

Prevalence, risk factors, and evaluation of ilio caval obstruction in advanced chronic venous insufficiency



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ABSTRACT

Objective: The aim of this study was to investigate the prevalence and clinical predictors of >50% ilio caval venous obstruction (ICVO) in Thai patients with lipodermatosclerosis and healed or active venous ulcers and the diagnostic accuracy of duplex ultrasound (DUS) compared with computed tomography venography (CTV).

Methods: Limbs with lipodermatosclerosis, healed venous leg ulceration, or active venous leg ulceration were prospectively evaluated by DUS and CTV. Loss of respiratory variation in the common femoral vein (CFV) and reversed flow in the superficial epigastric vein (SEV) were evaluated by DUS. Percentage of venous obstruction was measured by CTV. The prevalence and clinical predictors of >50% ICVO were determined, and the accuracy of DUS for diagnosis of >50% ICVO was compared with the diagnostic accuracy of CTV.

Results: A total of 106 patients (135 limbs) were enrolled. The mean age was 58 ± 12 years, and 57 (54%) patients were female. Previous history of deep venous thrombosis (DVT) in the symptomatic leg was documented in 21 (15.6%) limbs; >50% ICVO by CTV was found in 38 (28.1%) limbs. Independent predictors of >50% ICVO included left leg ($P = .001$) and previous history of DVT in the affected leg ($P = .001$). For diagnosis of >50% ICVO, the sensitivity and specificity of loss of respiratory variation in the CFV were 23.7% and 100%, respectively; the sensitivity and specificity of reversed flow in the SEV were 7.9% and 100%, respectively.

Conclusions: Limbs with lipodermatosclerosis or with healed or active venous ulceration, especially in the left limb or in limbs with a history of DVT in the affected limb, had a high prevalence of ICVO; these limbs should be routinely studied with DUS. Limbs with an abnormal finding on DUS, including loss of respiratory variation in the CFV or reversed flow in the SEV, should be routed for venous intervention, and those with normal DUS findings should be referred for CTV. (*J Vasc Surg: Venous and Lym Dis* 2019;7:441-7.)

Keywords: Iliocaval venous obstruction; Duplex ultrasound; CT venography; Deep venous thrombosis; May-Thurner syndrome

Patients in an advanced stage of chronic venous insufficiency (CVI), including lipodermatosclerosis, healed venous leg ulcer, and active venous leg ulcer (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical classes C4b, C5, and C6, respectively), have complex venous disease with involvement of superficial, perforator, and deep veins.¹ It was previously reported that patients with advanced CVI had a high incidence of ilio caval venous obstruction (ICVO) when studied with intravascular ultrasound (IVUS).² The two recognized major types of ICVO are nonthrombotic iliac vein lesions or May-Thurner syndrome and post-thrombotic iliac vein stenosis resulting from a prior episode of deep venous thrombosis (DVT).³

The “gold standard” method for diagnosis of ICVO is IVUS, but it is an invasive method that is unsuitable for screening and for deciding the best treatment strategy.³ Computed tomography venography (CTV) is a minimally invasive diagnostic method that is also an investigation of choice for detecting ICVO.⁴ Although the accuracy of duplex ultrasound (DUS) for diagnosis of ICVO may be improved by performing direct scanning,⁵ transabdominal DUS may fail to identify a vessel obstruction because the iliac vein may be obscured by intestinal gas in the pelvic cavity.⁶⁻⁸ Indirect signs, such as loss of respiratory variation in the common femoral vein (CFV), may be useful for detecting ICVO.^{8,9} Reversed flow in the superficial epigastric vein (SEV) as a collateral venous drainage

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system to circumvent the ICVO was also observed to be associated with ICVO in a retrospective study.¹⁰

The primary aim of this study was to determine the prevalence of >50% ICVO in patients with CEAP C4b, C5, and C6 disease. The secondary objectives were to identify clinical risk factors associated with >50% ICVO and to investigate the accuracy of DUS for diagnosis of >50% ICVO compared with CTV. In this study, all consecutive patients with CEAP C4b, C5, or C6 disease underwent both DUS and CTV to detect >50% ICVO.

