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Incidence of and risk factors for iliocaval venous obstruction in patients with active or healed venous leg ulcers

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Background: **Iliocaval venous obstruction (ICVO) can be a significant contributor to venous hypertension in patients with advanced disease. The incidence of ICVO in patients with CEAP clinical class 5 and 6 disease has not been reported. In this study, we reviewed a series of patients with healed or active venous leg ulcers to determine the incidence of ICVO and the risk factors related to its occurrence.**

Methods: **Patients with CEAP clinical class 5 and 6 venous insufficiency underwent evaluation with duplex ultrasound scan to identify the presence of venous reflux in the deep and superficial systems and either computed tomography (CT) or magnetic resonance (MR) venography to identify ICVO. The venograms were evaluated by two separate examiners to calculate the percentage of obstruction in the iliocaval outflow tract. Demographics and risk factors related to venous disease were collected and examined for their association with severe ICVO.**

Results: **A total of 78 CEAP clinical class 5 and 6 patients evaluated with either a CT or MR venogram were retrospectively reviewed. The average patient age was 59.3 years and 53.4% were men. The ulcer affected the left lower extremity in 46% of cases and 50% of patients reported a medical history of deep vein thrombosis (DVT). Overall, 37% of imaging studies demonstrated ICVO of at least 50% and 23% had obstruction of >80%. Risk factors that were found to be independently associated with a significantly higher incidence of >80% ICVO included female gender ($P = .023$), a medical history of DVT ($P = .035$), and reflux in the deep venous system ($P = .035$). No limb with superficial venous reflux (SVR) alone was found to have ICVO >80%.**

Conclusions: **ICVO is a frequent and underappreciated contributor to venous hypertension in patients with venous leg ulcers. Women and patients with a history of DVT or duplex scan-diagnosed deep venous reflux (DVR) have a higher incidence of outflow obstruction and should be routinely studied with CT or MR venography to allow correction in this high-risk group of patients. (J Vasc Surg 2011;53:1303-8.)**

Lower extremity chronic venous insufficiency (CVI) is a common cause of severe leg symptoms, including pain, swelling, and ulceration estimated to affect millions of people in the United States.[1] Although the majority of cases are generally believed to be related to venous valvular incompetence and abnormal reflux, awareness of the importance of iliac venous obstruction as a cause of lower extremity symptoms is increasing. In a cadaver study investigating the anatomy of the aortoiliac arterial and venous bifurcations, May and Thurner[2] reported compression of the left iliac vein against the fifth lumbar vertebra by the right iliac artery in 22% of cases. Variants of this syndrome have been described resulting in compression of the right iliac vein or distal vena cava by the aortic bifurcation as well.[3]

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Although May-Thurner syndrome is believed to be a contributing factor related to iliofemoral venous thrombosis, compression occurs in many asymptomatic patients as well. Kibbe et al[4] reviewed abdominal/pelvic computed tomography (CT) scans performed on patients with no lower extremity symptoms for the presence of iliocaval abnormalities. They reported that 24% of patients with no history of lower extremity deep vein thrombosis (DVT) or symptoms had at least 50% obstruction of the left common iliac vein. Conversely, it is known that anatomic compression of the iliac vein may predispose patients with other promoting factors to thrombosis of the iliofemoral system leading to a high risk of chronic venous insufficiency symptoms.

Patients at the end stage of chronic venous insufficiency (CEAP clinical class 5 and 6) have complex venous disease, with involvement of deep, superficial, and perforator veins in the majority of cases.[5] It has previously been reported that patients with severe symptoms of chronic venous disease have a high incidence of compression of the iliocaval system when studied with intravascular ultrasound (IVUS).[6] Symptomatic patients diagnosed with iliocaval outflow obstruction (iliocaval venous obstruction [ICVO]) may be treated with percutaneous stent insertion resulting in relief of iliac obstruction. Raju and Neglen[6] and others[7,8] have documented improvement in venous hemodynamics, patient symptoms, and quality of life after stenting for this condition.

The incidence and characteristics of iliac venous outflow obstruction have not been well described in patients with CEAP class 5 and 6 CVI. The majority of patients with venous ulceration in the United States are currently treated in wound clinics or primary care offices where this cause of correctible venous hypertension is poorly understood and rarely investigated. The primary purpose of this study was to identify the incidence and severity of venous outflow obstruction in the iliac veins and/or vena cava in patients with class 5 and 6 CVI and risk factors related to its occurrence. A secondary goal of the study was to examine the utility of duplex ultrasound scans of the common femoral vein (CFV) in predicting the presence of ICVO as identified by CT or magnetic resonance (MR) venography.

