The two-segment caliber method of diagnosing iliac vein stenosis on routine computed tomography with contrast enhancement



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#### ABSTRACT

**Background**: Iliac vein stenosis is a frequent pathologic process in advanced chronic venous disease. Intravascular ultrasound (IVUS) has emerged as the "gold standard" to diagnose iliac vein stenosis and to guide stent treatment. A pre-IVUS test is often obtained. Routine venography is deficient in several respects to fill this role; absence of an internal scale is a critical deficiency. Computed tomography venography (CTV) may be superior; its measurement capabilities can be used to precisely identify stenotic iliac vein caliber. Furthermore, the calibers of common iliac vein (CIV) and external iliac vein (EIV) can be individually assessed, yielding two data points instead of single-point assessment used in venography and current CTV protocols. We compared the diagnostic accuracy of the two-segment caliber method of CTV (arm vein injection of contrast material) with IVUS.

**Methods:** In patients who underwent computed tomography assessment of iliac vein segments before IVUS examination during a 5-year period, 91 limbs were analyzed. This is a single-center, retrospective analysis of prospectively collected data. CTV images of CIV and EIV segments were compared individually and in combination with IVUS planimetry images. A caliber diameter of <16 mm for CIV and <14 mm for EIV was considered stenotic with either imaging technique. Bland-Altman plots and receiver operating characteristic curves were used.

**Results:** On IVUS evaluation, 84% of CIVs and 78% of EIVs were stenotic and 16% and 22% were of normal caliber. These provided IVUS positive and negative controls for CTV comparison. On CTV, at least one of the two segments (CIV or EIV) was stenotic in 90% of the limbs, about 10% to 15% higher than single-segment involvement. Mean CTV caliber difference from IVUS was +2.5% for CIV and +7.3% for EIV. On Bland-Altman plot, single-segment diagnostic sensitivity of CTV was 83% and 73% for CIV and EIV, respectively, compared with IVUS. The sensitivity increased to 97% with a positive predictive value and accuracy of 93% and 91%, respectively, when a stenotic caliber in at least one of the two segments was considered diagnostic of iliac vein stenosis. Receiver operating characteristic analysis confirmed increased accuracy of the two-segment method over single-segment assessment with an area under the curve of 0.89 (P < .001).

**Conclusions:** Caliber diameter of <16 mm for CIV or <14 mm for EIV on routine CTV imaging appears to correlate with IVUS caliber stenosis with good diagnostic metrics of low false positives and false negatives. (J Vasc Surg: Venous and Lym Dis 2020;8:970-7.)

Keywords: Iliac vein stenosis; CT diagnosis; Iliac vein caliber

Iliac vein stenosis is a major pathologic process in advanced chronic venous disease. Stent correction of stenosis has been shown to be effective and safe, with excellent long-term patency.<sup>1,2</sup> Intravascular ultrasound (IVUS) has emerged as the tool of choice for diagnosis of iliac vein stenosis and for guidance of stent placement.<sup>3,4</sup> Contrast venography is widely used for

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preoperative iliac vein assessment. The technique has many shortcomings related to contrast enhancement, among them the obscuration of stenotic lesions and the underestimation of severity and extent, leading to poor choice of landing zones.<sup>5</sup> Lack of internal scale is a critical deficiency. Consequently, stenotic lesions are rated on a relative basis (percentage stenosis) using the adjacent "normal segment" as a reference.<sup>6</sup> This scheme is routinely used in grading arterial stenosis and is derived from it. This works on the arterial side because lesions are focal and the adjacent segment used as reference is usually of normal caliber. This may not work on the venous side as diffuse long lesions (Rokitansky stenosis) with or without focal elements are often found in iliac venous stenosis.<sup>7</sup> Using this segment as reference would result in underestimation of the stenosis.

