






Role of Imaging in Deep Vein Thrombosis: A Review Article

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Article Info	ABSTRACT
<p>Article type: Review article</p>	<p>Background and Aim: Venous Thrombo Embolism (VTE) refers to the formation of clots in blood vessels. The current study aimed to investigate deep vein thrombosis (DVT) by imaging modalities.</p> <p>Materials and Methods: In this review study, national databases, including Magiran, SID, IranMedex, as well as international ones, namely databases including PubMed, Google scholar, Scopus, and ISI, were searched for related books and articles. The keywords included thrombosis, deep vein thrombosis, imaging, and thrombosis detection.</p> <p>Results: In patients with suspected primary or recurrent deep vein thrombosis, CT venography (CTV) and Magnetic Resonance Venography (MRV) are rarely used on suspicion of iliac vein thrombosis or inferior vena cava (IVC) thrombosis in ultrasound. These examinations have relatively poor reliability, cause adverse side effects of radiation and contrast materials, and are undoubtedly more costly.</p> <p>Conclusion: As evidenced by the obtained results, different methods are available for the diagnosis of deep vein thrombosis. Moreover, it was revealed that ultrasound imaging is the most reasonable method for initial examination due to its sensitivity, specificity, costs, and adverse effects.</p>
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Introduction

Venous Thrombo Embolism (VTE) is the formation of clot in blood vessels which may appear as deep vein thrombosis (DVT) or pulmonary embolism (PE) (1, 2). Deep vein thrombosis occurs with the formation of venous blood clots in the deep veins of the lower and upper extremities, mainly one of the legs (such as the femoral or saphenous vessels) or the pelvis (iliofemoral vessels) (3,4).

Venous thrombosis usually occurs in one of the lower extremities which can be attributed to a higher rate of clot formation in the legs. Eventually, a part of the clot (such as an embolism) breaks off and may travel through IVC, the right cardiac cavity, and the pulmonary artery and causes obstruction

(in 13-4% of cases of deep vein thrombosis) (4). The present study aimed to investigate the diagnosis of deep vein thrombosis by imaging techniques.

Materials and Methods

In this review study, national databases, including Magiran, SID, IranMedex, as well as international ones, namely databases including PubMed, Google Scholar, Scopus and, ISI were searched for related books and articles. The keyword included thrombosis, deep vein thrombosis, imaging, and thrombosis detection. Related articles were searched simultaneously by two scholars from January to July 2019. Notably,

only full-text articles in English and Persian were included in the initial search (132 items).

Inclusion criteria entailed access to full-text and all the articles which were related to diagnostic procedures in deep vein thrombosis and the role of imaging in deep vein thrombosis (121 cases). On the other hand, the exclusion criteria included articles without available full-text, as well as articles whose abstract had been presented at conferences and congresses (11 cases).

Results

Diagnostic ultrasound for suspected primary deep vein thrombosis

Compression ultrasonography (CUS) along with Doppler is the diagnostic test of choice in patients with suspected DVT (Figure 1). Most of the following information is related to the accuracy of CUS in outpatients with suspected primary DVT. In general, the sensitivity and specificity of proximal CUS are greater than 95%. However, proximal CUS is less sensitive and practical in the following patients (5-9).

Tibial vein thrombosis: tibial veins are not assessed by the proximal CUS since they are harder to find, as compared to the proximal veins. While the whole-leg ultrasound can assess both tibial and proximal veins.

Iliac vein thrombosis: These vessels cannot be examined due to compression; therefore, Doppler or CT venographies are used for their assessment.

The method of choice and interpretation of ultrasound in these studies are consistent with those of other physicians. Nonetheless, according to these studies, some physicians prefer Doppler to proximal vascular ultrasound (10). The selection among these methods is made based on the radiologist's preference and the rules of each center.

Selection between proximal ultrasound and whole-leg ultrasound

The selection between proximal ultrasound and whole-leg ultrasound depends on the physicians. While some physicians prefer whole-leg ultrasound, some others confine the ultrasound to the proximal areas. On the other hand, proximal ultrasound is performed in certain groups of patients, either whole-leg or major-leg (e.g., patients with overt symptoms of the leg and negative proximal sonography). Although all approaches are acceptable, the selection between these two ultrasound procedures is highly dependent on medical centers. In this regard, physicians should be aware of the procedure performed at their center and its benefits and disadvantages.

