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The rate of missed diagnosis of lower-limb DVT by ultrasound amounts to 50% or so in patients without symptoms of DVT

A meta-analysis

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Abstract

Background: To assess whether the ultrasound (US) is a reliable approach in detecting lower-limb deep-vein thrombosis (DVT) in patients without symptoms of DVT.

Methods: The research team performed a systematic search in PubMed, Ovid, Cochrane, and Web of Science without language or date restrictions. Full-text reports on prospective diagnostic studies involve the detection of lower-limb proximal and distal DVT in patients without symptoms of DVT using US and venography. A meta-analysis was performed using Meta-DiSc (version 1.4), providing the pooled sensitivity, specificity, positive (LR+) and negative (LR–) likelihood ratios of the detection accuracy of US. There were 4 different classes of subgroup analysis—the class of patients stratified by location of US exam (proximal, distal, whole leg), the class stratified by technique (color/doppler, compression, both modalities), the class stratified by kind of surgery (orthopedic, otherwise hospitalized) and the class stratified by era of publishing (1980s, 1990s, 2000s). The study quality and the risk of bias were evaluated using QUADAS-2, with heterogeneity was assessed and quantified by the *Q* score and I^2 statistics, respectively.

Results: The meta-analysis included 26 articles containing 41 individual studies with a total of 3951 patients without symptoms of DVT. Using venography as the gold standard, US for proximal DVT had a pooled sensitivity of 59% (95% confidence interval (CI) = 51%–66%) and a pooled specificity of 98% (95% CI = 97%–98%), US for distal DVT had a poor sensitivity of 43% (95% CI = 38%–48%) and a pooled specificity of 95% (95% CI = 94%–96%), US for whole-leg DVT had a pooled sensitivity of 59% (95% CI = 54%–64%) and a pooled specificity of 95% (95% CI = 94%–96%), US for post-major orthopedic surgery patients had a pooled sensitivity of 52% (95% CI = 49%–55%), and US for other types of patients had a pooled sensitivity of 58% (95% CI = 43%–72%). Pure compression technique for DVT had a poor sensitivity of 43% (95% CI = 39%–48%), pure color/doppler technique for DVT had a pooled sensitivity of 58% (95% CI = 53%–63%), compression and color/doppler technique for DVT had a pooled sensitivity of 61% (95% CI = 48%–74%).

Conclusion: US could be a useful tool for diagnosing DVT, but it has a lower positive rate and a higher false negative rate. The rate of missed diagnosis of lower-limb DVT by US amounts to 50% or so in the patients without symptoms of DVT. The negative results do not preclude the possibility of DVT and if appropriate heightened surveillance and continued monitoring or try a more accurate inspection method is warranted. The whole leg evaluation and color/doppler technique should be the preferred approach.

Abbreviations: CI = confidence interval, DVT = deep-vein thrombosis, LR– = negative likelihood, LR+ = positive likelihood, MOOSE = Meta-analysis of Observational Studies in Epidemiology, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, US = Ultrasound.

Keywords: asymptomatic, lower-limb deep-vein thrombosis, meta-analysis, ultrasound

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1. Introduction

It is estimated that Deep-vein thrombosis (DVT) has an incidence of approximately 1 in 1000 and leads to more than 50,000 deaths annually in the USA.[1,2] DVT can occur in deep veins of the pelvis, thigh or calf, with the thrombus subsequently detaching as an embolus and lodging in the pulmonary vessels. Early accurate diagnosis is therefore essential to allow immediate treatment for avoiding potential consequences, such as pulmonary embolism and unnecessary anticoagulation treatment.

Contrast venography is accepted as the gold standard for the detection of DVT; however, this technique has its own disadvantages due to extravasation of the contrast medium, systemic reactions to the contrast medium and venous thrombosis at the catheter site.[3,4] Ultrasound (US) is widely recognized as a choice of the imaging methods for suspected DVT thanks to its noninvasiveness, low cost, ready availability, portability, safety, and operator-friendliness.[5] The McMaster Diagnostic Imaging Practice Guidelines Initiative reported that US had a sensitivity of 97% for proximal DVT and 73% for distal DVT, and a specificity of 96%.[6] Wells et al[7] performed a meta-analysis of patients after orthopedic surgery, and found that US had a low sensitivity of 62% for detecting proximal thrombi. But all of the studies in the meta-analysis included asymptomatic patients only after orthopedic surgery. The "asymptomatic" means that patients have signs and symptoms in their legs from the trauma of surgery or fracture, but no additional symptoms or signs of DVT at the time. The clinical symptoms in the presence of a larger embolus present an even more distinctive signal to the US operator. So, it is unknown whether the low value of the pooled sensitivity of US for lower-limb DVT would be the same in other asymptomatic patients. Goodacre[8] performed a meta-analysis, which included both asymptomatic and symptomatic patients. It should be noted that including both groups of patients in the same analysis introduced an obvious threshold effect and heterogeneity. We are not aware of any reported meta-analysis of the diagnostic accuracy of US for lower-limb proximal and distal DVT just in patients without symptoms of DVT.