There is a "critical" threshold of 60% to 70% in arterial stenosis that is a tipping point beyond which arterial perfusion declines steeply. This is related to

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autoregulation, whereby compensatory vasodilation in the runoff territory attempts to offset the effect of proximal stenosis. Such vasodilatation "maxes out" at the tipping point, beyond which there is an inexorable drop in perfusion.<sup>8</sup> Many have used a 50% stenosis on the venous side as a critical threshold. There is no hemodynamic basis for such a threshold. Autoregulation in response to stenosis is weak or absent on the venous side, with no consequent tipping point.<sup>9</sup> There is an early and continuous rise in peripheral venous pressure (the basis of chronic venous disease symptoms) with onset of stenosis in experimental simulations without a sudden inflection in pressure curve.<sup>10</sup> Iliac vein stenosis of <50% is sometimes symptomatic in the clinical setting, although most lesions are typically >60%.<sup>10</sup>

Computed tomography (CT) with contrast enhancement has the potential to overcome the deficiencies of plain venography. There is an internal scale that can be used to measure the caliber of iliac vein segments. A caliber less than normal at the narrowest point in the lumen is stenotic. The design of the cardiovascular system is such that many key parameters, such as cardiac output, regional perfusion, arterial and venous pressures, and resistances, are surprisingly within a narrow normal range across the human species, with only minor variations related to body size.<sup>11,12</sup> This is because the vessel radius enters the Poiseuille equation in the fourth power, whereas flow is in the first power. A 20% increase in cardiac output and regional flow related to body mass will require only 201/4% or 2.1% increase in the common iliac vein (CIV) caliber (eg, from 16 to 16.3 mm) to accommodate the increased flow. There is therefore uniformity of morphometrics across the human species to which most circulatory parameters are tightly interconnected. The normal caliber of iliac veins can be calculated from the Poiseuille equation and Young's scaling law. The calculated diameters closely correspond to IVUS measurements of nonstenotic vein segments.<sup>13</sup> Based on these, the minimum normal caliber was set at a diameter of 16 mm (area of 200 mm<sup>2</sup>) for the CIV and 14 mm (area of 150 mm<sup>2</sup>) for the external iliac vein (EIV).

CT-based measurements of the calibers of iliac vein segments have the potential to yield superior diagnostic accuracy compared with the relative stenosis method. Furthermore, the caliber method yields two data points, one each for the CIV and EIV. This two-segment caliber method has the potential to improve diagnostic accuracy over single-point assessment of stenosis at its narrowest location as used in venography and also in many CT venography (CTV) protocols.

The aim of this manuscript was to assess the diagnostic accuracy of routine CTV with administration of contrast material (through a vein in the arm) with focus on the two-segment caliber method. Subsequent IVUS measurements of iliac vein segments to determine suitability

## ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective analysis of prospectively collected cohort data
- **Key Findings:** Computed tomography venography caliber of common and external iliac veins yielded good diagnostic sensitivity and accuracy (97% and 91%, respectively) for stenosis vs intravascular ultrasound, considered to be the "gold standard," in 91 limbs with advanced chronic venous disease.
- **Take Home Message:** Diagnostic sensitivity of computed tomography venography measurement of vein diameters is boosted significantly when common and external iliac vein segments are measured separately than with single-segment measurement.

for stenting are used as the "gold standard" for comparison. This is a single-center (three surgeons) cohort study with retrospective analysis of prospectively collected data.

### **METHODS**

Patients. Of patients who had CT imaging before IVUS examination during a 5-year period (2014-2018), 91 limbs are included in the analysis. Comparison of CT with IVUS was segment specific, comparing CIV and EIV calibers separately and in combination. After exclusions, this netted 83 CIV segments and 91 EIV segments in 91 limbs for comparative analysis.

Informed consent from patients for the procedures was obtained. Institutional Review Board permission for publication of this deidentified analysis was granted.

**CT** with contrast enhancement. Contrast material (iohexol [Omnipaque 350]) was injected into the antecubital or other arm vein through a 20- or 18-gauge needle; 135 to 150 mL, depending on weight, was injected at a rate of 3.5 to 4 mL/s. Imaging of abdomen and pelvis was started after a standard delay of 120 seconds.

The CT scans were interpreted by a vascular radiologist on rotation (five radiologists) and reported on a preset standard template. The region of interest (vascular anatomy of abdomen and pelvis) was scanned in coronal, sagittal, and axial views to note anatomic course and variations if any. All measurements were taken with electronic calipers in the axial sections set at 5-mm intervals. The shortest diameter (any radial) of the CIV and the EIV at their narrowest point (focal or diffuse) was measured. The diameters were converted to areas for a circle ( $\pi r^2$ ).

**IVUS examination**. An IVUS catheter (Visions PV .035; Philips Volcano, San Diego, Calif) was used. The caliber perimeter of the CIV and EIV was traced at the narrowest point with an electronic pen; the machine planimetry software provided the area. Because the IVUS image was often an irregular circle, area measurement was thought to be less erroneous than reverse conversion from measured diameter.