METHODS

Study design. All venous leg ulcer cases at the University of North Carolina Wound Healing Center are entered into a database capturing demographic information and key variables related to wound management and healing. This database was accessed retrospectively for this study.

This research study was approved by the University of North Carolina School of Medicine Human Studies Subcommittee.

Between January 2008 and June 2009, all patients presenting with ulcers and duplex ultrasound scan evidence of venous insufficiency were identified at the University of North Carolina. Patients with morbid obesity and those unable to stand for venous duplex testing were excluded. Morbid obesity was defined as weight >400 pounds, which would preclude CT scanning using the scanners available to us at the start of the project. Patient information, including age, gender, medical comorbidity, ulcer location, etiology, duration, size, and type of treatment were collected and maintained in a prospective database. For patients with bilateral disease, each limb was entered into the database and considered separately in all statistical evaluations.

Each patient underwent a complete duplex scan evaluation by an experienced, registered vascular technologist. Duplex ultrasonography scans were performed with the patients in the supine position with 30 degrees of reverse Trendelenburg position. A 6- to 3-MHz linear array B-mode ultrasound scan probe (Acuson Sequoia, Mountain View, Calif) was used for the examination. Compression maneuvers and examination of flow patterns with augmentation allowed identification of both acute or chronic venous obstruction and incompetent perforating veins. Commencing at the saphenofemoral junction, the infrainguinal deep, superficial, and perforating veins were assessed with Doppler scan flow patterns and B-mode imaging as previously described.[9] The common femoral venous velocity patterns were examined carefully to evaluate for evidence of iliocaval outflow obstruction. Those not demonstrating typical respiratory variation were identified as patients with duplex scan evidence of outflow obstruction.

Venous reflux in the deep and superficial venous systems was evaluated with a rapid inflation/deflation system (Hokanson E20 Rapid Cuff Inflator and AG101 Cuff Inflator Air Source, Issaquah, Wash) and duplex ultrasound scan while the patient stood. This allowed measurement of valvular closure times with a cutoff valve closure period of 0.5 seconds as the criterion for significant venous reflux.[10] Systematic interrogation of the common femoral, femoral, popliteal, and great saphenous and small saphenous veins was conducted.

It has been the authors' impression that duplex scan of the CFV can identify ICVO in some cases, but may be falsely negative in cases with more proximal obstruction or if there is severe obstruction of the CFV itself. Our clinical protocol for treating patients with venous leg ulcers had changed to obtain CT or MR venography in all patients who were candidates for venous intervention to look for ICVO. This would allow comparison of duplex scan imaging of the CFV to the results of axial imaging. In all cases, CT or MR venography was performed to evaluate for anatomic compression of the iliac veins or vena cava. In our hospital, CT venography is readily available and local expertise has allowed highly detailed three-dimensional studies. CT venography was performed using the Seimens SOMATOM Sensation (Erlangen, Germany) 64-slice spiral CT. Axial images were obtained after the administration of 150 mL of Omnipaque 350 intravenous contrast (GE Healthcare Inc, Princeton, NJ) administered at 4 to 5 mL/second followed by 50 mL of saline solution. Venous phase imaging was obtained 3 minutes after contrast administration.

MR venography was performed in patients with a contraindication to CT venography using the Seimens MAGNETOM Avanto scanner (Erlangen, Germany). Axial and coronal images were obtained after the venous administration of 1 mL per 11 pounds of MultiHance Gadolinium (Bracco Diagnostics Inc, San Donato Milanese, Italy) administered at 2 mL/second. Arterial phase imaging was performed at 20 seconds after contrast administration and venous phase imaging was performed 40 seconds after contrast administration.[11]