Both ultrasound methods have high sensitivity and specificity for the diagnosis of proximal vein DVT. Following diagnosis, anticoagulant treatment is required to control symptoms, prevent progression and embolization, and reduce the risk of post-thrombosis syndrome (i.e., important clinical DVT). Moreover, the isolated distal DVT can be detected by whole-leg ultrasound. This DVT is either resolved or does not progress to proximal without any treatment. In addition, it develops fewer complications. Therefore, the routine use of whole-leg ultrasound helps identify DVTs that do not necessarily need treatment.

Proximal

CUS of proximal vein demonstrates uncompressed segments (thrombosis marker) in proximal veins (e.g., common femoral, femoral, and popliteal veins). Identification of proximal DVT is of paramount importance since it is more prone to progression and embolization, as compared to distal single DVT. Proximal CUS is highly sensitive to

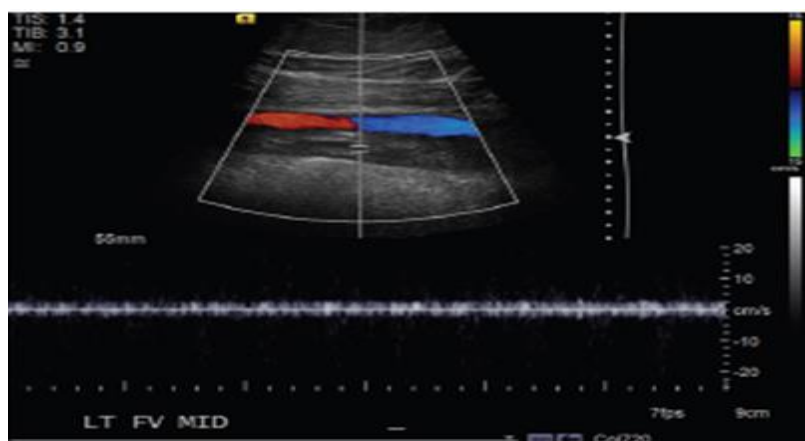


Figure 1. Staining of Venous Doppler. Doppler imaging of the femoral vein which demonstrates complete occlusion by heterogeneous thrombus with venous contraction at the site of thrombosis. There is no significant wave. The adjacent artery has been also displayed for reference (6).

proximal vein DVT diagnosis (over 95%). Moreover, it has high negative predictive value for proximal DVT rejection in all patients, and for rejection of all DVTs (including single distal DVT) in patients with low pre-test probability (PTP). In addition, proximal CUS ultrasound is easier to perform and its interpretation is less technician-dependent, compared to whole-leg ultrasound.

One limitation of proximal CUS is that unlike whole-leg sonography, the tibial veins are not assessed; therefore, isolated distal DVTs are not diagnosed. However, thrombosis in this place is rarely embolized, and these patients do not always need anticoagulation therapy. In addition, the risk of misdiagnosis of serious distal DVT is reduced by the application of D-dimer and serial proximal CUS in selected patients, which will be discussed separately.

Several randomized trials and continuous meta-analyses have reported that proximal CUS (as compared to contrast-enhanced venography) is a sensitive method for proximal DVT (95-100%) (11-17). In patients with low risk of DVT, a proximal CUS rejects the diagnosis, and the risk of VTE in these patients over the next 3 months will be approximately 0.5(1).

Nearly 2% of patients with moderate to high risk of DVT whose proximal CUS was negative at baseline had proximal DVT upon re-examination after 7 days (18). One re-examination within 5-7 days after the negative initial assessment showed less than 1% probability of VTE during 6 months follow-up in patients who did not receive anticoagulant (19). Randomized studies revealed that progressive VTE level was similar in patients who had undergone a whole-leg ultrasound and those who had proximal ultrasound 1 week after the initial examination (about 1-2%) (20).

A randomized trial study was conducted on 1002 patients with suspected DVT whose thrombosis was not ruled out in initial examination by clinical PTP and negative D-dimer or proximal CUS sonography (in the initial examination and first-week follow-up) or whole-leg ultrasound. The result of the mentioned study revealed that progressive VTE level during the 3-month follow-up was the same as those with negative examinations who did not receive anticoagulation (2 vs. 1%).

In another randomized study comparing whole-leg ultrasound with proximal ultrasound, it was reported that progressive VTE level was similar during the 3-month follow-up (0.9 vs. 1.2%)(20).

