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Review Paper

Diagnosis of Upper Extremity Deep Vein Thrombosis: A Review

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ABSTRACT

Background and Aim: Upper extremity deep vein thrombosis (UEDVT) accounts for 1% to 4% of deep vein thrombosis (DVT) cases and can be associated with complications and mortality. This study aims to review the upper extremity DVT diagnosis methods and evaluate the sensitivity and specificity of commonly available diagnostic tests for upper extremity DVT that can be used to provide a combined diagnosis strategy.

Materials and Methods: Articles in this study, national databases, including Magiran, SID, and IranMedex, as well as international databases, including PubMed, Google Scholar, Scopus, and ISI databases, were searched for related books and articles. Keywords, including upper extremity deep vein thrombosis, thrombolysis, diagnosis, upper extremity deep vein thrombosis, thrombolysis, and diagnosis were searched and finally, 50 articles were reviewed.

Results: The accuracy of the D-dimer test for the diagnosis of UEDVT was evaluated in two studies. The sensitivity and specificity of D-dimer with a cut-off value of 500 micrograms per liter are 100% (95% confidence interval [CI], 78% to 100%), 14% (95% CI, 4% to 29%), 92% (95% CI), 73% to 99%), and 60% (95% CI, 52% to 67%). Duplex ultrasound has become the first line of diagnosis. The combined sensitivity and specificity of different ultrasound methods were, respectively, 84% (95% CI, 72% to 97%) and 94% (95% CI, 86% to 100%) for non-compression doppler ultrasound, 97% (95% CI, 90 to 100%) and 96% (95% CI, 87 to 100%) for compression ultrasound, and 91% (95% CI, 85 to 97%) and 93% (95% CI, 80 to 100%) for compression doppler ultrasound.

Conclusion: UEDVT is an increasing clinical problem and requires accurate and rapid diagnosis to prevent complications. Clinical suspicion should be confirmed by diagnostic imaging methods, such as duplex ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI). A diagnostic strategy based on sequential evaluation of clinical factors and D-dimer test can avoid imaging in about a quarter of patients. Ultrasound is widely used as a first-line imaging test and, if inconclusive, may be followed by a second ultrasound, CT venography, or magnetic resonance imaging (MRI).

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1. Introduction

Upper extremity deep vein thrombosis (UEDVT) means the formation of a blood clot in the inner wall of a deep vein, which causes blood flow disturbance and partial or complete blockage of the veins. Thrombosis in the veins of the upper extremities accounts for 1% to 4% of the total causes of deep vein thrombosis (DVT) [1]. Today, UEDVT is classified into primary UEDVT (eg, Paget-von Schrötter syndrome) and secondary UEDVT, which is most often caused by a central venous catheter (CVC), a pacemaker lead, or cancer [2]. Among these, primary thrombosis is rare, and in most cases, UEDVT is secondary and related to central vein cannulation (central line, pacemaker) or prothrombotic conditions (such as thrombophilia, and malignancy). Mortality and complications of UEDVT are similar to lower extremity DVT. Specifically, 1-, 3-, 6-, and 12-month mortality rates were at least statistically equivalent between lower extremity DVT and UEDVT. Mortality of 1, 6, and 12 months in the upper limb is estimated as 4.4%, 14.5%, and 20.3%, and in the lower limb 5.8%, 12.1%, and 14.7% [3]. In the primary type, patients are often young and in the last years of their fourth decade, and the ratio of involvement in men to women is 1:2. Most patients refer to varying degrees of neck, shoulder, or armpit discomfort, arm heaviness, and pain associated with upper limb swelling. Additionally, upper limb thrombosis may present with asymptomatic or symptomatic pulmonary embolism. Most of the deaths are related to the secondary type and are affected by the underlying condition of the patient.

