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Factors related to the size of venous leg ulcers

A cross-sectional study

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Abstract

Venous leg ulcers (VLUs) are an important health problem, and the size of ulcers often affects patient care, healing time, and quality of life. However, the risk factors associated with ulcer size have been rarely reported. The aim of this study was to establish the risk factors for the size of venous ulceration by analyzing the patient demographics and the results of duplex ultrasonography.

This study was an in-patient population-based cross-sectional study conducted at a single center during the period from 2013 to 2017. Men and women aged >18 years, who consecutively presented to our hospital with VLU, were included. According to the size of the ulcer, patients were divided into two groups, those with ulcers≤2 cm and those with ulcers >2 cm. Demographic, anthropometric, and clinical data were collected. For the analysis, univariate and multivariate logistic regressions were used.

A total of 232 patients with VLUs were admitted to our hospital from 2013 to 2017, including 117 patients (50.4%) with ulcer diameters ≤2 cm and 115 patients (49.6%) with ulcer diameters >2 cm. According to the results of the multivariate analysis, the ulcer duration ($P = .001$), the diameter of perforating veins (PVs) around the ulcers ($P = .025$), the reflux time of common femoral veins (CFVs) ($P = .013$), the reflux time of great saphenous veins (GSVs) ($P = .021$), and the reflux time of PVs around the ulcers ($P = .001$) were independent risk factors for VLUs.

These findings provide evidence that the size of VLU was significantly related to the ulcer duration, the diameter of PV around the ulcers, the CFV reflux time, the GSV reflux time, and the PV reflux time.

Abbreviations: CEAP = Clinical-Etiology-Anatomy-Pathophysiology, CFV = common femoral vein, CI = confidence interval, CVI = chronic venous insufficiency, DVT = deep venous thrombosis, GSV = great saphenous vein, OR = odds ratio, PV = perforating vein, SFJ = saphenous femoral junction, VLU = venous leg ulcer.

Keywords: cross-sectional study, risk factors, venous leg ulcers

1. Introduction

VLU is a considerable health problem because of its high incidence and the high cost of treatment. Ulcers are the most serious consequence of chronic venous insufficiency (CVI), reaching the C5 and C6 levels in the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification.[1] More serious and large ulcers are associated with a longer healing time and a worsened quality of life for the patients.

Many studies have reported the influencing factors of VLUs, including gender, age, family history, childbirth, long periods of standing, physical inactivity, obesity, and deep venous thrombosis (DVT).[2–5] However, few studies have reported the risk factors related to the size of VLUs.

The severity of VLUs is mainly reflected in the size of the ulcer. Dragan et al found that an ulcer with an area >20 cm^2 was a risk factor for the failure of pressure treatment for VLUs.[6] Harding et al also found that the size and depth of ulcers affected the efficacy in the treatment of VLUs with special silver dressings.[7]

The aim of the study was to establish the risk factors for the size of venous ulceration by analyzing patient demographics as well as the results of duplex ultrasonography so that corresponding prevention and treatment measures may be proposed to reduce the severity of ulcers and to improve the prognosis of VLU patients.

2. Materials and methods

2.1. Case selection

The Medical Ethics Committee of Ganzhou People's Hospital approved the collection of case data for this clinical retrospective study. The study was based on an in-patient population cross-sectional sample and was conducted at a single center during the period from 2013 to 2017. Patients were identified using the procedure and using diagnosis codes of the International Classification of Diseases, Tenth Revision (ICD-10). By referencing the medical records, we identified consecutive patients with a primary diagnosis of VLU (ICD-10 I83.002 and I83.202). The patients were divided into two groups, those with ulcers ≤2 cm and those with ulcers >2 cm.[8]

Inclusion criteria: Patients aged 18 years or older with active or healing VLUs, reaching the C5 and C6 levels according to the CEAP C classification, were included.

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Exclusion criteria: Patients with calf ulcers caused by other conditions such as arteriosclerosis obliterans, diabetes, malnutrition and malignancy, and VLU patients for whom there were not complete duplex ultrasonography data were excluded.

