

Report

Venous ulcer: clinical characteristics and risk factorsLuciana P. F. Abbade¹, MD, PhD, Sidnei Lastória², MD, PhD, and
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Abstract

Background Lower limb venous ulceration ranks among the 10 most common medical problems in Western countries and has significant socioeconomic impact. The aim of this study was to identify the risk factors for unhealed, recurrent, and large ulcers and to characterize patients with active or recently healed venous ulcers.

Methods We identified 97 patients and assessed 103 ulcerated limbs in 90 patients. All patients underwent clinical examination, arterial and venous system evaluation, ankle-brachial index determination, and ultrasound of the affected limb. Clinical characteristics included age, gender, race, ulcer duration, time since first episode, history of recurrence, localization of ulcer, ulcer area, eczema, ochre dermatitis, lipodermatosclerosis, pain, body mass index, and medical history data. Risk factors were identified by univariate analysis and estimated odds ratios.

Results We assessed 90 patients (103 limbs) with active or healed venous leg ulcers, of whom 84.4% were Caucasian and 68.9% were female. Mean age was 56.0 ± 13.3 years. Ulcers had remained unhealed for <1 year in 40.7%. Lipodermatosclerosis, lower limb hyperpigmentation, edema, and eczema were seen in 96.7%, 95.6%, 94.4%, and 51.1% of patients, respectively. Pain was a frequent symptom in 74.4%. Body mass index was assessed in 85 patients: 30.6% were slightly, 36.5% moderately, and 7% severely obese. Patient age >60 years (odds ratio [OR] 4.0), extensive lipodermatosclerosis (OR 8.7), and previous history of ulceration (OR 19.9) were risk factors for unhealed ulcers. Time since first ulcer episode ≥ 2 years (OR 29.2) and incompetence of venous systems (OR 1.6) were risk factors for recurrence.

Conclusions Longstanding and large ulcers and recurrences are the main problems encountered by venous ulcer patients. Severe lipodermatosclerosis, previous ulcer history, and time since first ulcer episode ≥ 2 years are significant risk factors.

Introduction

Lower limb venous ulceration represents the most advanced stage of chronic venous disorder (CVD).¹ It is a common problem in Western countries and has a significant socioeconomic impact.^{2,3} In the USA, the estimated annual cost of treatment for venous ulcerations is US\$1.9–2.5 billion, and CVD is among the 10 most common reasons for seeking medical care.⁴

Prevalences of venous ulcers range from 0.06% to 2%^{4,5} and exceed 4% in the population aged >65 years.⁶ Venous ulcers usually remain unhealed for a long time, tend to be recurrent, and are of variable size, ranging from small to the full circumference of the leg.

Given the scarcity of information on the factors correlated with unhealed, large, and recurrent ulcerations, the aim of this study was to identify the risk factors for these

variables and to characterize patients with active or recently healed venous ulcers.

Materials and Methods

In this descriptive study, subgroup analysis was used to assess the risk factors correlated with unhealed, recurrent, and large ulcers. We assessed all patients with venous leg ulcers who were managed in the Ulcer Outpatient Clinic (Dermatology Department) at Botucatu Medical School Hospital, São Paulo State University (UNESP), between March 1998 and October 2003, with the exception of patients with associated peripheral arterial disease. We analyzed 103 ulcerated limbs in 90 patients.

Venous ulcer was defined as ulceration in the lower limb with one or more of the following symptoms: edema; hyperpigmentation; eczema; lipodermatosclerosis; and varices

(Fig. 1). A recently healed ulcer associated with the skin alterations described above was classified as C5 according to the CEAP (clinical, etiology, anatomy, pathophysiology) clinical severity score. All patients underwent a clinical examination and evaluation of the arterial and venous system carried out by a dermatologist and a vascular surgeon. The ankle-brachial index (ABI) was determined, and duplex ultrasound (US) scanning of the affected limb was performed.