Data collection and statistics. Contemporaneously entered data were extracted from an electronic medical program and analyzed retrospectively. Bland-Altman plot and receiver operating characteristic curves were used for method comparison. Two-tailed paired or unpaired *t*-tests as indicated were used for continuous data. The  $\chi^2$  test was used for comparison of categorical data and proportions. A commercial statistical program was used (MedCalc Software, Ostend, Belgium).

### RESULTS

There were 434 patients (436 limbs) who underwent IVUS examination of iliac vein segments during a 5-year period (2014-2018) who were analyzed in this study. Comparison was segment specific (CIV or EIV), allowing two data points in each limb.

**Exclusions.** There were 328 limbs that had other modes of assessment (magnetic resonance, duplex ultrasound, plain venography) before IVUS during the same time period and were excluded. Three limbs that had technically unsatisfactory CT imaging were excluded. Twelve CIV segments and four EIV segments were excluded from comparative analysis because IVUS could not provide a complete image ("missing border") of the lesion owing to lack of a centering mechanism in the IVUS catheter.<sup>5,7</sup> However, the CTV caliber of these segments is useful information and is provided.

After exclusions, 83 CIV segments and 91 EIV segments in 91 limbs were available for comparative analysis.

**Demographics**. The demographic features of the included patients are shown in Table I. Per IVUS, 63% of the limbs were classified as post-thrombotic syndrome (PTS) and 29% as nonthrombotic iliac vein lesion (NIVL). There was no stenosis in eight limbs (8%). Pathologic categorization as PTS was based on prior history of deep venous thrombosis and IVUS features (fibrosis, trabeculae). PTS usually involved the entire iliac vein segment, often extending to the adjacent segments as well. NIVL was typically focal and sub-segmental underneath the crossing artery (iliac or hypogastric artery).

**Definition of caliber stenosis.** An IVUS caliber area of 200  $\text{mm}^2$  (diameter of 16 mm) for the CIV and 150  $\text{mm}^2$  (diameter of 14 mm) for the EIV was considered minimum normal caliber. Values below these thresholds for the segments were considered stenotic.

The prevalence of IVUS stenosis based on these thresholds in CIV and EIV segments is shown in Table II. About 80% of either segment was stenotic; 16% of CIV Table I. Patients' demographics (N = 98 limbs)

Age, years, median (range)	62 (17-86)			
Male:female (n:n)	1:2 (32:66)			
Left:right (n:n)	1:1 (55:43)			
PTS cases	62 (63)			
NIVL cases	28 (29)			
No stenosis	8 (8)			
CEAP clinical class				
0-2ª	1 (1)			
3	19 (19)			
4-6	74 (76)			
Missing data	4 (4)			
<i>CEAP</i> , Clinical, Etiology, Anatomy, and Pathophysiology; <i>NIVL</i> , non-thrombotic iliac vein lesion; <i>PTS</i> , post-thrombotic syndrome.				

<sup>a</sup>Limbs with severe venous pain.

segments and 22% of EIV segments had normal caliber. This allowed the limbs to be categorized as IVUS positive and negative controls, respectively, for evaluation of the diagnostic accuracy of CTV.

Prevalence and caliber (IVUS) of PTS and NIVL involving the iliac vein segment either alone or in combination are shown in Tables III and IV, respectively. NIVL was slightly more prevalent (not significant) in CIV than in EIV, consistent with a previous report.<sup>14</sup> PTS was more prevalent than NIVL in either segment. Overall, at least one of the two segments was stenotic in 90% of the limbs. There was no significant difference between PTS and NIVL in caliber metrics.

**Comparison of IVUS vs CT.** Bland-Altman plots of mean difference in segment caliber as measured by CT and IVUS are shown in Fig 1 for the CIV and EIV. The data were normally distributed (D'Agostino and Pearson test). The mean difference was only 2.5% for the CIV and 7.3% for the EIV. CT caliber was larger than IVUS caliber in 51% of the limbs, smaller in 46%, and identical in 3%, suggesting random rather than systematic difference between the two techniques. Spearman correlations between caliber areas were r = 0.39 and 0.51 for CIV and EIV, respectively (P < .001). When the segment was categorized as normal or stenotic on the basis of the respective caliber area thresholds, Spearman correlation

Table II. Comparisor	of computed	tomography	(CT) vs
intravascular ultrasou	nd ( <i>IVUS</i> )		

Control groups	CIV (n = 83)	EIV (n = 91)
IVUS stenosis positive control <sup>a</sup>	70 (84)	71 (78)
IVUS stenosis negative control <sup>b</sup>	13 (16)	20 (22)

CIV, Common iliac vein; EIV, external iliac vein.

