0.36 (0.11-1.20)	.10	1.45 (0.08-25.20)	.80
Deep venous disease	**48 (22)**	**84 (16)**	**5.82 (1.49-22.72)**	**.011**	**37.0 (1.05-1.31 × 10^3)**	**.047**
Incompetent perforator	**24 (11)**	**5 (1)**	**0.17 (0.02-1.40)**	**.10**	**0.006 (9.27 × 10^{-5}-0.44)**	**.019**
History of superficial venous surgery	22 (10)	37 (7)	1.25 (0.65-6.74)	.21	5.83 (0.36-94.77)	.22
DVT	**11 (5)**	**63 (12)**	**14.06 (3.77-52.39)**	**<.001**	**122.4 (3.09-4.84 × 10^3)**	**.01**
Hypertension	65 (30)	63 (12)	0.91 (0.30-2.78)	.88	4.35 (0.36-52.11)	.25
Obesity	37 (17)	47 (9)	1.53 (0.52-4.53)	.43	0.96 (0.11-8.72)	.97
Diabetes mellitus	20 (9)	21 (4)	1.10 (0.29-4.11)	.89	0.68 (0.03-16.79)	.82
Congestive heart failure	17 (8)	5 (1)	0.26 (0.03-2.27)	.23	0.03 (3.49 × 10^{-5}-23.16)	.30
Depression	**13 (6)**	**37 (7)**	**3.89 (1.10-13.80)**	**.036**	**3.73 (0.21-66.99)**	**.37**
Smoking history	33 (15)	37 (7)	1.20 (0.39-3.69)	.74	10.56 (0.34-324.5)	.18
Inflammatory condition	4 (2)	11 (2)	2.59 (0.34-19.87)	.36	34.88 (0.49-2.49 × 10^3)	.10

CI, Confidence interval; *DVT*, deep venous thrombosis.
Categorical variables are presented as % (number). Continuous variables are presented as mean. Boldface values indicate statistical significance.

Table V. Access measures

	Whites (n = 42)	Nonwhites (n = 23)	*P*
No. of visits in 1 year	11.9	12.9	.71
Patients with procedure performed	62 (26)	65 (15)	.80
Patients with procedure performed before study	31 (13)	13 (3)	.11
Patients with private insurance	40 (17)	22 (5)	.13
Patients with Medicare	55 (23)	57 (13)	.89
Patients with Medicaid	5 (2)	22 (5)	**.04**

Categorical variables are presented as % (number). Continuous variables are presented as mean. Boldface values indicate statistical significance.

risk factor for failure to heal, as initially described by the St. Thomas' group[21] and subsequently by others.[8,11,19,22,23] In previous studies, however, a history of DVT is associated with inconsistent results. For example, Guest et al[13] and Moffatt et al[24] found history of DVT to be a poor prognostic factor, whereas Karanikolic et al[7] and Milic et al[9] had contradictory results. By contrast, our study demonstrates that duplex ultrasound-defined post-thrombotic VLUs fare worse, rather than a simple history of DVT used in previous studies. Given these results, it is crucial that acute DVT of the proximal venous outflow tract be treated appropriately by pharmacomechanical catheter-directed thrombolysis to prevent the development of deep venous reflux or obstruction. Whereas the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial[25] failed to show an impact on the overall frequency of post-thrombotic syndrome, it did show benefit in a subset of iliofemoral DVT patients who were treated, particularly in those with more severe symptoms. On the other hand, once deep venous reflux or proximal deep venous obstruction is identified, aggressive treatment is beneficial. Although it has not been shown in randomized trials, previous large observational studies have demonstrated that stenting for outflow obstruction aids in ulcer healing.[26] In addition, the recent Venogram vs IVUS for Diagnosing Iliac vein Obstruction (VIDIO) trial[27] showed clinical improvement in patients 6 months after stenting for outflow obstruction or stenosis. In regard to deep venous reflux, several older series have addressed open valve repair,[28,29] but most of the current attention has focused on the development of a novel therapy for deep venous reflux, such as a durable open[30] or percutaneous neovalve procedure. As the ESCHAR trial[31] showed, patients with "total deep venous reflux" fail to benefit from the treatment of superficial venous reflux in regard to lowering recurrence.