Arterial disease was defined by an ABI of <0.9 , which was determined using a portable 5-mHz continuous-wave Doppler US device. In patients with diabetes mellitus, the absence of distal pulses was considered indicative of arterial disease, because this disease results in arterial stiffness, despite normal ABI.^{7–9}

The clinical characteristics studied included age, gender, race, ulcer duration, time since first ulcer episode, history of recurrences, localization of ulcer(s), area of the ulcer, eczema, ochre dermatitis, lipodermatosclerosis (localized or extensive), and varicose veins associated with ulcer. Ulcer-related pain was classified as absent, mild to moderate (if the presence of pain did not interfere with daily activities), or severe (if pain interfered with daily activities). Body mass index (BMI), medical history (diabetes mellitus, arterial hypertension, congestive heart failure), number of pregnancies, previous deep venous thrombosis (DVT), and superficial thrombophlebitis (ST) in the lower limbs were also evaluated.

Each ulcer was measured by drawing its perimeter on transparent plastic film. The software KS-300 (Carl Zeiss Jena GmbH, Jena, Germany) was used for image analysis. In



Figure 1 Active venous ulcer in the region of the lateral malleolus with hyperpigmentation and lipodermatosclerosis (C_{4,6} according to CEAP [clinical, etiology, anatomy, pathophysiology] classification; area: 54 × 35 mm)

patients with more than one ulcer, individual areas of ulceration were added together and classified as small (<30 cm²), medium (30–60 cm²), large (60–90 cm²), or very large (>90 cm²).

Nutritional status was determined based on BMI¹⁰ estimated as weight (kg)/height² (m). Patients were classified as thin (BMI <18.5), eutrophic (BMI 18.5–24.9), slightly obese (BMI 25–29.9), moderately obese (BMI 30–39.9) or severely obese (BMI >40). Duplex US scanning was performed by qualified vascular surgeons using a Phillips Platinum CVI device and 5-mHz and 7.5-mHz linear transducers. During the duplex scan, anatomic localization and functional alterations of the venous system in the lower limb were evaluated. Valvular incompetence was diagnosed when reflux time in the superficial and/or deep venous system exceeded 0.5 seconds. Perforating vein incompetence was defined by the presence of bidirectional flow and/or diameter of a perforator >2.5 mm.¹¹ Reflux intensity was assessed in the great saphenous vein and, according to reflux time, was classified as slight (reflux time 0.5–1 second), moderate (reflux time 1–2 seconds) or severe (reflux time >2 seconds).

A database was created using SPSS for Windows Version 10.5 (SPSS, Inc., Chicago, IL, USA). The Chi-squared test was used to compare non-parametric variables, and the Student's *t*-test was used to compare parametric variables. Significance was set at $P < 0.05$. Data were analyzed using spss (v. 10.5). Risk factors were identified by univariate analysis and the estimation of the odds ratio (OR) at a 95% confidence interval (CI). The significant values resulting from this analysis were included in a multiple regression model where OR, 95% CI, and *P*-values confirmed the independent risk for some variables. This study was approved by the Research Ethics Committee of Botucatu Medical School-UNESP (280/2003).

Results

Ninety-seven patients with active or healed venous leg ulcers were assessed. Seven patients were excluded because of peripheral arterial insufficiency characterized by an ABI of <0.9 and/or reduced or absent distal pulses, which most probably indicated a mixed ulcer.

Overall, 76 patients (84.4%) were Caucasian, 62 (68.9%) were female, and 28 (31.1%) were male (female : male ratio 2.2 : 1). Mean age was 56.0 ± 13.3 years (range: 27–86 years). Only eight patients (8.9%) were aged <39 years, and 16 (17.8%) were aged ≥ 70 years. Active or healed ulcers were localized on the right side in 38 patients (42.2%), on the left side in 39 (43.3%), and bilaterally in 13 (14.4%). Of the 103 limbs examined, 87 showed an active ulcer (CEAP score: C₆), and 16 exhibited a healed ulcer (CEAP score: C₅). The medial malleolar region was the most frequently affected area, and 47 limbs (45.6%) had an active or healed ulcer in this region. The least frequently involved areas were: the

dorsal aspect of the foot (1.9%); the medial malleolus together with the dorsal foot (1.9%); the posterior aspect of the lower leg (1%), and the entire circumference of the leg (1%).

