Endovascular management of iliac vein compression syndrome: a prospective case series of 61 patients

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Context
Iliac vein compression syndrome (IVCS) or May–Thurner syndrome is an anatomically variable condition of venous outflow obstruction caused by extrinsic compression. The pathology of this condition is secondary to a partial obstruction of the common iliac vein by an overlying common iliac artery with subsequent entrapment of the left common iliac vein. Clinical presentations include, but not limited to, pain, swelling, venous stasis ulcers, and skin discoloration. With extensive deep venous thrombosis, postphlebitic syndrome, with all its sequelae, may also develop. Endovascular interventions of this syndrome have become first-line therapy.

Aims
To estimate the prevalence of IVCS in patients with unilateral left lower limb venous disease [chronic venous disease (CVD)], assess the sensitivity and specificity of modified computed tomography venography in the diagnosis of IVCS, and evaluate the feasibility and effectiveness of the endovascular treatment.

Settings and design
This was a prospective case series study. The study was performed at three tertiary referral centers in Kingdom of Saudi Arabia (Security Forces Hospital Program, Al-Noor Specialist Hospital, Makkah, Almoosa Specialist Hospital, Al-Ahsaa) and three hospitals in Egypt (Benha University Hospitals, Nile Insurance Hospital, and Kuwaiti Specialized Hospital, Benha).

Patients and methods
Between March 2015 and February 2018, we evaluated 369 patients with unilateral left lower limb symptomatic CVD in the outpatient clinic of vascular surgery in the study hospitals. Sixty-one symptomatic patients with IVCS who received endovascular treatment were included in our study.

Statistical analysis
used The initial data entry used Microsoft excel (2010 version) for logical proofreading and analysis. We expressed continuous data as mean±SD and compared continuous variables using two-sided Student's *t* tests. We estimated stent patency using Kaplan–Meier method. We considered *P* value less than 0.05 to be statistically significant. Statistical analysis was performed by using IBM Statistical Package for the Social Sciences software (version 22 for Windows program package).

Results
The 1-year patency rates in the nonthrombotic and thrombotic IVCS groups were 95.7 and 80%, respectively (P=0.146). The overall primary patency rate at 1 year after treatment was 93%. Complete pain relief was achieved in 76.7% of patients. The overall edema relief rate was 78.1%. Of the 12 limbs with active ulceration before treatment, 10 (83.3%) healed completely.

Conclusion
IVCS is not an uncommonly encountered condition, especially among patients with unilateral left lower extremity CVD. Computed tomography venography with three-dimensional reconstruction images was more sensitive and specific as a diagnostic approach for IVCS and provided useful information for the endovascular treatment planning. Moreover, endovascular therapy is feasible and effective for treating left-sided IVCS with high technical success rate and with an acceptable complication profile. So, we concluded that endovascular treatment should be considered as the first line of therapy for patients experiencing IVCS.

Keywords:
deep vein thrombosis, endovascular treatment, iliac vein compression syndrome, in-stent patency

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Introduction

Iliac vein compression syndrome (IVCS), also called May–Thurner syndrome (MTS) or Cockett syndrome, is a clinical syndrome comprising a series of symptoms, such as lower extremity swelling, pain, and varicosities [1–3].

Isolated left lower extremity swelling caused by left iliac vein compression was first described by McMurrich in 1908, but the nature of the disease was not fully understood until 1957. After the evaluation of 430 cadavers, May and Thurner found that intraluminal venous spurs existed in approximately 22% of this cohort, which was directly related to extensive deep venous thrombosis (DVT) of the left lower extremity caused by external compression by the right common iliac artery. The relation between iliac vein compression and postthrombotic syndrome was well illustrated by Cockett *et al.* [4]. Indeed, the majority of cases follow this classic description [5,6]; however, right-sided MTS cases have also been reported [7,8].

IVCS is characterized by an outflow obstruction (stenosis or occlusion) of the left common iliac vein (LCIV) caused either by extrinsic compression from the right overlying iliac artery against the pelvic rim or by internal lesions just like spurs or webs. Other factors such pelvic tumor, pregnancy, pelvic hematoma after trauma, and pelvic pregnancy, can cause IVCS too. IVCS commonly involves LCIV, usually manifested as hemodynamic-related obstruction *in situ* [9].

IVCS is of clinical significance because it can cause not only lower extremity DVT but also other chronic venous diseases (CVD) without thrombosis, such as asymmetrical edema of the left lower limb, pain, varicose veins, and venous ulcers [9–11]. With great progression made in recent decades, endovascular angioplasty and stent placement became a feasible and effective alternative to conventional surgery for the treatment of IVCS [1].

The purpose of this study was to estimate the prevalence of IVCS in patients with unilateral left lower limb venous disease (CVD), assess the sensitivity and specificity of modified computed tomography venography (CTV) in the diagnosis of IVCS, and evaluate the feasibility and effectiveness of the endovascular treatment of IVCS. In our study, we present the 1-year outcomes of stent placement associated with both thrombotic and nonthrombotic IVCS.

Patients and methods

Study design and patient selection

This was a prospective case series study. The study was performed at three tertiary referral centers in Kingdom of Saudi Arabia (Security Forces Hospital Program, Al-Noor Specialist Hospital, Makkah, Almoosa Specialist Hospital, Al-Ahsaa) and three hospitals in Egypt (Benha University Hospitals, Nile Insurance Hospital, and Kuwaiti Specialized Hospital, Benha). Our institutional review board in the enrolled centers approved the study protocol. Before enrollment, patients were informed of the risks and benefits of participating in the study and given written informed consent for all to sign. Between March 2015 and February 2018, we evaluated 369 patients with unilateral left lower limb symptomatic CVD in the outpatient clinic of vascular surgery in the study hospitals. Sixty-nine patients with IVCS were admitted in the enrolled hospitals according to inclusion and exclusion criteria demonstrated in Table 1. A flow chart of the study is demonstrated in Fig. 1. At last, 61 symptomatic patients with IVCS who received endovascular treatment were included in our study. Baseline data were collected from the medical records before endovascular treatment, including demographic data, clinical presentations, hypercoagulable disorders, and criteria of DVT if existed. The end point events included patient death, the deadline of the study (February 2018), and the last visit if the enrolled patient was lost to follow-up.

