Association between the degree of iliac venous outflow obstruction by intravascular ultrasound and lower limb venous reflux

Patrick Bastos Metzger, PhD, MD,[a,b] Fabio Henrique Rossi, PhD, MD,[c] Miguel Godeiro Fernandez, MS,[d] Sarah Fernandez Coutinho de Carvalho, MS,[d] Simone Lessa Metzger, MD,[d,e] Nilo Mitsuru Izukawa, PhD, MD,[c] Antonio Massamitsu Kambara, PhD, MD,[c] *and* Patricia Thorpe, MD,[f] *Salvador and São Paulo, Brazil; and Phoenix, AZ*

ABSTRACT

Objective: The present study aims to evaluate the association between the degree of iliac venous outflow obstruction (IVOO) identified by intravascular ultrasound (IVUS) and venous reflux presentation in the lower limbs on duplex ultrasound (DU).

Methods: Patients with bilateral chronic venous insufficiency, CEAP (clinical-etiology-anatomy-pathophysiology) C3 to C6, and a visual analog scale score for pain >5 underwent DU for reflux evaluation of the deep venous system (reflux ≥1 second); superficial system, great saphenous vein, and small saphenous vein (reflux ≥0.5 second); and perforator system (reflux ≥0.35 second). All patients underwent IVUS in the iliac venous territory. The area of the impaired venous segments was categorized as obstruction <50% (category 1), 50% to 79% (category 2), and ≥80% (category 3). The venous clinical severity score and reflux multisegment score (RMS) were assessed.

Results: A total of 51 patients (n = 102 limbs; age, 50.53 ± 14.5 years; 6 men) were included. The predominant clinical severity CEAP class was C3 in 54 of 102 limbs (52.9%). The mean VCSS was 14.3 ± 6.7. A severe RMS (≥3) was registered in 63.4% of the limbs. Of the 102 limbs, 51 (50%) presented with category 1, 27 (26.5%) with category 2, and 24 (23.5%) with category 3. Previous deep vein thrombosis (DVT) was associated with critical obstruction (odds ratio [OR], 3.65; 95% confidence interval [CI], 1.29-10.38; $P = .015$). The superficial and perforator venous systems had no association with the degree of IVOO. Deep venous reflux (DVR) had a significant association with significant IVOO (obstruction ≥50%; OR, 6.44; 95% CI, 2.19-18.93; $P = .001$) and critical IVOO (obstruction ≥80%; OR, 4.57; 95% CI, 1.70-12.27; $P = .003$) and a significant linear association with the IVOO degree and reflux in the femoral veins ($P < .001$) and popliteal vein ($P = .008$). Significant lesions were significantly more likely to develop in the left limb (OR, 5.76; 95% CI, 2.46-13.50; $P < .001$). After multivariate analysis, DVR remained a predictor for significant and critical obstruction ($P < .003$ and $P < .012$, respectively). Left limb and previous DVT remained as predictors for IVOO of ≥50% and ≥80% ($P < .001$ and $P = .043$, respectively).

Conclusions: We found a significant linear association between the degree of IVOO and reflux in the deep venous system on DU. Limbs with DVR, a severe RMS, loss of respiratory variation on DU, and previous DVT were more likely to be affected by IVOO of ≥50%, especially with left leg involvement. (J Vasc Surg Venous Lymphat Disord 2023;11:1004-13.)

Keywords: Duplex ultrasound; Iliac vein; Intravascular ultrasound; Lower limbs; Venous reflux

The diagnosis and treatment of reflux have been the main focus in managing symptomatic patients with chronic venous insufficiency (CVI) for more than a century.[1,2] However, it has been recognized that obstruction alone can cause symptoms in a small subset of CVI patients with post-thrombotic limbs and in those with primary disease, such as nonocclusive iliac vein lesions.[3,4] One pathophysiologic mechanism relating obstruction to venous reflux might be that increased pressure from the central obstructions leads to increased

From the Department of Interventional Radiology, Federal University of Bahia, Salvador[a]; the Department of Vascular Surgery, Hospital Cardiopulmonar - Rede D'Or, Salvador[b]; the Department of Vascular Surgery, Instituto Dante Pazzanese de Cardiologia, São Paulo[c]; the Bahiana School of Medicine and Public Health,[d] the Department of Geriatrics, Hospital Santo Antônio, Obras Sociais Irmã Dulce,[e] Salvador; and the Department of Vascular Interventional Radiology, Arizona Heart Institute, Phoenix.[f]

The present study was supported by the Fundação de Amparo a Pesquisa de São Paulo (FAPESP) (grant 2012/01021-9). The Fundação de amparo a Pesquisa do Estado de São Paulo had no involvement in the study design or data collection, analysis, or interpretation, was not involved in the decision to submit our report for publication, nor had any other involvement in the creation, artwork, or writing of the report.

Clinical Trail Registration: NCT02240914.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvsvenous.org.

Correspondence: Patrick Bastos Metzger, PhD, MD, Department of Interventional Radiology, Federal University of Bahia, Doutor Augusto Viana St, s/n Canela, Salvador, BA 40110-060, Brazil (e-mail: patrickvascular@gmail.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2023.05.018

pressurization, resulting over time in compromise to the peripheral vein valves.[4,5] This leads to venous hypertension in the lower extremity, contributing to clinical symptoms such as varicose veins, swelling, leg heaviness, lipodermatosclerosis, and venous ulcers in 15% after 5 years of follow-up.[5,6]

In this context, a meaningful correlation between iliac venous outflow obstruction (IVOO) and lower limb reflux presentation can be proposed, reinforcing the effects of proximal venous disorders on CVI origin and severity.[7,8] The relationship between obstruction and reflux, especially deep venous reflux (DVR), has not been well characterized.[9] Clinical benefit has also been reported for patients with CVI after the treatment of proximal venous lesions,[7-10] especially iliac vein stenting.[11,12]

The standard test for lower limb reflux, acute deep vein thrombosis (DVT), and CVI diagnosis is duplex ultrasound (DU) because DU is a noninvasive and easy-to-perform test with high accuracy to detect and quantify reflux.[13] However, for IVOO, the inaccuracy of single planar transfemoral venography in the delineation of the obstruction has been increasingly recognized.[14] Intravascular ultrasound (IVUS) is an imaging modality able to delineate the venous wall architecture and precisely measure the lumen diameter and area.[14,15] Consequently, IVUS provides renowned benefits for the diagnosis and management of iliofemoral venous disorders.[16-18]

The present study aims to evaluate the association between the degree of iliac venous obstruction found on IVUS and venous reflux presentation in lower limbs evaluated by DU to achieve a better understanding of the relationship between these disorders and early suspicion of IVOO with CVI evaluation.[11,19]

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, cross-sectional study of prospectively randomized collected data
- **Key Findings:** The prevalence of iliac venous outflow obstruction (IVOO) of ≥50% was 50% (51 of 102 limbs) and ≥80% was 23.5% (24 of 102 limbs) in patients with CEAP (clinical-etiology-anatomy-pathophysiology) class C3 to C6 disease. The independent predictors of IVOO ≥50% were deep venous reflux (DVR) and severe reflux multisegment score (≥3). For IVOO of ≥80%, the loss of respiratory variation in the common femoral vein, the presence of DVR, and previous deep vein thrombosis were significantly associated. Also, a significant linear association was found between the degree of IVOO and the presence of DVR.
- **Take Home Message:** Investigation for IVOO obstruction of ≥50% should be performed in symptomatic patients with CEAP class C3 to C6, especially with duplex ultrasound demonstrating DVR, a loss of respiratory variation in the common femoral vein, severe reflux multisegment score (≥3), and history of deep vein thrombosis in the affected leg, especially with left leg involvement.