Whole-leg ultrasound

The whole-leg sonography diagnoses proximal DVT (i.e., the common femoral, femoral, and popliteal veins) as the proximal CUS do. Its major

advantage over proximal CUS is the imaging of the tibial veins (peroneal, posterior tibial, anterior tibial, and muscle veins). Consequently, its negative evaluation rejects the isolated distal DVT (i.e., total DVT), and other diagnostic tests or repeated proximal CUS are not needed.

However, compared to the proximal CUS, whole-leg ultrasound is more difficult to perform and its interpretation depends on the operator. In addition, the clinical significance of the diagnosis of isolated distal DVT is unclear since it is less prone to embolization, and treatment is not required in all patients. Indications for anticoagulant administration in patients with distal DVT and the use of whole-leg ultrasound in patients with suspected DVT will be discussed later.

Findings that indicate high sensitivity (> 99%) of whole-leg sonography in patients with suspected DVT have been reported in several randomized studies and meta-analyses (> 99%). A meta-analysis of 7 studies revealed that the VTE level was very low (0.6%; 95% CI 0.25-0.89) within 3 months in patients who did not receive anticoagulant after negative whole-leg sonography (28). This rate was 0.3% in patients with low PTP, 0.8% in moderate PTP, and 2.5% in high PTP.

Interpretation of ultrasonography

The interpretation of CUS in patients with suspected primary DVT is described in the following sections.

Positive

While probe pressure is applied, the presence of thrombosis is detected if the vein is not compressed. The veins which are evaluated by pressure are proximal (such as the common femoral, femoral, and popliteal veins). However, distal veins (such as the peroneal, posterior tibial, anterior tibial, and muscle veins) and iliac veins cannot be examined by pressure measurement. Prospective studies have indicated that failure to compress a vein by ultrasound probe is the most sensitive (> 95%) and most specific (> 95%) ultrasound symptom of proximal vein thrombosis. The addition of color Doppler does not increase the sensitivity; nonetheless, it could confirm thrombosis or evaluate tibial veins (29-30).

Resizing the veins by Valsalva maneuvering is less sensitive and specific for diagnosis and is not performed in many centers. On the contrary, CUS is less sensitive to thrombosis of iliac and tibial veins since these veins are less compressible (specifically tibial veins).

Negative

Negative evaluation means the ability to squeeze

all the veins under examination.

Nondiagnostic

The nondiagnostic evaluation of the presence or non-presence of DVT is unknown. Non-diagnostic findings in outpatients are less than those of inpatients. Less than 5% of outpatients had non-diagnostic findings for proximal veins. Non-diagnostic findings are also less likely in the imaging of proximal veins, as compared to distal veins (i.e., using whole-leg ultrasound). Nonetheless, nondiagnostic findings are less important in distal veins and can be controlled by non-prescribing anticoagulant therapy and serial ultrasound.

There are three main reasons for a non-diagnostic finding:

Firstly, it may be difficult to see the deep veins due to obesity, edema, recent surgery or trauma, skin lesions, contractions, and leg cramps (i.e., technical limitations in evaluation) (31).

Secondly, small or abnormal findings (such as smaller than 2 mm) may be found since seep veins can be well observed.

Thirdly, in patients with previous DVT, the distinction between old and new thrombosis is difficult (old thrombosis can still persist). The features of each of them will be discussed later.

Further evaluations (such as proximal CUS on days 3 and 7) in patients with nondiagnostic findings depend on some factors. They include the patient, the reason for nondiagnostic ultrasound, status and extent of thrombosis (e.g., distal or proximal vein), clinical probability of PTP, D-dimer test results, and the doctor's overall assessment of the risks associated with undiagnosed DVT.

Suspected recurrent deep venous thrombosis

A previous episode of DVT is a risk factor for its recurrence. Suspected patients present with symptoms that they had experienced for the first time. However, swelling and persistent leg pains that may fluctuate are common in subsequent episodes (i.e., post-thrombosis syndrome (PTS)). The diagnostic approach to recurrence in the ipsilateral lower extremities is described in this section. Recurrence is diagnosed on the opposite leg as is in a person with suspected DVT for the first time.

Initial Examination

In most patients with recurrent DVT at the same foot, patient referral to sonography (proximal or whole-leg)(32) or an approach similar to that of DVT are efficient for the first time.

Findings confirming the above information are

as follows:

Predictive criteria, such as Wells or Modified Wells, (32-34) can help to reduce unnecessary ultrasounds and improve the control of the situation when the findings are undiagnostic.

