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υπό

ΜΙΧΑ ΒΑΣΙΛΕΙΟΥ

Ειδικευόμενου Ιατρού Ακτινολογίας

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»

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Τίτλος εργασίας στα αγγλικά: MULTIPARAMETRIC ULTRASOUND FOR THE EVALUATION OF LOWER LIMB DEEP VENOUS THROMBOSIS

TABLE OF CONTENTS

ΠΕΡΙΛΗΨΗ

Στόχος. Η υπερηχογραφική εξέταση θεωρείται βασικό μέρος της διαχείρισης της εν τω βάθει φλεβικής θρόμβωσης των κάτω άκρων (ΕΒΦΘ). Η εργασία αποτελεί μία βιβλιογραφική ανασκόπηση με στόχο να τονίσει τη σημασία των διάφορων διαθέσιμων υπερηχογραφικών τεχνικών (πολυπαραμετρικού υπερήχου) στη διάγνωση της ΕΒΦΘ των κάτω άκρων, στον καθορισμό της χρονιότητας του θρόμβου και να αναδείξει σημεία που χρειάζονται περαιτέρω μελέτες ώστε να εξαχθούν ασφαλή συμπεράσματα.

Μεθοδολογία. Πραγματοποιήθηκε βιβλιογραφική ανασκόπηση στην ηλεκτρονική βάση δεδομένων PubMed, χρησιμοποιώντας συγκεκριμένα κριτήρια και λέξεις-κλειδιά. Τα αποτελέσματα και συμπεράσματα των μελετών που συμπεριλήφθηκαν, περιεγράφηκαν και υπογραμμίστηκαν στην εργασία.

Αποτελέσματα. Συμπεριλήφθηκαν συνολικά 9 μελέτες. Δύο μετα-αναλύσεις για τις δοκιμασίες πιέσεως (CUS) έδειξαν ότι η εγγύς (κοινή, επιπολής μηριαία και ιγνυακή φλέβα) επαναληπτική και ολόκληρου-άκρου υπερηχογραφία είχαν υψηλότερο ποσοστό θετικών αποτελεσμάτων σε σύγκριση με την μη-επαναληπτική εγγύς υπερηχογραφία. Οι συγκεντρωτικές εκτιμήσεις της ευαισθησίας και ειδικότητας της εγγύς υπερηχογραφίας ήταν 90,1% και 98,5% αντίστοιχα, της ολόκληρου-άκρου 94% και 97,3% και της επαναληπτικής υπερηχογραφίας 97,9% και 99,8% αντίστοιχα. Μια μετα-ανάλυση ανέδειξε ότι το color-doppler για την ΕΒΦΘ είχε ευαισθησία 58% και ειδικότητα 96%. Τρεις μελέτες σχετικά με το spectral-doppler έδειξαν ότι 8 από 37 ασθενείς με μονοφασική ροή στην κοινή μηριαία και 47 από 124 ασθενείς με μονοφασική ροή στην επιπολής μηριαία φλέβα είχαν ΕΒΦΘ. Παθολογική κυματομορφή παρατηρήθηκε στη μηριαία φλέβα μετά από περιφερική συμπίεση σε 18/28 ασθενείς με ΕΒΦΘ. Για την υπερηχογραφία με ηχοενισχυτική ουσία(CEUS) και power-doppler, δύο μελέτες τόνισαν την ικανότητά τους στη βελτίωση των ποσοστών διάγνωσης της ΕΒΦΘ. Μια συστηματική ανασκόπηση για την ελαστογραφία διαπίστωσε ότι η σκλήρυνση του θρόμβου αυξάνεται με την χρονιότητα.

Συμπέρασμα. Πολλές τεχνικές υπερήχων είναι διαθέσιμες, μερικές από αυτές δυνητικά ικανές να βελτιώσουν την διαγνωστική αξιολόγηση της ΕΒΦΘ (CUS, color/spectral-doppler, CEUS) και να προσδιορίσουν την ηλικία των θρόμβων (ελαστογραφία) όπως υποδεικνύεται από την παρούσα έρευνά. Ωστόσο, απαιτείται περαιτέρω μελέτη για την επιβεβαίωση των αποτελεσμάτων.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ– Υπερηχογραφία, εν τω βάθει φλεβική θρόμβωση, ελαστογραφία, υπερηχογραφία με ηχοενισχυτική ουσία, κάτω άκρα

ABSTRACT

Objectives. Ultrasonography(US) is considered a substantial part of the work up of lower limb deep venous thrombosis(DVT). This paper consists of a literature review targeting to highlight the role of the various ultrasound techniques available, also referred to as multiparametric US, in diagnosis of lower limb DVT and the determination of thrombus chronicity, in addition to give prominence to domains that need further research for valid deductions.

Material and methods. A literature review via the electronic PubMed database was conducted using specific criteria and keywords. The results and conclusions of the included studies were reported and emphasized in this paper.

Results. In total 9 studies were included. Two meta-analyses related to compression ultrasonography(CUS) showed that serial limited and whole-leg CUS had higher proportion of positive results compared to single limited CUS. Pooled estimates for sensitivity and specificity of proximal CUS were 90,1% and 98,5% respectively, of whole-leg US 94% and 97,3% respectively and of serial US 97,9% and 99,8% correspondingly. A meta-analysis showed that color-doppler technique for DVT had a pooled sensitivity of 58% and a specificity of 96%. Three studies regarding spectral-doppler showed that 8 out of 37 patients with monophasic flow in the common femoral vein and 47 out of 124 cases with monophasic flow in the femoral vein(FV) had proximal DVT, while abnormal spectral waveform in SFV after augmentation was observed in 18/28 DVT cases. Regarding contrast enhanced US(CEUS) and power-doppler, two studies emphasized their capability in improving DVT diagnostic rates. A systematic review concerning elastography designated that thrombus stiffness increases with age progression.

Conclusion. Many US techniques are available, some of them potentially capable of improving current diagnostic assessment of DVT (CUS, color/spectral-doppler,

CEUS) and others of determining thrombus age (elastography) as indicated by our research. Still, more intensive research is needed to corroborate these results.

Keywords- Ultrasound, deep venous thrombosis, elastography, contrast enhanced ultrasound, lower limbs

1. INTRODUCTION

Lower limb deep venous thrombosis (DVT) is a serious and potentially fatal disease with an incidence of 1 in 1000 each year (1). If left untreated or unsuccessfully counteracted, it can lead to high-risk complications such as pulmonary embolism, or others significantly deteriorating the quality of life, such as the development of post thrombotic syndrome (PTS) or venous ulcerations. Lower limb DVT can develop in either the proximal veins (iliac, common femoral, superficial femoral, popliteal), thereby amplifying the risk of complications, or in the distal calf veins (2). The latter is a more challenging entity to diagnose in terms of imaging approach, particularly considering the increased possibility of anatomical variations, but bears a diminished possibility of complications to occur, unless the thrombus propagates and extends to the proximal deep veins (3). Key risk factors include malignancy, prolonged immobilization (for at least 3 days), trauma, surgery, obesity, systemic inflammation or infection, estrogen intake, pregnancy, recent hospitalization, antiphospholipid syndrome, non 0 blood type and genetic thrombophilia (factor V Leiden homozygote or heterozygote, protein C or S or antithrombin deficiency), whilst some cases are considered unprovoked/idiopathic. Virchow’s triad (flow stasis, vein wall injury and hypercoagulability) is considered the cornerstone of the pathophysiology mechanisms of venous thrombosis (4).

Suspected cases of DVT primarily undergo a meticulous diagnostic workup including clinical examination, blood serum analysis and imaging evaluation. Optimal diagnostic procedures are requisites for the minimization on the one hand of false negative results, which can lead to devastating implications, and on the other hand of false positive results which will lead to unnecessary anticoagulant medical therapy, thereby augmenting the risk of bleeding complications and increasing health costs and patient's anxiousness (5). On admission, patients can present with an edematous, extremely painful, warm, red and swollen leg, especially if thrombosis occurs proximally as calf veins thrombosis can sometimes be asymptomatic (2). Well's Score is a validated useful tool with high validity for clinical assessment of patients with suspected DVT (6). Differential diagnosis can be broad; including conditions like cellulitis, lymphedema, complicated baker's cyst and chronic venous insufficiency. Based on patients' history, clinical evaluation and pre-test probability assessment for DVT using validated scores like Well's score, a D-dimers test and/or imaging workup are usually recommended (6).