METHODS

From February 2013 to August 2014, 58 patients with bilateral lower limb (n = 116) CVI (CEAP [clinical-etiology-anatomy-pathophysiology] class C3-C6) and a score >5 for complaints or pain assessed using the visual analog scale (VAS) were evaluated.[20] The VAS is a validated, subjective measure for acute and chronic pain, with the score recorded by marking a 10-cm line that represents a continuum between "no pain" and "worst pain."[20] All 58 patients had undergone noninvasive treatment (drug therapy for CVI and elastic compression therapy) for ≥1 year with no relief of symptoms. The number of analyzed patients corresponds to 28% of the patients evaluated for CVI by us during the study period. Patients with limb symptoms of nonvenous etiology, patients with only unilateral involvement, and patients with bilateral CVI but with a VAS score of ≤5 were excluded. Bilateral involvement was an inclusion criterion to avoid an invasive evaluation with IVUS for healthy limbs. In addition, another two patients were excluded because of morbid obesity (body mass index >40 kg/m^2), three patients because of renal insufficiency (creatinine clearance <30 mL/min/1.73 m^2), and two because of concomitant chronic lower limb ischemia. Thus, the study enrolled 51 patients (102 limbs). All the patients provided written informed consent, and the institutional review board approved the present study, which was registered in ClinicalTrials.gov (NCT02240914).

The venous clinical severity score (VCSS) was assessed for each patient, and the limbs were classified using the revised CEAP classification.[21] The lower limb's superficial, perforator, and deep venous systems were evaluated by DU. Subsequently, all 51 patients underwent venography and IVUS on the same day. Two different examiners, who were unaware of the other's findings, performed DU and IVUS. Each limb was considered separately in all statistical evaluations.

Venous DU. DU evaluation was performed with linear transducers of 10 to 13 MHz (AplioXV; Toshiba), as previously described by Labropoulos et al[22] and Metzger et al.[13] The examination was performed with the patient in the upright position to evaluate the presence of reflux in the superficial venous system (reflux time, ≥0.5 second) and deep venous system (≥1 second) in the lower limbs. Venous reflux in the perforating system (≥0.35 second) was evaluated using a rapid inflation/deflation system (E20 Rapid Cuff Inflator and AG101 Cuff Inflator Air Source; Hokanson Inc).[23] Venous obstruction was evaluated with the patient in the supine position through compression maneuvers and examination of

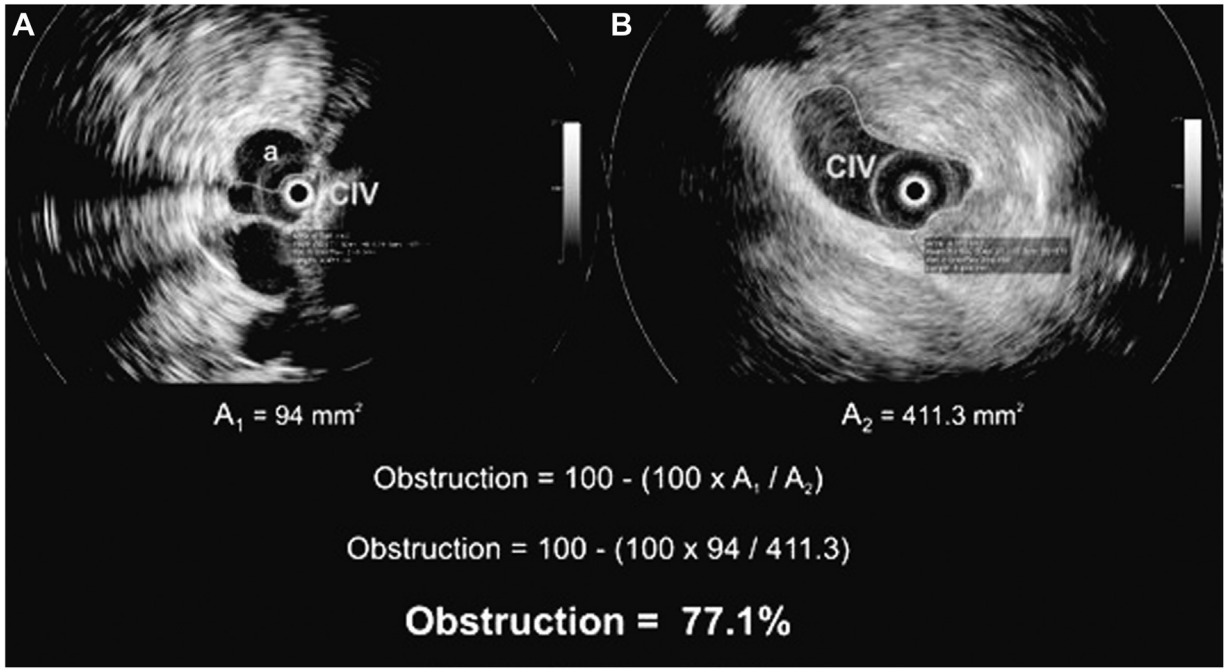


Fig 1. Assessment of left common iliac vein stenosis with intravascular ultrasound (IVUS). **A,** Area at site of stenosis (A_1). **B,** Area at common iliac vein bifurcation (A_2). *a,* Right common iliac artery; *CIV,* common iliac vein.

flow patterns with augmentation that allowed for identification of acute or chronic venous obstruction. The characteristics of the waveforms were analyzed in the common femoral vein (CFV).