2.2. Estimate of sample size and grouping

In the early observation of 50 cases with VLUs, we found that the diameters of ulcers ≤2 cm and >2 cm each accounted for approximately half of the cases. Values of 2 cm and 6 cm have been used as the group boundary values in other study,[8] and patients with VLUs were divided into light, medium, and heavy groups according to the diameter of the ulcer. Therefore, in the present study, the patients with VLUs were divided into two groups: light and heavy, using 2 cm as the cutoff value.

We estimated that there were approximately 10 indicators for comparison. According to the sample size of 1:10–20, we estimated that 100–200 cases were needed for each group.

2.3. Data extraction

The variables collected according to the medical records included the following: gender, age, varicose vein duration, ulcer location, ulcer duration, diameter of ulcer, GSV surgical history, lower limb trauma history or smoking history, comorbidities of patients, and a grade of C according to the CEAP classification. The variables compiled according to the results of the ultrasonography were as follows: the reflux time of CFV, the reflux time of GSV, the reflux time of PVs around the ulcers, and the diameter of the GSVs, SVs, and PVs around the ulcers. All the recorded variables were checked at least twice by two different people.

2.4. Methods of measurement and instructions of classification[9]

CFV and GSV reflux time: With the patients in a supine position, both CFV and GSV reflux time in the groin were measured during a Valsalva maneuver (a breath hold after forced exhalation for at least 3 s). A reflux time <1.0 s was normal, and a reflux time that lasted for the entire Valsalva maneuver was considered persistent reflux. To facilitate statistical comparisons, we classified the reflux time into four levels: <1.0 s, 1.0–2.0 s, 2.0–5.0 s, and persistent reflux.

PV reflux time around the ulcers: With the patients in a supine position, the pressure was relieved after pressing the calf muscle while measuring the reflux time of PVs around the ulcers. A reflux time <0.5 s was normal, and persistent blood flow from the deep to the superficial veins through the PVs was defined as persistent reflux. To facilitate statistical comparisons, we also classified this reflux time into four levels: <0.5 s, 0.5–1.0 s, 1.0–3.0 s, and persistent reflux.

2.5. Statistical analysis

Continuous data were compared by independent-samples *t*-tests, categorical data were compared by the χ^2 test, and the Spearman rank correlation was used to analyze the correlation between the ulcer diameter and the reflux of lower limb veins.

Univariate and multivariate logistic regression analyses were used to assess the influence of indicators on the size of VLUs. The indicators included gender, age, varicose vein duration, VLU duration, GSV diameter, PV diameter, superficial vein diameter, CFV reflux time, GSV reflux time, and PV reflux time around the ulcer. Factors with a *P* value of less than 0.1 according to the univariate analyses were entered into the multivariate analyses. Binary logistic regression with enter method for the covariates was used to perform the multivariate analysis to assess the independent factors related to the size of the venous ulceration.

All the tests were two-sided, with a significance level of 0.05, and were performed using SPSS software (ver. 22.0; IBM Corp; USA).

3. Results

3.1. Demographic characteristics of the patients

From 2013 to 2017, there were 219 patients with VLUs, including 13 patients with bilateral varicose veins, accounting for 232 limbs. The average age was 59.8 ± 11.8 years, with 114 males (49.1%) and 118 females (50.9%) (Table 1). Of these patients, 117 (50.4%) had ulcer diameters ≤2 cm, and 115 (49.6%) had ulcer diameters >2 cm. No statistically significant differences were found between the two groups in terms of gender, age, varicose vein duration, ulcer location, GSV surgical history, lower limb trauma history, or smoking history. In terms of coexisting diseases, such as ischemic heart disease, diabetes, high blood pressure, chronic obstructive pulmonary disease (COPD), lower limb arteriosclerosis occlusion, lower extremity DVT, superficial thrombophlebitis, and arthritis, no significant differences were found between the groups (Table 2). The demographic characteristics of the two groups were essentially balanced and comparable. The ulcer duration ($P = .000$) and the CEAP C categories, however, were significantly different between the groups ($P = .003$) (Table 1).