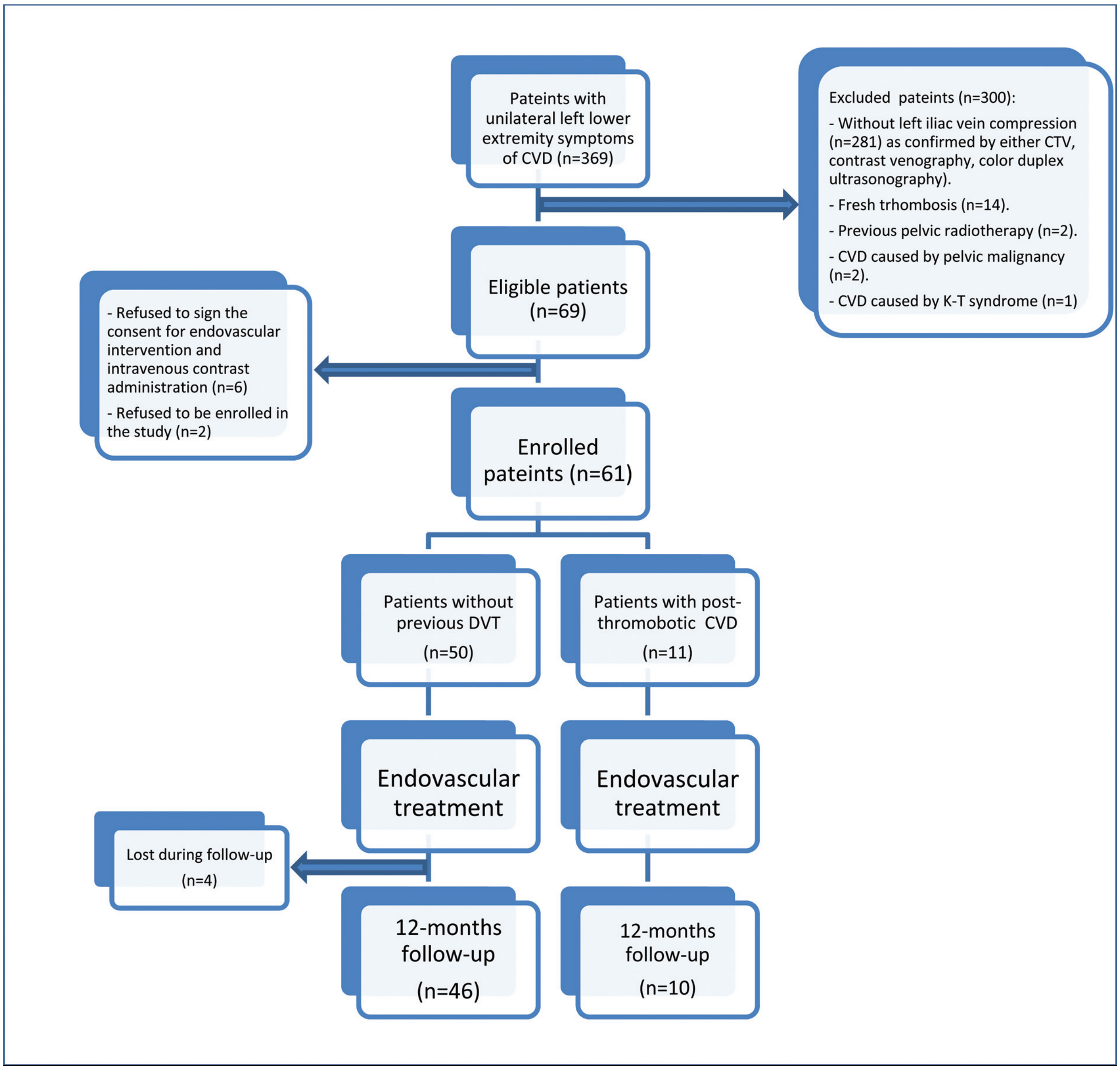
Diagnostic methods

The diagnosis of IVCS was established using history and physical examination, with the initial workup in

Table 1 Inclusion and exclusion criteria of the enrolled patients

Inclusion criteria	Exclusion criteria
Symptoms of unilateral left lower limb chronic venous disease	Age < 18 years
1. Unilateral significant lower limb edema	Pregnancy
2. Venous ulcer	History of pelvic surgery, pelvic radiation therapy, or traumatic iliac vein injury
3. Recurrent varicose veins	Contraindication to anticoagulation
4. Nonanatomical varicose vein	Contraindication to iodinated contrast media
5. Skin changes including lipodermatosclerosis	Chronic venous disease caused by pelvic tumor
	Chronic venous disease caused by Klippel–Trénaunay syndrome
	Malignancy with life expectancy < 1 year

Figure 1



Patient consort and flow chart of the study design. CVD, chronic venous disease; CTV, computed tomography venography; K–T syndrome, Klippel–Trénaunay syndrome; DVT, deep venous thrombosis.

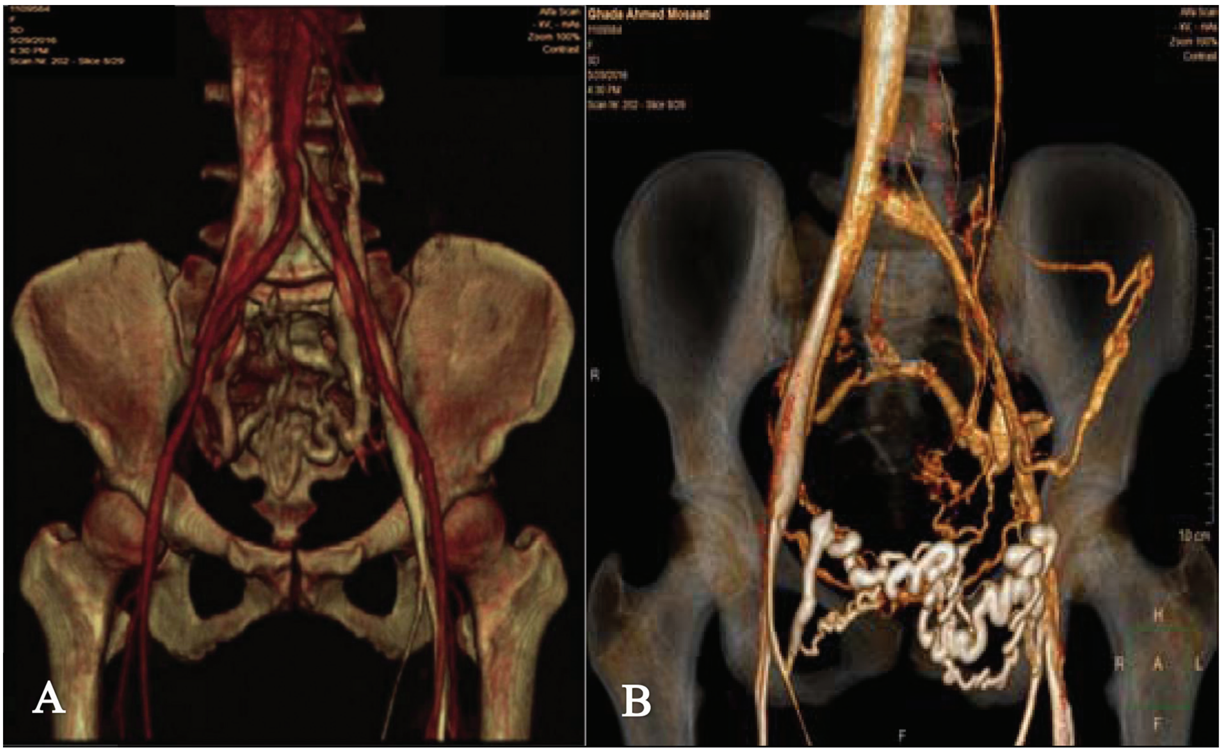
all patients consisted of color Doppler ultrasonography of the lower extremities and pelvis to identify obstructive lesions, presence or absence of DVT, and detect superficial and/or deep reflux and collateral pathways. We established the diagnosis of IVCS on the visualization of a more than 50% reduction in the luminal diameter of the vein and the formation of collateral circulation. Subsequently, all patients underwent direct CTV scans to assess the extent of obstruction, visualization of the collateral pathways, differential diagnosis of IVCS as well as the presence or absence of DVT. Before endovascular management, iliocavograpy was performed for all patients for further assessing the length of obstruction and the presence of collateral pathways. Obstruction involving the common iliac vein exclusively was considered focal, whereas extensive involvement of the common and external iliac veins and the proximal femoral vein was considered as a long-segmental obstruction.

Endovascular therapeutic techniques

The treatment procedures were performed in the operation room with mobile c-arm or endovascular suite with fixed imaging. All patients were under local anesthesia and intravenous sedation.