Ulcers had remained unhealed for <1 year in 42 limbs (40.7%), for 1–5 years in 30 limbs (29.1%), for 5–10 years in 12 limbs (11.7%), and for >10 years in 17 limbs (16.5%). Forty-five patients (50%) had experienced their first ulcer >10 years before their first clinical assessment.

Lipodermatosclerosis was the most frequent sign (96.7%) noted in these patients. It was sufficiently extensive to give the leg the appearance of an inverted bottle in 45 patients (50%). Lower limb hyperpigmentation or ochre dermatitis was observed in 86 patients (95.6%), whereas edema and eczema were seen in 85 (94.4%) and 46 (51.1%) patients, respectively. Varices occurred in 79 (87.8%) patients and were bilateral in 63 (70%) of them. Pain was a frequent symptom in 67 (74.4%) patients and was found to be severe in 22 (24.4%).

Diabetes mellitus was present in nine (10%) patients, arterial hypertension in 30 (33.3%), and congestive heart failure in six (6.7%). History of previous DVT was reported by 12 (13.3%) and ST by 26 (28.8%) patients. Of the 62 women participating in the study, 51 (82.3%) were multigravida, two (3.2%) were primigravida, and only five (8.1%) were nulligravida. Forty-six (74.2%) were multiparous. We had no information regarding pregnancies in four cases.

Body mass index was assessed in 85 patients, 63 (74.1%) of whom had a BMI above normal values: 26 patients (30.6%) were slightly, 31 (36.5%) moderately, and six (7.0%) severely obese.

Table 1 shows the factors correlated with longstanding ulcers (unhealed for >10 years). Univariate analysis revealed that patient age >60 years (OR 4.0, 95% CI 1.1–16.3), extensive lipodermatosclerosis (OR 8.7, 95% CI 1.8–41.4), and previous history of ulcer (OR 19.9, 95% CI 2.68–858.8) were risk factors correlated with unhealed ulcerations. Multiple regression analysis confirmed that extensive lipodermatosclerosis (OR 5.3, 95% CI 1.1–27.2) and previous history of ulcer (OR 13.7, 95% CI 1.7–113.6) were independent risk factors.

We recorded 87 active ulcers. An area of <30 cm² was observed in 65 limbs (74.7%). In five legs (5.7%), the ulcerated area was ≥90 cm². The median ulcer area was 12.5 cm².

Table 2 presents potential risk factors associated with a large or very large ulcer area. No single variable was identified as a risk factor for such large ulcers.

History of ulcer recurrence was reported by 57 (63.3%) patients. Table 3 shows some potential risk factors for recurrence. Univariate analysis revealed that time since first ulcer episode ≥2 years (OR 29.2, 95% CI

Table 1 Univariate analysis of the risk factors for an ulcer to remain unhealed for ≥10 years

Risk factor	Odds ratio	95% CI
Age		
≥50 years	3.9	0.8–37.4
≥60 years	4.0	1.1–16.3 ^a
≥70 years	1.3	0.2–5.9
Gender: female	0.3	0.09–1.16
Body mass index		
≥25	0.8	0.2–4.2
≥30	0.5	0.1–1.8
≥35	0.3	0.01–2.5
≥40	1.0	0.02–10.2
Large or very large ulcer area	0.4	0.1–2.6
Severe lipodermatosclerosis	8.7	1.8–41.1 ^a
Superficial thrombophlebitis history	0.1	0.0–1.0
Deep venous thrombosis history	0.7	0.01–6.2
Diabetes mellitus	2.9	0.4–15.6
Arterial hypertension	1.0	0.2–3.6
Previous history of ulcer	19.9	2.68–858.8 ^a
Multiparity	1.7	0.18–84.5
Isolated SVSI	0.4	0.01–3.5
Isolated DVSI	1.8	0.03–23.9
Isolated incompetence of perforators	0.8	0.02–7.3
SVSI + incompetence of perforators + DVSI	0.8	0.02–7.3
SVSI + incompetence of perforators	1.8	0.5–8.5
DVSI + incompetence of perforators	1.7	0.03–23.9
SVSI + DVSI	5.4	0.1–434.5
GSV severe reflux	1.1	0.3–4.4

^aP < 0.05 was considered to indicate statistical significance. 95% CI, 95% confidence interval; SVSI, superficial venous system incompetence; DVSI, deep venous system incompetence; GSV, great saphenous vein.