3.2. Ultrasonography results

The mean GSV diameters in the two groups were 6.8 ± 2.5 mm and 6.7 ± 2.9 mm, and the mean diameters of the superficial veins were 6.8 ± 2.5 mm and 7.4 ± 3.4 mm. No statistically significant differences were observed between the two groups, with *P* values of .861 and .132. However, the mean diameters of the PVs around the ulcers were 3.2 ± 1.4 mm and 3.8 ± 1.1 mm. Thus, a significant difference between the two groups was observed, with a *P* value of .001 (Table 3). The ultrasonography results of the classification of the vein reflux time of CFVs, GSVs, and PVs around the ulcer of the 232 limbs are shown in Table 4.

3.3. Relationship between ulcer diameter and venous reflux

There was a significant positive correlation between the ulcer diameter and the reflux time of CFVs, GSVs, and PVs around the ulcer; the correlation coefficients were 0.327, 0.272, and 0.347, respectively. With the prolongation of reflux time, the ulcer diameter gradually increased (Table 5).

3.4. Variables related to the size of venous ulceration

According to the univariate analysis of the ten variables, we found that gender, the duration of varicose veins, the diameter of the PVs around the ulcers, and the reflux times of CFVs, GSVs, and PVs around the ulcers were risk factors for VLU size. We assessed these factors in the multivariate regression analysis and found that the VLU duration ($P = .001$), the diameter of PVs

Table 1

Demographic characteristics of the patients.

Variable	Total n = 232 (%)	Ulcer diameter ≤2 cm n = 117 (50.4%)	Ulcer diameter >2 cm n = 115 (49.6%)	*P* value
Average age (years)	59.8 ± 11.8	58.6 ± 11.6	61.0 ± 11.9	.115[†]
Gender				.053[§]
Male	114 (49.1)	53 (45.3)	61 (53.0)	
Female	118 (50.9)	64 (54.7)	54 (47.0)	
Varicose vein duration (year)	20.7 ± 12.5	19.4 ± 12.7	22.1 ± 12.1	.091[†]
GSV surgical history	24 (10.3)	11 (9.4)	13 (11.3)	.671[§]
Lower limb trauma history	10 (4.3)	6 (5.1)	4 (3.1)	.749[§]
Smoking history	70 (30.2)	35 (29.9)	35 (30.4)	1.000[§]
Ulcer duration (m)	25.7 ± 62.7	10.4 ± 27.1	41.2 ± 82.0	.000[‡]
Ulcer location				.138[*]
Left inner ankle	81 (34.9)	42 (35.9)	39 (33.9)	
Right inner ankle	35 (15.1)	22 (18.8)	13 (11.3)	
Anterior tibia of left	21 (9.1)	6 (5.1)	15 (13.0)	
Anterior tibia of right	18 (7.8)	8 (6.8)	10 (8.7)	
Left leg	29 (12.5)	13 (11.1)	16 (13.9)	
Right leg	13 (5.6)	8 (6.8)	5 (4.3)	
Left external ankle	15 (6.5)	8 (6.8)	7 (6.1)	
Right external ankle	7 (3.0)	2 (1.7)	5 (4.3)	
Left foot back	10 (4.3)	7 (6.0)	3 (2.6)	
Right foot back	2 (0.9)	0 (0)	2 (1.7)	
Right plantar	1 (0.4)	1 (0.9)	0 (0)	
CEAP classification				.003[§]
C5, n (%)	54 (23.3)	37 (31.6)	17 (14.8)	
C6, n (%)	178 (76.7)	80 (68.4)	98 (85.2)	

CEAP = Clinical-Etiology-Anatomy-Pathophysiology, GSV = great saphenous vein.
[*] Chi-square test.
[†] Independent sample *t* test.
[‡] Separate variance estimation *t*-test.
[§] Fisher's exact test.

around the ulcers ($P = .025$), the reflux time of CFV ($P = .013$), the reflux time of GSV ($P = .021$), and the reflux time of PVs around the ulcers ($P = .001$) were independent risk factors for the size of VLU (Table 6).