D-dimers test, which measures degraded fibrinogen values in blood, is a non-specific blood serum biomarker test with a high sensitivity for DVT. Although different diagnosis such as cancer, infection and trauma may also raise D-dimers blood value, raised levels still yield a strong suspicion for DVT in the presence of even low level of clinical evidence. A negative D-dimer test can safely rule out DVT in cases with a low level of clinical evidence, but it is not accurate enough in patients with a strong pre-test probability where further diagnostic imaging is imperative (2).

Venography has long been deemed the gold standard for the diagnosis of DVT, albeit several shortcomings limit its role (4,7). Conventional venography uses ionizing radiation and is a highly invasive technique with an increased risk of complications, while CT angiography involves ionizing radiation and iodinated contrast enhancing agent. Although MR angiography does not suffer from these disadvantages it is limited by its high cost, low availability and long examination time (4).

US examination combined with clinical evaluation and patient's history, constitutes an invaluable method for the diagnosis of lower limb DVT (6). US is a non-invasive, well tolerated, cost effective, portable, time saving and reproducible technique for the diagnosis of lower limb DVT (8). The term multiparametric US includes various techniques available such as B-mode, color/power or pulsed wave doppler, non-doppler flow visualization US techniques such as b-flow or Superb Microvascular Imaging (SMI), elastography and contrast enhanced sonography (CEUS) (8). In B-mode CUS, acute thrombosis appears as echogenic or hypoechoic material inside the lumen of an enlarged and non-compressible vein, either completely occlusive or not (9) (Fig. 1.). Doppler or non doppler flow US techniques can visualize the blood flow inside the veins, thus discriminating between patent lumen and thrombus (Fig. 2.), while elastography estimates qualitatively and quantitatively tissue stiffness by interpreting acoustic energy interaction between tissue and probe and can potentially evaluate thrombus stiffness (9,10). As thrombus stiffness is suggested to increase with age, this fact may help infer exact thrombus age – a valuable parameter for the selection of the appropriate treatment (11). Regarding pulsed wave doppler mode, a monophasic waveform suggests a proximal venous occlusion, whereas a waveform that does not alter in augmentation indicates a peripheral venous occlusion located somewhere between the venous segment examined and the venous segment squeezed. In non-occlusive cases of DVT however, spectral doppler may demonstrate normal phasic waveforms (12–14). CEUS uses an inert intravascular contrast agent (microbubbles of gas) to augment US signal (Fig 3,4.). Its use has been validated so far for the examination of liver, kidneys and breast among other organs, primarily to characterize and stage tumors (15). Its significance in DVT diagnosis is assumed based on previous studies suggesting this technique improves visualization of distal deep veins, an asset especially in obese patients or extremely edematous limbs, where conventional US may be inferior (16,17).

Different CUS protocols have been developed for the examination of suspected cases of DVT. Some institutions prefer a limited CUS protocol, serial (repeated in 5 to 7 days) or not, which embodies evaluation of common femoral, superficial femoral and popliteal veins, while others adopt a whole-leg evaluation approach (3). The Society of Radiologists in Ultrasound (SRU) has recommended that a whole-leg CUS combined with color and spectral doppler (CDUS) should be the preferred diagnostic protocol for suspected DVT. In the case of a negative limited CUS result, whole-leg CDUS in 5 to 7 days is suggested for the safe exclusion of DVT (18). The patient lies in a supine position and lower limb deep veins are scanned, using a linear high frequency probe, in a transverse plane starting from the common femoral vein above the level of saphenofemoral junction and moving distally while compression technique is performed with intervals of 2 cm. Spectral and color doppler images of both the right and the left common femoral and popliteal veins are obtained in longitudinal planes to compare the symmetry between them. Along with the evaluation of veins, notice of any other pathology involving adjacent muscles and soft tissues is important, as symptoms resembling DVT may derive from different pathological conditions (9,18). It is deduced that CDUS can be a challenging and time-consuming examination, especially when evaluating calf veins in swollen legs, requiring a skilled and experienced sonographer and advanced US machinery. Thus, the feasibility of CDUS is not always assured, so in this setting, a limited protocol which includes CUS from the common femoral vein till the popliteal vein is recommended (18,19).

Apart from the prompt and valid diagnosis of DVT, a significant parameter capable of making the difference in the management of these patients is the ability to correctly evaluate thrombus age. This is due to the various treatment methods available nowadays besides anticoagulant medication, such as catheter directed thrombolysis (CDT), or catheter directed mechanical thrombectomy or combination of them, surgical thrombectomy or compression therapy (20–25).Each one of them including the different phases of anticoagulant therapy administered in DVT cases, have specific time spans that benefit the patient by dissolving the thrombus when administered. For example, CDT in UK and USA is indicated only within the first fourteen days after DVT incidence currently (10). Thus, knowledge of the exact thrombus age can help physicians chose the appropriate treatment, maximizing their beneficial effect and minimizing potential adverse effects (10).

2. AIM

Given the magnitude of the prompt and valid diagnosis of acute DVT and the importance of thrombus age estimation in the selection of the appropriate treatment strategy, a review of the literature was conducted regarding the role of multiparametric US, as it is considered a pivotal part of DVT investigation. Specifically, our research targets to identify the test accuracy of CUS, color/power/pulsed wave doppler, b-flow, MVI and CEUS for the diagnosis of lower limb DVT, as well as the ability of elastography to confidently assess the age of thrombus.

3. MATERIAL AND METHODS

3.1. Search Strategy

An in-depth literature review was performed via the electronic database of PubMed, using specific keywords and filters. An advanced search inserting the following combination of keywords with the intended Boolean operator in the query box was conducted: (CEUS) OR (contrast enhanced ultrasound) OR (waveform) OR (power doppler) OR (b-flow) OR (spectral doppler) OR (pulsed wave doppler) AND (deep vein thrombosis) AND (lower limbs)/ (spectral doppler sonography) AND (deep vein thrombosis) AND (proximal venous obstruction)/ (contrast ultrasound) AND (calf vein thrombosis)/ (Superb microvascular imaging) AND (ultrasound) AND (deep vein thrombosis) without adding any filters. With the implementation of additional filters like publication date within the last five years and article type selection of systematic reviews and meta- analysis, the following combination of keywords were introduced: (Ultrasound) OR (diagnostic imaging) OR (color doppler) AND (deep vein thrombosis) AND (Lower limbs). Furthermore, the keywords (Elastography) AND (deep vein thrombosis) including article type selection of systematic reviews and meta- analysis as a filter, was utilized as well.

3.2. Inclusion and Exclusion Criteria

According to our strategy, studies examining and reporting the test accuracy of the various US techniques available for the diagnosis of DVT and for the determination of thrombus chronicity were enrolled. Patients in the included studies were mainly adult women and men, symptomatic or not, excluding pregnant women and children or infants, since we wanted to examine the general population, without incorporating any specific target groups. All peer-reviewed publications not written in English language were excluded, as well as any experimental studies, posters or oral publications at scientific conferences, individual case reports, expert opinion and background information articles. Moreover, any type of study incorporating outcomes, different diagnostic imaging methods, treatment and thromboembolic data statistical processing, comparing and displaying were excluded, as well as studies embodying exclusively point of care CUS in critically ill patients, due to suspected increased risk of bias. Due to the excessive existing literature regarding the role of B- Mode CUS and color doppler US in DVT diagnosis and the rapid technologic evolution of US machines in recent years, we limited our search in relative systematic reviews and meta-analyses published within the last 5 years concerning these two US techniques. Our assessment was that overabundant studies published many years ago using inferior technologic level of US machines in comparison with nowadays, would not contribute much to the topic or even provide non representative results. Concerning the contribution of elastography in thrombus assess, all existing research studies eligible for inclusion, are incorporated in a systematic review published in 2023.

3.3. Information Extraction and Processing

A rigorous overview of the results was conducted by checking title and abstract relativity with the topic. Only relative prospective and retrospective studies, as well as systematic reviews and meta-analysis were selected for further evaluation. After careful review, all studies fulfilling the aforementioned criteria in "Inclusion and Exclusion Criteria" section were included. Additionally, all the references of the included studies were thoroughly examined for possible eligibility. Data extracted, processed and displayed from eligible studies, comprises of publication date, first author name, type of research article, title, search strategy, information about included participants (total number - n, demographics and clinical condition), diagnostic procedure followed, examination of reference if existed, inclusion and exclusion criteria, risk of bias assessment, possible limitations, rates of diagnostic test accuracy of available US techniques (for example sensitivity and specificity), definition of thrombus age phases and concomitant inferences mentioned.