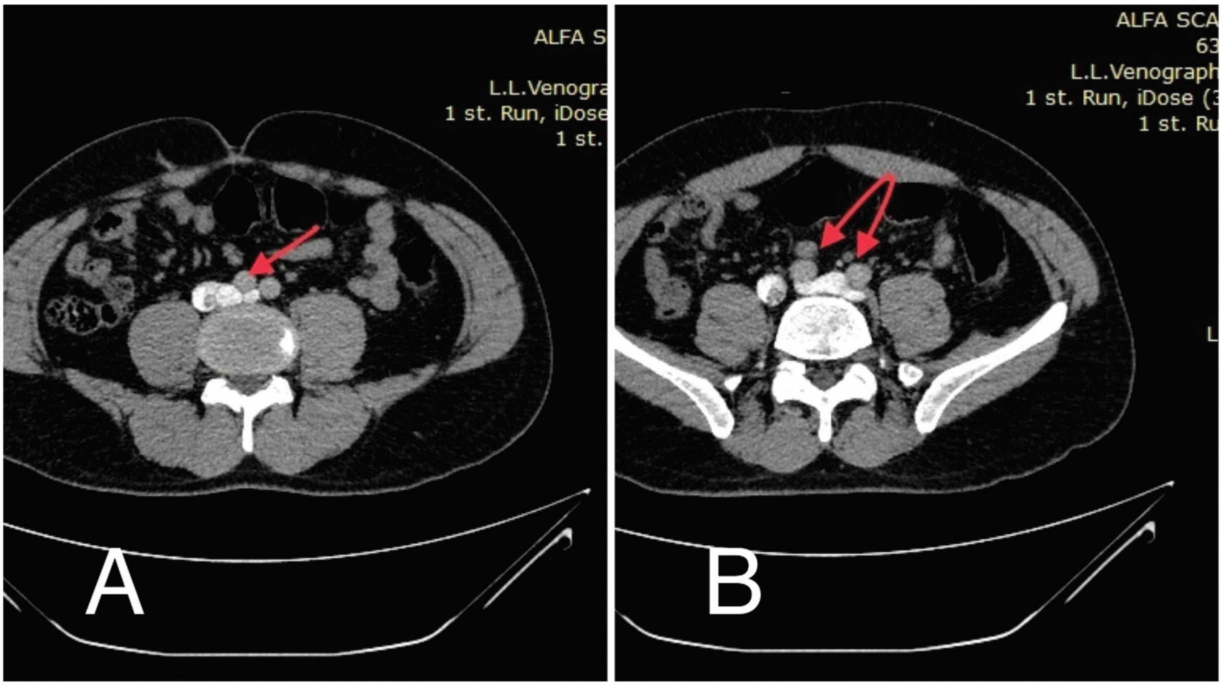
First in previously diagnosed focal common iliac vein lesions, the left common femoral vein (CFV) has been cannulated using the standard venous puncture needle, a single-wall puncture Seldinger needle, which was used under duplex guidance, followed by placement of a 6-Fr sheath into the vein to perform left iliac venography, which revealed compression of the central portion of the LCIV, stasis of the blood flow below the level of compression, and contralateral venous drainage via the pelvic collateral veins (Figs 2–4a). After confirming the presence of pathology, the 6-Fr sheath was replaced by 10-Fr sheath to allow stent deployment. In patients with postthrombotic stenosis or occlusion that involved the entire iliac vein extended to CFV, the access was achieved through the popliteal vein in prone position using a 10-Fr sheath under duplex guidance. Next after gaining a percutaneous access, we passed a vertebral catheter (Cordis Corporation, Miami, Florida, USA), and hydrophilic guidewire (Terumo Corporation, Tokyo, Japan) through the obstruction and advanced the guidewire-catheter combination up to the inferior vena cava. Additionally, we exchanged the vertebral catheter with multi side-hole catheter (Cook Medical Inc., Bloomington, Indiana, USA) followed by venography of the iliac vein and inferior venal cava to assess the location and severity of the iliac vein obstruction and ensure that the catheter was positioned in the true lumen. In cases of chronically occluded iliac vein, we used hydrophilic stiff wire (Terumo Corporation, Tokyo, Japan) over support catheter (CXI; Cook Medical Inc.). We used a high-pressure balloon catheter (XXL; Boston Scientific, Natick, Massachusetts, USA) and ATLAS (Bard Peripheral Vascular Inc., Tempe, Arizona, USA) for predilatation (Figs 2–4b,c) and deployed self-expanding stents (diameter, 12–18 mm; length 40–90 mm; Wallstent, Boston Scientific) across the stenotic lesion of the iliac and the CFV. We estimated the length of the stent based on the length of the lesion and the position of the proximal landing zone (>20 mm). The distal stent extended ~10 mm into the proximal vena cava. We performed postdilatation routinely in all patients. A postangioplasty venogram of individualized patient demonstrated a widely patent stent and good uninterrupted in-line contrast flow through the stent into the inferior vena cava without filling of the cross-pelvic collaterals (Figs 2d, 3b, and 4c). The initial technical success was defined as recanalization with antegrade flow and disappearance of collateral venous pathway after stent placement. Finally, we removed the access sheath and applied light external pressure to the angioplasty access site. All patients received unfractionated intravenous heparin at a dose of 5000 international units during the procedure.

Figure 2



A 33-year-old female presented with unilateral left lower limb swelling with history of old DVT and severe vulvar varices with progressive limb edema on standing. (a, b) Venography showing prominent collaterals of the pelvis with severe stenosis of the left common iliac vein. (c) Balloon dilatation of the left common iliac vein. (d) Poststent completion venogram with uninterrupted in-line contrast flow into the inferior vena cava. DVT, deep venous thrombosis.

Figure 3



A 38-year-old male presented with unilateral left lower limb ulcer with history of old DVT. (a) Venography showing prominent collaterals of the pelvis with severe stenosis of the left common iliac vein. (b) Poststent completion venogram with uninterrupted in-line contrast flow into the inferior vena cava. (c, d) Venous ulcer before and after procedure. DVT, deep venous thrombosis.

Follow-up and assessment criteria

Low-molecular-weight heparin was initially used in therapeutic dose as postprocedural anticoagulation therapy for not less than 2 weeks and then transferred to daily oral administration of warfarin or novel oral anticoagulants. This anticoagulation regimen was prescribed for 1 year to avoid stent occlusion by thrombosis. The targeted therapeutic range of international normalized ratio was 2–3 in patients who were on warfarin. In addition, wearing of graduated elastic compression stockings (30–40 mmHg) for more than 1 year was recommended for all patients and continued to receive venous ulcer wound care on an outpatient basis after intervention until the ulcer healed completely. Irregular postprocedure anticoagulation therapy was defined as that of disobedience to the anticoagulation therapy regimen, for example, intermittent anticoagulation drug administration, insufficient anticoagulation drug dosage that failed to reach the lower target level range of international normalized ratio, or a total duration of anticoagulation drug administration less than 6 months. Irregular postprocedure stockings wearing was defined as failure to follow the stockings-wearing regimen, for example, intermittent stocking wearing, or the duration of stocking wearing less than 1 year.

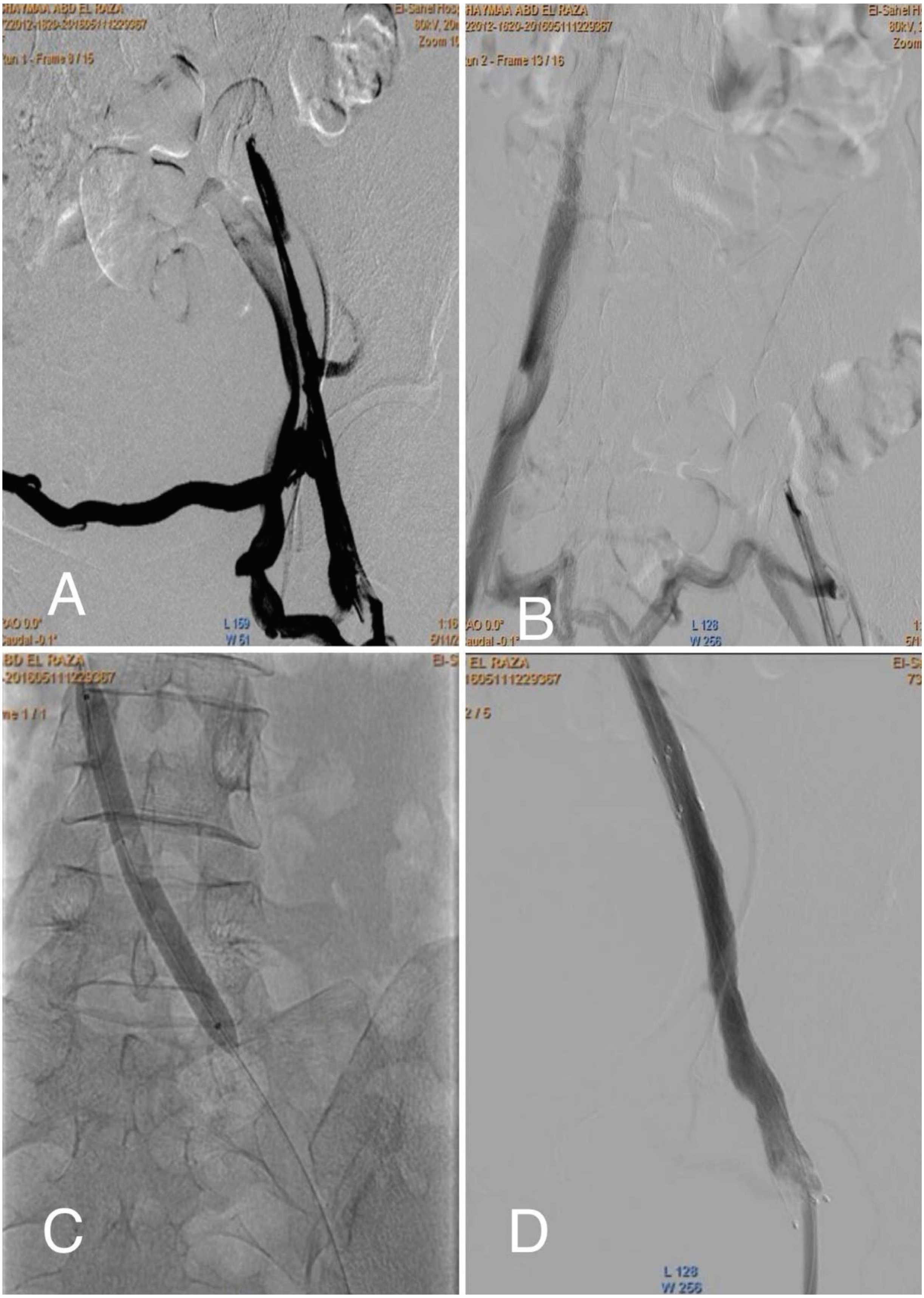
Some of our patients (9/61, 15%) were on daily acetyl salicylic acid because of extracranial carotid plaque or coronary artery disease, but it is not mandatory in the regimen after intervention.