Based on available evidence, similar to patients with DVT for the first time, a negative D-dimer level (e.g., less than 500 ng/ml) is sensitive for diagnosis and useful in DVT recurrence. However, it is less specific to patients with DVT for the first time (34-3). For instance:

A prospective study on 105 patients with suspected recurrent DVT demonstrated that the D-dimer had a sensitivity of 97%, the specificity of 30%, and a negative predictive value of 95%. However, D-dimer was only negative in 17% of patients.

Another study on 300 patients with suspected recurrent DVT with negative D-dimer (45% of patients) found that the rate of DVT within 3 months was less than 1% in those who did not receive anticoagulant therapy (Table 1) (35).

Ultrasound interpretation

Common femoral vein and popliteal thrombosis gradually resolve with a 50-60% decrease in residual vein diameter (RVD) over the first 3 months (36). Nearly 80% of proximal ultrasound during these 3 months and 25-30% within one year remain abnormal (36-38). Therefore, it is difficult to diagnose new or old thrombosis in patients with recurrent DVT. Consequently, the ultrasound specificity for the diagnosis of recurrent DVT is lower, as compared to DVT for the first time. On the other hand, this specificity is improved by access to information on previous thrombosis remnants from previous ultrasound examinations. Nonetheless, there is no clear consensus on this issue (39).

Previous ultrasound

If a previous ultrasound is available for comparison, there is a consensus on the following:

Positive ultrasound

For acute thrombosis, it is defined when a part of the vein is uncompressible which was not

Table 1. Summary of criterion for the diagnosis of deep vein thrombosis based on ultrasound

US diagnostic criteria of DVT	
Direct Signs	Indirect Signs
Intramural Thrombus	Loss of phasicity
Incompressibility+++	Proximal thrombosis
Increase in vein diameter	Venous compression
No flow in pulsed Doppler	Loss of augmentation:
No flow in color Doppler	Distal thrombosis

involved in the previous sonography (such as a popliteal vein or femoral joint). Moreover, a 4 mm increase is detected in the diameter of the compressible vein in the previous sonography. In addition, at the face of evidence of significant progression of the thrombus in the same segment of the vein (e.g., 10 cm in the femoral vein) with no new part of the vein involved.

Any evidence of compression in a new place in the vein suggests acute thrombosis and the patient should be treated. Nonetheless, recurrent DVT may be the cause only in 10-20% (small group) of patients (36).

Most physicians consider recurrent DVT in the face of evidence of an increase in $\text{mm4} \leq \text{VD4}$ and significant progression of (> 10 cm) thrombosis. The exact threshold for RVD is unknown; however, studies have reported that a 2 mm increase in RVD, 95% specificity, and $\text{mm4} \leq \text{increase in RVD}$ have 100% specificity (36-41). Accordingly, it is suggested to consider recurrent DVT in patients with an increase of $\text{mm4} \leq \text{RVD}$ (42).

Negative sonography

For acute thrombosis, it is defined when all venous segments are compressible or at the presence of less than 2 mm increase in RVD in the common femoral and popliteal veins, compared to the previous CUS ultrasound examinations.

If whole-leg ultrasound is negative for proximal and distal DVT, no further examination is needed. If proximal CUS is negative, patients should undergo re-CUS (usually) either whole-leg sonography or high-sensitivity D-dimer testing (if not performed) within a week. If any of these reviews were negative, no further investigation is needed. In the case of positive D-dimer, proximal CUS sonography should be repeated and treatment should be performed in case of new positive proximal CUS.

Patients with less than 2mm increase in RVD size are unlikely to have recurrent DVT. It is recommended to repeat the proximal CUS within 2 to 7 days and if CUS status improves or persists, no treatment is needed and vice versa. The clinical evidence for the use of increased RVD in CUS to discontinue anticoagulation therapy when CUS is stable or at the presence of an RVD increase of less than 2 mm is as follows:

In a study conducted on 205 patients with suspected recurrent DVT in the ipsilateral limb, proximal CUS findings were compared with CUS 3-12 months after receiving anticoagulant therapy (101). Patients who had negative CUS (i.e., non-compressive or increase of <2 mm; $n=153$) underwent ultrasound examination 2-7 days later without receiving anticoagulation, and CUS was

positive in 3 of 153 patients. Out of the remaining 149 patients who did not receive anticoagulation, 2 (1.3%) cases had VTE in the next 6 months. In a similar study performed on 284 patients with rejected recurrent DVT by similar criteria and did not receive anticoagulant therapy, 3% developed VTE within the next 3 months (42). A prospective study was conducted on 75 patients suspected of recurrent DVT. The results of the study revealed that no disease occurred during 3 months of VTE when negative D-dimer ($\text{ng/ml} 500 >$) was taken into account, apart from ultrasound criteria (43).