4. RESULTS

Using the aforementioned combinations of keywords and filters in 3.1 "Search Strategy" section, a total of 354 results were retrieved. After a thorough overview of article titles and abstracts, all duplicates were removed. Also, all articles not relevant with the topic of interest, or generally not fulfilling the defined criteria mentioned in 3.2. "Inclusion and Exclusion Criteria" section were excluded. Finally, after a thorough analysis, a total of 9 studies were included in our research. All 9 studies were available to us on full text mode, except one pertaining to power doppler US technique which was only available on abstract format. A brief summary of the included studies is presented on Table 1. Two out of nine eligible studies were meta-analyses refereeing to B- Mode CUS, one was a meta- analysis refereeing to color doppler US technique, one was a systematic review concerning elastography technique, two retrospective studies and one prospective study refereeing to pulsed wave doppler, one prospective study regarding CEUS and one prospective study concerning power doppler US technique. A flow chart describing our search method is shown in Fig. 5. B- Mode CUS and color doppler US techniques for the diagnosis of lower limb DVT have been extensively reported in the literature so far, thus studies published only within the last five years referring to these two US techniques were included. In terms of the other sought out US techniques, as far as we are aware after our rigorous research, to the best of our knowledge, there is not adequate literature research published available so far, especially for CEUS, power doppler, b-Flow and SMI techniques, so no additional time- limiting filters were added.

4.1. B- Mode CUS

4.1.1. Data Selection

B- mode CUS has long been considered the mainstay of diagnostic workup of lower limb DVT (26). As so, it is not surprising that many research articles about this US technique for the investigation of DVT have been published so far. Thus, we confined our search for B-Mode CUS using the filter of article type selection of systematic reviews and meta- analysis and the keywords (Diagnostic imaging) OR (Ultrasound) AND (Deep vein thrombosis) AND (Lower limbs), in an attempt to precisely investigate in depth the topic. Moreover, the implementation of temporal filter of publication date within the last 5 years, was an attempt to ensure a decreased risk of bias that would potentially originate from older publications that possibly used inferior technologic level of US machines with inferior spatial resolution. A total of 16 results were acquired for B-Mode CUS, from which 6 records were distinguished for full text analysis after the discard of duplicates and non-relevant articles by title and abstract overview. After full text preview of the 6 records, 4 were excluded due to ineligibility control and 2 meta- analyses were finally included.

4.1.2. Included CUS studies

A 2019 meta- analysis conducted by Meha Bhatt et all, estimated the diagnostic accuracy of 3 CUS techniques (proximal CUS – 4036 participants, whole- leg CUS – 1725 participants and serial CUS – 2415 participants) for the diagnosis of lower limb DVT (first episode or recurrent). The term serial US includes an initial negative CUS examination, followed by a repeat CUS examination and the whole diagnostic strategy is termed as serial US. By searching Embase, Medline and Cochrane Central registries and reference lists of eligible studies, without temporal and lingual limitations, authors came to a conclusion of pooled estimates for first DVT episode of 90,1 % for sensitivity, 98,5 % for specificity concerning proximal CUS, 94 % for sensitivity and 97,3 % for specificity concerning whole- leg CUS and 97,9% for sensitivity and 99,8 % for specificity regarding serial CUS. Overall, all three CUS techniques showed high levels of sensitivity and specificity, of whom serial CUS showed the highest of all. A total of 43 studies were included containing mostly adults, inpatients or outpatients, with a suspected first episode or recurrent episode of DVT. There was exclusion of asymptomatic patients or pregnant women, or patients suffering only from superficial thrombophlebitis. Studies with a small sample size were excluded as well due to increased concern of effectively determining test accuracy rates. Furthermore, studies focusing solely on calf DVT were excluded. Clinical follow-up and/or venography were the reference standards to establish the diagnosis. According to the authors, the organized and systematic methodology of study identification and selection, the absence of linguistic limitations and the identification of bias sources were the upsides of their project, whereas not defining whether doppler US techniques were utilized alongside CUS was a demerit.

A meta- analysis published in 2020 by Kraaijpoel et all, compared the accuracy tests of single limited CUS, serial limited CUS and whole- leg CUS for lower limb DVT diagnosis. Authors searched Medline, Central and Embase from 1989 up until 2019 for eligible studies. After discarding all duplicates, non-relevant and non-eligible studies, they came up with 40 studies (36 out of 40 were prospective and 4 out of 40 studies were retrospective studies) incorporating 21,250 participants. Eligible studies were those written in English, Dutch, Spanish, French, German and Italian language encompassing adult population (mean age of 60 years old, exclusion of studies encompassing participants younger than 18 years old), inpatients or outpatients, in whom lower limb DVT was suspected, based on pre- test probability assessment and/or D- dimer test. The reference standard diagnostic test was clinical follow up for a period of three months (except one study in whom the time period of follow up was six months) and venography. 27 out of 40 studies used clinical follow up, while the rest 13 studies used venography as a reference standard. The risk of bias was considered to be low in all included studies, an important asset. Regarding the 3 CUS techniques examined, single limited CUS was examined in 16 studies, serial limited CUS was assessed in 10 studies and whole-leg single CUS was evaluated in 19 studies. Prevalence of DVT among included studies ranged from 2,8 % to 59 %, with a median value of 25 %. Results revealed a similar rate of thromboembolic incidents after a negative single limited CUS, a negative serial limited CUS and a negative whole-leg CUS (1.4 %, 1.9 % and 1.0 % respectively). Moreover, the rates of positive results were higher with whole-leg CUS and serial limited CUS, than those with single limited CUS and they were similar between serial limited CUS and whole-leg CUS. However, due to a lower level of DVT prevalence in the single limited CUS group, these results are questionable, as it is hypothesized that in a potential group with a higher prevalence of DVT, negative result rates of single limited CUS could have been higher and positive results could have been lower.

4.2. Color doppler US

4.2.1. Data Selection

Color doppler US is not a novel technique. It is long considered a complementary tool for DVT diagnosis as it depicts blood flow inside patent venous lumen and absence of flow in case of thrombus existence (Fig. 6.). We inserted the following combination of keywords for literature search of this technique: (Color doppler) AND (Deep vein thrombosis) AND (lower limbs) with the addition of the temporal filter of publication date within the last 5 years and the filter of article type selection of systematic reviews and meta- analyses, in an attempt to confine our search on account of abundant literature research existence and the concern about possible technologic outdated US machines included in older published studies that would increase bias risk and lower the applicability of our findings to current technology. Only 1 result (a meta-analysis) was identified that fulfilled the relevance and eligibility criteria and it was included in our study.

4.2.2. Included Color Doppler Study

A meta-analysis published in 2019 by Yuhong Zhang et all, assessed the pooled estimates of sensitivity and specificity of pure color doppler US technique and the pooled sensitivity and specificity estimates of the combination of color doppler and CUS techniques in suspected asymptomatic DVT cases. Authors screened PubMed, Cochrane, Ovid and Web of Science databases for relevant and eligible articles without any lingual or temporal restrictions. Venography was defined as the reference standard. 14 studies examining color doppler technique yielded a pooled sensitivity of 58 % and a pooled specificity of 96 %, whereas pooled estimates for the combination of color doppler and CUS technique were 61 % and 95% for sensitivity and specificity respectively. Although authors recognized the shortcoming of inclusion of old studies that date back more than a decade ago in the meta-analyses, a parameter that increases bias due to outdated US machines used, they acknowledged that in asymptomatic populations the rates of missed diagnosis of lower limb DVT are high and further investigation in these cases is imperative if appropriate.

4.3. Pulsed Wave Doppler

4.3.1. Data Selection

Spectral doppler is recommended as an adjunct tool to lower limb DVT diagnosis, as a monophasic venous waveform implies a proximal obstruction, while the absence of response in augmentation maneuver implies a peripheral obstruction located in a site between the venous segment examined and the venous segment squeezed (12). Utilizing the following combination of keywords: (Spectral doppler) OR (Waveform) OR (Pulsed wave doppler) AND (Deep vein thrombosis) AND (Lower limbs)/ (spectral doppler sonography) AND (deep vein thrombosis) AND (proximal venous obstruction) we identified 33 results. A title and abstract screening were conducted and after discarding the duplicates, records were full text overviewed for eligibility delineation. Last, a total of three studies concerning pulsed wave doppler were included.