For postthrombotic patients, we usually recommend anticoagulant treatment for at least 1 year, and then decide whether to continue the treatment according to the symptom. We evaluated the stent patency using venous duplex ultrasonography every 3 months; we performed abdominal plain radiography film every 6 months to assess whether the stent had migrated or not. Each patient visited the vascular surgery outpatient clinic 1, 3, 6, and 12 months after treatment and yearly thereafter.

The patient's initial clinical-etiology-anatomy-pathophysiology score was recorded and compared at the most recent follow-up and by evaluating the relief of limb pain and edema using measuring tape together with the healing and absence of recurrence of ulceration. Pain level was measured using a visual analog scale [12]. Clinical severity of the edema was scored as follows: grade 0 = absent, grade 1 = pitting/nonobvious, grade 2 = visible ankle edema, and grade 3 = massive/encompassing the entire leg [13]. Ulcer healing was defined as complete re-epithelialization [14].

In case of clinical recurrence of symptoms or in-stent obstruction at duplex ultrasonography, the CTV or

Figure 4



A 40-year-old male presented with unilateral left lower limb edema and back pain without history of DVT. (a, b) Venography showing collaterals of the pelvis with severe compression of the left common iliac vein that was confirmed by severe balloon wasting during venoplasty. (c) Poststent completion venogram with uninterrupted in-line contrast flow into the inferior vena cava. DVT, deep venous thrombosis.

contrast venography was performed. Greater than 50% of in-stent restenosis with inflow obstruction was considered significant.

End points

The primary end points were improvement of symptoms and the cumulative patency rate with freedom from stent thrombosis; secondary end points included stent migration, iliac vein rupture, bleeding, hematoma, back pain, contrast-induced nephropathy, and DVT.

Statistical analysis

We evaluated data for all end points in an intention-to-treat analysis. The initial data entry used Microsoft excel (2010 version) for logical proofreading and analysis. We expressed continuous data as mean±SD and compared continuous variables using two-sided Student's *t* tests. We estimated stent patency using Kaplan–Meier method. We considered *P* value less than 0.05 to be statistically significant. Statistical analysis was performed by using IBM Statistical Package for the Social Sciences software (version 22 for Windows program package; SPSS Inc., Chicago, Illinois, USA).

Results

Between March 2015 and February 2018, we evaluated 369 patients with unilateral left lower limb symptomatic CVD in the outpatient clinic of vascular surgery in the study hospitals. We identified IVCS in 18.7% (69/369) of patients with unilateral left lower limb CVD. The 69 patients who met the inclusion criteria and became eligible for our study underwent duplex ultrasonography and contrast-enhanced direct CTV. Six patients refused to sign the consent for endovascular intervention and intravenous contrast administration with another two patients refused to be enrolled in the study.

We divided the total enrolled patients (n=61) into two treatment groups: nonthrombotic IVCS (n=50) and thrombotic IVCS (n=11). Figure 1 shows a flow chart of the study design. The mean ages of the nonthrombotic and thrombotic IVCS patient groups were 39.6 and 40.8 years, respectively; the respective mean disease durations were 14.6 and 20.7 years. The overall female : male ratio was 12 : 5. The patients' characteristics and clinical-etiology-anatomy-pathophysiology grades are demonstrated in Table 2.

We found that CTV has high sensitivity and specificity for diagnosis of IVCS and can distinguish between thrombotic and nonthrombotic IVCS (Fig. 5a and b). Using CTV, we clearly identified the precise iliac venous anatomy, the drainage of the pelvic collateral veins into the contralateral iliac vein, and the extension of thrombosis in the left external iliac vein. A transverse computed tomography scan of each patient revealed compression of the left iliac vein caused by the right

Table 2 Criteria and clinical-etiology-anatomy-pathophysiology classification of the studied patients

Characteristics	Iliac vein compression syndrome study groups		*P* value
	Group 1 (nonthrombotic) (*N*=50)	Group 2 (thrombotic) (*N*=11)	
Number of patients (limbs)	50	11	0.251
Mean age (year) (range)	39.6	40.8	0.440
Female : male	31 : 19	8 : 3	0.282
Duration of disease (years) (range)	14.6 (1?41)	20.7 (2? 48)	0.156
Pain [*n* (%)]*	22 (44)	8 (72.7)	0.032
Edema [*n* (%)]*	22 (44)	10 (90.9)	0.029
Smoking [*n* (%)]	7 (14)	2 (18)	0.674
Diabetes mellitus [*n* (%)]	19 (38)	5 (45.5)	0.294
Hypertension [*n* (%)]	18 (36)	3 (27.3)	0.267
Hypercholesterolemia [*n* (%)]	18 (36)	2 (18)	0.381
C0 (*n*)	0	0	
C1 (*n*)	0	0	
C2 [*n* (%)]	15 (30)	2 (18)	0.068
C3 [*n* (%)]	19 (38)	5 (45.5)	0.079
C4 [*n* (%)]	6 (12)	2 (18)	0.461
C5 [*n* (%)]	3 (6)	1 (9.1)	0.842
C6 [*n* (%)]*	4 (8)	1 (9.1)	0.029
Obstruction [*n* (%)]	19 (38)	11 (100)	0.896
Superficial reflux [*n* (%)]	23 (46)	0 (0.0)	0.904
Deep reflux [*n* (%)]	21 (42)	0 (0.0)	0.896
Combined superficial and deep reflux [*n* (%)]	6 (12)	11 (100)	0.089