While the diagnostic and therapeutic management of lower extremity (DVT) has been well established over the years, UEDVT is less well known due to its low prevalence. Nevertheless, UEDVT should not be ignored, as it accounts for approximately 5% of all DVTs [4, 5]. The prompt and accurate diagnosis followed by effective treatment of UEDVT is vital because patients may develop post-thrombotic syndrome (PTS) of an arm or pulmonary embolism (PE) [4, 6]. Diagnostic methods to identify UEDVT include D-dimer, duplex ultrasound, venography, computed tomography (CT) with contrast, and magnetic resonance imaging (MRI). The highly sensitive D-dimer is often elevated in the presence of inflammation, malignancy, and other systemic diseases and therefore it is nonspecific and requires additional testing if elevated (positive) or if the clinical probability of DVT is not low. Diagnosis of UEDVT by ultrasound is more complex due to the local anatomy of the lower extremities, particularly in the axillary and clavicular regions where vessels may be difficult to visualize and compress. A duplex ultrasound, a non-invasive and widely available technique that uses doppler technology to assess vascular flow, has become a first-line diagnostic tool [7]. Therefore, pressure ultrasound is usually used in combination with doppler ultrasound to diagnose or rule out UEDVT. Contrast venography is the diagnostic standard for UEDVT, but it is an invasive imaging test in which patients are exposed to intravenous contrast and radiation. Furthermore, because venography is no longer routinely performed, radiologists have limited experience in evaluating UEDVT with this method. In addition, CT venography may be less useful in patients with severe chronic kidney disease (e.g. stage 4) due to the need for intravenous contrast dye [7, 8]. This study aims to review the diagnostic methods of upper extremity DVT and to investigate the sensitivity and specificity of commonly available diagnostic tests for upper extremity DVT that can be used to provide a combined strategy for diagnosis.

2. Materials and Methods

This study was conducted as a review. Articles in this study, national databases, including IranMedex, SID, and Magiran as well as international databases, including PubMed, Google Scholar, Scopus, and ISI databases were searched for related books and articles. Keywords, including upper extremity deep vein thrombosis, thrombolysis, diagnosis, upper extremity deep vein thrombosis, thrombolysis, and diagnosis were searched. Relevant articles were searched simultaneously by two researchers from January to July 2019. It should be noted that only full-text articles in English and Farsi were included in the initial search (90 items). Inclusion criteria included access to the full text and all articles related to the diagnostic methods of deep vein thrombosis and the role of imaging in deep vein thrombosis (131 cases). On the other hand, the exclusion criteria included articles without available full text as well as articles whose abstracts were presented in conferences and congresses (20 cases). Of the 131 articles that were included in the study, 20 articles that were common in different databases and overlapped were left out and finally, 50 articles were examined

3. Results

Epidemiology

UEDVT (of any cause) accounts for 1% to 4% of all DVT causes [1]. Primary UEDVT is rare and has an annual incidence of 1 to 2 cases per 100000 people [1, 2,

10]. Most cases of UEDVT are secondary and related to central vein cannulation (e.g. central line, pacemaker) or prothrombotic conditions (such as thrombophilia, and malignancy) [2, 3, 9, 10]. A total of 60% to 80% of patients with primary UEDVT have a history of exercise or intense activity with a predominance of upper extremity movements before the onset of symptoms. Strenuous activities include lifting weights, rowing, or activities that involve repeated arm elevation, especially wide open arms [11, 12, 14]. The different age of manifestation is in the late 30s and the ratio of men to women is 1:2 [3]. The predominance of right-handed people explains why the axillo-subclavian vein is more involved

Clinical manifestations

Primary UEDVT can present with signs and symptoms of UEDVT or PE acutely or with chronic or intermittent symptoms. In the pediatric population, primary UEDVT occurs with similar symptoms and thrombotic complications similar to adults [13, 15, 16].