METHODS

Study design. All patients with advanced CVI of a lower extremity, including patients with lipodermatosclerosis, healed venous leg ulcer, or active venous leg ulcer (CEAP C4b, C5, or C6), who visited the outpatient clinic of Siriraj Hospital (Mahidol University, Bangkok, Thailand) during the study period of February 1, 2017, to January 31, 2018, were prospectively recruited. Patients with a history of allergy to iodinated contrast material, patients with chronic renal failure (estimated glomerular filtration rate <45 mL/min), and patients who were pregnant during the recruitment period were excluded.

Patients' data, including age, sex, body mass index, comorbidities, medical history of DVT, degree of clinical severity of CVI (CEAP C4b, C5, or C6), and Venous Clinical Severity Score, were collected and recorded. For patients with bilateral disease, both limbs were enrolled and analyzed as two separate affected limbs.

All patients underwent venous DUS evaluation by a qualified vascular surgeon. Compression ultrasound and evaluation of venous flow pattern, including CFV respiratory variation and direction of flow in the SEV, were performed using a GE Logiq 9 system (GE Healthcare, Chicago, Ill) with a 5- to 10-MHz linear transducer with patients in the supine position.^{7,10} Limbs with loss of respiratory variation in the CFV or with reversed flow in the SEV were identified as limbs with suspected >50% ICVO from DUS⁸⁻¹⁰ (Figs 1 and 2). Valvular reflux at the saphenofemoral junction and at the infrainguinal deep, superficial, and perforating veins was also carefully evaluated with patients in the standing position.¹¹ Cutoff values of 1000 milliseconds for deep venous reflux (DVR) and 500 milliseconds for superficial venous reflux (SVR) or perforator vein reflux were used to define significant venous reflux.¹¹

All patients underwent CTV in a 256-slice GE Revolution scanner (GE Healthcare). Axial images were obtained after intravenous administration of 100 mL of contrast material at 5 mL/s followed by 20 mL of normal saline solution through the same route. Venous-phase imaging was obtained at 80 and 180 seconds after administration of the contrast material. Measurement was performed after centerline reconstruction using OsiriX MD 2.9 software (Pixmeo SARL, Bernex, Switzerland). Analysis for the presence of obstructions in the iliac veins and the

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective observational study
- **Key Findings:** In 106 patients with C4 to C6 disease, >50% ilio caval venous obstruction (ICVO) was found with computed tomography venography in 28.1% of 135 limbs. Left leg and previous deep venous thrombosis predicted >50% ICVO. For diagnosis of >50% ICVO, sensitivity and specificity of loss of respiratory variation in the common femoral vein were 23.7% and 100%, respectively; the sensitivity and specificity of reversed flow in the superficial epigastric vein were 7.9% and 100%, respectively.
- **Take Home Message:** Left limbs with C4 to C6 disease, especially with a history of deep venous thrombosis, should be routinely studied with duplex ultrasound for ICVO. Limbs with an abnormal finding on duplex ultrasound, including loss of respiratory variation in the common femoral vein or reversed flow in the superficial epigastric vein, should be routed for venous intervention; those with normal findings should be referred for computed tomography venography.

vena cava and for arteriovenous relationships was conducted using multiplanar reconstruction.¹² Centerline reconstructions of the iliac vein and vena cava located ipsilateral to the affected limb were performed to provide true perpendicular cross-sectional images of the veins. The area of maximal compression was identified, and the smallest diameter of the vein was compared with the diameter of the normal-appearing vein located caudal to the area of obstruction. If the entire external or common iliac vein was affected, the diameter in the stenotic segment was compared with the contralateral vein if it appeared to be free of obstruction. Iliac stenosis >50% was described as >50% ICVO. CTV was evaluated by a qualified vascular surgeon who was blinded to the result of DUS.