5.5–205.9), time since first ulcer episode ≥10 years (OR 7.4, 95% CI 2.5–23.0) and incompetence of both deep and superficial venous systems (OR 1.6, 95% CI 1.4–1.9) were risk factors for recurrence. Multiple regression analysis revealed that only time since first ulcer episode ≥2 years (OR 16.1, 95% CI 3.0–85.6) appeared to be an independent risk factor for recurrence.

Discussion

Longstanding and large ulcers, as well as recurrences, are the main problems encountered by patients with venous ulcers. Ineffective and often inappropriate treatments may also account for the long duration of a venous ulcer.⁷ It is important to identify the factors that may influence these variables in order to improve the results of treatment.

Active or recently healed venous ulcers were more frequently seen in Caucasian, obese females aged >40 years.

Table 2 Univariate analysis of risk factors for a large or very large ulcer area

Risk factor	Odds ratio	95% CI
Age		
≥50 years	3.0	0.3–143.3
≥60 years	1.4	0.2–8.4
≥70 years	0.5	0.01–4.5
Gender: female	0.2	0.03–1.3
Body mass index		
≥25	0.7	0.1–4.9
≥30	0.4	0.01–3.9
≥35	0.6	0.01–5.78
≥40 ^a	–	–
Active ulcer ≥5 years	2.3	0.4–13.7
Active ulcer ≥10 years	2.8	0.4–16.9
Ulcer recurrence	2.0	0.3–11.8
Severe lipodermatosclerosis	1.4	0.3–6.5
Superficial thrombophlebitis history ^a	–	–
Deep venous thrombosis history ^a	–	–
Diabetes mellitus	1.7	0.03–18.3
Arterial hypertension	0.6	0.1–3.9
Time since first ulcer episode ≥10 years	1.2	0.2–9.3
Multiparity ^a	–	–
Isolated SVSI	4.7	0.1–75.6
Isolated DVSI	3.2	0.05–46.4
Isolated incompetence of perforators	–	–
SVSI + incompetence of perforators + DVSI	–	–
SVSI + incompetence of perforators	1.9	0.3–21.4
DVSI + incompetence of perforators	–	–
SVSI + DVSI	–	–
GSV severe reflux	1.1	0.1–6.8

^aOdds ratio could not be estimated.

95% CI, 95% confidence interval; SVSI, superficial venous system incompetence; DVSI, deep venous system incompetence; GSV, great saphenous vein.

However, whether or not race is a risk factor for the development of venous ulcers remains controversial. Caucasian subjects predominated in this study, and 84.4% of ulcer patients were Caucasian, a result similar to our previous study.¹² Considering that 83% of people in our region are Caucasian,¹³ race does not seem to be a significant risk factor for venous ulcers. Scott *et al.*,¹⁴ in a community study in the USA (Boston), found similar frequencies in Caucasian and African-American individuals, whereas Margolis *et al.*¹⁵ observed a slight predominance of Caucasian subjects, who accounted for 62% of cases. Perhaps the predominance of a certain race in a study is influenced by the type of population. The patients assessed in this study came from a predominantly Caucasian population.

Duplex US scanning was performed in the affected limbs to evaluate the anatomic localization and functional