The reflux in each limb was categorized according to the reflux multisegment score (RMS).[1,24] Reflux in the great saphenous vein (GSV) above the knee, GSV below the knee, small saphenous vein, perforator veins, femoral veins, deep femoral veins, and popliteal veins were each given a score of 1. The total reflux score for the limb was calculated (maximum score, 7). Next, we categorized each limb as presenting with moderate reflux (RMS <3) or severe reflux (RMS ≥3).[1]

IVUS examination. Bilateral venous access (femoral or popliteal) was performed using ultrasound. The vein anatomy and obstruction zones were evaluated with digital subtraction venography, followed by bilateral IVUS. The 9F Sonicath Ultra 6 IVUS system (Sonicath Ultra; Boston Scientific) was inserted into the venous segment through the appropriate sheath size. Images were obtained with catheter pullback from the infrarenal cava to the femoral veins to assess the venous size, degree of stenosis, and presence of intraluminal lesions.[11,13]

The built-in software program measured the obstructed areas at the maximum compression point and the healthy vein below the stenosis. Neglén et al[15] recognized that the nonconcentric shape of the iliac vein makes measuring its diameter difficult and that the area measurements must be more precise. In the present study, the degree of obstruction was recorded using the following formula: $100 - (100 \times A_1/A_2)$, where A_1 is the area at the point of maximum compression, and A_2 is the area at the common iliac vein confluence caudal to the obstruction (Fig 1).

The common iliac vein confluence caudal to the obstruction was used as the denominator for several reasons.[15,25] First, the area of the iliac vein immediately caudal to the obstruction site is typically free from compression by surrounding structures and sustains a nearly circular shape. Second, in some cases, the location of the arterial crossing over the iliac vein is near the vena cava confluence, leaving little or no space to measure the diameter of the cranial iliac vein. Third, the cranial iliac vein segment near the confluence is often considerable, which would result in an overestimation of the proper degree of obstruction.

When the entire iliac vein was affected, the area in the stenotic segment was compared with that of the contralateral vein if it appeared free from obstruction.[15] If both iliac veins were affected, the area was compared with the normal iliac vein area of 150 mm^2 ($r = 6.5$ mm).[1,15]

The degree of iliac vein compression or obstruction was then qualitatively classified into three categories: obstruction <50% (category 1), 0% to 49%, category 2; 50% to 79%, and category 3, ≥80% (Fig 2, *A-E*).[11,13,19] If venography showed occlusion, the iliac vein was classified as category 3. Iliac venous stenting was performed in all patients in whom IVUS found significant IVOO (obstruction of ≥50%).[11]

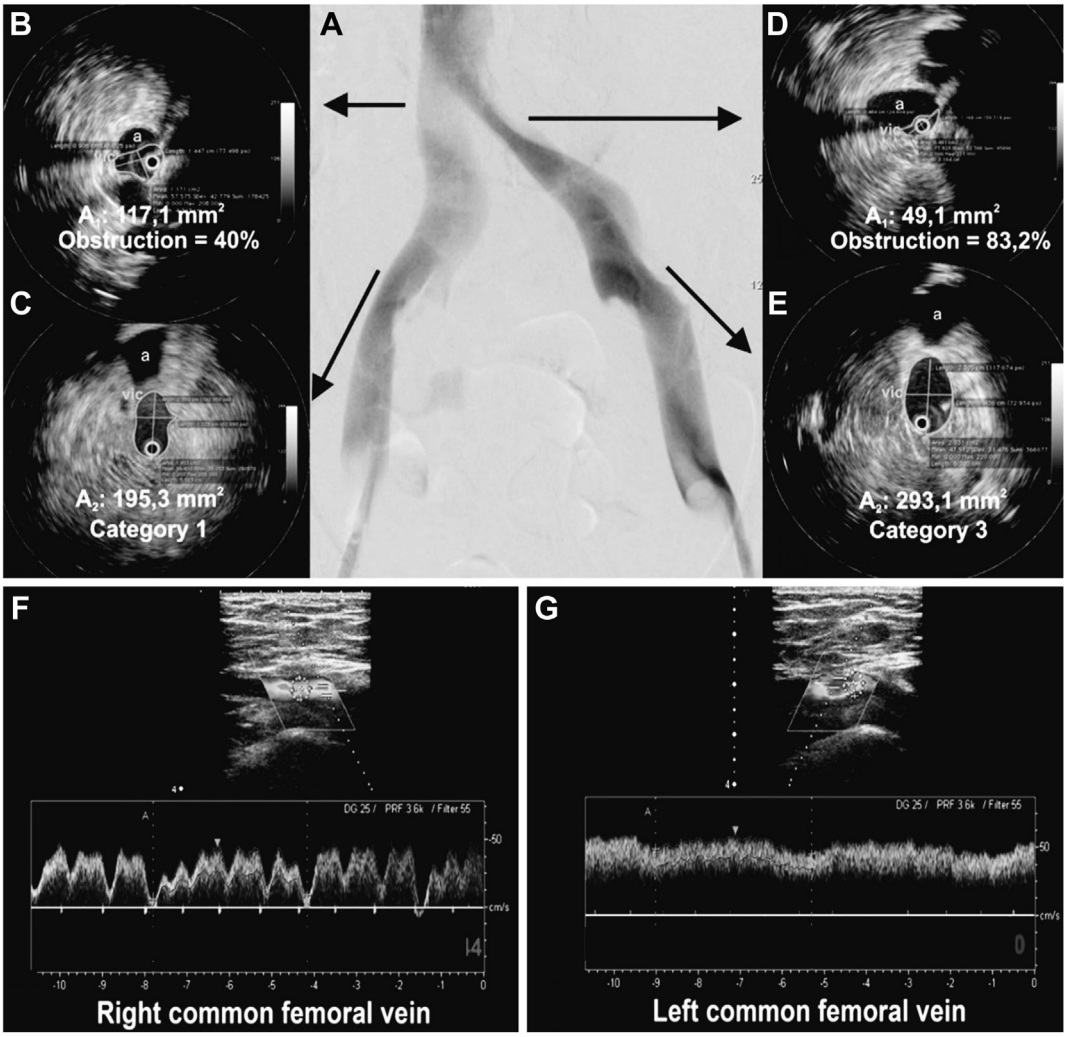


Fig 2. Venography, categories of obstruction on intravascular ultrasound (IVUS), and evaluation of venous flow phasicity. **A,** Iliocaval venography. **B,** Area of point of maximum compression in right iliac vein. **C,** Area of right common iliac vein confluence. **D,** Area of point of maximum compression in left iliac vein. **E,** Area of left common iliac vein confluence. **F,** Phasic waveform in common femoral vein. **G,** Monophasic waveform in common femoral vein.

Calculation of sample size and power of the study. As described by Marston et al,[26] we used a prevalence of 23% of ≥50% IVOO in the general population with CVI and an estimated superior limit of 37% in the studied population, because the study was performed at a tertiary center with a higher prevalence of patients with advanced disease. Based on data reported by Metzger et al,[13] for an estimated difference in the femoral velocity index of 0.1 on DU (the index between the maximum velocity of the femoral veins between patients with and without significant IVOO) and applying the Wilcoxon-Mann-Whitney test, we estimated a total sample of 64 limbs would be needed for a power of 95% with a standard deviation of 0.1.