The overall goal of the present meta-analysis was therefore to determine the diagnostic accuracy of US for clinically suspected lower-limb DVT patients without symptoms of DVT.

2. Materials and methods

This meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist.[9] Our work was done before the knowledge of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist, but the study steps appears to be in compliance with the requirements of PRISMA.[10] Our study, a meta-analysis, does not require an ethics committee or institutional review board confirmation.

2.1. Search strategy

We sought to identify all patients without symptoms of DVT who underwent testing for lower-limb DVT using US and venography. Two investigators (LC and SNL) independently performed systematic searches of the MEDLINE (PubMed), Ovid, Cochrane and Web of Science without applying language or date restrictions. We used a combination of controlled vocabulary, Mesh, and keywords associated with venous thrombosis, US, phlebography, sensitivity, and specificity. Search strategy in the PubMed database: ((Phlebothrombosis[Title/Abstract] OR Phlebothromboses[Title/Abstract] OR "Thrombosis, Venous"[Title/Abstract] OR "Thromboses, Venous"[Title/Abstract] OR Venous Thromboses[Title/Abstract] OR Deep Vein Thrombosis[Title/Abstract] OR "Thromboses, Deep Vein"[Title/Abstract] OR "Vein Thromboses, Deep"[-Title/Abstract] OR "Vein Thrombosis, Deep"[Title/Abstract] OR Deep-Venous Thrombosis[Title/Abstract] OR Deep-Venous Thromboses[Title/Abstract] OR "Thromboses, Deep-Venous" [Title/Abstract] OR "Thrombosis, Deep-Venous"[Title/Abstract] OR Deep-Vein Thrombosis[Title/Abstract] OR Thromboses, Deep-Vein[Title/Abstract] OR "Thrombosis, Deep-Vein"[Title/Abstract] OR Deep-Vein Thrombosis[Title/Abstract] OR "Venous Thrombosis"[MeSH]) AND ("Ultrasonography"[MeSH] OR Echography [Title/Abstract] OR Sonogram[Title/Abstract] OR Echogram[Title/Abstract] OR Echoscopy[Title/Abstract] OR Sonography[Title/Abstract] OR Echoschopy[Title/Abstract] OR Echogram [Title/Abstract] OR Sonogram[Title/Abstract] OR Ultra sound [Title/Abstract]) AND (Sensitivity[Title/Abstract] OR Specificity [Title/Abstract] OR "Sensitivity and Specificity"[MeSH])). Two systematic reviews[8,11] related to our meta-analysis were reviewed for other potential studies that met the inclusion criteria. Publications with titles and abstracts relevant to our study were screened independently by 2 reviewers (YXW and IA). Bibliographies from all of the selected articles were manually evaluated to identify additional relevant studies for inclusion in the analysis. The results of the searches were reviewed jointly by the search team.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were applied:

(1) original studies that compared the performances of US and venography in detecting clinically suspected lower-limb DVT in patients without symptoms of DVT,
(2) original prospective blinded clinical studies (practitioners performing US and contrast venography did not know each other's result),
(3) original studies that provided detailed information of the US checking method: the types of US, scanning methods, scanning position, and detecting veins, and
(4) studies that included true-positive, true-negative, false-positive, and false-negative results.

If such data were not provided in the report, we attempted to contact the authors to obtain this information.

The exclusion criteria were as follows: studies that were reported as abstracts or letters only, without additional information.

2.3. Data extraction

Two reviewers (YW and HFX) independently extracted data from the final set of articles using standardized forms, and resolved disagreements by discussion. The following data were extracted from each study include: first author, country, publication year, sample size, gender proportion or number of adults by gender, mean age, US technique, areas of the limbs that were evaluated, type of patient, experience of the operator and the numbers of true positives, true negatives, false positives and false negatives.

2.4. Methodological quality assessment

Two reviewers (YHZ and YS) independently assessed the quality of each study, with disagreements resolved by discussions. The methodological quality was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) criterion.[12] The studies that meet consistent with the eligibility criteria were included in the meta-analysis.