Acute symptoms

In the history of these patients, intense use of the arm before the onset of swelling and arm pain is mentioned in 40% to 80% of patients, and symptoms usually appear within 24 hours after intense activity [2, 15, 16, 17]. In most patients (70% to 80%) with varying degrees of discomfort in the neck, shoulder, or armpit, arm heaviness, and pain associated with upper limb swelling occur [18-20]. Swelling and pain often improve by resting and raising the arm at heart level, while lifting the limb above the head aggravates the symptoms [21]. In the physical examination, the predominant finding is limb edema, mainly with cyanosis of the hands and fingers. Mild degrees of fever may be found. A palpable venous cord (superficial thrombophilia) may be evident in associated superficial veins (such as the proximal cephalic vein). Subcutaneous collateral veins titled Urschel's sign in the upper chest and proximal upper limbs may be significant, especially in patients with chronic venous stenosis [11, 17, 19]. Examination of the arterial vessels of the upper limbs should be normal. Decreased arterial blood flow due to venous congestion (phlegmasia ceroladolens), which is rare in the lower limbs, is rarer in the upper limbs [22, 23], although if present, it is considered an emergency and needs treatment as soon as possible. Associated symptoms associated with pressure on the brachial plexus (ie. neurogenic thoracic outlet syndrome), with paraesthesia or pain in the ulnar nerve region, tendentiousness in the supraclavicular fossa, and internal palmar muscle atrophy may be present.

Chronic or intermittent symptoms

In patients with partial thrombosis with venous stenosis due to repeated injury that causes activity-related obstruction, symptoms may be intermittent and less severe. If the venous obstruction is prolonged, edema with pain is minimal, and Urschel's sign or increased lateral flow of chest pain may be the only symptom.

Diagnosis

The diagnosis of upper extremity venous obstruction (i.e. deep vein thrombosis or venous stenosis) is suspected in the clinical manifestations but must be confirmed by imaging, usually ultrasound. D-dimer is useful to rule out thrombosis as an etiology but does not rule out venous stenosis without thrombosis. In a patient who refers with classic symptoms, if the diagnosis of venous obstruction is confirmed, no other action is necessary except for a simple chest radiograph to identify any bone abnormality before intervention. In the absence of a specific bony abnormality, the specific structural abnormality is not identified until surgical exploration. Its most common clinical symptoms include pain, swelling, and skin discoloration. Since the diagnosis of UEDVT based on signs and symptoms alone is not reliable due to poor clinical manifestations, imaging is necessary to confirm or reject the diagnosis. To reduce the burden of imaging in all patients with clinical suspicion, UEDVT risk stratification with clinical probability assessment and D-dimer testing may be valuable to select low-risk patients in whom imaging can be withheld [5].

Clinical probability

In patients with a low clinical probability, the diagnosis of UEDVT can be ruled out with a negative D-dimer, while patients with a high clinical probability undergo an ultrasound. For patients with clinically suspected UEDVT, Constans et al. combined clinical signs with UEDVT risk factors to obtain a clinical decision score comparable to those used for lower extremity DVT [24]. This score was made in a derived group of 140 patients with suspected UEDVT, of which 50 patients (36%) objectively confirmed the diagnosis. Patients were assigned 1 point for the presence of venous material (e.g. catheter in subclavian or jugular vein or pacemaker), localized pain, or unilateral cavitary edema, while another diagnosis was considered at least as acceptable as UEDVT, 1 point reduced. The total score ranges from -1 to 3. Patients with a score of 0 or less were considered to be at low risk of UEDVT, those with a score of 1 were considered to be at moderate risk, and those with a score of 2 or more were considered to be at high risk (Table 1). These

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findings suggest that the diagnostic accuracy is not high enough to justify the use of Constans' law as an independent tool, nevertheless it can help physicians to identify high-risk patients for whom imaging is essential.