**P* value less than 0.05 (nonthrombotic versus thrombotic iliac vein compression syndrome groups).

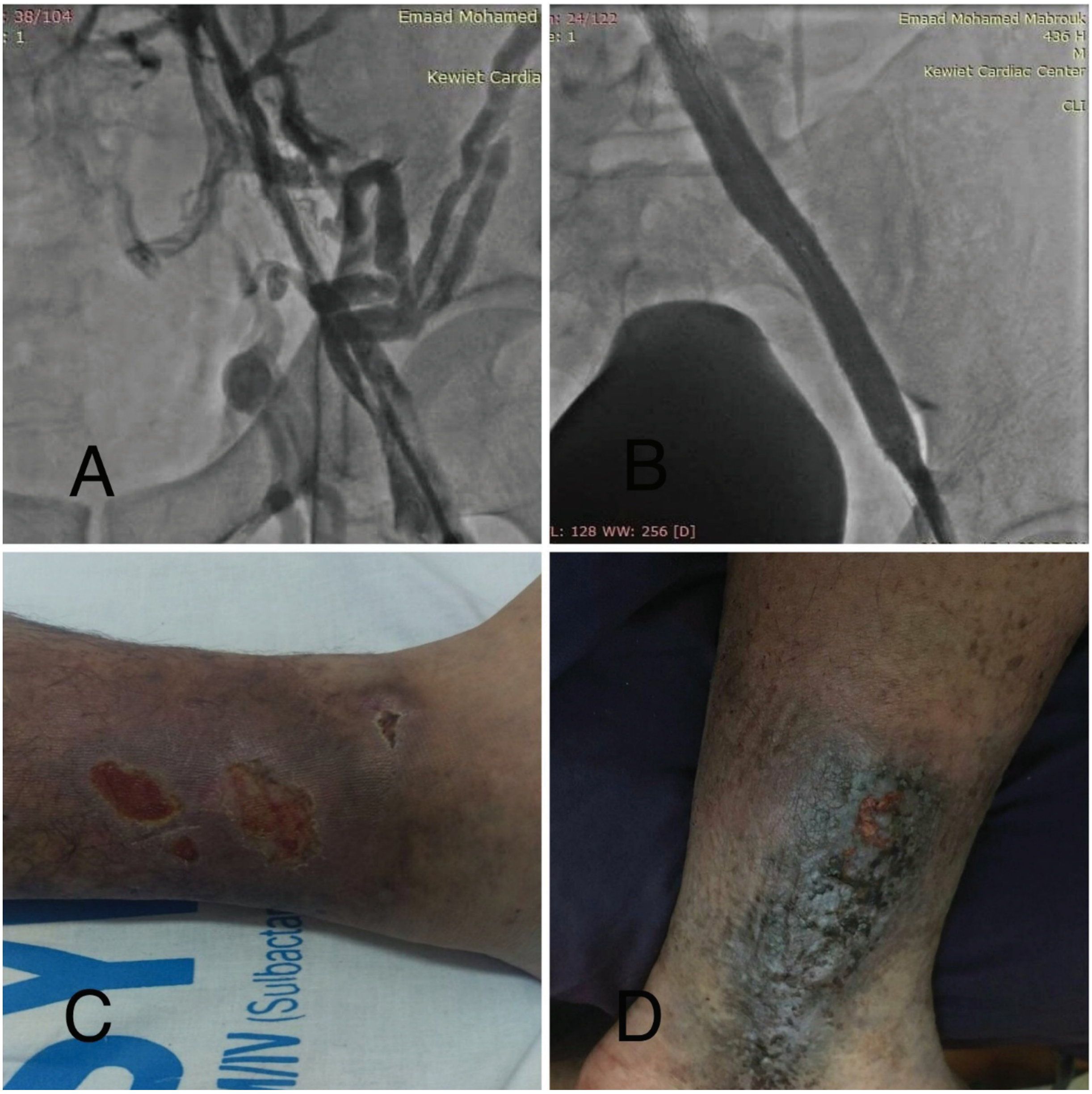
common iliac artery and in some cases by both right and left common iliac artery (Fig. 6a and b). Transfemoral venography during the endovascular treatment revealed obstructive outflow of the LCIV and collateral veins with pooling of the contrast in the pelvic veins which are dilated, tortuous, and elongated.

Intraprocedural outcomes

We administered endovascular therapy to 61 patients and deployed 74 stents in 60 patients. Our technical success rate was 98.4% (60/61). Table 3 shows the peri-interventional complications that had encountered during our trial; none of the patients died or experienced pulmonary embolism or contrast-enhanced nephropathy. All the patients experienced back pain during the process of predilatation and stent placement; however, all of the patients tolerated the procedure well. CFV access was used in 82% (50/61), popliteal vein access was used in 9.8% (6/61), mid-thigh femoral vein access in 3.3% (2/61), great saphenous vein access in 4.9% (3/61), and right internal jugular access in 6.6% (4/61).

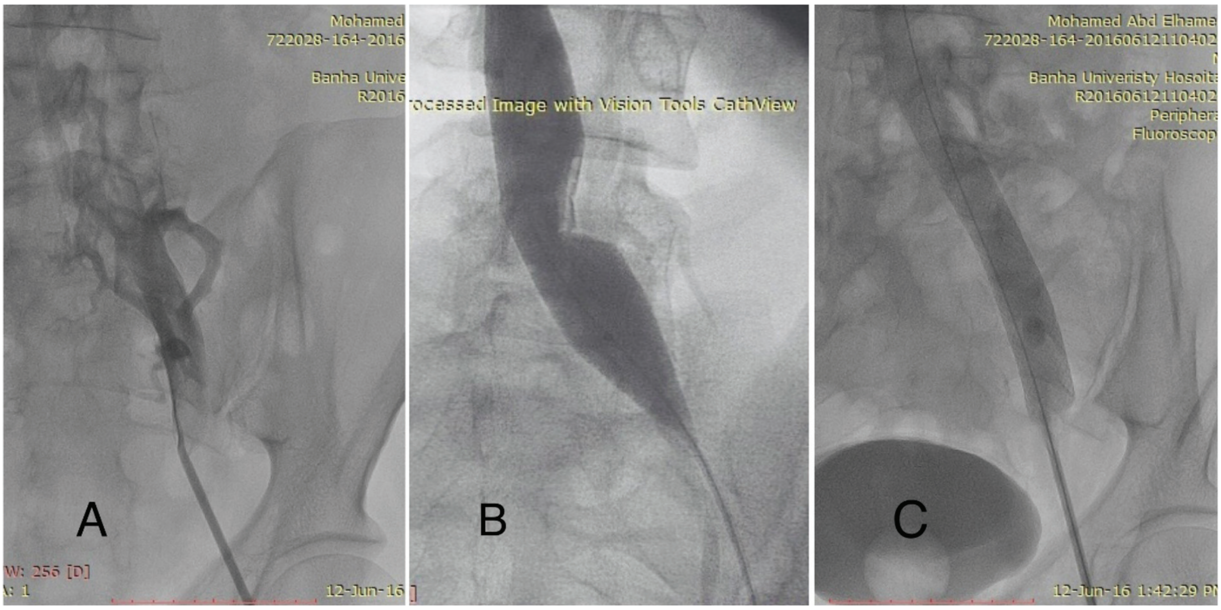
The antegrade cannulation failed in four patients; when the cannulation failed, we treated the patients with transjugular retrograde cannulation that succeeded to cross the targeted lesion in three of

Figure 5



(a) CTV scan of a patient with nonthrombotic IVCS shows the left common iliac vein compression by the right CIA and revealed the dilated ipsilateral both external iliac and common femoral veins. (b) CTV scan of a patient with thrombotic IVCS reveals dilated collateral veins and pelvic congestion. CTV, computed tomography venography; IVCS, Iliac vein compression syndrome.

Figure 6



(a) A transverse CTV scan of a patient with nonthrombotic IVCS showing the left common iliac vein is being compressed by right CIA. (b) Compression of left iliac vein by both right and left CIA. CTV, computed tomography venography; IVCS, Iliac vein compression syndrome.

Table 3 Peri-interventional, 30-day, and 1-year complications

Complications	Immediate postprocedural		24 h–30 days		1-year follow-up	
	NIVC	TIVC	NIVC	TIVC	NIVC	TIVC
Stent fracture	0	0	0	0	0	0
Stent migration	1	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0
Iliac vein rupture	0	0	0	0	0	0
Hematoma	1	0	1	1	0	0
Back pain	12	9	10	19	0	0
Contrast-induced nephropathy	0	0	0	0	—	—
Deep venous thrombosis	0	0	0	0	1	2

NIVC, Nonthrombotic iliac vein compression; TIVC, thrombotic iliac vein compression.

four patients. We implanted two stents in eight of the patients: one patient of nonthrombotic group as the initial stents migrated, and we deployed secondary stents to prevent further primary stent migration and the other seven patients belonged to thrombotic group. Three stents were deployed in three patients owing to involvement of CFV.