2.5. Outcome measures

The primary objective was to summarize the evidence on the diagnostic accuracy of US for clinical suspected lower-limb DVT in asymptomatic patients. The primary outcomes were the sensitivity and specificity of US in identifying asymptomatic lower-limb DVT using venography as the reference standard. The positive (LR+) and negative (LR–) likelihood ratios were analyzed. The following secondary outcomes were also assessed: area being examined, type of US, year of publication and experience of the operator. The feasibility was defined as the degree of being easily or conveniently done.

Subgroup analyses were performed with the stratification by the specific examined area (proximal DVT, distal DVT, and whole-leg DVT), type of patient (post-major orthopedic surgery and other patients), US technique (compression, pure color/doppler and the 2 together technique), year of publication (before and after 2000). A US operator was considered to be experienced if the authors emphasized it. The methodology of lower-limb evaluation: the proximal limb veins were examined with the patient in the supine position, and the popliteal vein and calf veins were examined with the patient in the sitting position with the leg hanging down. The veins were evaluated for intraluminal echoes and compressibility in both the sagittal and transverse planes. Whole-leg evaluation: the external iliac (distal part), common femoral, superficial femoral, popliteal, tibiofibular trunc, posterior tibial and peroneal veins. Proximal limb evaluation: the external iliac, common femoral, superficial femoral vein. Distal limb evaluation: the tibiofibular trunc, posterior tibial and peroneal veins. Criteria for DVT were: in the sagittal and transverse planes, visible thrombus, lack of compressibility, or absence of blood flow in a venous segment previously seen normal. The diagnosis of DVT was usually a result of a combination of criteria and ultrasonographic characteristics, rather than a question of presence or absence of one single criterion.

2.6. DATA analysis

The meta-analysis was performed using the statistical software Meta-DiSc (version 1.4, Unit of Clinical Biostatistics team, Ramón y Cajal Hospital, Madrid, Spain). We generated combined estimates for diagnostic accuracy by applying a random-effects model in Meta-DiSc. The random-effects model was used when a high degree of heterogeneity was detected ($I^2 \geq$ e ran while the fixed-effects model was used when no significant clinical or statistical heterogeneity was present ($I^2 < 50\%$).[13] For each diagnostic test we used a bivariate random-effects model to calculate the 95% confidence intervals (CIs) and the pooled sensitivity and specificity of proximal, distal and overall lower-limb DVT. Software Review Manager (version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used to construct a flowchart of the articles retrieved and summary graphs of the methodological quality. Heterogeneity was assessed and quantified using the Cochrane Q and I^2 statistics, respectively.[14,15] Publication bias was assessed using funnel plots.[16] The cut-off for statistical significance was set at $P < .05$ in all analyses.

3. Results

3.1. Literature search

The characteristics of the included and excluded articles are presented in Figure 1. In total, 767 papers were identified after applying the initial search strategy, of which 43 were considered potentially eligible based on close reading of the titles and abstracts. Seventeen publications were excluded: 8 were review articles, 2 were letters, 2[17,18] reported retrospective studies, 1[19] did not provide detailed information on the US checking method, 1[20] included superficial veins, 1[21] included symptomatic patients and 2[22,23] did not report the available date for analysis, and we could not contact the authors since no telephone number or e-mail address was provided. Finally, 26 articles[24–49] containing 41 individual studies were included in this meta-analysis.

3.2. Study characteristics

The characteristics of the included studies are presented in Table 1. The 41 individual studies involved 3951 patients without symptoms of DVT and were reported between 1988 and 2007. The number of participants in each of the studies ranged from 36 to 1140. The meta-analysis involved 3351 postoperative hip or knee patients,[24,26–32,35–37,39–42,45–49] 180 postoperative ankle fracture patients,[25] 116 postoperative intertrochanteric or femoral neck fracture patients,[38,43] 122 hospitalized patients,[44] 100 patients who received a craniotomy and who participated in a venous thrombosis prophylaxis study,[33] and 82 postoperative major elective abdominal or thoracic operations with an expected duration of more than 1 hour.[34] Different authors take different language expression ways in their original studies. Various types and names of US were used. Compression: using a Grey scale US to look for compression of the vessel. Color Duplex, color Doppler and triplex US: the combination of Grey scale US, gated Doppler and color flow. Compression and Duplex: mixing compression with a Doppler waveform. Compression and Color Doppler: mixing compression with a Doppler waveform and color flow. Duplex and Color Doppler: mixing a Doppler waveform with color flow. Fifteen individual studies (36.6%) involved an experienced physician, radiologist, sonographer or technologist performing the US investigations, while the experience of the operator was not reported for the other 26 individual studies (63.4%). The overall quality of studies included in this meta-analysis was high (Fig. 2).