Values are reported as number (%).

<sup>a</sup>Lumen area/diameter: <200 mm<sup>2</sup>/16 mm for CIV; <150 mm<sup>2</sup>/14 mm for EIV.

<sup>b</sup>Lumen area/diameter: >200 mm<sup>2</sup>/16 mm for CIV; >150 mm<sup>2</sup>/14 mm for EIV.

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	Prevalence								
	CIV (n	= 83)	EIV (n	= 91)	Combination CIV	and EIV (n $=$ 79)			
	Stenosis (n = 70)	Normal (n $=$ 13)	Stenosis (n = 71)	Normal (n = 20)	Stenosis (n = 71)	Normal (n = 8)			
NIVL	21 (25)	7 (8)	16 (18)	14 (15)	22 (28)	5 (6)			
PTS	49 (59) <sup>a</sup>	6 (7)	55 (60) <sup>a</sup>	6 (7)	49 (62) <sup>a</sup>	3 (4)			
Prevalence	84%	15%	78%	22%	90%	10%			
CIV. Common iliac vein; EIV, external iliac vein. Values are reported as number (%). $^{\circ}P < 0.001$ PTS vs NIVI									

**Table III.** Intravascular ultrasound (IVUS) stenosis prevalence of nonthrombotic iliac vein lesion (NIVL) vs post-thromboticsyndrome (PTS) by segment

for both segments (either/or) was 0.44 (P < .001). When a 50% stenosis threshold was used to define stenosis (IVUS calibers of <100 mm<sup>2</sup> and <75 mm<sup>2</sup> for CIV and EIV, respectively), Spearman correlation was poor and not significant (r = 0.1; P = .3).

The incidence of true and false positives with segment detail by CT is shown in Table V. Identical caliber stenosis thresholds for the respective segment were used for both methods. More detailed diagnostic accuracy statistics are shown in Table VI. Diagnostic statistics are significantly improved when stenosis in either the CIV or EIV was considered diagnostic of iliac vein stenosis compared with single-segment analysis. This mirrors the prevalence data of single-segment vs eithersegment involvement shown in Table III.

Receiver operating characteristic curves for diagnosis of iliac vein stenosis based on the single-segment vs eithersegment criterion are shown in Fig 2. The area under the curve for either-segment analysis (CIV or EIV) yields the greatest area under the curve (0.89).

Because of the missing border feature on IVUS resulting in the inability to accurately measure caliber, 15 CIV segments and seven EIV segments in 22 limbs (Table VII) were excluded from this analysis.<sup>5,7</sup> CT caliber was able to be measured in all of these 22 segments; 13 of 15 CIV segments and 3 of 7 EIV segments were stenotic (area/diameters of <200 mm<sup>2</sup>/16 mm and <150 mm<sup>2</sup>/14 mm, respectively); two CIV segments and four EIV segments were of normal caliber.

# DISCUSSION

CT vs IVUS. Routine CTV of the pelvis with contrast enhancement appears to have broad dimensional parity with IVUS to differentiate stenosis from normal caliber. This results in reliable diagnosis of iliac vein stenosis with involvement of at least one of the two segments. Sensitivity based on single-segment calibers is  $\approx 80\%$ . When caliber of either of the two segments is considered, the sensitivity increases to 97% with a positive predictive value of 93%. This powerful boost to diagnostics is based on the fact that the  $\approx$  20% diagnostic misses in single-segment evaluation has about 80% chance of being rectified when the second segment is considered. This is because one of the two segments is involved in disease in 90% of limbs (prevalence, Table III), whereas single-segment involvement is less. Although it is considered a gold standard, current IVUS instrumentation is unable to completely image venous caliber in  $\approx$ 20% of subsets.<sup>5,7</sup> This is related to absence of a centering mechanism in the IVUS probe, resulting in tilt of the transducer tip at lesion sites near confluences. CT was able to provide useful caliber information in 22 iliac vein segments with a missing border on IVUS imaging.