Statistical analysis. Data from clinical and complementary evaluations were entered prospectively into an electronic medical record program. Unless otherwise indicated, continuous data were entered as the mean ± standard deviation and analyzed using a *t* test or nonparametric Wilcoxon rank test, depending on normality. Fisher's exact test was used to investigate the association between deep, superficial, and perforating venous reflux with the categories of iliac venous obstruction diagnosed by IVUS. The Kappa index was used to evaluate the degree of agreement between the C class of the CEAP classification and the RMS. The performance of RMS in detecting significant IVOO was assessed by the receiver operating characteristic (ROC)

Table I. Patient characteristics

Parameter	Value
Age, years	
Mean ± SD	50.53 ± 14.5
Median (range)	51 (25-77)
BMI, kg/m^2	
Mean ± SD	28.6 ± 5.55
Median (range)	27.6 (19.6-40.0)
Pregnancies, No.	
Mean ± SD	2.66 ± 1.96
Median (range)	2 (0-7)
OCP use	14 (13.7)
Race	
White	58 (56.6)
Black	12 (11.8)
Mixed	32 (31.6)
VCSS	
Mean ± SD	14.3 ± 6.7
Median (range)	14 (5-26)
CEAP class	
C3	54 (52.9)
C4	21 (20.6)
C5	9 (8.8)
C6	18 (17.6)
Previous DVT	20 (19.6)

BMI, Body mass index; *DVT*, deep vein thrombosis; *OCP*, oral contraceptive; *SD*, standard deviation; *VCSS*, venous clinical severity score. Data presented as number of limbs (%), unless noted otherwise.

curve and area under the ROC curve (AUC). The selection of the cutoff point was determined by the best value of sensitivity and specificity.

Logistic regression was performed to determine the independent association of risk factors with the presence of IVOO. Significant predictors on univariate analysis were also evaluated in a multivariate model. Odds ratios (ORs) were calculated from the parameters with the 95% confidence intervals (CIs). The commercially available SPSS program, version 19.0 (IBM Corp) was used for statistical analysis. The results are reported using *P* values, and $P < .05$ was considered statistically significant.

RESULTS

Most of the patients were women (88.2%) and White (56.6%), with an average age of 50.53 ± 14.5 years (range, 25-77 years). All previous DVTs were in the iliac (50%) or femoropopliteal (50%) veins. The main clinical data and CVI CEAP class are shown in Table I. The presence and location of venous reflux on DU, RMS, and distribution of ≥50% IVOO localization are shown in Table II.

Venous reflux and clinical severity. DVR was present in 26 of the 102 limbs (25.5%). The CEAP class for these 26 limbs was C3 in 4 (15.38%), C4 in 6 (23%), C5 in 7 (26.9%), and C6 in 9 (34.6%). Axial DVR was more prevalent in limbs with CEAP class C5-C6 (61.5%).

We evaluated the RMS and observed that 75 of 102 limbs (73.5%) showed reflux. The score ranged from 1 to 7. Moderate reflux (RMS <3) was demonstrated in 29 limbs (38.6%), with severe reflux (RMS ≥3) in 46 (61.4%). Significant agreement was found between the clinical CEAP class and the RMS (kappa = 0.603; $P < .001$).

Venous reflux and IVOO degree. Venography showed that 10 limbs (9.8%) were occluded. Regarding the classification of the degree of obstruction, 51 limbs (50%) were category 1 (obstruction, <50%), 27 (26.5%) were category 2 (obstruction, 50%-79%), and 24 (23.5%) were category 3 (obstruction, ≥80%). The left/right ratio for significant lesions was 2.4:1.

Monophasic waveforms were present in limbs with category 2 and category 3 (7.7% vs 62.5%; $P < .001$) but not in limbs with category 1. The presence of monophasic waveforms demonstrated high accuracy in discriminating against critical obstruction (≥80%; Fig 2, *F* and *G*; Supplementary Table, online only).

Univariate analysis of the reflux in the superficial, perforator, and deep venous systems identified by DU with an IVOO of ≥50% and ≥80% showed that only the deep venous system demonstrated a significant association ($P < .001$). Previous DVT was associated with critical obstruction (OR, 3.65; 95% CI, 1.29-10.38; $P = .015$), and left limbs were associated with both significant and critical obstruction ($P < .001$ and $P < .049$, respectively). After multivariate analysis, DVR remained a predictive factor for significant and critical obstruction ($P < .003$ and $P < .012$, respectively). Previous DVT remained a predictive factor for IVOO of ≥80% (OR, 3.16; 95% CI, 1.04-9.37; $P = .043$), and lesions in the left limb remained a predictive factor for IVOO of ≥50% ($P < .001$; Table III).

A positive linear association was found between the degree of IVOO and DVR evaluated in the femoral veins ($P < .001$) and popliteal vein ($P = .008$). No association was found between the degree of venous obstruction and reflux in the superficial venous system (GSV, $P = .546$; small saphenous vein, $P = .235$) or perforator system ($P = 1.0$; Supplementary Fig, *A*, online only). In particular, patients with axial DVR (femoral and popliteal veins) were more likely (OR, 5.25; 95% CI, 1.07-25.66; $P = .041$) to be affected by significant IVOO. Significant lesions were also more likely (OR, 5.76; 95% CI, 2.46-13.50; $P < .001$) to occur in the left limb.

RMS and IVOO. The RMS evaluation revealed different mean values for patients with and without significant IVOO (2.73 ± 1.98 vs 1.94 ± 1.76; $P = .037$). A ROC curve to evaluate RMS accuracy in detecting significant iliac venous lesions showed an AUC of 0.616 (95% CI, 0.506-0.725; $P = .044$; Supplementary Fig, *B*, online only).

Table II. Reflux and distribution of significant iliac venous outflow obstruction locations

Parameter	Value
Venous reflux on DU	
Femoral veins	21 (20.6)
Popliteal vein	16 (15.7)
Great saphenous vein	57 (55.9)
Small saphenous vein	30 (29.4)
Perforator vein	51 (50)
Type of reflux	
DVR alone	4/26 (15.4)
DVR plus superficial reflux	5/26 (19.2)
DVR plus perforator reflux	2/26 (7.7)
DVR plus superficial and perforator reflux	15/26 (57.7)
Axial deep reflux	11/26 (42.3)
Reflux multisegment score	
1	7 (6.9)
2	22 (21.6)
3	20 (19.6)
4	13 (12.7)
5	5 (4.9)
6	6 (5.9)
7	2 (2)
IVOO ≥50% location	
Left common iliac vein	34 (33.3)
Right common iliac vein	13 (12.7)
Left external iliac vein	2 (1.96)
Right external iliac vein	2 (1.96)
Bilateral common iliac veins	20 (19.6)

DU, Duplex ultrasound; *IVOO*, iliac venous outflow obstruction.
Data presented as number (%) or number/total (%).