D-dimer

Since the clinical scoring system (Constans) cannot rule out the diagnosis of UEDVT alone, it should be used in conjunction with the D-dimer test. D-dimer, the minimal degradation product of fibrin, is produced by hydrolysis of the fibrinolytic protein fibrin. D-dimer has been established as a sensitive biomarker for fibrinolytic system activation [25]. D-dimer levels may be elevated in patients with UEDVT, similar to lower extremity DVT with PE. Accordingly, the determination of D-dimer levels can be effective in helping with diagnosis. Among patients with a low risk of DVT and D-dimer levels less than 0.5 mg/L, DVT can be ruled out without the need for color doppler ultrasound or other imaging tests, and unnecessary anticoagulant treatment can be avoided [26, 27, 28]. Patients with UEDVT often have abnormal D-dimer test results, but patients with cancer, old age, or indwelling catheters may also have false-positive results. Also, although plasma D-dimer above 0.5 mg/L is sensitive for thrombosis and has a high estimated value, it is not specific for the anatomical location of thrombosis and cannot rule out venous compression stenosis as a source of symptoms [28]. The accuracy of the D-dimer test for the diagnosis of UEDVT was evaluated in two studies. Merminod et al. prospectively enrolled 52 patients with suspected UEDVT; 23 people (44%) had active cancer and 18 people (35%) had fixed catheters. The sensitivity and specificity of D-dimer with a cut-off value of 500 µg/L were 100% (95% confidence interval [CI], 78% to 100%) and 14% (95% CI, 4% to 29%), respectively. Accuracy was consistent in subgroups of patients with cancer or CVC [28]. In another prospective study by Sartori et al., D-dimer testing was performed in 239 patients with suspected UEDVT, of whom 39 patients (16.3%) had active cancer and 14 (5.9%) had CVC. UEDVT was confirmed in 24 patients (10%) and superficial vein thrombosis in another 35 patients (14.6%). Using a cut-off value of 500 ng/mL, the D-dimer test had a sensitivity and specificity of 92% (95% CI, 73% to 99%) and 60% (95% CI, 52% to 67%), respectively [29] (Table 2).

These two studies show that the sensitivity of the D-dimer test is as high as in patients with suspected lower extremity DVT, making it a suitable test to rule out UEDVT in patients with low clinical suspicion and normal D-dimer concentrations. In patients with high D-dimer levels or patients with high clinical suspicion, additional imaging is necessary to confirm the diagnosis.

Imaging

As lower extremity DVT, clinical history and physical examination are essential for the diagnosis of UEDVT [30]. The D-dimer test is used to rule out thrombosis with a high negative probability (unlikely probability) [28]. Since the yield of physical examination in the diagnosis of UEDVT is very low [28], imaging techniques should be used. While venography used to be considered the diagnostic gold standard, nowadays, it is rarely used because it is time-consuming, exposes patients to ionizing radiation, and requires the use of intravenous contrast with the potential for renal complications and allergic reactions. Due to these disadvantages, ultrasound has replaced venography as the preferred imaging method [31]. The diagnosis of UEDVT is confirmed by the presence of an intraluminal thrombus, venous flow abnormalities, or incompressibility of a venous segment.

Ultrasound

Ultrasound (B-mode ultrasound, color doppler ultrasound, and duplex ultrasound) is widely used in the diagnosis of deep vein occlusion. Because it is simple, available, non-invasive, and reliable without radiation or injection of nephrotoxic contrast agents, we use ultrasound as a primary test in the diagnosis of upper limb venous obstruction because it is non-invasive and cheap, and in observational studies, it has acceptable sensitivity and specificity in diagnosing UEDVT [32, 33].