The maximum percentage of venous stenosis in the outflow tract of the ulcerated limb was determined in each case by examination of the vessel in two planes. First, the axial images were examined following the iliac veins and cava throughout their course through the retroperitoneum. Centerline reconstructions focused on the iliac vein and vena cava ipsilateral to the ulcerated limb were performed to provide true perpendicular cross-sectional images of the veins. The area of maximal compression was identified and the diameter of the vein was compared to the diameter of the normal-appearing vein caudal to the area of obstruction. If the entire external or common iliac vein was affected, the diameter in the stenotic segment was compared to the contralateral vein if this seemed to be free from obstruction. Then, sagittal reconstructions based on the iliac vein were reviewed and the site of maximal vein compression was identified in the longitudinal plane. This was also compared to the diameter of the noncompressed vein distal to the obstructed area. The greater of the two mea-

Table I. Patient demographics (n = 64)

Average age	59.3 ± 12.8
Male gender	36 (56%)
Percent white	46 (72%)
Percent African American	13 (21%)
Diabetes	18 (28%)
Average BMI	32.3 ± 9.0
Medical history of DVT	31 (49%)
Limb affected	Left, 38 (49%)/right, 40 (51%)

BMI, Body mass index; *DVT,* deep vein thrombosis.

sures of iliac vein stenosis was chosen as the final measure of percent narrowing for data analysis. Veins completely obstructed due to previous thrombosis were characterized as 100% stenosed. Each study was evaluated by two observers separately. Discrepancies of measured stenosis >15% were examined by a third observer and the mean of the two or three observations was used for data analysis.

Statistical methods. Accumulated data are expressed as means ± SD. Patient demographics and risk factors were compared to the presence of high-grade iliocaval venous obstruction defined as stenosis of ≥80% on CT or MR venography. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). The dependent variable for these analyses was the presence or absence of iliac stenosis. Logistic regression was performed to determine independent association of risk factors to the presence of ICVO. These risk and comorbidity factors were age, gender, ethnicity (white or non-white), body mass index, which limb (right or left), diabetes status, presence of deep venous reflux, and a history of DVT. The parsimonious model that includes all risk factors is preferred, as the risk factors are evaluated together reducing the probability of false-positive results. Odds ratios were calculated from the parameters of the model following Agresti.[12] For all tests, a *P* value of <.05 was required to demonstrate significance.

RESULTS

During the 18-month study period, 78 CEAP clinical class 5 or 6 limbs in 64 patients who were studied with either CT (n = 62) or MR (n = 2) venography were identified for study inclusion. Patient demographics are summarized in Table I. The patterns of venous reflux identified on standing duplex scan examination are specified in Table II. Duplex ultrasonography scan identified deep venous reflux (DVR) only in 13% of ulcerated limbs, superficial venous reflux (SVR) only in 38%, and combined DVR and SVR in 49% of limbs. Overall, complete obstruction of the iliocaval outflow tract was identified in 7 cases (9%) and 80% to 99% obstruction was identified in another 11 cases (14%). The complete listing of the incidence of varying degrees of iliocaval obstruction is listed in Table III. Overall, 29 of 78 limbs (37%) were found to have ICVO of 50% or more. The cause of venous obstruction in cases with >50% venous obstruction was external compression alone in 18 cases, thrombosis alone in 2 cases and combined external compression and thrombosis in 9 cases.

Table II. Patterns of venous reflux identified on standing duplex scan examination

GSV reflux only	4 (5.1%)
SSV reflux only	2 (2.6%)
GSV and SSV reflux	6 (7.7%)
CFV and superficial (GSV and/or SSV) reflux	18 (23.1%)
Popliteal reflux only	2 (2.6%)
CFV and popliteal reflux	4 (5.1%)
CFV, FV, and popliteal vein reflux	4 (5.1%)
Superficial reflux and popliteal vein reflux	11 (14.1%)
Superficial reflux and multisegment deep venous reflux	27 (34.6%)

CFV, Common femoral vein; *CT,* computed tomography; *FV,* femoral vein; *GSV,* great saphenous vein; *MR,* magnetic resonance; *SSV,* small saphenous vein.

Table III. Incidence of iliocaval venous obstruction on CT or MR venography

Iliocaval stenosis	*Number of total cases (%)*
100%	7 (9)
80% to 99%	11 (14)
50% to 79%	11 (14)
30% to 49%	4 (5)
10% to 29%	13 (17)
0% to 10%	32 (41)

CT, Computed tomography; *MR,* magnetic resonance.