4. Discussion

In the present retrospective study, we found that the VLU duration ($P = .001$), the diameter of PVs around the ulcers ($P = .025$), the reflux time of CFVs ($P = .013$), the reflux time of GSVs ($P = .021$), and the reflux time of PVs around the ulcers ($P = .001$) were independent risk factors for the size of VLU. These findings have not yet been reported in the literature.

Table 2

Comorbidities of the patients.

Disease	Ulcer diameter ≤2 cm n = 117 (%)	Ulcer diameter >2 cm n = 115 (%)	*P* value
Ischemic heart disease	2 (1.7)	5 (4.3)	.278[*]
Diabetes	4 (3.4)	3 (2.6)	1.000[*]
High blood pressure	24 (20.5)	22 (19.1)	.870[*]
COPD	2 (1.7)	5 (4.3)	.278[*]
Arteriosclerosis occlusion	1 (0.9)	2 (1.7)	.620[*]
DVT	1 (0.9)	5 (4.3)	.118[*]
Superficial thrombophlebitis	9 (7.7)	5 (4.3)	.409[*]
Arthritis	1 (0.9)	5 (4.3)	.118[*]

COPD = chronic obstructive pulmonary disease, DVT = deep venous thrombosis.
[*] Fisher's exact test.

CVI was related to gender, particularly women.[4,10] The univariate analysis in this study showed that gender was also an influential factor for the size of venous ulcers. However, when excluding confounding factors by the multivariate analysis, gender was not an independent risk factor for venous ulcers. One explanation is that women may be more likely to focus on the symptom of CVI, prompting them to treat the CVI in time and thereby preventing the occurrence of venous ulcers and the deterioration of ulcers.[2,10]

One of the unique aspects of our study was the inclusion of ulcer duration. The results of our analysis showed that when the duration of the ulcer was longer, the ulcer was larger in size. This finding may be associated with neglecting the presence of ulcers and not properly treating ulcers for a long period of time. No similar reports have been reported in previous clinical studies. The revised VCSS,[11] which is used to assess the criteria for CVI, consists of 10 assessment indicators, including ulcer duration and

Table 3

Results of ultrasonography in the diameter of lower extremity veins.

Variables (mm)	Total n = 232	Ulcer diameter ≤2 cm n = 117	Ulcer diameter >2 cm n = 115	*P*[*] value
GSV	6.8 ± 2.6	6.8 ± 2.5	6.7 ± 2.9	.861
Superficial vein	7.1 ± 3.0	6.8 ± 2.5	7.4 ± 3.4	.132
PV	3.5 ± 1.3	3.2 ± 1.4	3.8 ± 1.1	.001

GSV = great saphenous vein, PV = perforating vein.
[*] Independent sample *t* test.

Table 4

Classification of the vein reflux time.

Classification of the vein reflux time	Ulcer diameter ≤2 cm n=117 (%)	Ulcer diameter >2 cm n=115 (%)
CFV reflux time (s)		
<1.0	43 (36.6%)	20 (17.4%)
1.0–2.0	32 (27.4%)	20 (17.4%)
2.0–5.0	29 (24.8%)	34 (29.6%)
Persistent reflux	13 (11.1%)	41 (35.7%)
GSV reflux time (s)		
<1.0	23 (19.7%)	12 (10.4%)
1.0–2.0	21 (17.9%)	6 (5.2%)
2.0–5.0	21 (17.9%)	15 (13.0%)
Persistent reflux	52 (44.4%)	82 (71.3%)
PV reflux time (s)		
<0.5	67 (57.3%)	36 (31.3%)
0.5–1.0	27 (23.1%)	11 (9.6%)
1.0–3.0	12 (10.3%)	29 (25.2%)
Persistent reflux	11 (9.4%)	39 (33.9%)

CFV = common femoral vein, GSV = great saphenous vein, PV = perforating vein.

ulcer size. The standard score is as follows: 1 point for ulcers <3 months, 2 points for ulcers between 3 and 12 months, and 3 points for ulcers >12 months. However, the relationship between time and ulcer diameter was not reported.