Statistical analysis. Continuous variables are described as mean \pm standard deviation, and categorical variables are shown as number and percentage. Mann-Whitney *U* test or *t*-test was used to compare continuous variables, and χ^2 test or Fisher exact test was used to compare categorical variables. Multivariate logistic regression was performed to identify independent clinical risk factors associated with the presence of >50% ICVO, and the results of that analysis are reported as odds ratio (OR) and 95% confidence interval (CI) and adjusted OR and 95% CI. All *P* values were two tailed with a significance level of .05. Accuracy of DUS, including loss of respiratory variation in the CFV and reversed flow in the SEV, for diagnosis

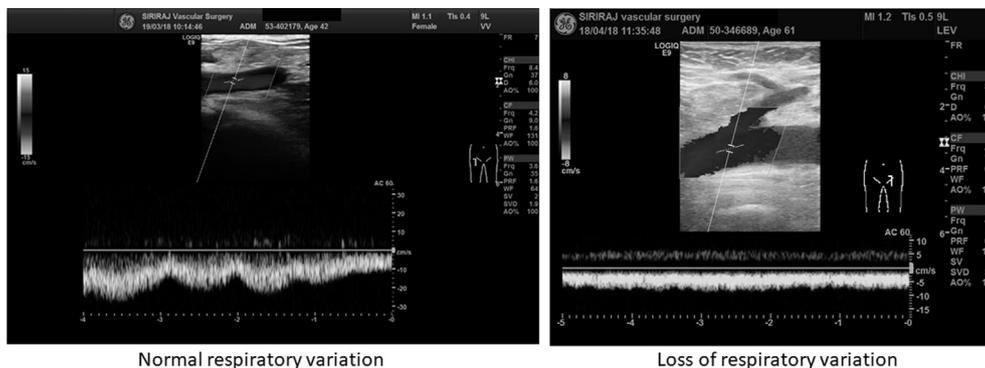


Fig 1. Duplex ultrasound (DUS) images of the common femoral vein (CFV) showing normal respiratory variation (left) and loss of respiratory variation (right).

of >50% ICVO was evaluated. Data were recorded and analyzed using PASW Statistics version 18.0 (SPSS Inc, Chicago, Ill).

The study protocol was approved by the Ethical Review Committee of the Siriraj Institutional Review Board (COA No. 689/2559(EC1)). Written informed consent was obtained from all patients.

RESULTS

A total of 106 patients and 135 affected limbs were enrolled. Demographic and clinical characteristics of patients and affected limbs are summarized in Table I.

For CTV findings, >50% ICVO was found in 38 (28%) limbs, as follows: complete occlusion in 14 (10%) limbs, 81% to 99% ICVO in 5 (3.7%) limbs, and 51% to 80% ICVO in 19 (14.1%) limbs. The complete listing of the prevalence of varying degrees of ICVO is shown in Table II.

ICVO sites included the initial portion of the left iliac vein (May-Thurner syndrome) in 16 (42%) limbs, the left external iliac vein in 12 (31%) limbs, the right external iliac vein in 9 (24%) limbs, and the vena cava in 1 (3%) limb.

Thirty-eight limbs had >50% ICVO, as follows: lipodermatosclerosis in 4 (10%) limbs, healed venous leg ulcer in 11 (29%) limbs, and active venous leg ulcer in 23 (61%) limbs. There was no statistically significant difference in the prevalence of >50% ICVO among patients with

lipodermatosclerosis, healed venous leg ulcer, or active venous leg ulcer ($P = .97$).

From 135 limbs, DUS identified isolated SVR in 46 (34%) limbs, isolated DVR in 10 (7%) limbs, and combined SVR and DVR in 18 (13%) limbs; isolated >50% ICVO was found in 7 (5%) limbs. Combined >50% ICVO and SVR was observed in 21 (15%) limbs. The patterns of venous reflux and >50% ICVO are specified in Table III. Univariate analysis for risk factors significantly associated with >50% ICVO is shown in Table IV. Multivariate analysis revealed left leg (adjusted OR, 6.02; 95% CI, 2.10-17.26; $P = .001$) and previous history of DVT in the affected leg (adjusted OR, 4.35; 95% CI, 1.77-10.69; $P = .001$) to be independent risk factors for >50% ICVO (Table V).