The dimensional parity of CTV with IVUS is not good enough to identify stenosis on a percentage basis, such as >50%. However, the variance between the two techniques is not large enough to breach threshold boundaries that could change categorization of stenosis/no stenosis classification. The lack of perfect dimensional parity between

 Table IV. Intravascular ultrasound (IVUS) caliber of nonthrombotic iliac vein lesion (NIVL) vs post-thrombotic syndrome (PTS) by segment

		Caliber, mm <sup>2</sup>					
	CIV (n = 8	3)	EIV (r	n = 91)			
	Stenosis (n = 70)	Normal (n $=$ 13)	Stenosis (n = 71)	Normal (n = 20)			
NIVL	131 (±46)	255 (±36)	118 (±19)	181 (±29)			
PTS	118 (±37) <sup>a</sup>	230 (±27) <sup>a</sup>	109 (±22) <sup>a</sup>	169 (±14) <sup>a</sup>			
CIV, Common Values are rep <sup>a</sup> Not significa	n iliac vein; <i>EIV</i> , external iliac vein. ported as mean ± standard deviation. nt, PTS vs NIVL.		-				





Table V.	Computed	tomography	venography	(CTV)	true	and	false	positives	and	negatives	compared	with	intravascular
ultrasoun	id (IVUS)												

Diagnostic CTV stenosis threshold	No.	True positives	True negatives	False positives	False negatives
CIV area <200 mm <sup>2</sup> (diameter <16 mm)	83	58 (70)	6 (7)	7 (8)	12 (14)
EIV area <150 mm² (diameter <14 mm)	91	56 (62)	14 (15)	6 (7)	15 (16)
CIV area <200 mm <sup>2</sup> (diameter <16 mm) or EIV area <150 mm <sup>2</sup> (diameter <14 mm)	79	69 (87) P < .01 vs CIV P < .001 vs EIV	3 (4) P < .05 vs EIV	5 (7)	2 (3) P < .05 vs CIV P < .01 vs EIV
<i>CIV</i> , Common iliac vein; <i>EIV</i> , external iliac vein. Values are reported as number (%). Two-segment diagnostic comparison was significant	y superio	or to single-segment a	inalysis.		

the two techniques is likely due to several reasons. The techniques employ fundamentally different physics for imagery; the definition of tissue-fluid interface of the lumen is likely to be different as ultrasound is more subject to tissue attenuation and flow velocity. The measurement sites are likely to be different as well as IVUS provides a continuous image, whereas CTV views are axial sections 5 mm apart. "Axial" CTV views are axial to the centerline of the body, not to the axis of the vein. The iliac vein traces a complex spiral course in the pelvis with continuous variations in the medial-lateral and anterior-posterior planes as shown in the three-dimensional reconstruction in Fig 3. A CTV axial cut will yield an oval section of the vein of variable dimension, depending on the anatomic location. The oval will be larger than a true orthogonal cross section. Nevertheless, the CTV technique as described empirically appears to yield good diagnostics despite these inherent variances from IVUS. Postprocessing has the potential to offer greater dimensional parity with IVUS as thin slices can be used for constructing the three-dimensional image.

Some centers use pedal injection of contrast material to increase iliac vein resolution. This technique, however, comes at the cost of greater technical difficulties with foot venous access and timing issues.

High diagnostic yield of IVUS in advanced chronic venous disease. IVUS has a diagnostic yield of  $\approx 80\%$  in patients with advanced chronic venous disease symptoms.<sup>1,4,14,15</sup> This is because iliac vein stenosis is a

permissive lesion that is often silent in the general population. The silent prevalence has been reported to variably range from 30% to 60%, depending on the diagnostic method used.<sup>16-18</sup> Symptoms are precipitated when there is perturbation of the compensated state by trauma, infection, thrombosis, or onset of new reflux below the lesion.<sup>16-19</sup> High incidence of the lesion in the symptomatic subset compared with silent prevalence in the general population is a characteristic of permissive lesions in human disease.

**Clinical application**. Because silent lesions are common, it is critically important to reserve diagnostic investigation for appropriately selected patients with symptoms. Silent lesions are benign, and there is no role for prophylactic correction in these.