Evaluating the RMS for the deep venous assessment, higher accuracy was identified for both significant lesions (AUC, 0.657; 95% CI, 0.551-0.764; $P = .006$) and critical lesions (AUC, 0.661; 95% CI, 0.528-0.794; $P = .017$; Supplementary Fig, *C* and *D*, online only).

Investigation algorithm. We developed an investigation algorithm for CVI patients with symptomatic CEAP class C3 to C6 (Fig 3). In a symptomatic patient with previous axial DVT in the left limb and with DVR, DVT, or a severe RMS (≥3) found on DU, cavoiliac DU or computed tomography venography should be performed to evaluate for IVOO. If the study findings are negative for IVOO, or a loss of respiratory variation is found in the CFV, a workup for IVOO, consisting of venography with IVUS, should be considered. However, if no DVR, no loss of respiratory variation in the CFV, or no previous DVT is found on DU, no workup for IVOO is necessary. In our study, none of the legs without one or more independent risk factors had significant IVOO.

DISCUSSION

The degree of IVOO attested by IVUS is associated with worse limb venous reflux, especially in the deep system. A severe clinical CVI presentation and its evaluation by DU might allow for early suspicion of IVOO before the patient requires further invasive intervention.

Reflux is considered the dominant pathology in patients with CVI.[27] Venous reflux generated by valvular incompetence, especially in the deep venous system, is often found in patients with advanced CVI.[28] In the present study, the occurrence of reflux in the deep venous system was 25.5%, and 61.3% of the limbs demonstrated severe reflux (RMS, ≥3). We found a significant positive correlation between the RMS and the clinical CEAP classification ($r = 0.603$; $P < .001$).[23] Thus, a worse RMS for venous reflux of the limb is associated with a more advanced CVI class. Raju et al,[1] in a retrospective study, found a 33% prevalence of DVR and a 59% prevalence of severe reflux (RMS ≥3) in 528 analyzed limbs with CEAP class C3 to C6 and CEAP class C2 with a VAS score of ≥5.

IVOO has been increasingly recognized as an important etiologic factor for CVI. It can present acutely (iliofemoral DVT) or cause chronic disabling CVI symptoms, including edema, leg heaviness, lipodermatosclerosis, pain, varicose veins, and ulceration, and venous hypertension.[1,29-31] The recognition of its importance and a better understanding of pelvic venous disorders are increasing globally.[32-34] For IVOO evaluation, single planar transfemoral venography was considered the gold standard but has since been continuously defined as inaccurate. The extent and severity of obstructive lesions appear worse using IVUS than using venography, and severe obstruction can remain undetected using venography.[35,36] Contrast dye injection can hide details, such as intraluminal webs, and, on average, venography underestimates the stenosis degree by 30%.[15] We found a prevalence of IVOO of ≥50% in 51 of 102 limbs (50%) and of ≥80% in 24 of 102 limbs (23.5%).

No accurate noninvasive or invasive hemodynamic tests are available for defining when venous obstructions become critical, and the diagnosis of occlusive or nonocclusive obstructions is based on morphologic studies. Venous obstructions of ≥50% are considered significant, arbitrarily determined by the clinical outcomes.[1,2] Nevertheless, recent studies have reported that the degree of iliac obstruction can categorize significant IVOO (≥50%): 50% to 79% and ≥80% using invasive and noninvasive methods.[11,13,19,26]

Several reports have suggested an obstructive component is commonly present in limbs with CVI of both post-thrombotic and nonthrombotic etiologies.[2,37] In limbs with a primary nonthrombotic disease, obstructive lesions occur at arterial crossover points, not only at the "classic" proximal location,[38] but also at distal locations, including the hypogastric artery crossing and behind

Table III. Univariate and multivariate analysis results stratified by reflux on duplex ultrasound and significant (≥50%) and critical (≥80%) iliac vein outflow obstruction (IVOO) on intravascular ultrasound

	IVOO ≥50%		IVOO ≥80%	
Analysis	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Univariate				
Superficial venous reflux	1.30 (0.57-2.95)	.532	1.36 (0.50-3.68)	.544
Perforator venous reflux	1.27 (0.58-2.75)	.553	0.80 (0.32-2.01)	.641
DVR	6.44 (2.19-18.93)	**<.001**	4.57 (1.70-12.27)	**<.003**
Previous DVT	2.15 (0.78-5.94)	.140	3.65 (1.29-10.38)	**<.015**
Left limb	5.76 (2.46-13.5)	**<.001**	2.69 (1.03-6.41)	**<.049**
Multivariate				
DVR	5.74 (1.80-18.27)	**<.003**	3.75 (1.34-10.50)	**<.012**
Previous DVT	1.41 (0.43-4.593)	.56	3.16 (1.04-9.37)	**<.043**
Left limb	5.28 (2.13-13.09)	**<.001**	1.84 (0.66-5.14)	.24

CI, Confidence interval; *DVR,* deep venous reflux; *DVT,* deep vein thrombosis; *OR,* odds ratio.
Boldface *P* values represent statistical significance ($P < .05$).

the inguinal ligament.[2] In the present study, the most frequent point of significant obstruction was the cranial common left iliac vein in 33.3% of the limbs; however, in 16.6% of the cases, other iliac vein segments were obstructed. The left/right ratio in the present study was 2.4:1. In a retrospective study of 528 patients, Raju et al[1] observed a left/right ratio of 2:1. In a consecutive study of 304 limbs, Neglén et al[15] found a ratio of 2.7:1. These findings demonstrate that obstruction caused by iliac vein compression syndrome or thrombosis can occur in sites other than the classic crossover point at the right common iliac artery and left common iliac vein, as described by May and Thurner[39] and Cockett et al.[40]

We found that 50% of the studied limbs had ≥50% IVOO and 23.5% had ≥80% IVOO when verified by IVUS. Raju and Neglen[2] found that IVUS-detectable lesions are present in >90% of CVI patients, demonstrating a high prevalence of iliac obstruction and the importance of IVOO screening in highly symptomatic patients with CVI.