4.3.2. Included Spectral Doppler Studies

A retrospective study by Edward P. Lin et all published in 2007, examined the significance of monophasic waveforms found in the common femoral vein in patients suffering from DVT. From 2000 to 2005, a total of 2963 adult spectral doppler exams of the common femoral vein were conducted and correlated with computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis. 65 participants were female and 59 were male, with a mean age of 51 years old (patients younger than 18 years old were precluded). Out of the 2963 exams, 124 displayed a monophasic waveform – 47 of which suffered from DVT propagating into the iliac veins. In the rest 77 patients, the monophasic waveform was attributed to different medical conditions, such as extrinsic compression and hypoplastic veins among others. Out of the 47 patients with a monophasic waveform, DVT was diagnosed by spectral doppler in 23, whereas the rest 24 DVT cases were identified by MRI or CT. 14 out of 47 DVT cases were isolated to iliac veins, 1 involved the iliac veins and inferior vena cava (IVC), 17 involved the common femoral and iliac veins and 15 involved the popliteal, superficial femoral, common femoral and iliac veins. Author's conclusion was that monophasic lower limb venous waveforms indicate a proximal obstruction, warranting further investigation in such cases.

A prospective study published by Ariadne M. Bach et all in 1996, aimed to investigate the correlation between monophasic common femoral waveforms and proximal venous obstruction. Authors examined between 1993 and 1995 2,138 cancer patients with pulsed wave doppler and ended up to 37 patients with monophasic common femoral waveforms, who consequently underwent follow up (up to 30 days) diagnostic imaging using venography, abdominal and pelvic CT or MRI, ultrasonography or both CT and venography. 8 out of 37 patients revealed proximal venous obstruction, whereas other causes like extrinsic compression were identified as the source of monophasic waveforms in the rest of the patients. 24 out of 37 patients were women and the rest were men with a median age of 56 years. All 37 patients suffered from cancer, did not have a history of previous DVT incident and were symptomatic or not. Authors concluded that pulsed wave doppler US of the common femoral vein should be routinely performed in the investigation of lower limb DVT, as a monophasic waveform may reliably suggest a proximal venous occlusion.

Another prospective study by A.S. McQueen published on 2008, aimed to highlight the value of single point augmentation in spectral doppler US examination for the diagnosis of lower limb DVT. For a period of 8 months, 158 symptomatic and asymptomatic patients with a median age of 65,4 years old were examined with this technique. The reference standard was CUS and author's strategy was to assess firstly the asymptomatic leg and after that the symptomatic leg in terms of comparison. This study showed a specificity rate of 91 % and a sensitivity rate of 64 % regarding single point augmentation technique for DVT diagnosis. Most missed DVT cases were revealed to be isolated calf deep vein thrombosis. According to authors, single point augmentation technique showed poor sensitivity levels for DVT diagnosis, thus it should not be routinely applied to CUS, which is recognized as a technique with high levels of accuracy for the diagnosis of this pathological condition.

4.4. CEUS

4.4.1. Data Selection

CEUS is a versatile asset with applicability in many pathologic conditions and the potential to play a role in lower limb DVT workup. We applied the following combination of keywords to acquire the existing literature about this topic: (CEUS) OR (Contrast enhanced ultrasound) AND (Lower limbs) AND (Deep vein thrombosis/ (Contrast ultrasound) AND (Calf vein thrombosis). 239 records were acquired and after removing duplicates and non-relevant records and implementing eligibility criteria we came up with one eligible prospective study that was included.

4.4.2. Included CEUS Study

A prospective study by Robert Alexander Bucek et all published in 2000, emphasized the role of CEUS in calf DVT diagnosis. Authors examined 20 patients (13 males and 7 females with a mean age of 53,3 years) with suspected calf DVT. Well’s score was utilized as a pre-test probability assessment and along with D-dimers value measurement, patients were selected for inclusion. The reference standard was defined as venography and patients underwent a CUS and color doppler evaluation as well. In comparison to CUS and color doppler US, CEUS showed an increased specificity (from 25 % to 67 %) and reduced percentage of indeterminate exams (from 55 % to 20 %), with comparative rates of sensitivity. Hence, authors stressed that albeit CEUS showed an improved visualization of calf veins compared to B-Mode and color doppler US, it should not be the first line method for lower limb DVT diagnosis.

4.5. Power Doppler

4.5.1 Data Selection

Power doppler US is a well-known technique that can detect slight blood flow velocities, therefore a potentially useful technique for DVT diagnosis (27) (Fig. 7.). The combination of keywords (Power doppler) AND (Deep vein thrombosis) AND (Lower limbs) identified 16 results and after thorough analysis, one prospective comparative study met the eligibility criteria and was included. Nevertheless, the study was available to us only on abstract format.

4.5.2. Included Power Doppler Study

I Baumgartner et all, in 1998 conducted a study to evaluate the role of power doppler US technique in diagnosis of suspected cases of calf DVT. 50 patients with suspected DVT underwent color doppler and power doppler examination of lower limb deep veins, whereas 47 out of 50 underwent venography as a reference imaging method. Results showed significantly improved rates of identification of paired calf veins using power doppler compared to color doppler US (from 80,5 % to 97,9%). Despite the fact that overall accuracy rates of detecting acute thrombosis were similar between the two techniques (96 % and 95 % for color and power doppler respectively) regardless of the calf vein examined (posterior/ anterior tibial and peroneal veins) authors deemed power doppler US a complementary asset for lower limb DVT diagnosis.

4.6. Elastography

4.6.1. Data selection

Elastography has the potential to precisely establish thrombus age by interpreting thrombus stiffness (Fig. 8.). There has been some literature research over the years concerning this topic. The combination of keywords (Elastography) AND (Deep vein thrombosis) AND (Lower limbs) with the application of systematic review and meta- analysis article type selection as a filter identified 2 records (both systematic reviews). One of them used MRI techniques along elastography as index diagnostic test, so it was excluded for ineligibility and only one record was included concerning elastography.

4.6.2. Included Elastography Study

A systematic review published in 2023 by Paolo Santini et all, demonstrated the significance of elastography application in lower limb DVT and delineation of thrombus chronicity. Authors conducted a systematic search of Medline, Embase and Web of science databases for appropriate articles as well as reference lists of retrieved records. The primary aim of their project was to evaluate the ability of elastography to differentiate between acute, subacute and chronic thrombus.

Retrospective and prospective studies were eligible for inclusion, whereas any experimental or non-English language studies were excluded. Only qualitative analysis of the information gathered was feasible, as the significant heterogeneity between studies included, hampered valid quantitative analysis. Hence, no pooled estimates for sensitivity or specificity were acquired and only data concerning elastography's ability to distinguish between acute, subacute and chronic thrombus were emphasized. Acute thrombosis was defined as thrombus formation up until 72 hours from DVT diagnosis, subacute thrombosis from 72 hours up until 30 days and chronic thrombosis was defined from 30 days to 6 months from DVT diagnosis. In total, 7 studies were enrolled with a variable risk of bias within them mainly in the topics of index test and patient population selection. In 5 out of these 7 studies, elastography techniques, both strain elastography (SE) and shear wave elastography (SWE), were able to discriminate between the different thrombosis phases (acute, subacute and chronic), by displaying increasing stiffness values of thrombus with age progression. Authors recommended that SWE should be the preferred technique for future studies for the diagnostic workup of DVT as it offers increased feasibility and impartiality in terms of results interpretation compared to SE. They concluded that elastography has a role to play in distinguishing DVT chronicity and should be routinely performed in this setting, as there is augmented evidence of the association of thrombus stiffness and the progression of thrombus age.

5. DISCUSSION

Studies included in our study are analyzed in the results section underlined the importance of the various techniques of multiparametric US for the diagnostic algorithm of lower limb DVT. Specifically, CUS and its various strategies showed a strong evidence- based applicability and validity for DVT diagnosis.

Color doppler US technique showed a poor sensitivity performance when used alone, but the outcomes were improved when used in combination with CUS techniques. Nevertheless, the relevant study had an increased bias risk, mainly due to the outdated US machines used in the study, so these results regarding color doppler should be under dispute.

In terms of pulsed wave doppler, 2 studies emphasized the need for its adoption into a routine US examination of lower limb DVT, as a monophasic waveform correlates with proximal venous occlusion and it should be warranted. On the contrary, according to another study, single- point augmentation should not be a part of the routine US investigation of DVT as indicated by the poor sensitivity rates, especially when calf vein thrombosis is suspected. The latter due to the normal augmentation response observed in some cases of calf vein thrombosis as blood flow is not impeded proximally.