Undiagnosed ultrasound: is considered at the presence of an RVD increase of ≥ 2 mm and > 4 mm or a longitudinal thrombus extension of less than 10 cm. Evaluation of these findings is performed similarly to the abovementioned information (e.g., PTP, D-dimer, repeated CUS, or venography).

- No previous sonography available
- In the absence of previous ultrasound findings for comparison, the results are as follows:
- Ultrasound examination showing incomplete femoral vein or uncompressible popliteal vein indicates a new or old thrombosis.

New thrombosis (i.e., acute) is more likely if: thrombosis is widespread, vein with low compression is dilated, D-dimer is positive and significantly high ($\text{ng/ml } 2000 <$), or PTP is high. Patients will be treated in case of a positive estimation and diagnosis of the high probability of DVT. If acute DVT is unlikely in general estimation, anticoagulation therapy may be refused and ultrasound is re-performed (2 and 7 days later).

Negative ultrasound is defined when all venous segments can be compressed.

The approach with nondiagnostic findings varies from person to person and is similar to the abovementioned approaches (e.g., PTP, D-dimer evaluation, serial CUS, or venography)

Alternative imaging techniques

In patients with suspected primary or recurrent DVT, CT venography (CTV) and magnetic resonance venography (MRV) are rarely used in suspicion of iliac vein thrombosis or inferior vena cava thrombosis in ultrasound.

These examinations are relatively less reliable, cause adverse side effects of radiation and contrast material, and are more costly. Nonetheless, they may be more useful than ultrasound in the differentiation between new and old thrombosis. Ascending contrast-enhanced venography which has long been the gold standard for DVT diagnosis and impedance plethysmography are rarely available today and are not used.

The clinical features and diagnostic value of these methods are as follows:



Figure 2. CT venography: CT imaging shows bilateral neuromuscular thrombosis as dense hypodense masses with an increased venous wall. This thrombosis has spread around the IVC (45).

Computed tomography

Thrombosis in the CT is diagnosed as a defect in the filling with contrast material enhancement (Figure 2). The major drawbacks of CT are the limitations and possible side effects associated with the contrast agent.

CT is not accurate in the diagnosis of lower extremity DVT. Its sensitivity and specificity have been reported in studies that simultaneously performed CTV and CT pulmonary angiography (CTPA) in patients with suspected pulmonary embolism (PE)(44-48). In CTPA which do not need extra contrast, deep veins below the diaphragm, including the veins of the foot, are simultaneously imaged.

(in the venous phase of imaging) the high sensitivity of up to 95% for the CT detection of femur popliteal thrombosis has been reported in small-scale studies. However, large-scale studies are needed to confirm CT for the detection of lower extremity DVT.

Magnetic resonance imaging

While contrast-free thrombosis appears as a filling defect on MRI, intravenous gadolinium is preferred. Magnetic resonance direct thrombus imaging (MRDTI) can detect DVT of the lower extremity due to the changes in the structure of the hemoglobin in red blood cells in the injured vein. Nevertheless, it is mostly regarded as a research technique (Figure 3) (49).

Fewer studies have been conducted on MRV, as compared to CTV, and sensitivity of > 95% has been reported in small-scale studies for proximal lower limb DVT diagnosis by MRV. In addition, the application of MRV is discouraged by the adverse effects of contrast agent, high cost, and patient's anxiety when placed in a confined space cause MRV. Small prospective studies have reported that

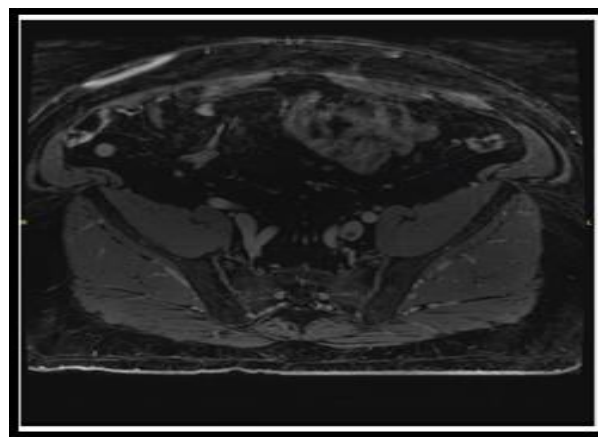


Figure 3. MR venography: MR imaging demonstrates focal thrombosis in the left iliac vein extending to the upper IVC. There is no thrombosis on the opposite side (49).