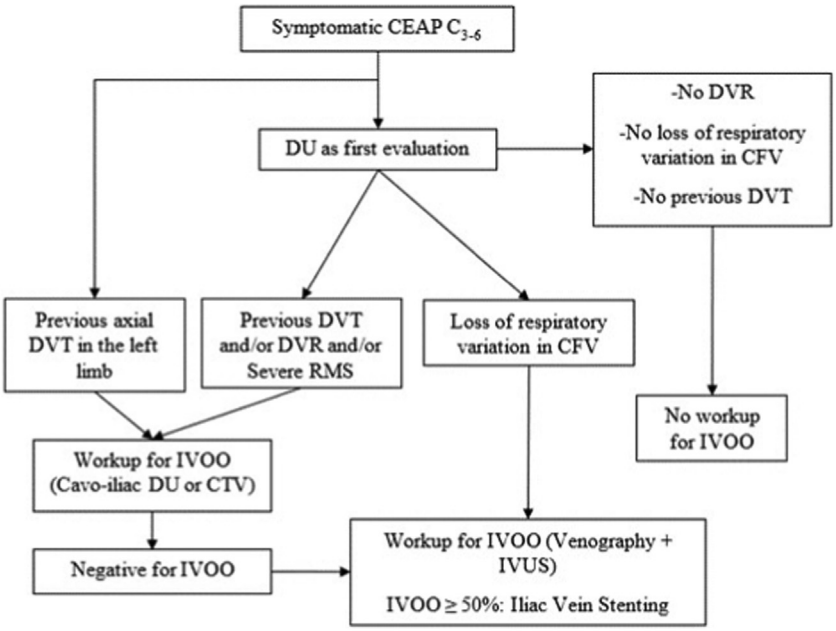


Fig 3. Investigation algorithm for patients with chronic venous insufficiency (CVI) with symptomatic CEAP (clinical-etiology-anatomy-pathophysiology) class C3 to C6. *CFV,* Common femoral vein; *CTV,* computed tomography venography; *DU,* duplex ultrasound; *DVR,* deep venous reflux; *DVT,* deep vein thrombosis; *IVOO,* iliac venous outflow obstruction; *IVUS,* intravascular ultrasound; *RMS,* reflux multisegment score.

Some studies have suggested a peak systolic velocity ratio of >2.5 across stenosis at the common iliac vein to be the most accurate variable for determining the presence of significant IVOO.[13,22] However, abdominal DU could be subject to limitations exerted by body habitus or intestinal gas. Indirect findings from DU, such as loss of respiratory variation within the CFV, could be suggestive of significant IVOO.[13] Monophasic waveforms result from dampened transmission of fluctuating intrathoracic pressures to distal venous structures. The loss of the phasic variation can result from (1) iliac nonocclusive thrombus; (2) extrinsic compression; (3) intrinsic luminal narrowing; or (4) cardiac factors or other causes.[41] Lin et al,[41] in a retrospective study, showed that 124 limbs had monophasic waveforms in the CFV, with iliac venous thrombosis the most common cause (38%). However, 36% had no discernable explanation for the loss of phasic variation. In our study, monophasic waveforms were present in 62.5% of the limbs categorized with IVOO of ≥80% and in just 7.7% of the limbs (two limbs) categorized with IVOO of 50% to 79%. Monophasic waveforms were the result of iliac venous thrombosis in 10 of 17 limbs (58.8%), extrinsic compression (35.3%), and intrinsic narrowing (5.9%). The loss of respiratory variation in the CFV had high specificity (100%) and a high positive predictive value but low sensitivity (34%) and a low negative predictive value for the detection of IVOO of ≥50%, similar to findings reported by other investigators.[28,42,43] However, for critical IVOO of ≥80%, the detection of monophasic waveforms showed better sensitivity (62.5%), with high specificity (97.4%), positive predictive value (93.4%), and accuracy (89.1%), suggesting that the loss of respiratory variation in the CFV better detected critical IVOO.

Neglén et al[37] conducted a retrospective study of 429 patients with CVI and proximal venous obstruction alone and others with associated venous reflux. They demonstrated that patients with signs of obstruction and reflux had a worse clinical presentation and RMS compared with the proximal obstruction group alone.[37] Proximal venous obstruction aggravated the patients' symptoms but did not worsen their reflux. Pergamo et al,[10] in a retrospective study of 275 patients who underwent iliofemoral stenting for venous obstruction, 58 had DVR before intervention, and 17 of those 58 patients experienced resolution of their reflux after the procedure ($P = .0001$). Pergamo et al[10] suggested that iliofemoral stenting might improve DVR.

Marston et al,[26] in a cross-sectional study of 78 limbs (CEAP class C5-C6), investigated the origins of reflux and obstruction and categorized IVOO into three categories, just as in our study. DVR and a history of DVT were associated with a high incidence of critical IVOO (obstruction of ≥80%). Therefore, it was postulated that patients with persistent DVR are more likely to experience major iliofemoral DVT associated with IVOO, resulting in a higher incidence of leg ulceration compared with that in patients with superficial involvement. In the present study, the left leg and DVR were identified as independent predictors of IVOO of ≥50%, and previous DVT demonstrated an association with IVOO of ≥80% ($P = .015$). In addition, Oğuzkurt et al[43] reported an increased average percentage of iliac vein obstruction in patients presenting with left leg DVT compared with asymptomatic controls. Other studies also found previous DVT to be a risk factor.[11,28,44]

Our study showed a significant linear association between the degree of IVOO and the presence of axial DVR evaluated in the femoral and popliteal veins. This reflux was more predominant in limbs classified as CEAP class C5 to C6 (61.5%). It is essential to consider proximal venous obstruction as a contributing factor for all patients with CVI, even if reflux in the deep venous system is evident and venous obstruction is not apparent.[1,37]

Study limitations. The present study is limited by its cross-sectional design and sample size, which might impair the detection of significant independent factors. In accordance with the recommendations in the current guidelines for investigating CVI, we identified venous reflux using the reflux time only.[45,46] Previous studies have suggested that the quantification of reflux, including both reflux flow and velocity, is better than the reflux time alone for determining the clinical severity of venous reflux.[47,48] Further studies to compare these two different methods of quantifying venous reflux are warranted.

CONCLUSIONS

We found a significant linear association between the degree of IVOO and reflux in the deep venous system in lower limbs using DU. Limbs with DVR, a severe RMS, the loss of respiratory variation on DU in the CFV, and previous DVT were more likely to be affected by significant and critical IVOO, especially with left leg involvement. A severe clinical CVI presentation (CEAP C3-C6) and evaluation using DU might allow for early suspicion of significant IVOO (>50%) before the patient requires further invasive intervention.