In studies, several ultrasound methods, including pressure ultrasound, Doppler, and pressure doppler ultrasound have been evaluated in people suspected of UEDVT [32]. The diagnostic and screening performance of ultrasound is high, with accuracy that appears to be best when pressure ultrasound is used alone or in combination with Doppler. In a systematic review of eleven studies that compared different methods of ultrasound with venography, the combined sensitivity and specificity were 84% (95% CI, 72% to 97%) and 94% (95% CI, 86% to 100%), respectively, for an ultrasound of non-compression Doppler, 97% (95% CI, 90 to 100%) and 96% (95% CI, 87 to 100%) for pressure ultrasound, and 91% (95% CI, 85 to 97%) and 93% (95% CI, 80 to 100%) was for pressure doppler ultrasound [32] (Table 3). These results should be interpreted with caution because the included studies were small and had poor methodological quality, limiting the validity and generalizability of the findings. Furthermore, these comparisons in ultrasound methods may have limited relevance in clinical practice where both doppler and pressure ultrasound are often used simultaneously during the examination. Evaluation of UEDVT

Table 1. Clinical scoring

Symptoms	Score
Venous materials including subclavian or jugular vein catheters or local pacemakers	+1
Local pain	+1
One-sided edema	+1
Other diagnoses are at least as reliable	-1
Score ≤1: Unlikely UEDVT Score ≥2: Probable UEDVT	
UEDVT risk	Total Score
Low risk	<0
Moderate risk	1
High risk	2<

*Advanced imaging is necessary in case of clinical suspicion to determine abnormal venous pressure.

can be performed by B-mode ultrasound with compression and by assessment of venous flow using doppler or color doppler for central veins that are not under direct pressure. Non-compressibility of the vein on B-mode ultrasound with or without intraluminal thrombosis is the main criterion in the diagnosis of venous thrombosis. On B-mode imaging, acute thrombus may appear as areas of variable echogenicity in the vessel lumen. The non-compressibility of a venous segment indicates the presence of DVT [33]. Pressure ultrasound is performed by applying pressure to the covering tissues to compress the vein observed in the transverse plane. Veins should easily collapse under applied pressure, while failure to collapse as expected indicates thrombosis. Because this technique requires direct manual compression, it cannot be used to evaluate the centrally located brachiocephalic vein and the superior vena cava (SVC), as well as the internal portion of the subclavian vein below the bony clavicle [33]. The absence of flow, especially in a vein that cannot be pressurized, indicates DVT. Venous blood flow can be assessed by doppler ultrasound and color doppler flow [34, 7]. Despite the mentioned advantages and features of ultrasound, it has several disadvantages. The interpretation of ultrasound depends on the operator; therefore, an inexperienced operator may miss the correct diagnosis, in addition, the invisibility of mural thrombi and proximal subclavian thrombi or innominate veins due to shadowing of the clavicle and sternum can be mentioned [32, 33].

Contrast venography

The gold standard for diagnosing UEDVT is contrast venography, which images the entire deep venous system of the arm. Unfortunately, venography is invasive, it is difficult to perform and interpret, inconvenient for patients and may cause allergic reactions and thrombosis associated with contrast dye, hence it is not our first choice in imaging, and ultrasound is often preferred as a cheaper and available alternative [7]. Therefore, contrast venography is widely considered for use when initial noninvasive imaging results (such as ultrasound) are insufficient to reach a diagnostic conclusion or are technically inadequate, or when ultrasound is negative for DVT but high clinical doubt exists for DVT.

Contrast venography images the thoracic outlet veins and can be used to confirm the diagnosis of thoracic outlet stenosis and plan possible interventional treatment [10]. In patients with chronic or intermittent symptoms,

Table 2. Sensitivity and specificity of combined D-dimer for the diagnosis of upper extremity deep vein thrombosis

Study	D-dimer Test	Specificity (95% CI)	Sensitivity (95% CI)	Cut-off Values
Sartori et al. [25]	STA liatest	0.600(0.533-0.663)	0.917(0.721-0.979)	500 ng/mL
Meriminod et al. [24]	VIDAS	0.145(0.064-0.295)	0.969(0.650-0.998)	500 ng/mL

Table 3. Evaluation of sensitivity and specificity of diagnostic imaging tests for upper extremity deep vein thrombosis

Study	Modality	Sensitivity	Specificity	Reference Modality
Di Nisio et al. [28]	Pressure ultrasound	97%	96%	Most contrast venography
	Doppler ultrasound without compression	84%	94%	
	Pressure doppler ultrasound	91%	93%	
Baarslag et al. [39]	Time-of-fligh	71%	89%	
	Gadolinium-enhanced	50%	80%	

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the external pressure of the vein is determined by venography and dynamic examinations by placing the arm in different positions during the study. A venogram may be abnormal at rest and with arm abduction of varying degrees of venous compression with "new" collateral veins, although venous compression with arm abduction may be a normal finding [35].