Table 3 Univariate analysis of risk factors for ulcer recurrence

Risk factor	Odds ratio	95% CI
Age		
≥50 years	1.0	0.4–2.7
≥60 years	0.6	0.2–1.8
≥70 years	0.8	0.2–3.0
Gender: female	0.9	0.3–2.6
Body mass index		
≥25	0.9	0.3–2.7
≥30	1.4	0.5–3.9
≥35	1.5	0.9–6.4
≥40	1.0	0.2–8.1
Active ulcer ≥5 years	0.4	0.1–1.2
Active ulcer ≥10 years	0.4	0.1–1.5
Large or very large ulcer area	0.5	0.1–2.7
Severe lipodermatosclerosis	2.4	0.9–5.8
Superficial thrombophlebitis history	1.5	0.5–4.4
Deep venous thrombosis history	1.8	0.3–14.0
Diabetes mellitus	0.4	0.1–2.0
Arterial hypertension	1.9	0.7–5.7
Time since first ulcer episode ≥2 years	29.2	5.5–205.9 ^a
Time since first ulcer episode ≥10 years	7.4	2.5–23.0 ^a
Multiparity	0.8	0.1–4.1
Isolated SVSI	0.4	0.1–1.5
Isolated DVSI	0.6	0.04–8.1
Isolated incompetence of perforators	0.8	0.1–5.7
SVSI + incompetence of perforators + DVSI	1.2	0.2–13.9
SVSI + incompetence of perforators	1.6	0.6–4.4
DVSI + incompetence of perforators	1.2	0.1–72.6
SVSI + DVSI	1.6	1.4–1.9 ^a
GSV severe reflux	1.3	0.4–3.3

^a $P < 0.05$ was considered to indicate statistical significance. 95% CI, 95% confidence interval; SVSI, superficial venous system incompetence; DVSI, deep venous system incompetence; GSV, great saphenous vein.

abnormalities of the venous system in the lower limb and to differentiate between patients with primary varices, in whom alterations occur mainly in the superficial venous system, and patients with secondary varices, in whom physiopathological alterations occur in the deep venous system. Valvular incompetence was diagnosed when reflux time in the superficial and/or deep venous systems exceeded 0.5 seconds. Perforating vein incompetence was defined by the presence of bidirectional flow and/or diameter of a perforator >2.5 mm.¹¹ As our study began in 1998, we used these values, but it is important to consider a more recent recommendation in which the cut-off value for reflux in the superficial and deep calf veins remains at 0.5 seconds, but that for reflux in the femoropopliteal veins is 1.0 second and outward flow in the perforating veins is considered abnormal if it exceeds 0.35 seconds.¹⁶

The prevalence of ulcers was similar on the right and left sides. Nelzen *et al.*¹⁷ found that 72% of venous ulcers were localized on the right leg, although this was not statistically significant. In our study, the most frequently affected area was the medial malleolus, whereas ulcers on the posterior aspect of the leg and the dorsal aspect of the foot were infrequent.

These findings are in line with those reported by Adam *et al.*,¹⁸ who analyzed 689 limbs with venous ulcers and found ulcerations in the dorsal aspect of the foot and posterior aspect of the lower leg only in 1.9% and 3.4% of cases, respectively. Baker *et al.*¹⁹ also observed that only 3.1% of limbs exhibited isolated venous ulcers in the dorsal aspect of the foot. Although the exact localization of venous ulcerations varied, they usually occurred in the gaiter area (from 2.5 cm below the malleoli to the point at which the calf muscles become prominent posteriorly). Venous ulcers affecting only the dorsal aspect of the foot or posterior aspect of the leg are less frequent, and other diagnoses should be considered when ulcerations are observed in these areas.

Venous ulcers are usually chronic and almost always take a long time to heal. One of the objectives of this study was to identify risk factors for delayed healing. Factors such as BMI, large ulcer area, diabetes mellitus, and deep venous system incompetence, which may seem important, were assessed but were not confirmed as risk factors. By contrast, multiple regression analysis showed that severe lipodermatosclerosis and previous history of an ulceration were independent risk factors.

It would be interesting to study venous ulcers in patients with uncontrolled diabetes, because poor glyce-mic control may impair wound healing through cyto-kines, growth factors, and synthesis of collagen abnormalities.¹⁵ However, as the number of patients with diabetes mellitus in our study was small, we did not perform such an analysis.

Another important factor that might interfere with the wound healing process concerns the presence of bacteria in the wound bed. Chronic ulcers are often characterized by bacterial and fungal colonization, which is associated with inactivation of growth factors, increased activity of matrix metalloproteinases, and altered proliferative and migratory properties of cells, especially fibroblasts.²⁰ All wounds contain bacteria at levels ranging from contamination, through colonization and critical colonization (also known as 'increased bacterial burden' or 'occult infection') to infection.²¹ It is important to determine the type and level of infection or colonization in the ulcer bed by microbiological examination of tissue samples obtained by a biopsy or by a validated quantitative swab technique. As microbiological tests were not performed routinely in our study, we were unable to evaluate any

correlation between failure to heal and the presence or absence of critical colonization.