Concerning CEUS included prospective study, it indicated it improved diagnostic rates for lower limb DVT, as well as the visualization of deep calf veins, although this tool can be reserved for more complicated cases. A study by AGW Smith et all. including 12 patients, showed the ability of CEUS to improve visualization of lower limb deep venous system compared to conventional CUS/color doppler technique, therefore providing a better imaging method to safely exclude potential lower limb DVT (17). Another prospective study by Mathias Kaspar et all. indicated that microvascular perfusion around the thrombosed deep venous segment, measured quantitively and qualitatively by CEUS, was increased at the baseline, after the first 2 weeks and after 3 months from DVT incidence, compared to the respective venous segment of the unaffected leg. In this study which encompassed 20 mainly male patients with unilateral popliteal vein thrombosis, the increased levels of perivascular perfusion as indicated by CEUS imaging, reflected the increased levels of perivascular inflammation associated with thrombus formation. Authors suggested that this perivascular inflammation due to thrombus formation can be a pathogenetic mechanism of PTS syndrome, hence CEUS could play a role in risk stratification of DVT patients for PTS development, nonetheless more studies need to confirm the association between perivascular inflammation and the development of PTS (28).

Power doppler US study, likewise, pointed out the improved identification of paired calf veins utilizing this technique, nonetheless it did not substantially improve diagnostic rates of DVT compared to color doppler.

CEUS and power doppler US techniques, as extracted from the two studies included, could play a key part in suspected cases of calf deep vein thrombosis, where the rest of US techniques are inferior, especially when the matter comes to edematous swollen calves, often encountered in venous thrombosis, or patients with increased body- mass index. There is a lot of debate lately about the necessity of treatment in calf venous thrombosis, as some physicians advocate that the condition bears a low thromboembolic potential, mainly owing to the small caliber of calf veins and they point out the increased bleeding effect, costs and patient anxiousness of unnecessary anticoagulant therapy or adverse effects of other regimens as a deterring agent (3,6,9). Other authors however, point out the need to treat selected calf DVT cases that bear an increased risk of proximal propagation and extension and consequently of thromboembolic incidents (for example hospitalized patients, or patients with active malignant disease, patients in bad general condition with comorbidities and/or loud symptoms, patients with unprovoked thrombosis, or patients with a history of previous thromboembolic incident, or if thrombosis involves a long, large venous segment (> 5 cm in length and > 7 mm in diameter), or if involves multiple veins (3,6,9). Hence, CEUS and power doppler US can offer an adjunct tool in the diagnostic workup of such cases.

When the matter comes to SMI and b-flow US techniques, we weren't able to identify any relevant patient studies in PubMed electronic database, except one case report pertaining to the utilization of SMI for the diagnosis of lower limb DVT. In this relatively recent case report (published in 2018) by Yuta Hagiwara et all, a 69 year-old patient woman was admitted to the hospital due to acute brain ischemic infarction (MRI showed a right putamen infarct). After gradual D-dimer level elevation, a lower limb DVT was suspected and ultrasonography was requested. CUS implicated left peroneal vein thrombosis but couldn't safely establish the diagnosis because of low thrombus echogenicity. The definite visualization of peroneal vein thrombus was achieved with the utilization of SMI technique, since it detected low velocity blood flow surrounding the thrombus and delineated its outline. In this case, thrombosis appeared as a low echogenicity structure inside the venous lumen, surrounded by high echogenicity venous blood flow. Consequently, a CT scan confirmed the diagnosis of peroneal vein thrombosis. In principle, SMI allows visualization of blood flow with low velocity due to the minimization of motion artifacts, thus venous thrombus surrounded by low-velocity blood flow can be potentially depicted, an asset especially when thrombosis is in the acute phase, where thrombus echogenicity is low and B-Mode examination is challenging (29)(Fig. 9,10.). According to authors, SMI technique can be a valuable implement for DVT diagnosis even in the hands of low- skilled examiners. In our knowledge, no other MVI or b-flow US studies regarding lower limb DVT in humans have been published.

Regarding the elastography systematic review included, it showcased its ability to detect increasing thrombus stiffness values, while age of thrombus advances, a potentially important element in precisely determining thrombus age, provided that cut-off values of stiffness are established accurately, according to authors. The physiological evolution of thrombus has many stages. In the first phase (first 5 to 7 days), they mainly consist of fibrin, which after polymerization forms a web- like structure that ensnares blood cells (red blood cells and platelets) (11). Gradually, cellularity in the thrombus increases as activated platelets facilitate the infiltration of white blood cells (11). In this stage (7 to 10 days from the beginning), thrombus becomes more resistant to anticoagulant therapies and as time passes deposition of collagen appears, while fibrinolysis decreases (11). The thrombus now organizes and forms stable, adhesive to the vessel wall structures, rich in collagen and poor in cellular components – highly therapy resistant (11). As time progresses (more than 6 months from beginning), thrombus remodels and assimilates in the vein wall, forming a post- thrombotic scar which can occlude the vessel lumen (11). For the time being, an unreliable method of thrombus age determination is the combination of estimating the date of patient’s onset of symptoms, along with some ultrasonographic criteria such as thrombus echogenicity, so it is important to establish a more reliable method for this regimen- directing matter and elastography exhibits this potential.

The studies included in our paper showed a high level of heterogeneity among them in various aspects, such as study designs, index tests and the participants populations included inter alia. Therefore, statistical processing and comparing between them was not applicable and quantitative analysis was not feasible. As a result, only intensive and descriptive analysis of the included studies was applied and presented.

6. CONCLUSION

Multiparametric ultrasound encompasses all various techniques available with modern technologic advanced US machines. As a compact and safe modality, offering well-tolerated reproducible examinations, it is corollary that its significance in lower limb DVT diagnostic workup should be rigorously investigated. We tried to analyze the various aspects of this modality and to showcase its usefulness in this setting. Even though CUS is generally accepted as a valid technique for the diagnosis of DVT, the role of the various Doppler and non- Doppler US techniques available nowadays, for lower limb DVT diagnosis should be clarified. For that reason, more high- quality large surveys and studies in humans should be conducted, especially concerning spectral doppler, CEUS, SMI and power doppler, which were found to be the least referred US techniques in the literature regarding this topic. As for elastography, even though studies depict increasing values of thrombus stiffness while its age progresses, there is need for establishment of accurate cut- off stiffness values for precise staging of thrombus age, hence future studies should aim for this achievement.

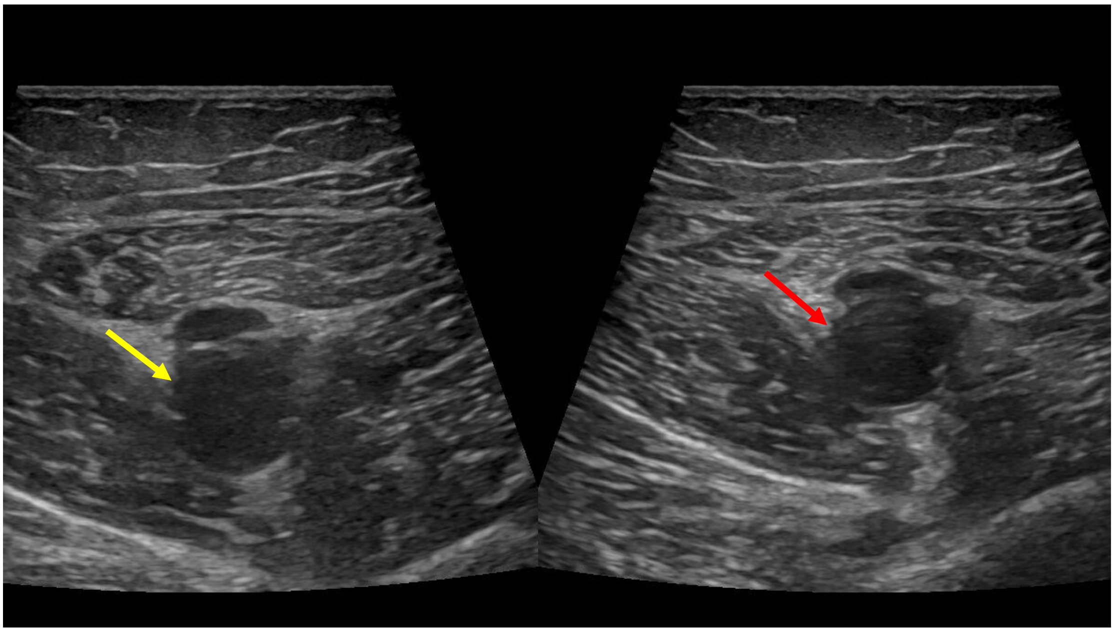

Fig. 1. Axial plane. On the right an enlarged common femoral vein (yellow arrow) on B-Mode, which does not collapse when pressure is applied via the probe (red arrow) on the left. This is indicative of DVT on CUS.