Computed tomography (CT) venography

Less invasive modalities include CT venography and magnetic resonance (MR) [36-38]. These tools are usually not used for the initial diagnosis of upper limb venous obstruction. However, in the setting of aseptic symptoms or ultrasound obscurity, these tools offer non-invasive methods to evaluate the central veins and surrounding structures. These studies are also useful for diagnosing other secondary causes of deep vein thrombosis (such as a tumor) [39]. Currently, CT venography has no role in the routine diagnostic process for suspected UEDVT. The main reasons for this are the use of radiation and iodinated contrast materials and relatively high costs compared to ultrasound. However, due to the use of multi-detector CT equipment in which coronal and sagittal slice correction and 3D reconstruction are possible, it may play a more crucial role in the evaluation of UEDVT [40, 41].

CT venography is performed by imaging the veins during the equilibrium phase of contrast injection. CT venography has not been adequately studied in terms of sensitivity and specificity, and there is limited information on its use in the upper limb. A small study on 18 patients compared CT venography and digital subtraction venography in terms of the ability to detect the severity of venous occlusion, the cause of UEDVT, and the possibility of treatment. CT venography provides more information than digital subtraction venography and in half of the patients, CT venography findings have changed the treatment plan [36]. Larger prospective comparative studies should be conducted to accurately assess the possible role of CT in the diagnosis of patients with suspected UEDVT.

Magnetic resonance imaging (MRI)

MRI does not expose the patient to ionizing radiation and can be a useful option in the diagnosis of UEDVT. MRI was evaluated in a study in which two techniques, time-of-flight and gadolinium-enhanced three-dimensional (3D) MR venography were used [42]. Of 31 eligible patients with suspected UEDVT, MRI was not performed in 10 for various reasons (inability to lie down, claustrophobia, too large for MR scanner, presence of osteosynthesis, or pacemaker). Overall sensitivity and specificity were poor for both MRI modalities, 71% and 89% for time-of-flight, and 50% and 80% for gadolinium-enhanced three-dimensional (3D), compared to contrast venography (Table 3).

Another remarkable MR-based technique can directly image the clot without the need for intravenous contrast. Direct thrombus imaging is based on the principle that the blood signal changes over time as the blood clots and is moderated by the production of methaemoglobin. Methemoglobin decreases T1 and increases the signal on a T1-weighted sequence. This technique is particularly sensitive to newly formed thrombi, which can help distinguish between old and new clots [43]. Early studies have used this technique for lower extremity thrombosis [44], and it can be concluded that this sequence works equally well in the upper extremity. Recently, a study with direct MRI thrombus imaging was completed in 63 subjects with suspected UEDVT and its results are being evaluated and have the potential as an alternative tool in the future in the diagnostic management of UEDVT [45].

Although MRI can be a valuable modality for the diagnosis of UEDVT, it is unlikely to become a first-line imaging test because it is expensive, not widely available,