The sensitivity and specificity of loss of respiratory variation in the CFV for diagnosis of >50% ICVO were 23.7% (95% CI, 11.4-40.2) and 100% (95% CI, 97.1-100), respectively. The accuracy of loss of respiratory variation in the CFV for diagnosis of >50% ICVO was 82.3% (95% CI, 75.6-87.8). Nineteen percent of patients who had normal respiratory variation in the CFV had >50% ICVO. All limbs with $\leq 50\%$ ICVO on CTV had normal respiratory variation on DUS evaluation of the CFV (Table VI).

The sensitivity and specificity of reversed flow in the SEV for diagnosis of >50% ICVO were 7.9% (95% CI, 1.7-21.4) and 100% (95% CI, 88.1-100), respectively. The accuracy of reversed flow in the SEV for diagnosis of >50% ICVO

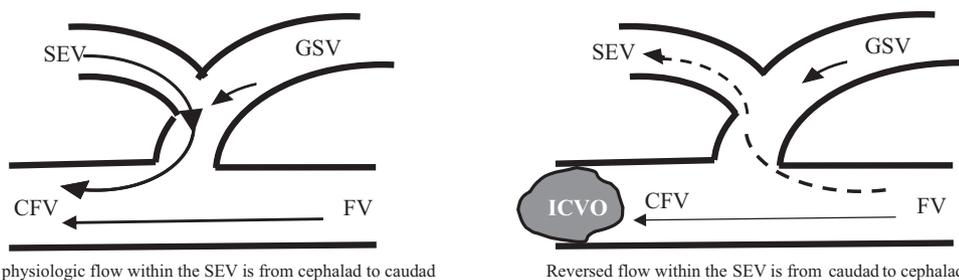


Fig 2. Left, Normal cephalad to caudad flow in the superficial epigastric vein (SEV), which is opposite to normal common femoral vein (CFV) flow. Right, Reversal of physiologic flow (flow in the same direction as CFV flow) is demonstrated within the SEV. FV, Femoral vein; GSV, great saphenous vein; ICVO, ilio caval venous obstruction.

Table I. Demographic and clinical characteristics of patients and affected limbs

Patients (n = 106)	
Age, years	58.8 ± 12.8
BMI, kg/m ²	28.3 ± 6.8
Female sex	57 (53.8)
Affected limbs (n = 135)	
Right leg	65 (48.1)
History of DVT in affected leg	21 (15.6)
CEAP clinical class	
C4b	15 (11.1)
C5	37 (27.4)
C6	83 (61.5)

BMI, Body mass index; *CEAP*, Clinical, Etiology, Anatomy, and Pathophysiology classification; *C4b*, lipodermatosclerosis; *C5*, healed venous leg ulcer; *C6*, active venous leg ulcer; *DVT*, deep venous thrombosis. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

was 47.8% (95% CI, 35.4-60.3). Fifty-five percent of patients who had normal flow in the SEV had >50% ICVO. Reversed flow in the SEV was not found in any limbs with ≤50% ICVO (Table VI).

DISCUSSION

ICVO may be due to a variety of mechanisms, including post-thrombotic chronic venous fibrosis and external compression caused by May-Thurner syndrome. Venous hypertension caused by the ICVO may result in lipodermatosclerosis or venous ulcer.⁹ We found that the majority of limbs with ICVO had SVR or DVR below the inguinal ligament, which is similar to the finding of a previous study.¹³ Both obstructive and reflux pathologic mechanisms cause microvascular injury by peripheral venous hypertension.¹⁴

The gold standard method for diagnosis of ICVO is IVUS, but the invasive nature of this method makes it unsuitable for screening for ICVO.³ Less invasive methods, such as transabdominal DUS, may fail to identify ICVO because ultrasound has significant limitations in visualizing abnormalities of the iliac veins owing to the deep location of the veins within the pelvis.¹⁵

Kibbe et al¹⁶ found that two-thirds of asymptomatic patients had ≥25% ICVO. The prevalence of >50%

Table II. Prevalence of ilio caval venous obstruction (ICVO) on computed tomography venography (CTV)

Degree of obstruction, %	No. of limbs (%)
100	14 (10.4)
81-99	5 (3.7)
51-80	19 (14.1)
31-50	40 (29.6)
11-30	38 (28.1)
0-10	19 (14.1)

Table III. Venous reflux characteristics in 135 limbs with >50% ilio caval venous obstruction (ICVO)

Finding	No. (%)
>50% ICVO only	7 (5.2)
>50% ICVO and SVR	21 (15.6)
>50% ICVO and DVR	3 (2.2)
>50% ICVO and SVR and DVR	7 (5.2)
SVR only	46 (34.1)
DVR only	10 (7.4)
SVR and DVR	18 (13.3)

DVR, Deep venous reflux; *SVR*, superficial venous reflux.