Table IV. Logistic model with all variables and association with ≥80% ICVO

Variable	*DF*	*B*	*SE*	X^2	P *value*	*Odds ratio*
Age	1	0.02	0.03	0.29	.5917	1.02
BMI	1	0.09	0.06	2.34	.1260	1.10
White	1	−0.23	0.95	0.06	.8047	0.79
Male	1	−2.04	0.90	5.13	.0235	0.13
Right limb	1	−0.99	0.86	1.32	.2509	0.37
Diabetes	1	0.87	1.04	0.70	.4029	2.40
Reflux	1	2.87	1.36	4.46	.0347	17.69
Thrombosis	1	2.51	1.19	4.43	.0353	12.33

B, Regression coefficient; *BMI,* body mass index; *DF,* degrees of freedom; *ICVO,* iliocaval venous obstruction.

Variables studied for independent association with high-grade ICVO are listed in Table IV with their *P* values and odds ratios. Men had a significantly lower incidence of high-grade ICVO (odds ratio, 0.13). Patients with a history of DVT were 12.3 times more likely and those with DVR were 17.7 times more likely to be affected by high-grade ICVO (Figs 1 and 2). In particular, patients found to have axial DVR (CFV, femoral vein, and popliteal vein) had a high incidence of ICVO (60%). All of the limbs found on duplex scan to have pure SVR were negative for high-grade ICVO on CT or MR venography.

The correlation between duplex ultrasound scan criteria for ICVO and anatomic obstruction on CT or MR venography was high. CFV duplex scan could be ob-

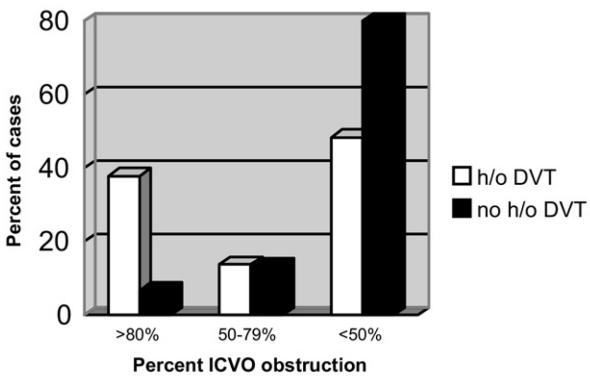

Fig 1. Incidence of iliocaval venous obstruction (*ICVO*) in patients with and without a history of deep venous thrombosis (*h/o DVT*).

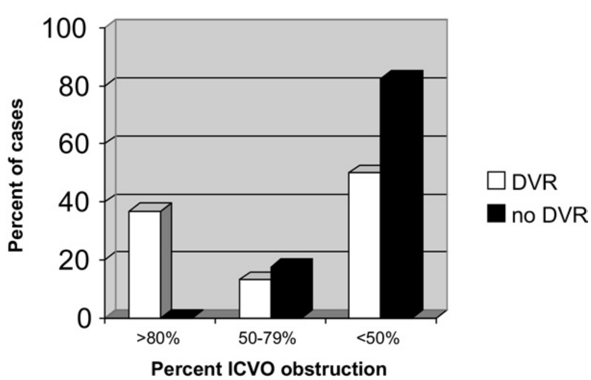

Fig 2. Incidence of iliocaval venous obstruction (*ICVO*) in patients with and without a history of deep venous reflux (*DVR*).

tained in 75 of 78 limbs. All patients with <50% obstruction on CT or MR had normal common femoral duplex scan waveforms, including respiratory variation and flow augmentation with compression. Seventy-seven percent of patients with >80% outflow obstruction had abnormal common femoral duplex scan examinations suggesting outflow obstruction. Sensitivity, specificity, and positive and negative predictive values are summarized in Table V.

Table V. Sensitivity and specificity of common femoral vein duplex ultrasound scan findings for identifying ICVO >80%

	ICVO ≥ 80%	*ICVO < 80%*	*Total*
CFV duplex positive	10	0	10
CFV duplex negative	3	62	65
Total	13	62	75
Sensitivity		77%	
Specificity		100%	
Positive predictive value		100%	
Negative predictive value		95%	

CFV, Common femoral vein; *ICVO,* iliocaval venous obstruction.

DISCUSSION

Obstruction of the iliac veins or vena cava may occur due to a variety of mechanisms, including postphlebitic venous thickening, external compression due to May-Thurner syndrome, or external compression by abnormally enlarged structures such as the intestines or ovaries. A combination of these mechanisms is also seen in many patients, in particular with May-Thurner syndrome and iliofemoral DVT. The late results of venous hypertension from obstruction and/or reflux may result in severe complications such as ulceration. Although numerous studies have reported on methods of treatment for iliocaval obstruction, little information is available concerning the prevalence of this problem in patients with venous insufficiency.