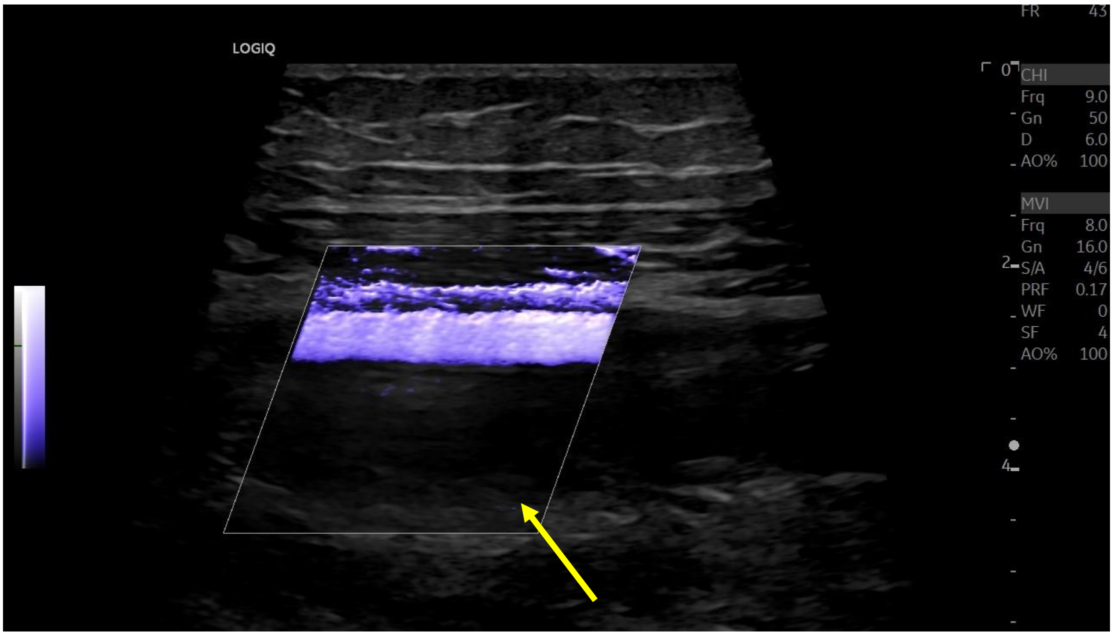

Fig. 2. SMI, longitudinal plane image showing no flow inside the thrombosed CFV lumen (yellow arrow).

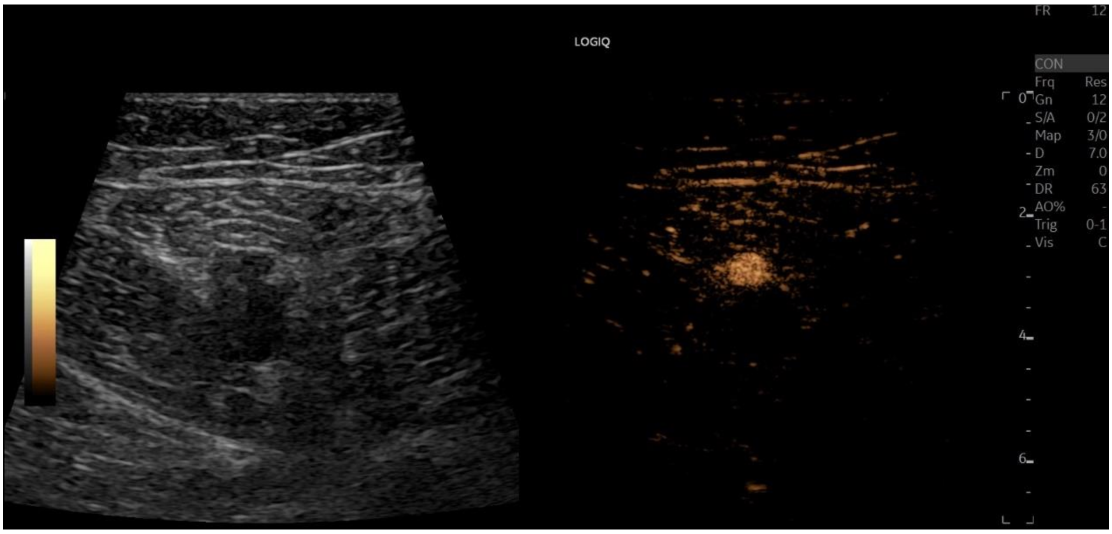

Fig. 3 CEUS exhibiting DVT in axial plane. No contrast is depicted inside the venous lumen, in contrast to the patent artery full of enhancing microbubbles of gas.

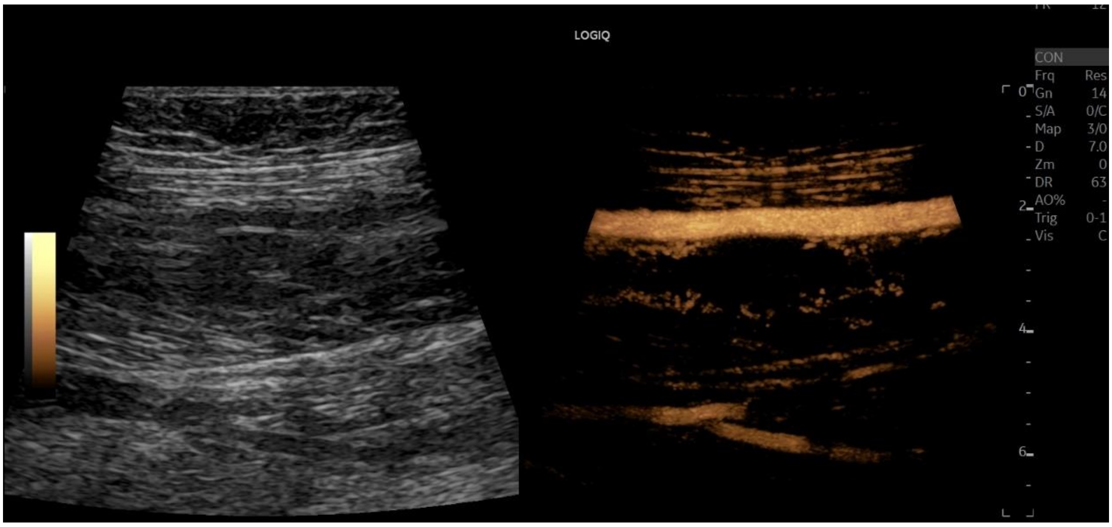

Fig. 4. The same thrombosed vein as in Fig. 3 in a longitudinal plane, clearly exhibiting the lack of enhancing contrast inside its lumen.