One-month outcomes

None of the patients died or experienced severe complications by the time of their 30-day follow-up. Most patients reported back pain relief 6 months after receiving treatment. Two patients in each group had self-limiting minor groin hematomas, the symptoms of which were relieved within 2 weeks after the 30-day follow-up. Fifty-five patients encountered back pain, but the back pain was self-limiting in most patients. As shown in Table 3, none of the patients experienced stent fracture, stent migration, pulmonary migration, pulmonary embolism, contrast-induced nephropathy, or DVT within 30 days of receiving treatment.

Twelve-month outcomes

The 1-year patency rates in the nonthrombotic and thrombotic IVCS groups were 95.7 and 80%, respectively (P=0.146; Fig. 7). The overall primary patency rate at 1 year after treatment was 93%. None of the patients died or experienced pulmonary embolism, stent fracture, or stent migration within 1 year of receiving treatment. Three patients, however, experienced DVT (Table 3): stent thrombosis occurred after the withdrawal of warfarin in two patients, and the other patient developed DVT in the right calf. Table 4 shows that the severity of the symptoms decreased after treatment, and the physical signs of IVCS generally went into remission. We did not

Table 4 1-year follow-up of patients with iliac vein compression syndrome

	Nonthrombotic IVCS		Thrombotic IVCS	
	Pretreatment (*N*=50)	Posttreatment (*N*=46)	Pretreatment (*N*=10)	Posttreatment (*N*=10)
Pain[a]				
Limbs [*n* (%)]	22 (44)	6 (13)	8 (80)	1 (10)
Score [mean (range)]	3.4 (0–8)	0.4 (0–3)	4.5 (1–9)	1.4 (0–4)
Edema [*n* (%)]				
Limbs	22 (44)	4 (8.7)	10 (100)	3 (30)
Ulcer				
Limbs	6 (12)	0 (0.0)	6 (60)	2 (50)
Varicose veins [*n* (%)]				
Limbs	50 (100)	35 (76.1)	8 (80)	6 (60)
Color duplex ultrasound [*n* (%)]				
Patency	–	44 (95.7)	–	8 (80)
Restenosis	–	2 (4.3)	–	1 (10)
Re-occlusion	–	0 (0.0)	–	1 (10)
Abdominal plain radiography film [*n* (%)]				
Stent migration	–	0 (0.0)	–	0 (0.0)

IVCS, iliac vein compression syndrome.

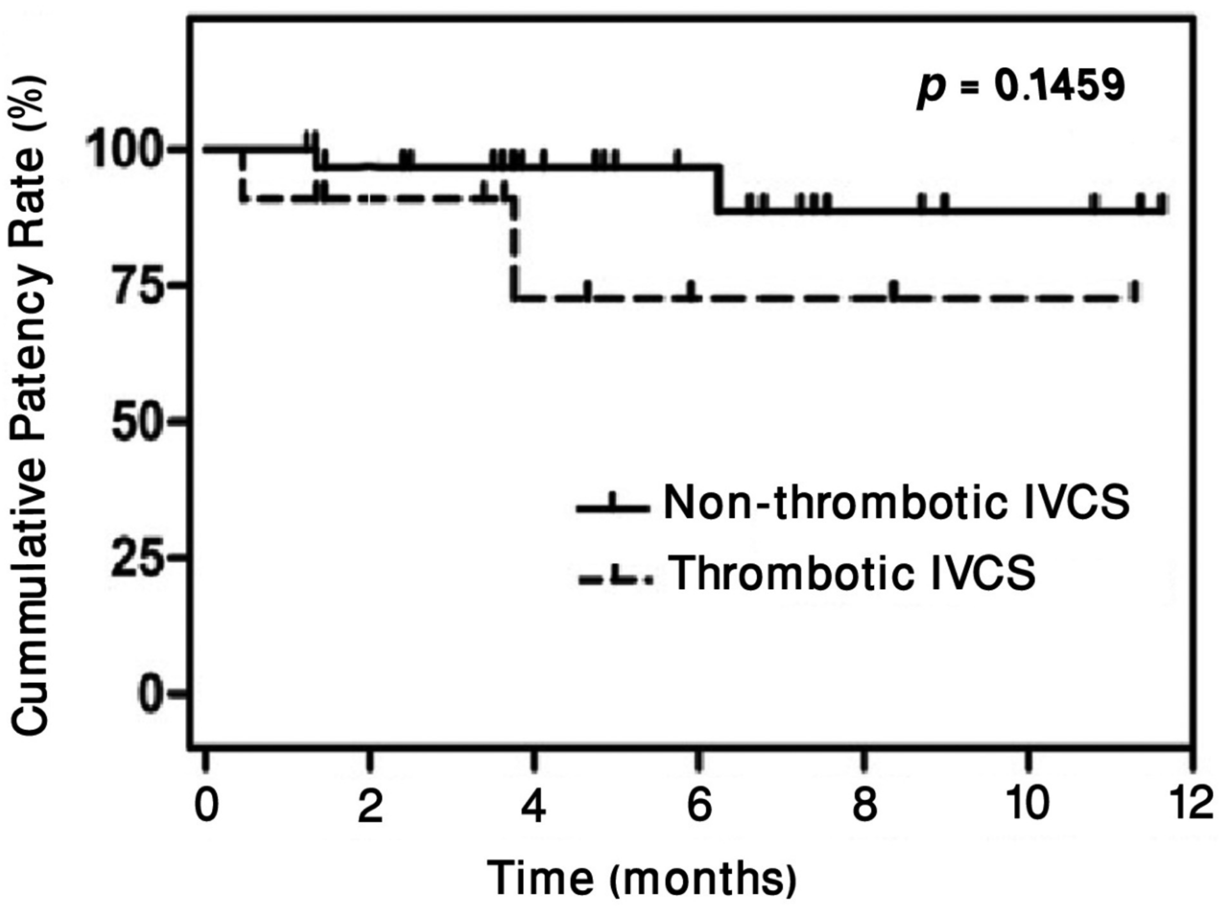
observe any significant improvement of varicose veins in either group.

The median degree of swelling and pain was significantly reduced: complete pain relief was achieved in 76.7% of patients. The median pain level recorded on a visual analog scale declined from 3.4 to 0.4 ($P<0.05$) in the nonthrombotic ICVS group and from 4.7 to 1.4 ($P<0.05$) in the thrombotic IVCS group. The edema relief rates in the nonthrombotic and thrombotic IVCS groups were 81.8 and 70%, respectively. The overall edema relief rate was 78.1%. Of the 12 limbs with active ulceration before treatment, 10 (83.3%) healed completely without recurrent ulceration 12 months after treatment (Table 4) (Fig. 3c and d). The median duration of venous stasis ulcer disease after treatment was 5.5 months. One patient continued to have recurrent ulcers until receiving endovenous laser ablation of the great saphenous vein with duplex-guided injection sclerotherapy of feeding perforators 1 year after stent placement. In one another patient who experienced IVCS and peripheral arterial disease, SFA and tibial angioplasty had been done for revascularization of the left lower limb with relief of pain and healed the ischemic ulcers.