Similarly, the severity of varicose veins was related to the duration of varicose veins. Some researchers have compared the damage of varicose veins to the skin of lower limbs, and they found that a longer duration of varicose veins resulted in more damage to the skin.[12] However, our findings regarding the relationship between variceal duration and varicose vein severity were not consistent with the results reported in the previous study: the values of p and 95% confidence interval (CI) of odds ratio (OR) in the multifactor analysis were 0.386 and 1.013 (0.984–10.42), respectively (Table 6). This may be related to the characteristics of the inpatient cases and sample size of this study.

Reflux is considered the dominant pathology in CVI.[13,14] Lower extremity venous reflux causes superficial venous hypertension, especially around the ankle, resulting in skin swelling, pigmentation, and nutritional disorders, culminating in skin damage and ulceration. The venous system of the lower extremity includes the superficial venous system, the deep venous system, and the penetrating venous system. Reflux affects the pressure of each system. We also found a significant correlation

Table 5

Correlations between the ulcer diameter and reflux time of lower extremity veins.

Variables			Ulcer diameter (cm)	CFV reflux time (s)	GSV reflux time (s)	PV reflux time (s)
Spearman's rho	Ulcer diameter (cm)	Correlation coefficient	1.000	.327*	.272*	.347*
		Sig. (2-tailed)	.	.000	.000	.000
		N	232	232	232	232

CFV = common femoral vein, GSV = great saphenous vein, PV = perforating vein.
* Correlation is significant at the 0.01 level (2-tailed).

Table 6

Univariate and multivariate logistic regression analysis of the risk factors related to the size of venous leg ulcer.

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
Variable	Odds ratio	95% CI	*P* value	OR	95% CI	*P* value
Gender	1.742	1.006–3.018	**.048**	0.604	0.299–1.220	.160
Varicose vein duration	1.018	0.997–1.040	**.092**	1.013	0.984–10.42	.386
Ulcer duration	1.022	1.009–1.034	**.001**	1.045	1.019–1.072	**.001**
GSV diameter	0.991	0.899–1.093	.860			
Diameter of superficial vein	1.070	0.980–1.157	.132			
Diameter of PV around the ulcers	1.514	1.183–1.937	**.001**	1.428	1.047–1.948	**.025**
CFV reflux time			**.000**			**.013**
CFV reflux time (0)	1.0 (reference)		.000	1.0 (reference)		
CFV reflux time (1)	1.344	0.622–2.903	.452	1.309	0.489–3.504	.592
CFV reflux time (2)	2.521	1.220–5.209	.013	1.691	0.668–4.276	.267
CFV reflux time (3)	6.781	2.990–15.379	.000	4.976	1.809–13.682	.002
GSV reflux time			**.000**			**.021**
GSV reflux time (0)	1.0 (reference)			1.0 (reference)		
GSV reflux time (1)	0.548	0.174–1.720	.303	0.842	0.206–3.439	.810
GSV reflux time (2)	1.369	0.523–3.584	.522	2.969	0.881–10.003	.079
GSV reflux time (3)	3.022	1.386–6.591	.005	3.386	1.231–9.312	.018
PV reflux time			**.000**			**.001**
PV reflux time (0)	1.0 (reference)			1.0 (reference)		
PV reflux time (1)	0.758	0.337–1.704	.503	0.437	0.150–1.273	.129
PV reflux time (2)	4.498	2.051–9.863	.000	2.226	0.851–5.817	.103
PV reflux time (3)	6.598	3.018–14.425	.000	4.448	1.780–11.115	.001

CFV = common femoral vein, CI = confidence interval, GSV = great saphenous vein, OR = odds ratio, PV = perforating vein.

between VLUs in the lower limbs and venous reflux. For easy comparison, the reflux results of the ultrasonography in this study were subjected to hierarchical processing, which has not been reported in the literature previously. The results revealed that the reflux time of CFVs, GSVs, and PVs around the ulcers were independent risk factors for the size of venous ulcers. Kanchanabat et al achieved good results by eliminating reflux to cure refractory venous ulcers.[14]