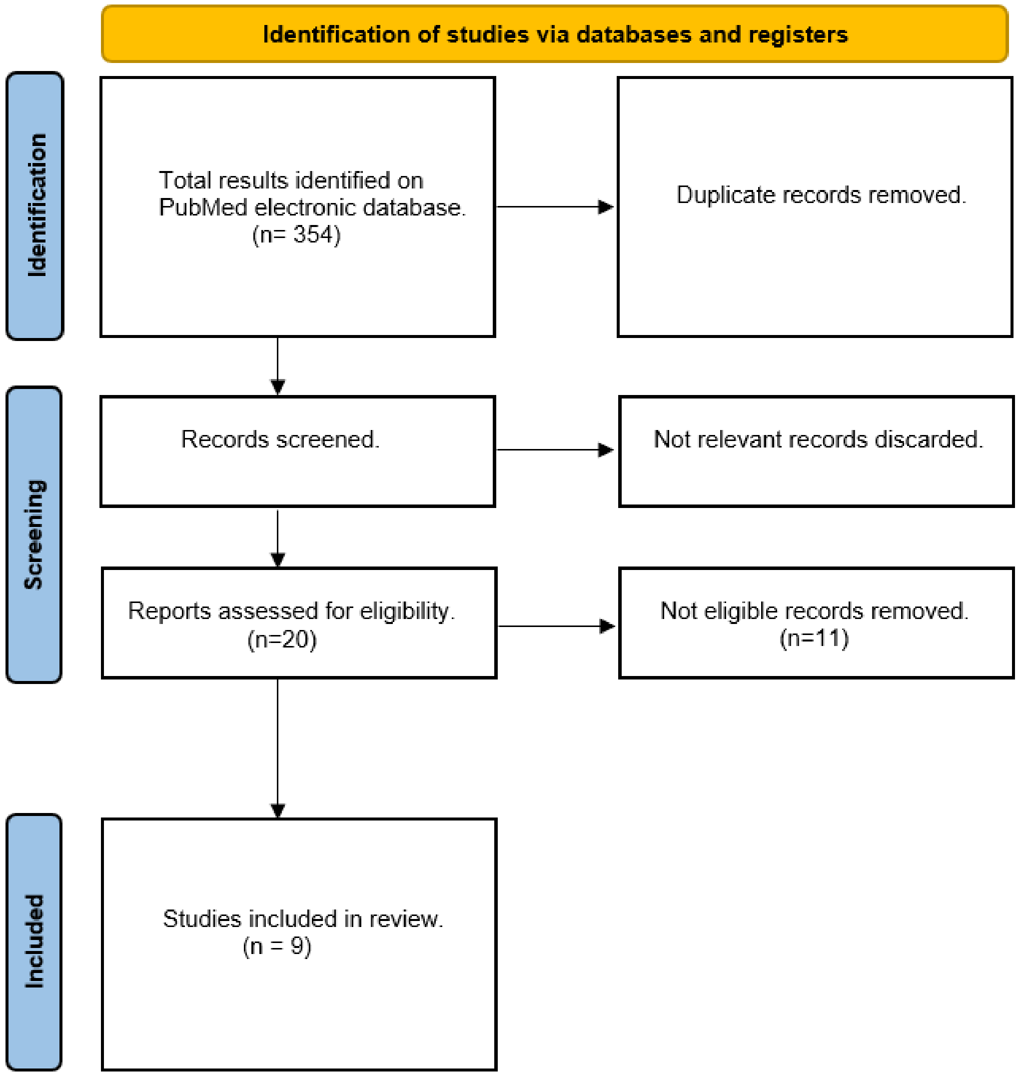

Fig. 5. Flowchart exhibiting study methodology.

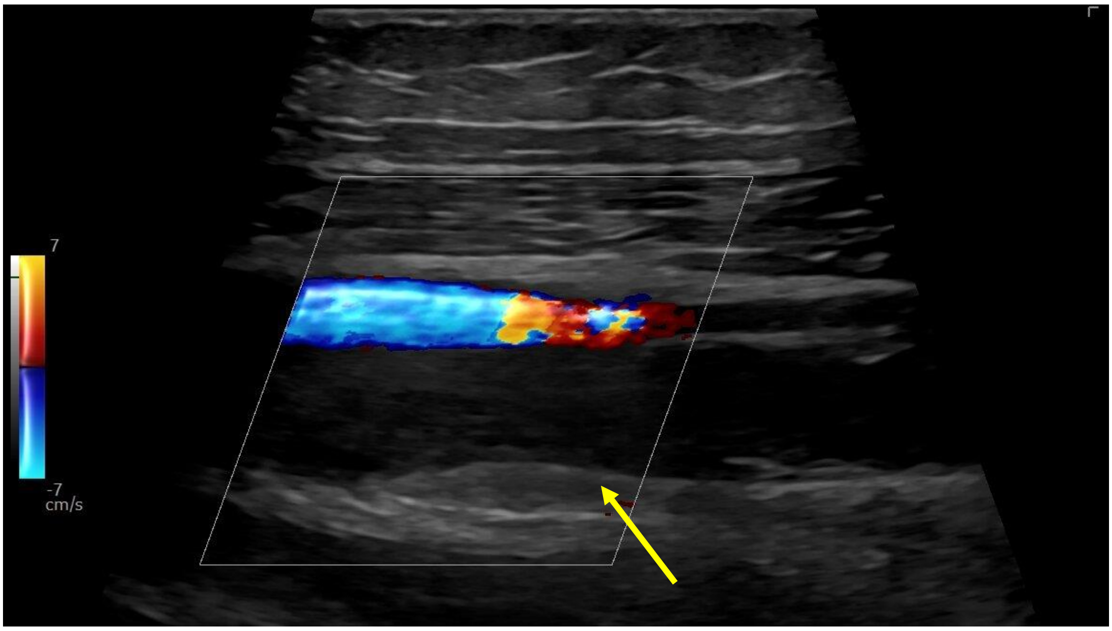

Fig. 6. Longitudinal plane, displaying blood flow inside the patent common femoral artery (yellow arrow) but no detectable blood flow inside the enlarged thrombosed common femoral artery.

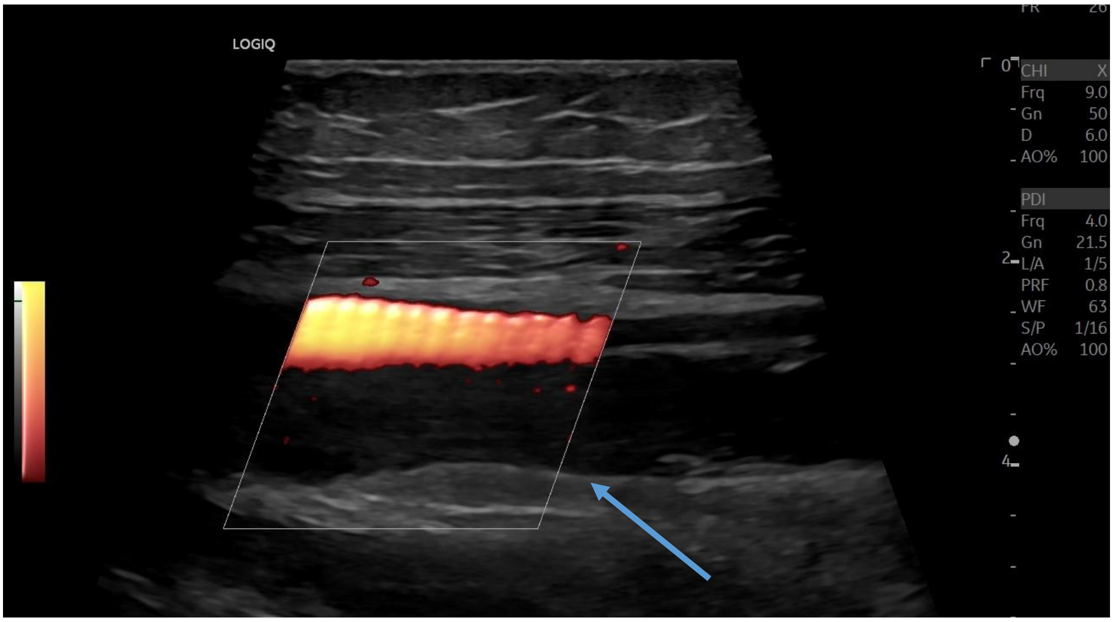

Fig. 7. Power doppler image on longitudinal plane exhibiting the absence of flow inside the thrombosed CFV (blue arrow).