3.3. The subgroup analyses of US for proximal, distal and whole-leg DVT

Sixteen individual studies of proximal DVT that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that when using venography as the reference, US for proximal DVT had a moderate sensitivity of 59% (95% CI=51–66%; Fig. 3A) with moderate heterogeneity (I^2=66.2%, $P < .001$), and a higher specificity of 98% (95% CI=97%–98%; Fig. 3B) with significant heterogeneity (I^2= 75.1%, $P < .001$).

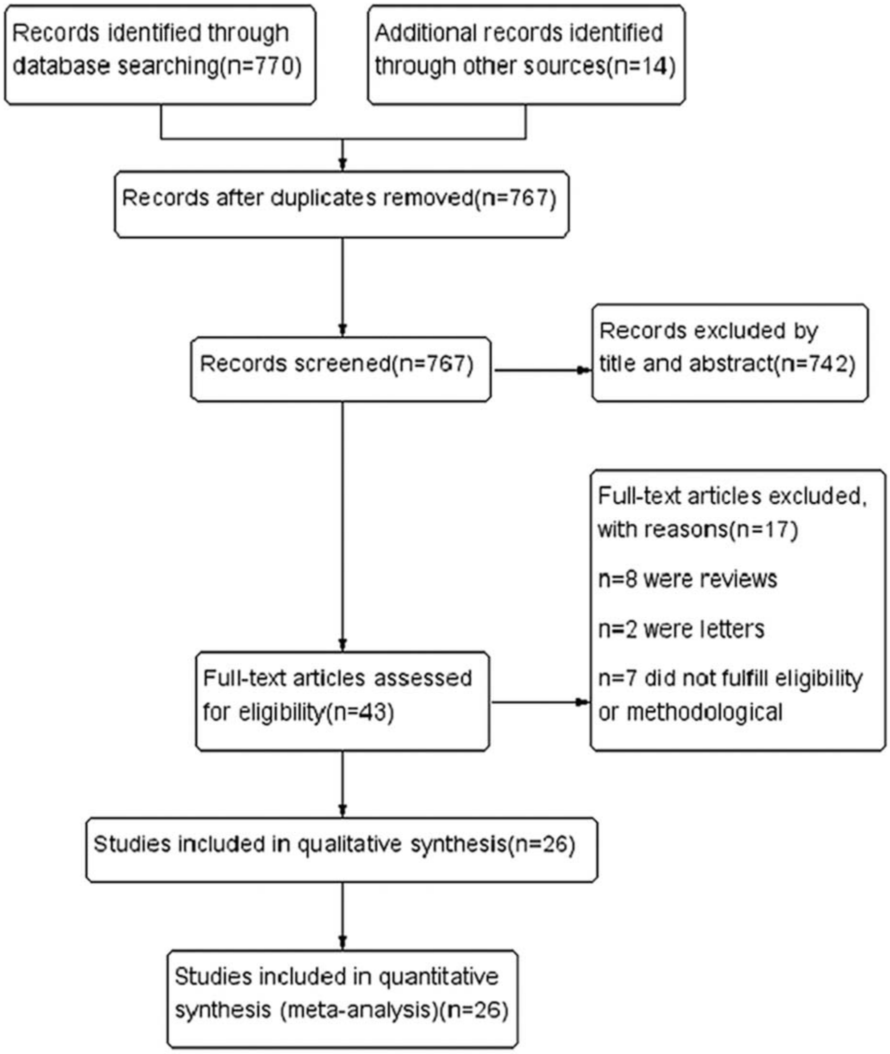

Figure 1. Flowchart of articles retrieved from the search of databases and reasons for exclusions.

Eleven individual studies of distal DVT that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that when using venography as the reference, US for distal DVT had a poor sensitivity of 43% (95% CI=38%–48%; Fig. 3C) with significant heterogeneity (I^2=93.0%, $P<.001$), and a higher specificity of 95% (95% CI=94%–96%; Fig. 3D) with significant heterogeneity (I^2=89.5%, $P<.001$).

Fourteen individual studies of whole-leg DVT that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that when using venography as the reference, US for whole-leg DVT had a moderate sensitivity of 59% (95% CI=54%–64%; Fig. 3E) with significant heterogeneity (I^2=87.6%, $P<.001$), and a higher specificity of 95% (95% CI=94%–96%; Fig. 3F) with significant heterogeneity (I^2=80.0%, $P<.001$).

3.4. The subgroup analyses of US for post-major orthopedic surgery and other kinds of surgeries

Thirty-seven individual studies of post-major orthopedic surgery patients that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that when using venography as the reference, US for post-major orthopedic surgery patients had a pooled sensitivity of 52% (95% CI= 49%–55% Fig. 4 A) with significant heterogeneity (I^2=88.1%, $P<.001$), and a pooled specificity of 96% (95% CI=96%–97%; Fig. 4 B) with significant heterogeneity (I^2=82.4%, $P<.001$).