MRDTI can differentiate between new and old thrombosis and is also useful in the diagnosis of recurrent DVT (49,50).

Contrast venography

It is performed by the injections of iodinated contrast into tibial vein to demonstrate the entire deep vein system of the lower limb (Figure 4). This technique is invasive, expensive, and technically (the tibial vein cannot be cannulated in 5% of people) difficult. Moreover, its interpretation is difficult, and it is associated with such complications as allergic reactions to contrast and renal failure (50-56).



Figure 4. Contrast venography. Upper left vein angiography imaging shows a partial obstructive thrombosis with irregular margins and reduced contrast. This thrombosis was treated after catheter treatment (50).

Discussion

Selection among available methods for the diagnosis of deep vein thrombosis depends on the opinion of the clinician and radiologist, as well as the rules of each center. Ultrasound is usually the first choice. Preference for proximal ultrasound or whole-leg ultrasound depends on the physician.

Both ultrasound methods have a high sensitivity and specificity for the diagnosis of proximal vein

DVT. After the diagnosis, anticoagulation is required to control symptoms, prevent progression and embolization, and reduce the risk of post-thrombotic syndrome. Whole-leg ultrasound also detects isolated distal DVT which is either resolved or does not progress to proximal without any treatment. In addition, it is associated with fewer complications.

Therefore, the routine use of whole-leg ultrasound helps identify DVTs that do not necessarily need treatment. CUS of proximal vein shows uncompressed segments (thrombosis marker) in proximal veins (e.g., common femoral, femoral, and popliteal veins). The identification of proximal DVT is of utmost importance since it is more prone to progression and embolization, as compared to isolated distal DVT.

Proximal CUS is highly sensitive to proximal DVT diagnosis (over 95%) and has high negative predictive value for proximal DVT rejection in all patients and for the rejection of all DVTs (including isolated distal DVT) in patients with low PTP.

Similar to proximal CUS, the whole-leg ultrasound recognizes the proximal DVT (i.e., common femoral, femoral, and popliteal veins). Its major advantage over proximal CUS is the imaging of the leg veins (peroneal, posterior tibial, anterior tibial, and muscle veins). Consequently, its negative evaluation rejects the isolated distal DVT (i.e., total DVT) and other diagnostic tests or repeated proximal CUS are not needed.

In most patients with recurrent DVT at the same foot, referral for ultrasound (proximal or whole leg) or a similar approach to DVT is appropriate for the first time. In patients with suspected primary or recurrent DVT, CT venography (CTV) and magnetic resonance venography (MRV) are rarely used in suspicion of iliac vein thrombosis or inferior vena cava thrombosis in ultrasound. These investigations are relatively less reliable and cause adverse side effects of radiation and contrast agent, and definitely, more expensive.

Nonetheless, it can be more practical and efficient in the differentiation of new and old thrombosis may be more useful, as compared to ultrasound. Ascending contrast-enhanced venography, which has long been the gold standard for DVT diagnosis and impedance plethysmography are rarely available today and are not use

Conclusion

In patients with suspected primary or recurrent DVT, CT venography (CTV) and magnetic resonance venography (MRV) are rarely used on suspicion of iliac vein thrombosis or inferior vena cava thrombosis in ultrasound. These investigations are relatively less reliable, cause adverse side effects of

radiation and contrast agents, and are more expensive. Nevertheless, they can be more useful in the differentiation of new and old thrombosis. Ascending contrast-enhanced venography which has long been the gold standard for DVT diagnosis and impedance plethysmography are rarely available today and are not used. The results of the current study indicated that different methods are available for the diagnosis of deep vein thrombosis.

Ultrasound is seemingly the most logical method for initial examination due to sensitivity, specificity, adverse side effects, and financial costs. The selection between proximal and whole-leg ultrasound depends on physician' opinion and the approach of the medical center to the treatment of deep vein distal thrombosis.

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Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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