AUTHOR CONTRIBUTIONS

Conception and design: PM, FR
Analysis and interpretation: PM, FR, MF, SC, SM, NI, PT
Data collection: PM, FR, AK
Writing the article: PM, FR, MF, SC
Critical revision of the article: PM, FR, SM, NI, AK, PT
Final approval of the article: PM, FR, MF, SC, SM, NI, AK, PT
Statistical analysis: PM, MF
Obtained funding: Not applicable
Overall responsibility: PM

REFERENCES

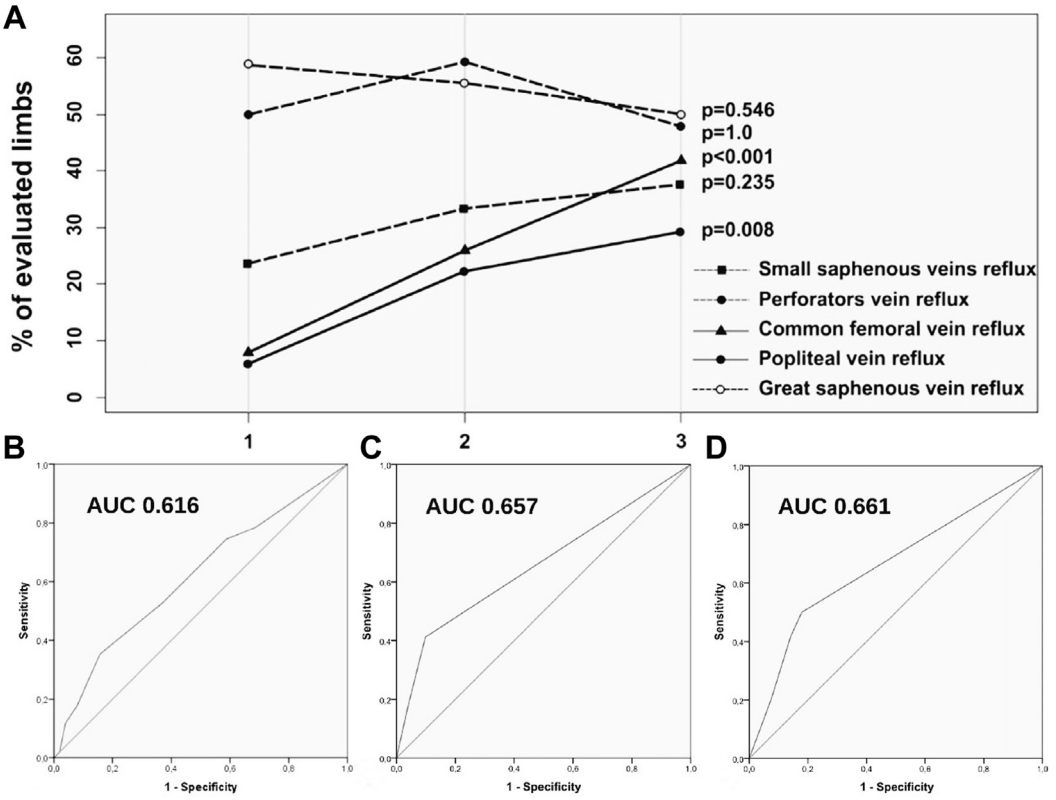
1. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. J Vasc Surg 2010;51:401-9.
2. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136-43.
3. Benfor B, Peden EK. A systematic review of management of superficial venous reflux in the setting of deep venous obstruction. J Vasc Surg Venous Lymphat Disord 2022;10:945-54.e2.
4. Rossi FH, Kambara AM, Rodrigues TO, et al. Comparison of computed tomography venography and intravascular ultrasound in screening and classification of iliac vein obstruction in patients with chronic venous disease. J Vasc Surg Venous Lymphat Disord 2020;8:413-22.
5. Wrona M, Jöckel KH, Pannier F, Bock E, Hoffmann B, Rabe E. Association of Venous Disorders with Leg Symptoms: results from the Bonn Vein Study 1. Eur J Vasc Endovasc Surg 2015;50:360-7.
6. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004;239:118-26.
7. Raju S, Owen S Jr, Neglen P. The clinical impact of iliac venous stents in the management of chronic venous insufficiency. J Vasc Surg 2002;35:8-15.
8. Raju S, Lucas M, Luke C, Peeples H, Saleem T, Jayaraj A. Long-term improvement of limb reflux prevalence and severity after iliac vein stent placement. J Vasc Surg Venous Lymphat Disord 2022;10:640-5.
9. Vasan V, Bai H, Chen J, et al. Iliac vein stenting outcomes for patients with superficial venous insufficiency concurrent with deep venous disease. J Vasc Surg Venous Lymphat Disord 2022;10:1215-20.
10. Pergamo M, Kabnick LS, Jacobowitz GR, et al. Relationship between iliofemoral venous stenting and femoropopliteal deep venous reflux. J Vasc Surg Venous Lymphat Disord 2023;11:346-50.
11. Rossi FH, Kambara AM, Izukawa NM, et al. Randomized double-blinded study comparing medical treatment versus iliac vein stenting in chronic venous disease. J Vasc Surg Venous Lymphat Disord 2018;6:183-91.
12. Abdul-haqq R, Novak Z, Pearce BJ, et al. Routine extended follow-up surveillance of iliac vein stents for iliocaval venous obstruction may not be warranted stent pra ompressão. J Vasc Surg 2017;5:500-5.
13. Metzger PB, Rossi FH, Kambara AM, et al. Criteria for detecting significant chronic iliac venous obstructions with duplex ultrasound. J Vasc Surg Venous Lymphat Disord 2016;4:18-27.
14. Raju S. Best management options for chronic iliac vein stenosis and occlusion. J Vasc Surg 2013;57:1163-9.
15. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg 2002;35:694-700.
16. Saleem T, Knight A, Raju S. Diagnostic yield of intravascular ultrasound in patients with clinical signs and symptoms of lower extremity venous disease. J Vasc Surg Venous Lymphat Disord 2019;8:634-9.
17. Tran LM, Go C, Zaghloul M, et al. Intravascular ultrasound evaluation during iliofemoral venous stenting is associated with improved midterm patency outcomes. J Vasc Surg Venous Lymphat Disord 2022;10:1294-303.
18. How GY, Quek LHH, Huang IKH, et al. Intravascular ultrasound correlation of unenhanced magnetic resonance venography in the context of pelvic deep venous disease. J Vasc Surg Venous Lymphat Disord 2022;10:1087-94.
19. Jayaraj A, Powell T, Raju S. Utility of the 50% stenosis criterion for patients undergoing stenting for chronic iliofemoral venous obstruction. J Vasc Surg Venous Lymphat Disord 2021;9:1408-15.
20. Huskisson EC, Jones J, Scott PJ. Application of visual-analogue scales to the measurement of functional capacity. Rheumatol Rehabil 1976;15:185-7.
21. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's choice - European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. Eur J Vasc Endovasc Surg 2022;63:184-267. Erratum in: Eur J Vasc Endovasc Surg. 2022 Aug-Sep;64(2-3):284-285.
22. Labropoulos N, Borge M, Pierce K, Pappas PJ. Criteria for defining significant central vein stenosis with duplex ultrasound. J Vasc Surg 2007;46:101-7.
23. Labropoulos N, Tiongson J, Pryor L, et al. Definition of venous reflux in lower-extremity veins. J Vasc Surg 2003;38:793-8.
24. Neglén P, Raju S. A rational approach to detection of significant reflux with duplex Doppler scanning and air plethysmography. J Vasc Surg 1993;17:590-5.
25. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic patient population. J Vasc Surg 2004;39:937-43.
26. Marston W, Fish D, Unger J, Keagy B, Hill C. Incidence of and risk factors for iliocaval venous obstruction in patients with active or healed venous leg ulcers. J Vasc Surg 2011;53:1303-8.
27. Lawrence PF, Hager ES, Harlander-Locke MP, et al. Treatment of superficial and perforator reflux and deep venous stenosis improves healing of chronic venous leg ulcers. J Vasc Surg Venous Lymphat Disord 2020;8:601-9.
28. Sermsathanasawadi N, Pruekprasert K, Pitaksantayothin W, et al. Prevalence, risk factors, and evaluation of iliocaval obstruction in advanced chronic venous insufficiency. J Vasc Surg Venous Lymphat Disord 2019;7:441-7.
29. Jayaraj A, Powell T, Raju S. Effect of body mass index on initial presentation and outcomes after stenting for quality of life-impairing chronic iliofemoral venous obstruction. J Vasc Surg Venous Lymphat Disord 2022;10:325-33.e1.
30. Masuda E, Ozsvath K, Vossler J, et al. The 2020 appropriate use criteria for chronic lower extremity venous disease of the American Venous Forum, the Society for Vascular Surgery, the American Vein and Lymphatic Society, and the Society of Interventional Radiology. J Vasc Surg Venous Lymphat Disord 2020;8:505-25.e4.
31. Taha MAH, Busuttil A, Bootun R, et al. A clinical guide to deep venous stenting for chronic iliofemoral venous obstruction. J Vasc Surg Venous Lymphat Disord 2022;10:258-66.e1.
32. Esposito A, Charisis N, Kantarovsky A, Uhl JF, Labropoulos N. A Comprehensive review of the pathophysiology and clinical importance of iliac vein obstruction. Eur J Vasc Endovasc Surg 2020;60:118-25.
33. Meissner MH, Khilnani NM, Labropoulos N, et al. The symptoms-varices-pathophysiology classification of pelvic venous disorders: a report of the American Vein & Lymphatic Society International Working Group on Pelvic Venous Disorders. J Vasc Surg Venous Lymphat Disord 2021;9:568-84.
34. De Carvalho SFC, Metzger PB, Fernandez MG, Ribeiro WB, Nogueira AKS, e Souza JPR. Pelvic venous reflux embolization in the treatment of symptomatic pelvic congestive syndrome: a systematic review with meta-analysis. J Vasc Surg Venous Lymphat Disord 2023;11:412-21.
35. Montminy ML, Thomasson JD, Tanaka GJ, Lamanilao LM, Crim W, Raju S. A comparison between intravascular ultrasound and venography in identifying key parameters essential for iliac vein stenting. J Vasc Surg Venous Lymphat Disord 2019;7:801-7.
36. Saleem T, Raju S. Comparison of intravascular ultrasound and multidimensional contrast imaging modalities for characterization of chronic occlusive iliofemoral venous disease: A systematic review. J Vasc Surg Venous Lymphat Disord 2021;9:1545-56.e2.
37. Neglén P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. J Vasc Surg 2003;38:879-85.
38. Cockett FB, Thomas ML. The iliac compression syndrome. Br J Surg 1965;52(10):816-21.
39. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology 1957;8:419-27.
40. Cockett FB, Thomas ML, Negus D. Iliac vein compression.–Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. Br Med J 1967;2:14-9.
41. Lin EP, Bhatt S, Rubens D, Dogra VS. The importance of monophasic Doppler waveforms in the common femoral vein: a retrospective study. J Ultrasound Med 2007;26:885-91.
42. Kayılıoğlu SI, Köksoy C, Alaçayır İ. Diagnostic value of the femoral vein flow pattern for the detection of an iliocaval venous obstruction. J Vasc Surg Venous Lymphat Disord 2016;4:2-8.
43. Oğuzkurt L, Ozkan U, Tercan F, Koç Z. Ultrasonographic diagnosis of iliac vein compression (May-Thurner) syndrome. Diagn Interv Radiol 2007;13:152-5.
44. Larkin TA, Hovav O, Dwight K, Villalba L. Common iliac vein obstruction in a symptomatic population is associated with previous deep venous thrombosis, and with chronic pelvic pain in females. J Vasc Surg Venous Lymphat Disord 2020;8:961-9.