There are only scarce data in the literature on the risk factors associated with prolonged healing of ulcers. Nemeth *et al.*²² found severe lipodermatosclerosis to be a poor prognostic factor because patients who did not respond to treatment with topical and systemic antibiotics and occlusive dressings presented with this condition.

In a study of 260 patients with venous ulcers, Margolis *et al.*¹⁵ found that a large wound area (OR 1.19, 95% CI 1.11–1.27) and long ulcer duration (OR 1.09, 95% CI 1.04–1.16) were important risk factors. They suggested that the time during which the ulcer remained unhealed could predict healing time because the longer the duration of an ulcer, the longer it took to heal. In another multi-center study, Margolis *et al.*²³ developed a prognostic model based on a multivariable logistic regression analysis. Initial measurements of wound size and duration accurately predicted the clinical outcome. The authors suggested, therefore, that it is possible to predict, given good wound care, whether an ulcer will heal within 24 weeks.

Skene *et al.*²⁴ reported similar results. They observed that, in a group of patients managed with compression therapy, healing rates after four months were higher in the patients with smaller ulcers, shorter duration of ulcerations, in young patients, and in individuals with no involvement of the deep venous system.

To corroborate these data, Phillips *et al.*²⁵ analyzed the results of a large, multicenter study on venous ulcers to establish retrospectively prognostic factors for ulcer healing. They concluded that ulcers that are large, longstanding, and heal slowly after three weeks of optimal therapy are unlikely to heal quickly, and such ulcerations might benefit from alternative therapies. Taylor *et al.*²⁶ used the artificial neural network, which accurately predicted healing time and demonstrated that poor healing was significantly related to history of a previous ulceration, highly exuding ulcers, obesity, large initial ulcer area, patient age, and male gender.

Another objective of this study was to identify risk factors associated with large ulcers. Less than 10% of active ulcers were >60 cm². No risk factor studied (i.e. BMI, duration of an ulcer, lipodermatosclerosis, history of DVT, diabetes mellitus, and involvement of the superficial and/or deep venous systems) was correlated with the presence of a large ulceration. It is possible that the relatively small number of patients precluded a statistically significant finding. To the best of our knowledge, there are no papers reporting risk factors for large venous ulcers. Thus, such studies are warranted.

Most of our patients had a history of ulcer recurrence. This finding is in line with the natural history of venous

ulcers, which is characterized by frequent recurrence.²⁷ Erickson *et al.*²⁸ observed a 56% recurrence rate during a 10.4-month follow-up. According to these authors, inadequate management results in recurrence in 30% of healed venous ulcers during the first year and in 78% within two years.²⁹ These high recurrence rates may be associated with non-compliance with compression treatment following ulcer healing and a lack of surgical correction of the sources of venous reflux. Nonetheless, keeping the patient free from ulcer recurrence after successful healing is challenging.

Very few studies have assessed the risk factors associated with the recurrence of venous ulcers. In this study, elapsed time ≥ 2 years since the first ulcer episode was the only independent risk factor for recurrence identified. Factors such as BMI, history of previous DVT, and incompetence of the deep or superficial venous systems were not found to be correlated with recurrences. McDaniel *et al.*³⁰ studied 99 limbs with venous ulcerations and followed them up for long periods after healing. Based on anatomic characteristics assessed by duplex US scanning, they observed that patients with deep venous incompetence (DVI) had significantly higher recurrence rates (66% in 48 months) than patients without DVI (29% in 48 months). They also found that patients who underwent venous surgery had a significantly lower recurrence rate (27% in 48 months) than patients who did not undergo surgery (67% in 48 months).

Conclusions

Venous ulcers were most frequent in female, Caucasian and obese patients aged >40 years. These ulcers were longstanding. Nearly all ulcer patients exhibited lipodermatosclerosis. Severe lipodermatosclerosis and a previous history of an ulcer were found to be risk factors for unhealed ulcerations. Elapsed time ≥ 2 years since the first ulcer episode was found to be a risk factor for recurrence.

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