ICVO by CTV in asymptomatic patients was reported to range from 9.8% to 24%.^{16,17} As such, compression of the left iliac vein may be a common anatomic finding in asymptomatic patients. Symptomatic ICVO can be manifested with a wide range of clinical features, including all clinical CEAP classes.¹⁸ Our study found a 28% prevalence of >50% ICVO in limbs with CEAP C4b, C5, or C6 disease. Marston et al⁹ observed ≥50% ICVO in 37% of limbs with CEAP C5 or C6 disease. Rossi et al¹² identified ≥50% ICVO in 57% of limbs with advanced CVI (CEAP C3-C6). Raju and Neglen² studied patients with severe CVI using IVUS and found that 53% of patients had >50% ICVO.

In this study, left leg and previous history of DVT were identified as independent predictors of >50% ICVO. The prevalence of >50% ICVO increased to 40% if the affected limb was a left leg and to 60% if the affected limbs had previous history of DVT. Oguzkurt et al¹⁹ also reported an increased average percentage of iliac vein obstruction in patients presenting with left leg DVT compared with asymptomatic controls. Marston et al⁹ and Rossi et al¹² also found history of DVT to be a factor

Table IV. Univariate analysis for clinical risk factors significantly associated with limbs with >50% ilio caval venous obstruction (ICVO)

Clinical risk factors	Without >50% ICVO (n = 97)	With >50% ICVO (n = 38)	P value
Side			.001
Right leg	55 (56.7)	9 (23.7)	
Left leg	42 (43.3)	29 (76.3)	
History of DVT in affected limb	8 (8.2)	13 (34.2)	<.001
Venous Clinical Severity Score	13.2 ± 5.1	12.3 ± 4.9	.34
SVR	58 (59.8)	28 (73.7)	.19
DVR	23 (23.7)	7 (18.4)	.68

DVR, Deep venous reflux; *DVT*, deep venous thrombosis; *SVR*, superficial venous reflux. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation. A P value in boldface indicates statistical significance (P < .05).

Table V. Multivariate analysis for risk factors independently associated with limbs with >50% ilio caval venous obstruction (ICVO)

Risk factors	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Left leg	4.30 (1.84-10.03)	.001	4.35 (1.77-10.69)	.001
History of DVT in affected leg	5.79 (2.16-15.51)	<.001	6.02 (2.10-17.26)	.001

CI, Confidence interval; DVT, deep venous thrombosis; OR, odds ratio.
A P value in boldface indicates statistical significance (P < .05).

predictive of ICVO. Although female sex and DVR were reported to be clinical risk factors for ICVO in previous studies,^{9,10} both factors failed to demonstrate statistical significance in our study. The number of patients included in our study was relatively small, so it is possible that our study lacked sufficient statistical power to identify all significant associations and differences.

Patients having both history of DVT in the affected leg and CEAP C4b, C5, or C6 disease of the left leg had a high prevalence of >50% ICVO in this study. Accordingly, we recommend routine study of these patients with CTV. Because concomitant SVR or DVR with >50% ICVO was found in 23% of patients with C4b, C5, or C6 disease in this study, it is important to consider obstruction as a contributing factor in all patients with CEAP C4b, C5, or C6 disease—even in patients in whom obvious SVR or DVR was detected. Labropoulos et al⁵ suggested peak systolic velocity ratio of >2.5 across the stenosis at the common iliac vein to be the most accurate variable for determining the presence of a significant ICVO; however, DUS of the abdomen may be subject to limitations exerted by body habitus or intestinal gas.⁵ Indirect findings from DUS examination, including loss of respiratory variation within the CFV and reversed flow within the SEV, may be suggestive of ICVO.^{6,7,10} In this study, loss of respiratory variation in the CFV had high specificity and positive predictive value (PPV) but low sensitivity and negative predictive value (NPV) for the detection of >50% ICVO. This result is similar to the finding published by Kayilioglu et al.²⁰ However, the sensitivity observed in our study is lower than that reported by Kayilioglu et al.²⁰ Differences between and among studies may be explained by differences in the populations of patients and in the skill level of the ultrasound operator.