45. Chinchalongporn W, Tanmit P, Pruekprasert K, et al. Prevalence and predictors of combined >50% iliocaval venous obstruction and superficial venous reflux in chronic venous insufficiency patients with healed or active venous leg ulcer. J Vasc Surg Venous Lymphat Disord 2023;11:502-9.
46. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53:2S-48S.
47. Morbio AP, Sobreira ML, Rollo HA. Correlation between the intensity of venous reflux in the saphenofemoral junction and morphological changes of the great saphenous vein by duplex scanning in patients with primary varicosis. Int Angiol 2010;29:323-30.
48. Singh AK, Karmacharya RM, Vaidya S, Thapa P. Quantification of superficial venous reflux by duplex ultrasound - role of peak reflux velocity and reflux time in the assessment of varicose vein. J Nepal Health Res Counc 2020;18:442-7.

Submitted Mar 17, 2023; accepted May 23, 2023.

Additional material for this article may be found online at www.jvsvenous.org.

APPENDIX (online only).



Supplementary Fig (online only). A, Linear association between severity of iliac venous outflow obstruction (IVOO) on intravascular ultrasound and venous reflux locations in the lower limb. **B,** Receiver operating characteristic (ROC) curve for evaluation of reflux multisegment score (RMS) for detection of IVOO of ≥50%. **C,** ROC curve for evaluation of deep venous reflux for detection of IVOO of ≥50%. **D,** ROC curve for evaluation of deep venous reflux for detection of IVOO of ≥80%.

Supplementary Table (online only). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of presence of monophasic waveform

Phasicity	S %	E %	PPV %	NVP %	A %	IVOO %
Present	62.5	97.4	93.4	81.6	89.1	≥80
Absent	34	100	100	72	67.3	≥50

A, Accuracy; *E,* specificity; *IVOO,* iliac venous outflow obstruction; *NVP,* negative predictive value; *PPV,* positive predictive value; *S,* sensitivity.