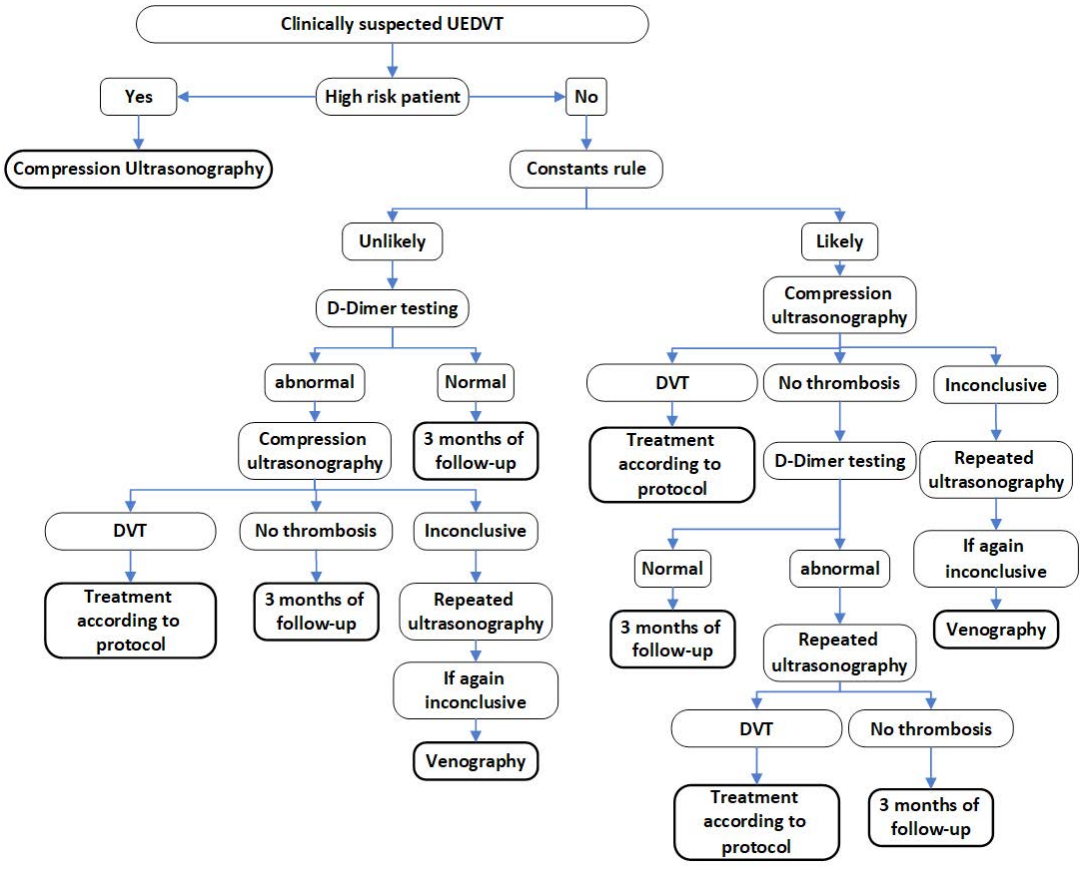

Figure 1. Diagnostic algorithm for upper extremity deep vein thrombosis based on the Armor study

*High-risk patients: Patients with a clinical score greater than or equal to 2, such as patients with malignancy, central venous catheter or pacemaker, hospitalized or elderly patients (over 75 years old).

time-consuming, and unsuitable for patients with claustrophobia or carrying internal devices, such as pacemakers. However, it can be useful in patients in whom ultrasound remains useless after repeated measurements or in cases where there is doubt about the diagnosis in patients with previous UEDVT.

Diagnostic algorithm

In patients with suspected lower extremity DVT or PE, the diagnostic approach is well established and includes the sequential use of a clinical decision rule, D-dimer test, and imaging [46]. A similar algorithm was prospectively evaluated in the multinational ARMOR study, which evaluated the safety and efficacy of sequential use of Constans' law, D-dimer test, and pressure doppler ultrasound in a large group of inpatients and outpatients with suspected UEDVT [47] (Figure 1). The clinical probability of UEDVT in all patients was assessed by the Constans score, which was divided by combining low and moderate clinical probability categories. UEDVT was considered "unlikely" in patients with a score of 1 or less and "probable" in patients with a score of 2 or more (Table 1).