Oguzkurt et al[13] reported an increased average percentage of iliac vein obstruction (mean, 74%; range, 45% to 100%) for patients presenting with left leg DVT compared to asymptomatic controls (mean, 28%; range, 0% to 68%). Two-thirds of the patients with DVT had >70% obstruction of the iliac outflow tract. Chung et al[14] also reported a high incidence of iliac obstruction on CT venography, with a significant number of cases affecting the right side. However, no other reports have specifically looked at the prevalence of this condition in patients with venous insufficiency.

A significant problem in treating ICVO relates to the lack of a noninvasive screening study to identify the problem. Although venography and intravascular ultrasound scan have been reported to be the gold standard for diagnosis,[15] these are invasive, expensive studies that cannot be used to screen large numbers of patients who are potentially at risk for ICVO. Duplex ultrasound scan examination of the femoral vein may provide evidence of outflow obstruction with loss of respiratory variation in the femoral tracing or poor augmentation of the signal with distal limb compression. In a study of nearly 3000 limbs with duplex ultrasound scans, Lin et al[16] found abnormal monophasic CFV waveforms in 124 patients. One hundred eight of the 124 patients were studied with abdominal/pelvic CT scans for further evaluation. Forty-five of the 108 CT scans revealed evidence of DVT in the iliac system and another 6 cases were found to have diffuse stenosis or hypoplasia of the iliac vein. Forty-five cases seemed to have no iliac outflow obstruction on CT despite the abnormal monophasic waveforms in the CFV. In another report, abnormal CFV waveforms were studied in patients with cancer. Patients found to have monophasic waveforms and no response to Valsalva's maneuver were all found to have outflow obstruction, either by external iliac compression or proximal DVT.[17]

We hypothesized that patients with CEAP clinical class 5 and 6 venous insufficiency would have a significant incidence of obstruction of the iliocaval outflow tract. To test this hypothesis, we chose to perform CT or MR venography using a protocol allowing detailed three-dimensional reconstructions and measurement of venous obstruction in multiple planes. We believe that this method provides a good estimation of the findings that would be obtained on venography. However, it is notable that this method of measurement on axial imaging has not yet been validated by direct comparison to venography or IVUS.

Our results indicate that nearly one-fourth of limbs which are affected with ulceration have ICVO of 80% or more. Patients with a history of DVT or DVR were positive for high-grade ICVO in nearly 40% of cases. We believe that patients with persistent DVR are more likely to have suffered a major iliofemoral DVT associated with ICVO resulting in later leg ulceration in comparison to patients with superficial venous disease as a cause of leg ulceration. Given the incidence of ICVO in these groups, we believe that a history of DVT and DVR should be used as a pathway step in a diagnostic algorithm for ICVO as outlined below.

Female patients with leg ulcers also had a higher risk for ICVO, possibly due to the anatomy of the pelvis narrowing the space between the iliac artery and anterior spine. The number of patients studied in this report was limited, and it is possible that studying a larger patient cohort would identify other risk factors for ICVO. We believe that in symptomatic patient populations with a high risk of ICVO, diagnostic studies such as CT or MR venography are justified to identify patients who may benefit from intervention.

Duplex ultrasound scan examination of the CFV was assessed as a screening study and was found to be useful when the study was positive with a lack of respiratory variation or response to augmentation maneuvers. If the duplex scan was positive, all patients were found to have high-grade ICVO on CT or MR venography. However, a negative duplex scan for outflow obstruction was unreliable, as 23% of cases of high-grade ICVO on CT or MR had a normal venous duplex.

The accuracy of duplex ultrasound scans in diagnosing iliac or caval obstruction may be improved by performing direct duplex scan examination of these vessels as described by Labropoulos et al.[18] They found duplex scan examination with their technique to correlate closely with both phlebography and intravascular ultrasound scan in the diagnosis of ICVO. Duplex scan examination in the abdomen may be subject to limitations, including body habitus and intestinal gas, but the experienced technologists in this study were able to adequately image the iliac system in nearly all cases. Other noninvasive screening tests for proximal venous obstruction have been described, including the venous outflow fraction using air plethysmography.[19] However, air plethysmography is not widely used, limiting its usefulness as a screening modality.