Discussion

Rudolf Virchow described the famous Virchow's triad of thrombosis in the setting of iliofemoral DVT and venous stasis in 1851. He noted DVTs occurring five times more commonly in the left lower extremity compared with the right [15]. McMurrich [16] identified chronic obstructive lesions at iliocaval junction and described multiple types of such lesions in his publication in 1908. May and Thurner in 1956 confirmed the pathological iliac vein compression by the right common iliac artery (CIA) against the spine and pelvic brim for this left-sided propensity as MTS [17]. The syndrome is repeatedly seen in ~18–49% of patients with left-sided lower extremity DVT, more commonly involving middle-aged females [15,18]. May and Thurner hypothesis was the lesion arising owing to chronic compression of a vein by a large pulsatile artery against a stiff bone may produce endothelial injury leading to intimal hyperplasia. This in long term may cause fibrotic changes within the venous wall in the form of bands and spurs creating a fixed intrinsic mechanical obstruction [19]. Most of these lesions are silent, manifesting symptoms related to chronic venous stasis ranging from pain and swelling to hyperpigmentation, dermatitis, and ulceration following a 'second hit,' these lesions have been described as 'permissive pathology' that precipitates symptoms when a secondary insult as trauma, hormonal contraception, and DVT occurs, addressing the permissive pathology first providing definitive cure [20]. Patients may also present with pulmonary embolism in absence of lower extremity DVT, according to the pelvic venous source or embolus. Extensive clot burden may result in excessive swelling, increasing the risk of compartment syndrome and rarely common iliac vein perforation [21]. Although the IVCS was previously thought to be a rare condition, the wider use of catheter-directed intrathrombus thrombolysis, now revealing IVCS, is more common than previously thought, especially among patients with symptomatic left lower extremity DVT [22,23]. The prevalence of IVCS ranges from 18 to 49% among patients with left lower extremity DVT [2]. A conservative therapy such as compression stockings and tight compression bandage may be tried for symptomatic relief [24]. Owing to the invasive nature of surgery, endovascular therapy becomes the current standard care and surgical decompression is preferentially a second line of treatment in cases of endovascular treatment failure and technically complicated cases. Endovascular therapy for acute iliofemoral DVT includes urgent catheter-directed thrombolysis using a pharmacologic agent or a mechanical device or both. This is followed by venoplasty and common iliac venous stenting [25]. Retrievable IVC filter may be used to prevent embolization and thrombus propagation [20,25]. Primary and secondary patency rates after venous stenting are reported as high as 78 and 95% at 2-year follow-up evaluation [3,20]. Venoplasty and venous stenting can also be used in treating MTS in the absence of thrombosis. After the procedure, these patients are generally treated with anti-platelet agents instead of anticoagulants [26]. Our study results suggest that IVCS is not uncommon, especially among patients with unilateral left lower limb CVD. We identified IVCS in 18.7% of patients enrolled in our study, with 1-year patency rates in the nonthrombotic and thrombotic IVCS groups being 95.7 and 80%, respectively. We found that IVCS is an independent etiological factor in all studied patients that affects the pathogenesis of iliac venous outflow obstruction and has an important role in the clinical expression of chronic venous insufficiency, particularly by producing pain as a common symptom. The symptoms and physical signs of unilateral lower limb CVD are helpful in the diagnosis of IVCS; imaging, however, is necessary for diagnosis in most patients. Because of its widespread availability, duplex ultrasonography is the most common modality of investigations for screening patients with DVT and diagnosing venous disease, but it is neither 100% sensitive nor 100% specific in the detection of lower extremity DVT [27]. Sonographic findings of CFV can often suggest proximal obstruction. Loss of collapsibility of CFV, lack of respiratory variations, and absence of response to Valsalva maneuver even in the absence of CFV thrombosis can be suggestive of potential compression or obstruction [19]. Its utility is limited in examining iliac veins given their deep pelvic location and highly operator dependent, however, especially in obese patients and cases of poor visibility caused by bowel gas

Figure 7



Kaplan–Meier curve shows the cumulative patency rate in comparison between the nonthrombotic and the thrombotic iliac vein compression patients at 12-month follow-up.

[19,20]. In addition, Doppler waveforms in the CFVs can indicate normal spontaneous flow and respiratory variation despite the presence of DVT because of large collateral vessels around the site of the proximal obstruction [28]. In our study, we used duplex ultrasonography to detect lower limb DVT but not to diagnose IVCS. In all of our cases in the study with unilateral lower extremity pain and edema, especially after a normal lower extremity venous duplex ultrasonography scan, direct imaging of the pelvic veins should be considered. We utilized CTV in the transverse plane that accurately revealed iliac vein compression caused by the overlying artery. We found that CTV with three-dimensional reconstruction had the highest sensitivity and specificity for diagnosing IVCS, and the images also added useful information for planning endovascular treatment. Our diagnosis was based on CTV findings that demonstrated diagnostic findings in the form of venous collateralization, pancaking sign, and significant compression with more than or equal to 50% reduction of lumen diameter in axial cuts of CTV. The advantages of CTV over venous duplex ultrasonography are its short examination time, its lack of operator dependency, and its superior visualization of the pelvic veins. CTV requires large volume of contrast medium and cannot be used on patients who are pregnant or who have impaired renal function. Because of its convenience and accessibility, unilateral left iliac vein CTV is used in our study institutions as an established, routine examination for patients with suspected IVCS. We performed predilatation digital subtraction venography in all patients, with the typical findings include reversal of flow within the left internal iliac vein, pancaking of common iliac vein, and collateral formation. An important finding of our study is that in cases of IVCS, clinical symptoms and physical signs do not always correlate with imaging results. Several young women in our study who experienced intermittently from slight left lower limb edema were found to have extensive collateral veins and strong pressure gradients across stenosis of the LCIV. The absence of symptoms could have results of good venous valve function. We must remain vigilant to avoid misdiagnosis; if left untreated, such patients who are misdiagnosed will progress from a less severe condition to a more serious one in which the venous valves are destroyed by the venous hypertension caused by the outflow obstruction. When the combination of reflux and obstruction emerges, such patients could experience severe venous insufficiency and DVT. There is no criterion standard for identifying patients who need treatment for iliac vein compression. Venographic evidence of collateral vessels certainly strengthens the case for intervention, but significant lesions can be present without collateralization. Hemodynamic significant venous lesions should always be stented, because patients with extrinsic causes of obstruction usually tend to respond poorly to balloon angioplasty alone [28]. If the underlying obstruction is not treated with stent placement, there is a 73% recurrence rate in patients with acute, left-sided iliac/femoral DVT [29]. Percutaneous iliac venous stenting is a safe and efficient method of correcting pelvic venous outflow obstruction [30]. The overall primary patency rate in our study was 93% at 1 year after treatment, with no death, pulmonary embolism, or contrast-induced nephropathy in any of the patients. Only a small number of limbs had late occlusion after stent placement: one stented limb became occluded at 12 months, and more than 50% within-stent recurrent stenosis developed in two limbs during the follow-up period. Our findings are consistent with those of previous reports [31]. There, it appears that balloon venoplasty and stenting of the iliac vein in chronically obstructed limbs is a safe, minimally invasive method with a minimal complication rate, no mortality, and an acceptable 1-year patency rate. The midterm patency rate of stents in the iliocaval venous system is considerably higher than those of self-expanding stents in other medium-sized veins, such as the subclavian vein [32]. The possible reasons for the high patency rate include the relatively immobile nature of the pelvic placement compared with placement in the freely mobile subclavian vein, and the absence of adjacent bony structures, such as clavicle or the first rib, which might compress a stent. In treating iliac vein compression, we found that self-expanding stents have the advantages of long length, large diameter, and low susceptibility to permanent deformation by the pulsatile artery and the inguinal ligament. Self-expanding stents can be initially deployed in the inferior vena cava, and the entire device can then be pulled caudally until the proximal end of the stent is flush with iliofemoral junction. Therefore, the recommendation that the stent be placed well into the inferior vena cava when the obstruction is close to the iliocaval junction, as it is in IVCS, appears to be safe [2]. Overall, balloon angioplasty and stenting is safe and effective, and the complication rate is likely to decrease as technology evolves and experience increases. The known complications of venous stents placed in the superior caval vein include dislodgement and migration into the right ventricle. Such stents are therefore mostly used in patients with superior vena cava syndrome in end-stage malignant disease. The migration of venous stents placed in the iliac vein in cases of IVCS, however, is rarely reported [33]. In our case series, we reported one patient with stent migration in nonthrombotic group. It was owing to undersizing of stent diameter with stent shortening that was treated with deployment of second larger stent. Although several reports suggest that venous