Four individual studies of other kind of surgery that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that when using venography as the reference, US for other kind of surgery had a pooled sensitivity of 58% (95% CI=43%–72%; Fig. 4C) with significant heterogeneity (I^2=81.4%, $P<.001$) and a pooled specificity of 94% (95% CI=91%–96%; Fig. 4D) with significant heterogeneity (I^2=92.9%, $P<.001$).

3.5. LR+ and LR– likelihood ratios of lower-limb DVT

According to the results obtained in the 41 individual studies, the pooled LR+ of 16.99 (95% CI=12.04–23.96) with significant heterogeneity (I^2=76.6%, $P<.001$) indicates that US can be used to identify lower-limb DVT, while the LR– of 0.39 (95%

Table 1

Characteristics of patients enrolled from studies retrieved for meta-analysis.

Study	Origin	Year	Ultrasound	Location	Male/ female	Mean age	Sample size	True-positive	False-positive	False-negative	True-negative	Sensitivity %	Specificity %
Atri M[24,*]	Canada	1996	Compression	Distal	101/105	65	130	24	0	2	104	92.0	100
Lapidus, L1[25,†]	Sweden	2006	Color Duplex	Overall	83/97	47	116	23	13	1	79	96.0	86.0
Lapidus, L2[25,†]	Sweden	2006	Color Duplex	Distal	83/97	47	116	17	13	1	85	94.0	87.0
Lensing, A W1[26,*]	Netherlands	1997	Compression/ Color Doppler	Proximal	65/138	65	178	15	6	10	147	60.0	96.0
Lensing, A W2[26,*]	Netherlands	1997	Color Duplex	Distal	65/138	65	122	11	8	22	81	33.0	91.0
Ching-JW[27,*]	China	2004	Compression/ Duplex	Overall	12/41	61	55	20	3	12	20	87.0	63.0
S.M.Schellong1[28,*]	Germany	2007	Compression	Overall	1140	UC	731	43	41	95	552	31.1	93.0
S.M.Schellong2[28,*]	Germany	2007	Compression	Proximal	1140	UC	879	4	11	15	849	21.0	98.7
S.M.Schellong3[28,*]	Germany	2007	Compression	Distal	1140	UC	785	42	43	94	606	30.8	93.3
Monreal M[29,*]	Spain	1989	Compression	Proximal	16 /23	70	36	3	1	3	29	50.0	96.7
Elliott CG[30,*]	USA	1993	Duplex	Overall	49/70	68	119	17	10	7	85	63.0	92.4
Mattos MA1[31,*]	USA	1992	Color Duplex	Overall	34/65	68	190	24	3	20	143	54.5	97.9
Mattos MA2[31,*]	USA	1992	Color Duplex	Proximal	34/65	68	190	2	0	1	187	66.7	100
Mattos MA3[31,*]	USA	1992	Color Duplex	Distal	34/65	68	190	24	3	19	144	55.8	98.0
Tremaine MD[32,*]	USA	1992	Compression	Overall	28/32	66	62	6	3	1	52	66.7	98.1
Jongbloets LM1[33,¶]	Netherlands	1994	Compression	Proximal	37/63	61	100	5	4	8	83	38.5	95.4
Jongbloets LM2[33,¶]	Netherlands	1994	Compression	Distal	37/63	61	71	8	15	8	40	50.0	72.7
Lausen I[34,||]	Denmark	1995	Color Doppler	Overall	82	UC	82	3	1	4	74	42.8	98.7
Evi Kalodiki1[35,*]	UK	1997	Color Duplex	Proximal	38/40	69	23	5	2	4	33	55.6	94.3
Evi Kalodiki2[35,*]	UK	1997	Color Duplex	Proximal	38/40	69	55	13	1	1	92	92.8	98.9
Evi Kalodiki3[35,*]	UK	1997	Color Duplex	Distal	38/40	69	55	15	3	4	85	78.9	96.5
M.Mantoni[36,*]	Denmark	1997	Triplex	Overall	26/107	76	133	20	1	7	208	74.1	99.5
Barnes RW[37,*]	USA	1988	Duplex	Overall	26/52	66	309	12	8	2	287	85.7	97.3
Cronan JJ[38,‡]	USA	1991	Compression	Overall	76	82	76	12	0	4	60	75.0	100
Davidson BL[39,*]	USA	1992	Color Doppler	Proximal	319	UC	319	8	23	13	275	38.1	92.3
Westrich GH1[40,*]	USA	1998	Color Doppler	Distal	100	68	65	20	1	4	40	83.3	97.6
Westrich GH2[40,*]	USA	1998	Color Doppler	Proximal	100	68	65	6	1	1	57	85.7	98.3
Westrich GH3[40,*]	USA	1998	Color Doppler	Overall	100	68	195	28	5	5	157	84.8	96.9
Robinson KS[41,*]	UK	1998	Compression	Proximal	45/41	69	86	5	2	1	78	83.3	97.5
Ginsberg JS1[42,*]	Canada	1991	Compression	Distal	130	UC	226	5	2	35	184	12.5	98.9
Ginsberg JS2[42,*]	Canada	1991	Compression	Proximal	130	UC	207	11	2	10	184	52.4	98.9
Froehlich JA[43,*]	USA	1989	Compression	Overall	40	82	40	5	1	0	34	100	97.1
Bressollette L[44,§]	France	2001	Compression	Overall	54/68	69	115	12	0	0	103	100	100
Borris LC1[45,*]	Denmark	1990	Compression	Overall	61	UC	61	10	3	4	44	71.4	93.6
Borris LC2[45,*]	Denmark	1990	Compression	Proximal	61	UC	61	8	2	3	48	72.7	96.0
Woolson ST[46,*]	USA	1991	Compression	Proximal	22/39	70	61	10	1	5	72	66.7	98.6
Grady-B JC1[47,*]	USA	1994	Duplex	Proximal	44/56	71	130	7	0	0	123	100	100
Grady-B JC2[47,*]	USA	1994	Duplex	Distal	44/56	71	123	7	2	1	113	87.5	98.2
Garino JP[48,*]	USA	1996	Compression	Proximal	84	UC	87	5	2	0	80	100	97.6
Ciccone WJ1[49,*]	USA	1998	Duplex/Color Doppler	Distal	123/79	64	343	5	1	47	290	9.6	99.7