CT and MR venography have improved markedly in recent years. The capability of centerline reconstructions based on the iliac veins and vena cava can provide high-quality anatomic information concerning the degree of narrowing of the iliac outflow tract. These modalities are the preferred method of evaluation for aneurysmal disease given the high degree of detail and accuracy at determining vessel and lumen dimensions. Although our institution has preferred CT for pelvic venous imaging, other authors have reported excellent results using MR for examining ICVO.[20] However, neither CT nor MR venography provide useful hemodynamic information indicating the relevance of the anatomic findings to venous function in the lower limb. In addition, CT and MR venography may not identify intraluminal webs or other chronic abnormalities that may contribute to poor venous function. Further validation of CT and/or MR venography requires comparison to percutaneous venography and IVUS. Given that there is no validated hemodynamic test for ICVO, our designation of venous stenosis ≥80% as high-grade for risk factor analysis is arbitrary. However, in studies of asymptomatic patients, the higher limit of iliocaval obstruction identified was 70%, so we believe that iliac venous obstruction ≥80% is more likely to be associated with symptoms.[5]

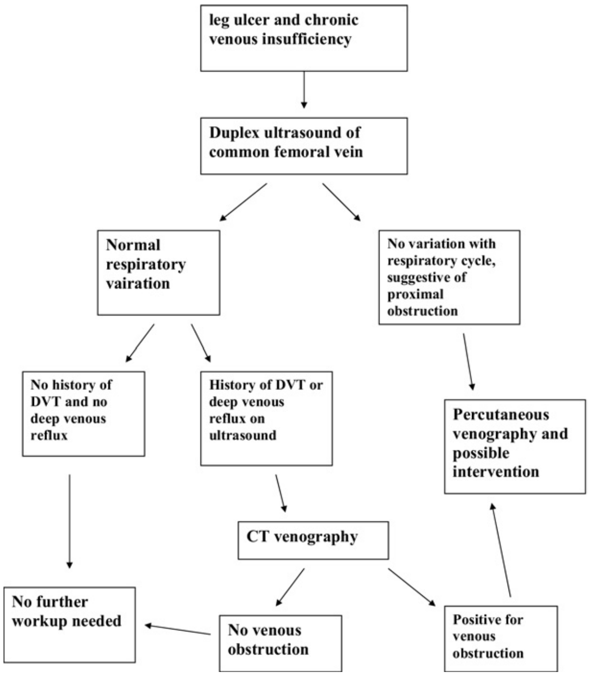

Fig 3. Algorithm for evaluation of patients with venous leg ulcers to identify iliocaval venous obstruction. *CT,* Computed tomography; *DVT,* deep venous thrombosis.

Based on the results of this analysis, we suggest the following protocol for diagnosis and treatment of ICVO in symptomatic patients who are candidates for venous intervention (Fig 3). Due to the high specificity of duplex ultrasound scan for diagnosing outflow obstruction, limbs with a positive duplex scan may go directly to percutaneous venography and intervention if confirmed on venography and/or IVUS. Limbs with a negative duplex scan for outflow obstruction require further evaluation, given the low sensitivity of this modality for ICVO. Limbs with reflux only in the superficial venous system require no further evaluation, as they have a low incidence of ICVO. Limbs with a history of DVT or DVR may be studied with CT or MR venography to evaluate for obstruction. Those who have high-grade obstruction should be considered for percutaneous venography and intervention. Validation of this algorithm will be required in a larger patient cohort.

CONCLUSIONS

Patients with limb ulceration and chronic venous insufficiency have a high incidence of iliac venous outflow obstruction. Women, patients with a history of DVT, and those with DVR have a significantly higher incidence of ICVO. Duplex ultrasound scan is a useful screening modality, but high-risk patients should undergo axial imaging with CT or MR venography if treatment of ICVO is warranted.

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AUTHOR CONTRIBUTIONS

Conception and design: WM, DF, JU, BK
Analysis and interpretation: WM, DF, JU
Data collection: WM, DF, JU
Writing the article: WM, JU
Critical revision of the article: WM, JU, DF, BK
Final approval of the article: WM, DF, JU, BK
Statistical analysis: WM, DF
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Overall responsibility: WM

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