A DUS finding of physiologic flow reversal within the SEV was reported from a retrospective study by

Kolluri et al¹⁰ as a new sign of ICVO, and most cases of reverse flow in the SEV were found in limbs with 100% ICVO. In contrast, we did not find this parameter to be a sensitive tool in our prospective study. By way of explanation, this parameter may be dependent on the amount of collateral circulation around the ICVO.

Given the high PPV of loss of respiratory variation in the CFV and the presence of flow reversal within the SEV for diagnosis of >50% ICVO in this study, limbs with an abnormal finding on DUS may bypass CTV and proceed directly to percutaneous venography and intervention.

Because the NPV of DUS is low, a DUS scan negative for >50% ICVO was unreliable; 76% percent of limbs with >50% ICVO had normal respiratory variation, and 92% of limbs had normal flow in the SEV. Given the high prevalence of >50% ICVO in limbs with CEAP C4b, C5, or C6 disease, especially in left legs or limbs with prior history of DVT, limbs with a DUS scan negative for >50% ICVO (normal respiratory variation in the CFV or no reversed flow in the SEV) require CTV because of the low sensitivity of DUS for diagnosis of >50% ICVO. Based on the results of this analysis, we recommend the protocol shown in Fig 3 for diagnosis and treatment of >50% ICVO in patients with advanced CVI who are candidates for venous intervention.

Nevertheless, the decision to perform venoplasty in the patients with >50% ICVO is also justified by the patient's symptoms. Therefore, the decision to investigate with DUS depends not only on the sensitivity, specificity, PPV, and NPV of the DUS evaluation but also on the physician's willingness to treat, the patient's willingness to be treated, and the physician's judgment as to the patient's ability to withstand treatment and potential complications.

Significant obstruction, defined as a stenosis of >50%, was derived from observations of and data from the arterial system; however, this criterion may not be applicable

Table VI. Diagnostic accuracy parameters for loss of respiratory variation at common femoral vein (CFV) and reversed flow at superficial epigastric vein (SEV) for diagnosis of >50% ilio caval venous obstruction (ICVO) by duplex ultrasound (DUS) compared with computed tomography venography (CTV)

DUS for >50% ICVO	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, % (95% CI)	Accuracy, % (95% CI)
Loss of respiratory variation at CFV	23.7 (11.4-40.2)	100 (97.1-100)	100	81.3 (78.5-83.8)	82.3 (75.6-87.8)
Reversed flow at SEV	7.9 (1.7-21.4)	100 (91.0-100)	100	45.3 (43.0-47.6)	47.8 (35.4-60.3)

CI, Confidence interval; NPV, negative predictive value; PPV, positive predictive value.