UC: unclear.

Compression: using a Grey scale ultrasound to look for compression of the vessel.

Color Duplex, color Doppler and triplex ultrasound: the combination of Grey scale ultrasound, gated Doppler and color flow.

Compression/ Duplex: mixing compression with a Doppler waveform.

Compression/Color Doppler: mixing compression with a Doppler waveform and color flow.

Duplex/Color Doppler: mixing a Doppler waveform with color flow.

* Postoperative hip or knee surgery patients.

† Postoperative ankle fracture surgery patients.

‡ Postoperative intertrochanteric or femoral neck fracture patients.

§ Hospitalized patients.

¶ Patients who had craniotomy and who participated in a venous thrombosis prophylaxis study.

|| Postoperative major elective abdominal or thoracic operations with an expected duration of more than 1 hour patients.

CI=0.32–0.48) with significant heterogeneity (I^2=91.1%, P <.001) suggests that the use of US is very likely to result in misdiagnoses of positive and negative patients as the absence and presence of lower-limb DVT, respectively.

3.6. The subgroup analyses of pure compression, pure color/Doppler and compression + color for DVT

Eighteen individual studies of pure compression technique that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that pure compression technique for DVT had a poor sensitivity of 43% (95% CI= 39%–48%; Fig. 6A) with significant heterogeneity (I^2=87.3%, P=.00), and a higher specificity of 96% (95% CI=95%–97%; Fig. 6B) with significant heterogeneity (I^2=85.3%, P=.00).

Fourteen individual studies of pure color/doppler technique that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that pour color/doppler technique for DVT had a moderate sensitivity of 58% (95% CI=53%–63%); Fig. 6C) with heterogeneity (I^2=88.5%, P=.00), and a higher specificity of 96% (95% CI=96%–97%; Fig. 6D) with significant heterogeneity (I^2=85.4%, P=0.00).

Two individual studies of compression and color/doppler technique that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that compression and color/doppler technique for DVT had a moderate sensitivity of 61% (95% CI=48%–74%; Fig. 6E) with heterogeneity (I^2=0.00%, P>.84), and a higher specificity of 95% (95% CI=91%–98%; Fig. 6F) with heterogeneity (I^2= 61.7%, P>.10).

Figure 2. QUADAS-2 risk of bias assessment.

3.7. The subgroup analyses of 2000s, 1990s, and 1980s for DVT

Five individual studies of 2000s that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that 2000s for DVT had a poor sensitivity of 0.57% (95% CI=53%–61%; Fig. 7A) with significant heterogeneity (I^2=84.2%, P=.00), and a higher specificity of 96% (95% CI=95%–96%; Fig. 7B) with significant heterogeneity (I^2=92.5%, P=.00).