In patients classified as "unlikely UEDVT", D-dimer was measured and if normal, UEDVT was ruled out. Patients with abnormal D-dimer levels were referred for pressure ultrasound, which was repeated after 3 to 5 days if no result was obtained. Patients with the status of "probable UEDVT" were directly subjected to ultrasound and, if normal, the subsequent D-dimer test was performed. Normal D-dimer levels were considered to rule out UEDVT, while abnormal values or inconclusive ultrasound were an indication for repeat ultrasound after 3 to 5 days. Venography or CT venography was mandatory for those with inconclusive serial ultrasound. All patients in whom UEDVT was excluded by the diagnostic algorithm had a 3-month follow-up for symptomatic venous thromboembolic events.

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This study included 406 patients, of whom 137 patients (34%) had active cancer and 92(23%) had a CVC or pacemaker. UEDVT was diagnosed in 103 patients (25% prevalence). The diagnostic algorithm ruled out UEDVT based on "unlikely" UEDVT on clinical scoring and normal D-dimer level in 87 patients (21%) in which anticoagulant therapy was discontinued without further imaging. None of these patients had venous thromboembolism during the 3-month follow-up. Among all patients excluded by the UEDVT strategy, one case of UEDVT developed during the 3-month follow-up, corresponding to a failure rate of 0.4% (95% CI, 0 to 2.2). This upper limit of the 95% CI was below the pre-defined safety threshold of 3%, indicating that this diagnostic algorithm could safely rule out UEDVT without additional imaging. As a result, unnecessary imaging in one-fifth of patients compared to a strategy using ultrasound in all unclassified patients with clinical probability and D-dimer was avoided [48].

Differential diagnoses

Differential diagnoses of upper extremity edema unrelated to primary UEDVT include edema related to other etiologies, secondary causes of thrombosis, and lymphedema. Primary UEDVT is distinguished by secondary causes, such as the absence of venous manipulation, the patient being young and healthy, and the sudden onset of symptoms. The clinical features of UEDVT are similar in other ways and include pain and swelling of the limb and cyanosis of the skin due to venous congestion for venous thrombosis (such as oral contraceptives), it raises the concern of a hidden malignancy. Up to 25% of patients are diagnosed with thromboembolism in the first year [20, 49]. If the primary cause for UEDVT is not evident in imaging studies, no history of venous manipulation, and no risk factors from the above for thrombosis, we propose a more serious laboratory evaluation to rule out secondary causes of thrombosis, such as a coagulation profile that should be performed before starting anticoagulation. Patients with venous thrombosis due to structural pressure of the thoracic outlet may show signs of the passage of neurological and arterial structures in this space. Many causes of limb swelling are irrelevant to pulmonary obstruction. Clinical history usually gives a clue to finding the source of swelling (such as a history of heart failure). Although systemic etiologies usually manifest as bilateral limb swelling, this feature does not help in diagnosis, because thoracic outlet disorders are common and symptoms appear in patients with primary bilateral UEDVT. Critical routine tests in the clinic in evaluating patients with limb edema include complete blood count, electrolytes, and liver function. These tests may point to other causes of upper limb swelling. Swelling of the upper limb can be caused by lymphedema, although the swelling caused by acute venous thrombosis has a sudden onset and does not have the risk of predisposing factors, such as previous axillary lymph node dissection.

4. Conclusion

UEDVT is an increasing clinical problem and requires accurate and prompt diagnosis to prevent complications, such as recurrence, PTS, and PE. A diagnostic strategy based on sequential evaluation of clinical factors and D-dimer test can avoid imaging in about a quarter of patients. When imaging is required, ultrasound is widely used as the first-line imaging test and, if inconclusive, it can be followed by a second ultrasound, CT venography, or MRI. For clinical decision-making, the prevalence or clinical probability (based on clinical scoring) of DVT in a population, along with estimates of sensitivity and specificity, affect how patients are managed. Future research and studies are needed to continue to identify safe and cost-effective diagnostic strategies.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors contributed equally to preparing this study.

Conflict of interest

The authors declared no conflict of interest.

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