Because of the high yield in the symptomatic subset, IVUS alone can be used without other confirming tests before IVUS in properly selected patients. Not only will IVUS be needed for confirming diagnosis, but it is the best available procedural guide at present. Nevertheless, it is a fact of current practice patterns that such pretests are more often performed than not. Current data show that CTV is an excellent pretest but is not good enough to replace IVUS as the gold standard.

The good diagnostic sensitivity of CTV as reported here is dependent on high prevalence of the lesion, which increases this statistic. With proper selection of patients, false positives and negatives should be rare but are

Table VI.	Diagnostic accurac	y detail of compute	d tomography vend	ography (CTV) assess	sment for iliac vein stenosis
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Diagnostic CTV stenosis threshold	No.	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Accuracy, %
CIV area <200 mm <sup>2</sup> (diameter <16 mm)	83	83	62	92	40	80
EIV area <150 mm² (diameter <14 mm)	91	79	70	90	48	77
CIV area <200 mm <sup>2</sup> (diameter <16 mm) or EIV area <50 mm <sup>2</sup> (diameter <14 mm)	79	97 P < .01 vs CIV P < .01 vs EIV	38 P < .01 vs CIV P < .001 vs EIV	93	60 P < .05 vs CIV	91 P < .05 vs CIV P < .05 vs EIV

CIV, Common iliac vein; EIV, external iliac vein.

Two-segment diagnostic comparison was significantly superior to single-segment analysis.



**Fig 2.** Receiver operating characteristic (*ROC*) curve showing sensitivity for common iliac vein (*CIV*), external iliac vein (*EIV*), and combination (*CIV and/or EIV*). The combination yields the largest area under the curve (*AUC*; see text). \*Compared with intravascular ultrasound (IVUS) "gold standard." *CTV*, Computed tomography venography.

occasionally inevitable. These diagnostic misses will be corrected if followed by IVUS after CTV. This is likely if CTV is positive for stenosis. CTV may be a useful adjunct to IVUS in cases with the missing border feature, in which stenotic caliber cannot be accurately measured.

A CTV negative for stenosis may be a true or false negative. Extensive PTS in the periphery, cardiac dysfunction, and obesity are among the more common causes of a true negative on CTV. A CTV negative for iliac vein stenosis should prompt a search for these and numerous other conditions that mimic venous symptoms. There is an occasional risk of delaying treatment when the pretest is a false negative that is not followed by IVUS examination. In summary, CTV, when it is used as described, appears to be a useful adjunctive pre-IVUS test. IVUS should follow the pretest as a rule and remains the definitive test of choice for final disposition of the patient.

### CONCLUSIONS

Routine CTV imaging with arm injection of contrast material has broad dimensional parity with the IVUS gold standard to differentiate stenotic caliber from normal. CIV and EIV should be assessed individually and in combination, which boosts sensitivity and positive predictive value. Proper selection of patients for investigations is key as this increases diagnostic yield and

 Table VII.
 Computed tomography (CT) mean caliber of limbs with intravascular ultrasound (IVUS) missing borders

	Missing border CIV (n = 15)	Missing border EIV ( $n = 7$ )
CT caliber, mm <sup>2</sup>	118 (±45)	143 (±52)
<i>CIV,</i> Common iliac vein Values are reported as		



**Fig 3.** Three-dimensional reconstruction of computed tomography venography (CTV) image. The iliac vein has a complex spiral course with continuous variation in all three axes. A traditional axial cut on CTV is axial to body centerline, not to the axis of the iliac vein. A CTV axial cut will yield an oval, slightly larger lumen than the true orthogonal cross section of the vein (see text). *CFV*, Common femoral vein; *CIV*, common iliac vein; *EIV*, external iliac vein; *IVC*, inferior vena cava.

reduces false positives and false negatives. CTV is a good pretest, but it is not a suitable instrument for definitive disposition of patients, and it cannot discriminate a lesion >50% from lesser lesions.

## **AUTHOR CONTRIBUTIONS**

Conception and design: SR Analysis and interpretation: SR, WW, CN, RK Data collection: SR, WW, CN, RK, AJ Writing the article: SR, WW, CN, RK Critical revision of the article: SR, WW, CN, RK, AJ Final approval of the article: SR, WW, CN, RK, AJ Statistical analysis: SR, WW, CN, RK, AJ Obtained funding: SR Overall responsibility: SR

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