stenting in IVCS patients is both safe and cost-effective, the possibility of migration has to be kept in mind. Anticoagulant therapy should be continued after stent implantation, especially in patients with thrombotic IVCS. It is, however, worth questioning how long the anticoagulant therapy is necessary; two patients with thrombotic IVCS in our study experienced recurrent thrombus after the oral anticoagulant therapy was withdrawn. We observed that varicose veins did not remit spontaneously; even 1 year after the obstruction was relieved by the stent implantation, we thought that when proximal outflow obstruction is relieved, axial retrograde reflux through the distal incompetent valves increases. It is reported that ambulatory venous pressure, venous filling time, and venous filling index, however, do not improve after stent insertion in patients with preoperative reflux [13,30]. In our patient cohort, the removal of the iliac vein outflow obstruction did not result in decreased axial reflux with clinical deterioration. Therefore, performing varicosity operation and endovascular treatment during the same hospital stay should be considered for patients experiencing IVCS and severe subsequent varicose vein disease.In our study, most of the patients with IVCS who had ulcers had previously exhausted conservative treatment options, such as ulcer dressings and compression stockings. Five of the seven patients with active ulcers healed after iliac vein stent placement and duplex-guided injection sclerotherapy of ulcer feeding perforators. In this study, we planned to evaluate intimal hyperplasia of iliac vein after implantation of the stent. Therefore, all the patients received duplex ultrasonography examinations during the follow-up period. We also offered venography to the patients upon follow-up when there was doubt about the patency of the iliac vein. However, there is limitation for duplex ultrasonography to detect iliac vein intimal hyperplasia, and not all patients received CTV. Therefore, it is hard to know the exact rate of stenosis. Our study was limited by a small number of patients, a nonrandomized study design, and a relatively short follow-up period. Prospective analyses with larger study groups to further evaluate the use of endovascular treatment for IVCS in patients with unilateral left lower limb CVD should be conducted in the future.

Conclusion

IVCS is not an uncommonly encountered condition, especially among patients with unilateral left lower extremity CVD. CTV with three-dimensional reconstruction images was more sensitive and specific as compared with venous duplex ultrasonography and ascending venography as a diagnostic approach for IVCS, and the constructed images provided useful information for the endovascular treatment planning. Moreover, endovascular therapy is a minimally invasive approach to treat venous lesions and is feasible and effective for treating left-sided IVCS with high technical success rate and with an acceptable complication profile. So, we concluded that endovascular treatment appears to be superior to conventional surgical treatment and should be considered as the first line of therapy for many patients suffering from IVCS.

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Conflicts of interest

There are no conflicts of interest.

References

1 Lou WS, Gu JP, He X, Chen L, Su HB, Chen GP, *et al.* Endovascular treatment for iliac vein compression syndrome: a comparison between the presence and absence of secondary thrombosis, Korean J Radiol 2009; 10:135–143.

2 O'sullivan GJ, Semba CP, Bittner CA, Kee ST, Razavi MK, Sze DY, *et al.* Endovascular management of iliac vein compression (May-Thurner) syndrome. J Vasc Interv Radiol 2000; 11:823–836.

3 Patel NH, Stookey KR, Ketcham DB, Cragg AH. Endovascular management of acute extensive iliofemoral deep venous thrombosis caused by (May-Thurner) syndrome. J Vasc Interv Radiol 2000; 11:1297–1302.

4 Cockett FB, Thomas ML, Negus D. Iliac vein compression. Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. Br Med J 1967; 2:14–19.

5 Hassell DR, Reifsteck JE, Harshfield DL, Ferris EJ. Unilateral left leg edema: a variation of the May-Thurner syndrome. Cardiovasc Intervent Radiol 1987; 10:89–91.

6 Steinberg JB, Jacocks MA. May-Thurner syndrome: a previously unreported variant. Ann Vasc Surg 1993; 7:577–581.

7 Burke RM, Rayan SS, Kasirajan K, Chaikof EL, Milner R. Unusual case of right-sided May-Thurner syndrome and review of its management. Vascular 2006; 14:47–50.

8 Abboud G, Midulla M, Lions C, El Ngheoui Z, Gengler L, Martinelli T, Beregi JP. "Right-sided" May-Thurner syndrome. Cardiovasc Intervent Radiol 2010; 33:1056–1059.

9 Bulger CM, Jacobs C, Patel NH. Epidemiology of acute deep vein thrombosis. Tech Vasc Interv Radiol 2004; 7:50–54.

10 Virchow R. About the expansion of small vessels. Anatomy 1851; 3:427.

11 Fazel R, Froehlich JB, Williams DM, Saint S, Nallamothu BK. Clinical problem-solving a sinister development-a 35-year-old woman presented to the emergency department with a 2-day history of progressive swelling and pain in her left leg, without antecedent trauma. N Engl J Med 2007; 357:53–59.

12 Scott J, Huskisson EC. Graphic representation of pain. Pain 1976; 2:175–184.

13 Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007; 46:979–990.

14 Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006; 44:136–143.

15 May R, Thurner J. The cause of the predominantly sinister occurrence of thrombosis of the pelvic veins. Angiology 1957; 8:419–427.

16 McMurrich JP. The occurrence of congenital adhesions in the common iliac veins and their relation to thrombosis of femoral and iliac veins. Am J Med Sci 1908; 135:342–346.

17 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al.* Antithrombotic therapy for VTE disease. Chest 2016; 149:315–352.

18 Oğuzkurt L, Ozkan U, Tercan F, Koç Z. Ultrasonographic diagnosis of iliac vein compression (May-Thurner) syndrome. Diagn Interv Radiol 2007; 13:152–155.

19 Lamba R, Tanner DT, Sekhon S, McGahan JP, Corwin MT, Lall CG. Multidetector CT of vascular compression syndromes in the abdomen and pelvis. Radiographics 2014; 34:93–115.

20 Titus JM, Moise MA, Bena J, Lyden SP, Clair DG. Iliofemoral stenting for venous occlusive disease. J Vasc Surg 2011; 53:706–712.

21 Hosn MA, Katragunta N, Kresowik T, Sharp WJ. May-Thurner syndrome presenting as spontaneous left iliac vein rupture. J Vasc Surg Venous Lymphat Disord 2016; 4:479–481.

22 Oguzkurt L, Tercan F, Ozkan U, Gulcan O. Iliac vein compression syndrome: outcome of endovascular treatment with long-term follow-up. Eur J Radiol 2008; 68:487–492.

23 Kasirajan K, Gray B, Ouriel K. Percutaneous angiojet thrombectomy in the management of extensive deep venous thrombosis. J Vasc Interv Radiol 2001; 12:179–185.

24 Cockett FB, Thomas ML. The iliac compression syndrome. Br J Surg 1965; 52:816–821.

25 Suwanabol PA, Tefera G, Schwarze ML. Syndromes associated with the deep veins: phlegmasia cerulea dolens, May-Thurner syndrome, and nutcracker syndrome. Perspect Vasc Surg Endovasc Ther 2010; 22:223–230.

26 Meissner MH. Indications for platelet aggregation inhibitors after venous stents. Phlebology 2013; 28 Suppl 1:91–98.

27 Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 1993; 329:1365–1369.

28 Hurst DR, Forauer AR, Bloom JR, *et al.* Diagnosis and endovascular treatment of iliocaval compression syndrome. J Vasc Surg 2001; 34:106–113.

29 Mickley V, Schwagierek R, Rilinger N, Görich J, Sunder-Plassmann L. Left iliac venous thrombosis caused by venous spur: treatment with thrombectomy and stent implantation. J Vasc Surg 1998; 28:492–497.

30 Neglen P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. J Vasc Surg 2003; 38:879–885.

31 Neglen P, Raju S. In-stent recurrent stenosis in stents placed in the lower extremity venous outflow tract. J Vasc Surg 2004; 39:181–187.

32 Lumsden AB, MacDonald MJ, Isiklar H, Martin LG, Kikeri D, Harker LA, Allen RC. Central venous stenosis in the hemodialysis patient: incidence and efficacy of endovascular treatment. Cardiovasc Surg 1997; 5:504–509.

33 Mullens W, De Keyser J, Van Dorpe A, Meuris B, Flameng W, Herregods MC, Van de Werf F. Migration of two venous stents into the right ventricle in a patient with May-Thurner syndrome. Int J Cardiol 2006; 110:114–115.