The influence of depression on overall poor outcomes in vascular patients is not novel,[32] but it is unique as a specific risk factor for delayed healing of VLUs. Patients with a history of depression were shown to be at risk for not closing their ulcer within the study period; this was significant only in univariate analyses. One explanation may be that depressed patients are more likely to be noncompliant with treatment, which can further delay healing.[33]

Interestingly, our study demonstrated that the presence of an incompetent perforator, specifically around the ulcer site, was a favorable independent prognostic factor for healing. We hypothesize the reason for this is that an incompetent perforator in isolation represents a treatable cause of ulceration. Eleven of 12 incompetent perforators were in the healed cohort, with 8 of 12 treated. Gloviczki et al,[34] Iafrati et al,[35] and Nelzen and Fransson[36] have previously shown the treatment of incompetent perforators around the ulcer site to be beneficial. The recent 10-year follow-up of the Dutch subfascial endoscopic perforator surgery (SEPS) randomized controlled trial[37] demonstrated a greater ulcer-free period of 58.9%, its primary outcome measure, for the SEPS group vs the control compression-only group (39.6%; $P < .00$). This finding has important implications for resource utilization and costs, as the SEPS group has a healed VLU for a longer time. Perforator treatment is currently recommended in SVS/AVF VLU guidelines.[10]

The Institute of Medicine defines health care disparities as "differences in the quality of health care that are not due to access-related factors or clinical needs, preferences or appropriateness of intervention."[38] Being nonwhite was independently associated with nonhealing in our study. The relationship between race/ethnicity and VLU is severely limited by the lack of inclusion of this factor in previous epidemiologic surveys on venous disease. Only the San Diego Population Study[39] and the AVF Screening Survey[40] provided data on race and ethnicity. Our observations contrast with the findings of Criqui et al,[39] whose cross-sectional multiethnic survey found that there is no increased risk for advanced venous disease in Asian, Hispanic, and non-Hispanic whites and African American men. They did note, however, a significantly lower risk for advanced venous disease in African American women. In our study, the population of nonwhites was broader and consisted of African Americans, Hispanics, and Asian Americans. Whereas the nonwhite category had a higher proportion of Medicaid coverage, it appears there was no treatment disparity at our wound center, as both the number of visits in the study and the number of appropriate interventions performed on each patient were the same between whites and nonwhites. This suggests that these patients may have an unidentified biologic risk or are experiencing additional risk factors not measured in this study, such as environmental stressors or poor nutrition. For example, previous studies have identified specific genetic factors in white patients with VLU, such as the "Viking gene,"[41] prevalent in northern European coastal areas, the northern

United Kingdom, Scotland, and Ireland—areas where the Vikings conquered, settled, and intermarried. One gene mutation, the hemochromatosis C282Y gene, is associated with disorders in iron metabolism, specifically in VLU, whereby mutated macrophages may release more iron from inside the cell, with this effect being related to ulcer appearance.[41] Only a few previous studies have analyzed race as a risk factor for delayed VLU healing, with results being contradictory; however, these studies again used a time frame of 24 weeks or less. In the study of Jones,[14] being nonwhite was shown to be a poor prognostic factor for VLU healing, whereas in the study of Phillips et al,[17] race was nonsignificant. Looking even more broadly, previous studies with vascular patients, such as that of Loja et al,[42] addressing prognoses of peripheral artery disease have demonstrated similar results to our study, with nonwhites experiencing worse outcomes than whites. With race becoming a more prevalent risk factor, it is imperative that future studies consider including race in their analyses; and more important, a larger and more in-depth study looking specifically at race in regard to VLU healing should be conducted to parse out what specifically is placing nonwhites at risk.

One major limitation of this study is the relatively small sample size of 65 patients. Whereas a total of 121 patients were identified to have been treated for CEAP C6 VLUs for a minimum of 1 year in our center, 56 of these patients were excluded for various reasons. Although it was unfortunate to exclude these patients, the multivariate statistical analysis requires exclusion of patients with missing variables, in this case, ulcer size and the duplex ultrasound-derived valve closure times required for the diagnosis of deep vs superficial reflux. In addition, a large proportion of patients were excluded because their ulcer recurred during the 1-year follow-up period. Because this study was focused on ulcer healing and not on ulcer recurrence, recurrent ulcer patients were excluded. As has been demonstrated in several studies, such as those of Gohel et al[6] and Labropoulos et al,[8] healing and recurrence are two individual events, with a separate set of risk factors.

CONCLUSIONS

This study demonstrates that history of DVT and presence of deep venous disease continue to be important risk factors associated with nonhealing of a VLU despite maximal therapy for 52 weeks. Novel risk factors identified, which would benefit from larger studies, include depression and the patient's race.

AUTHOR CONTRIBUTIONS

Conception and design: TO
Analysis and interpretation: RM, TO, LS, MI
Data collection: RM
Writing the article: RM
Critical revision of the article: TO, LS, MI
Final approval of the article: RM, TO, LS, MI
Statistical analysis: RM, MI
Obtained funding: Not applicable
Overall responsibility: RM

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