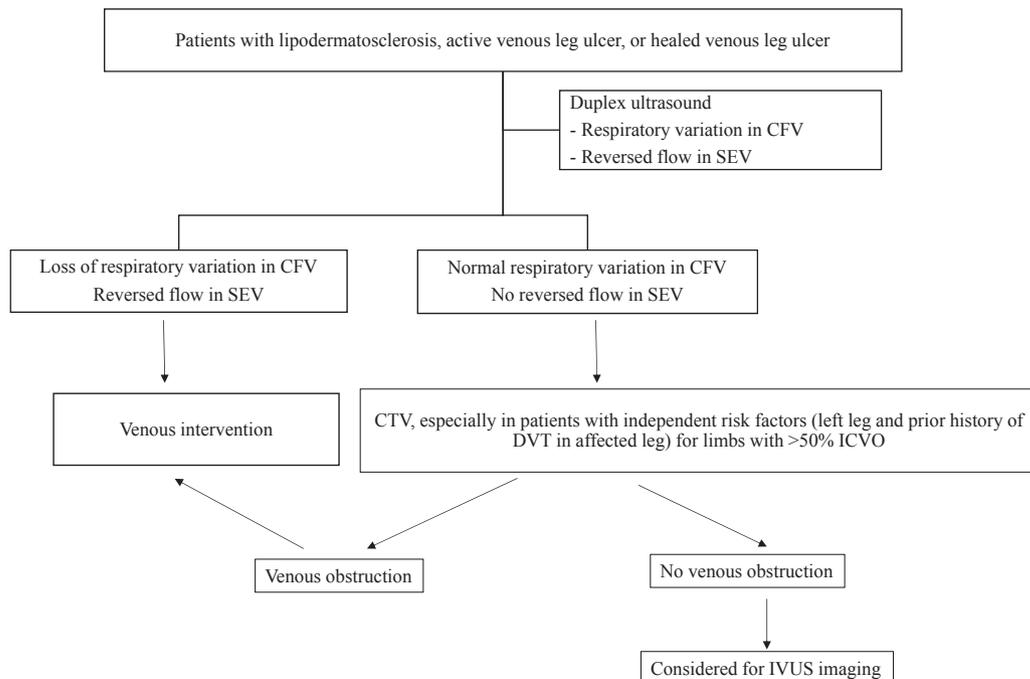


Fig 3. Flow diagram describing the algorithm used to evaluate patients with lipodermatosclerosis, healed venous leg ulcer, or active venous leg ulcer for ilio caval venous obstruction (ICVO). CFV, Common femoral vein; CTV, computed tomography venography; DVT, deep venous thrombosis; IVUS, intravenous ultrasound; SEV, superficial epigastric vein.

to the venous system because there are many notable differences between the two systems.^{2,21} An arterial stenosis has high peripheral resistance downstream; however, an iliac vein stenosis has low downstream resistance.¹⁸ The effects of a venous obstruction are upstream (lack of emptying) rather than downstream (lack of perfusion), the venous velocity is lower at rest, and the geometry of the narrowing may be more important in the venous system.³ Despite the lack of hemodynamic studies to determine the degree of obstruction necessary to cause symptoms of CVI, many practitioners adhere to a guideline of >50% stenosis diameter by multiplanar venography and >50% stenosis cross-sectional area by IVUS as thresholds that suggest clinically significant lesions.^{12,15,21-23} A study by Gagne et al²⁴ found that a >50% cross-sectional area threshold by IVUS defined a clinically significant iliofemoral stenosis that, when stented, had significant predictive value for symptom improvement.

The limitation of this study is that CTV is incapable of identifying membranes, spurs, and fibrosis that could be present in CVI patients, which means that CTV could underestimate the prevalence of treatable ICVO. IVUS determination of morphologically significant stenosis is presently the best available method for the diagnosis of clinically significant chronic iliac vein obstruction.¹⁸ The incidence of ICVO stenosis identified by IVUS was greater than the incidence of ICVO stenosis identified by both

traditional multiplanar venography and CTV.^{24,25} However, IVUS was not available at our center during the study period, so we used CTV instead. Further studies in IVUS should include a comparison of IVUS results with CTV results.

CONCLUSIONS

Limbs with lipodermatosclerosis or with healed or active venous ulceration, especially in the left limb or in limbs with a history of DVT in the affected limb, had a high prevalence of ICVO; these limbs should be routinely studied with DUS. Limbs with an abnormal finding on DUS, including loss of respiratory variation in the CFV or reversed flow in the SEV, should be routed for venous intervention, and those with normal findings should be referred for CTV.

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AUTHOR CONTRIBUTIONS

Conception and design: NS, KP, WP, KC, CW, CR, PM

Analysis and interpretation: NS, KP

Data collection: KP, WP

Writing the article: NS, KP

Critical revision of the article: NS, KP, WP, KC, CW, CR, PM

Final approval of the article: NS, KP, WP, KC, CW, CR, PM

Statistical analysis: KP

Obtained funding: NS

Overall responsibility: NS

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