The reflux of CFVs is a part of deep venous reflux, located at the saphenous femoral junction (SFJ), and it is primarily caused by deep venous valve insufficiency. The SFJ of the groin plays an important role in the development of venous reflux in the superficial venous system of the leg. Zollmann et al analyzed 2019 legs with CVI and found that in 1348 legs (66.8%), reflux originated exclusively in the CFV.[15] A case-control study of ulcerated and nonulcerated lower extremity varicose veins in two centers also identified deep vein reflux as an independent risk factor for venous ulcers.[16]

The reflux of the GSV also originates from the SFJ, which is associated with deep venous reflux and GSV valve insufficiency.[17] To clarify the route of venous reflux associated with local leg ulcers and its origin, 183 limbs with VLUs were examined using ultrasonography, and 64 (35%) medially located ulcers were found to exhibit reflux in the GSV.[18]

PV reflux is known as a high risk factor for venous ulcers in the lower extremities,[19] and our study produced similar results. The occurrence, development, and even postoperative recurrence of venous ulcers are all related to the existence of PV reflux. After the treatment of PV reflux around the ulcer, the ulcer healed well, and the recurrence rate was low.[20–24]

Venous reflux is related to the superficial vein diameter. Generally, the more serious the reflux is, the larger the superficial vein diameter, and the more serious the CVI.[25] Special studies were conducted to measure the diameter of the superficial veins.[9,26] In the standard Valsalva maneuver to measure the superficial vein diameter of insufficiency veins and normal veins, the authors believed that with the prolongation of reflux time, the superficial vein diameter would increase accordingly. The present study also found that CVI of varying severity was associated with different superficial vein diameters. However, after eliminating confounding factors from the logistic regression analysis, we did not find that the superficial vein diameter was a risk factor for ulcer diameter.

Generally, the larger the diameter of the PV is, the greater the chances of PV reflux, and the greater the severity of CVI. Labropoulos et al compared 30 asymptomatic limbs and 103 venous insufficient limbs using duplex ultrasonography and found that the PV diameters of grades 4 to 6 CVD were >3.9 mm,[27] while those of grade 4 or less were less than 3.9 mm in one-third of patients.[28] In addition, Seren et al used laser and pressure to treat a group of patients with refractory VLUs.[22] The mean diameter of the perforating veins was 4.6 ± 0.3 mm. Prasad et al also reported a group of patients with recurrent CVI with a minimum diameter of 3 mm of PVs in the fascial layer.[21] In our study, the average diameter of the PVs of ulcers ≤ 2 cm was 3.2 ± 1.4 mm, the average diameter of the PVs of ulcers >2 cm was 3.8 ± 1.1 mm, and the comparison between the two groups was statistically significant ($P < .001$). Single factor and multiple factor logistic regression analyses were used, confirming that the diameter of PVs around ulcers was an independent risk factor for ulcer diameter.

Our study had several limitations. First, it was performed at a single center and a relatively small number of patients. Second, this was a retrospective study, performed using electronic medical records, possibly introducing selection bias. In addition, ultrasonography was conducted by different personnel, and there might be measurement bias in the interpretation of the results. Therefore, a multicenter prospective randomized controlled study is required to further evaluate the risk factors related to the size of VLUs (Supplementary file: http://links.lww.com/MD/C807).

5. Conclusion

Gender, ulcer duration, PV diameter, CFV reflux time, GSV reflux time, and PV reflux time were risk factors for the size of VLUs. Ulcer duration, PV diameter, CFV reflux time, GSV reflux time, and PV reflux time were independent risk factors for ulcer size. Special attention should be paid to patients in whom postulated risk factors for venous ulceration are present.

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Author contributions

Xiaochun Liu contributed to the study design, data analysis, and the writing and translation of the manuscript. GZ, HX, and TZ contributed to data collection, and BY and WC revised the manuscript. All authors agreed with the decision to submit the manuscript for publication.

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