Thirty-three individual studies of 1990s that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that 1990s for DVT had a moderate sensitivity of 57% (95% CI=53%–61%); Fig. 7C) with heterogeneity (I^2=84.2%, P=.00), and a higher specificity of 97% (95% CI=97%–98%; Fig. 7D) with significant heterogeneity (I^2=81.2%, P=.00).

Three individual studies of 1980s that provided available DATA were included in the quantitative meta-analysis. Subgroup analysis showed that 1980s for DVT had a moderate sensitivity of 80% (95% CI=59%–93%; Fig. 7E) with heterogeneity (I^2= 61.7%, P=.07), and a higher specificity of 97% (95% CI=95%–99%; Fig. 7F) with heterogeneity (I^2=0.0%, P=.98).

3.8. Heterogeneity analysis

No significant threshold effect or publication bias was found, and significant heterogeneity between the included studies was observed. Our use of a meta-regression analysis searching for heterogeneous sources revealed that heterogeneity was not related to the examined part, the type of US, the year of publication or the experience of the operator.

4. Discussion

This meta-analysis evaluates the use of US in detecting suspected lower-limb proximal and distal DVT in patients without symptoms of DVT, and it has yielded evidence for the need to re-evaluate the guidelines in this area. This meta-analysis demonstrates that US has a low sensitivity, in that approximately half of the patients without symptoms of DVT with lower-limb DVT were detected: 59% for proximal DVT, 43% for distal DVT, 59% for lower-limb, 52% for post-major orthopedic surgery patients, 58% for other types of patients, 43% for pure compression technique and 58% for pure color/doppler technique. A highly sensitive test means that there are few false negative results; few actual cases are missed. Ceteris paribus, tests with high sensitivity have potential value for screening, because they rarely miss subjects with the disease. While the specificity of US for identifying lower-limb DVT was nearly 95%, there was evidence of a high degree of statistical heterogeneity. The pooled LR+ of 16.99 (95% CI=12.04–23.96) indicates that US can be used to identify lower-limb DVT, while the LR– of 0.39 (95% CI=0.32–0.48). Internationally, a useful diagnostic test is 1 where the LR+ is greater than 10 (diagnosis) and the LR- is smaller than 0.1 (exclusion). This means that US can be a useful tool for diagnosing DVT, but it has a lower positive rate and a higher false negative rate.

In this paper, 92.3% of the 3951 patients were orthopedic patients and they seemed not truly "asymptomatic patients" as they have signs and symptoms in their legs from the trauma of surgery or fracture. However, we considered that they had no additional symptoms or signs of DVT at the time. Hence being "asymptomatic" means that the patients without symptoms of DVT. Wells et al[7] performed a meta-analysis of patients after orthopedic surgery, and found that US had a sensitivity of 62% for detecting proximal thrombi. All of the included studies involved asymptomatic patients after orthopedic surgery. Our study included hospitalized patients and patients after orthopedic surgery. We exclude the 7.7% that are not orthopedic patients, the post-major orthopedic surgery patients had a pooled sensitivity of 52% and a pooled specificity of 96%. We analyzed this 7.7% separately, the 7.7% patients had a pooled sensitivity of 58% and a pooled specificity of 94%. Form all of the patients without symptoms of DVT, US for whole-leg DVT had a