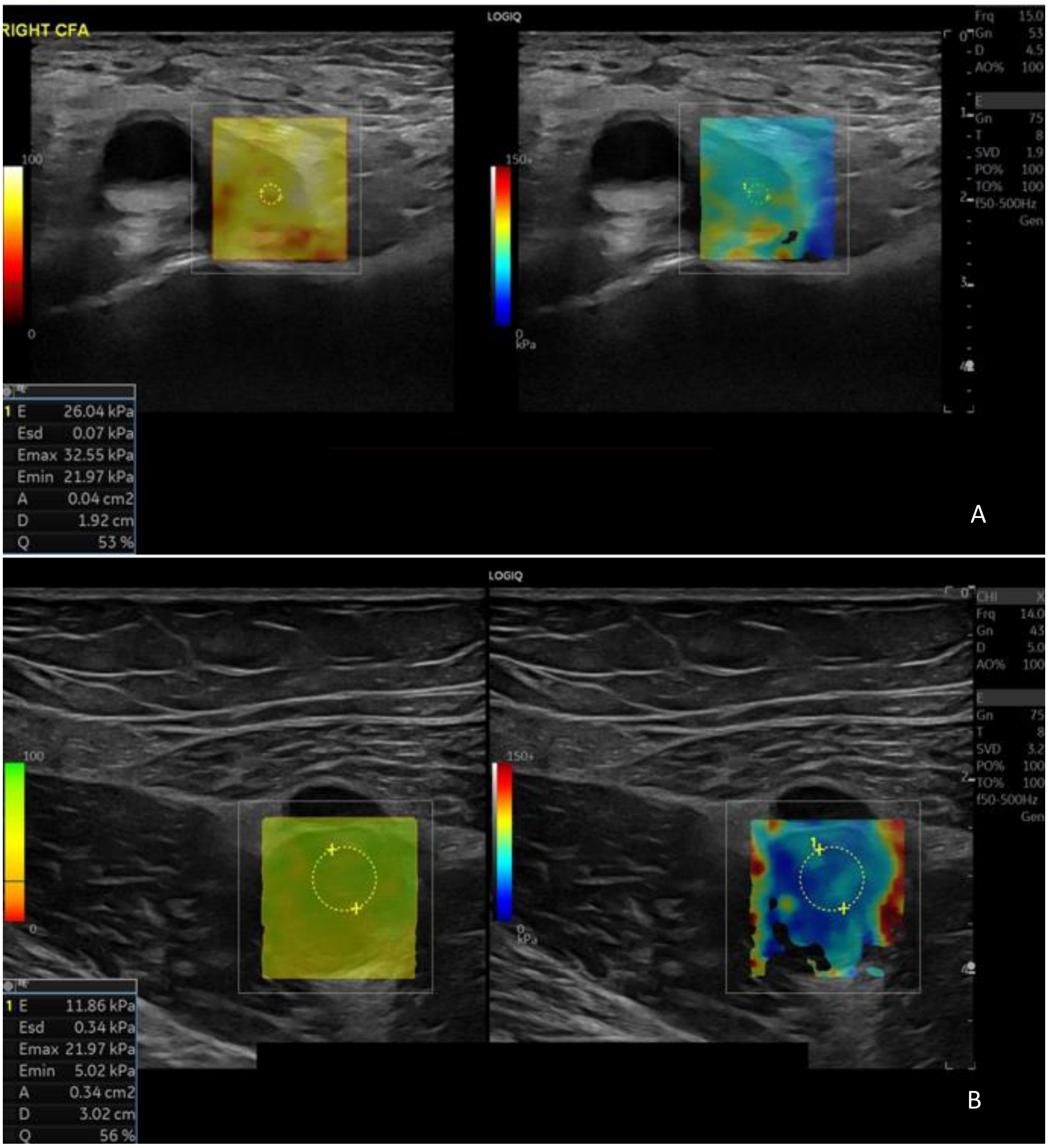

Fig. 8. Elastography (in axial plane) accurately measures thrombus stiffness as displayed in these two completely thrombosed CFVs (A and B).

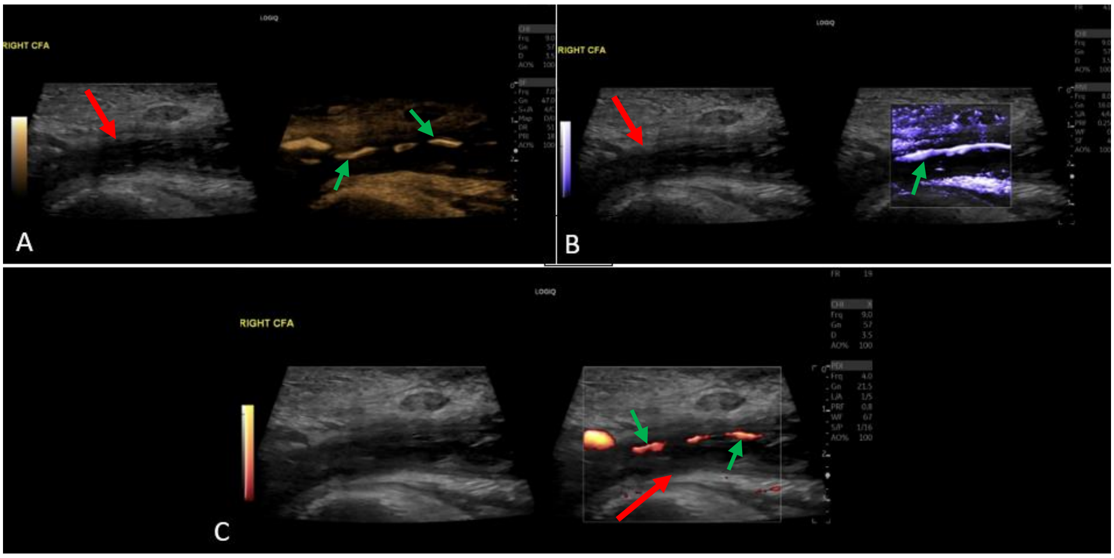

Fig. 9. Partially thrombosed CFV with hypoechoic thrombus (red arrows) in longitudinal plane. CEUS in A (right), SMI in B (right) and Power doppler in C (right) techniques depicting low-velocity blood flow in the periphery of the partially thrombosed lumen (green arrows).

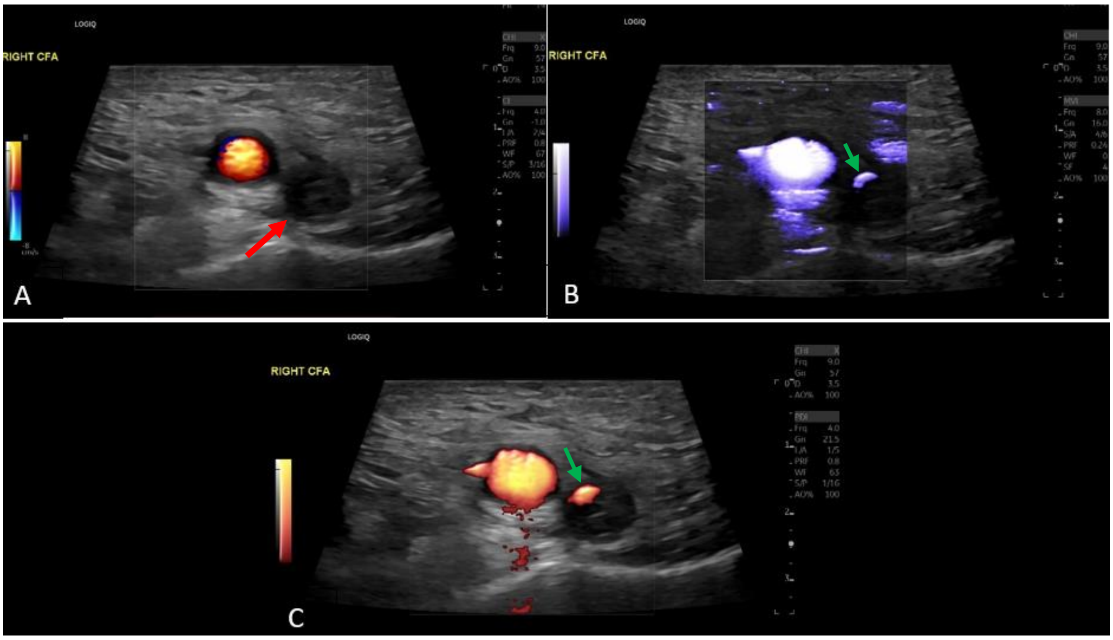

Fig. 10. CFV DVT in axial plane. Color doppler in A displaying no visible flow inside the lumen of the CFV (red arrow). SMI in B and Power doppler in C techniques at the same level with A, showing a small pocket of low-velocity blood flow in the periphery of the partially thrombosed lumen not visible in color doppler technique (green arrows). SMI and Power doppler techniques can detect flow of lower velocity compared to color doppler, an asset to differentiate between complete and partial venous thrombosis.

YEAR/FIRST AUTHOR	INDEX TEST	STUDY DESIGN	PURPOSE
2020/Meha Bhatt	CUS	Meta-analysis	To assess CUS strategies' validity for lower limb DVT diagnosis
2020/Noemie Kraaijpoel	CUS	Meta-analysis	To assess CUS strategies' validity for lower limb DVT diagnosis
2019/Yuhong Zhang	Color Doppler	Meta-analysis	To identify CUS and color Doppler validity for lower limb DVT diagnosis
1996/Ariadne M. Bach	Spectral Doppler	Prospective Study	To determine the role of spectral doppler for lower limb DVT diagnosis
2007/Edward P. Lin	Spectral Doppler	Retrospective Study	To determine the role of spectral doppler for lower limb DVT diagnosis
2008/A.S. McQueen	Spectral Doppler	Prospective Study	To determine the role of spectral doppler for lower limb DVT diagnosis
2000/Robert Alexander Bucek	CEUS	Prospective Study	To ascertain whether CEUS is helpful in lower limb DVT diagnosis
1998/I Baumgartner	Power Doppler	Prospective Study	To investigate the role of Power doppler in lower limb DVT investigation
2023/Paolo Santini	Elastography	Systematic Review	To evaluate elastography's ability in distinguishing lower limb DVT chronicity

Table 1. A brief overview of included studies.

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