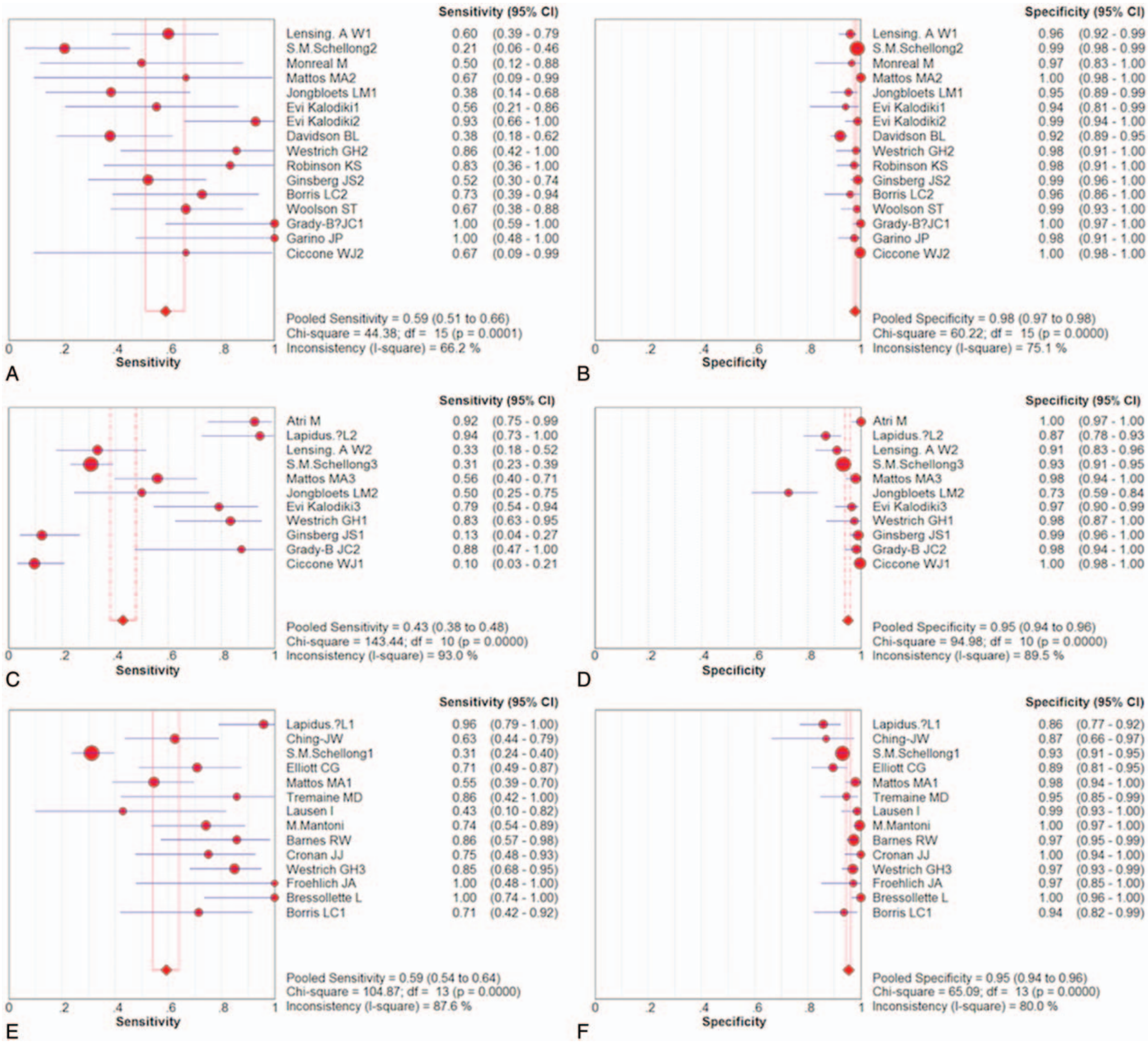

Figure 3. Pooled sensitivity and specificity of ultrasound for the diagnosis of asymptomatic lower limbs deep-vein thrombosis. (A) Proximal pooled sensitivity. (B) Proximal pooled specificity. (C) Distal pooled sensitivity. (D) Distal pooled specificity. (E) Whole-leg pooled sensitivity. (F) Whole-leg pooled specificity.

moderate sensitivity of 59% and a higher specificity of 95%. As US technology spread, the physicians use the bedside US to screen the lower extremity DVT in high-risk patients with DVT. Orthopedic patients and the asymptomatic patients, such as gynecological surgery, Tumors, immune diseases, hyper-coagulation state, slow blood flow, obesity, braking, dehydration, infection, or oral contraceptives. Orthopedic patients have signs and symptoms in their legs from the trauma of surgery or fracture. However, we considered that they had no additional symptoms or signs of DVT at the time. Hence being “asymptomatic” means that the patients without symptoms of DVT. Through this meta-analysis, we can recognize that in reality the rate of missed diagnosis of lower extremity DVT amounts to 50% or so in the patients without symptom of DVT.

We found that the sensitivity was significantly lower (59%) compared with that found in the meta-analysis performed by Goodacre[8] (90%), which included both asymptomatic and symptomatic patients. It should be noted that including both asymptomatic and symptomatic patients in the same analysis as performed by Goodacre introduced a marked threshold effect and heterogeneity. Clinical symptoms in the presence of a larger embolus provide an even more distinctive signal to the US operator. Our meta-analysis focused on asymptomatic patients, and no significant threshold effect or publication bias was found. Therefore, the presence of symptoms might have influenced the significant heterogeneity and threshold effect found in the study of Goodacre. However, many more asymptomatic patients than symptomatic patients are seen in clinical practice. Since some of the patients correctly identified by venography in the included trials were excluded from US investigations due to technically difficulties or an indeterminate result was obtained, the diagnostic accuracy of US might have been overestimated. Similarly, some patients who were correctly identified by US in the included trials were excluded from venography due to technical difficulties or obtaining an indeterminate result, which may have led to an underestimation of the diagnostic accuracy of US. However, the overall quality of studies included in this meta-analysis was high. Finally, the results of our analysis show that US

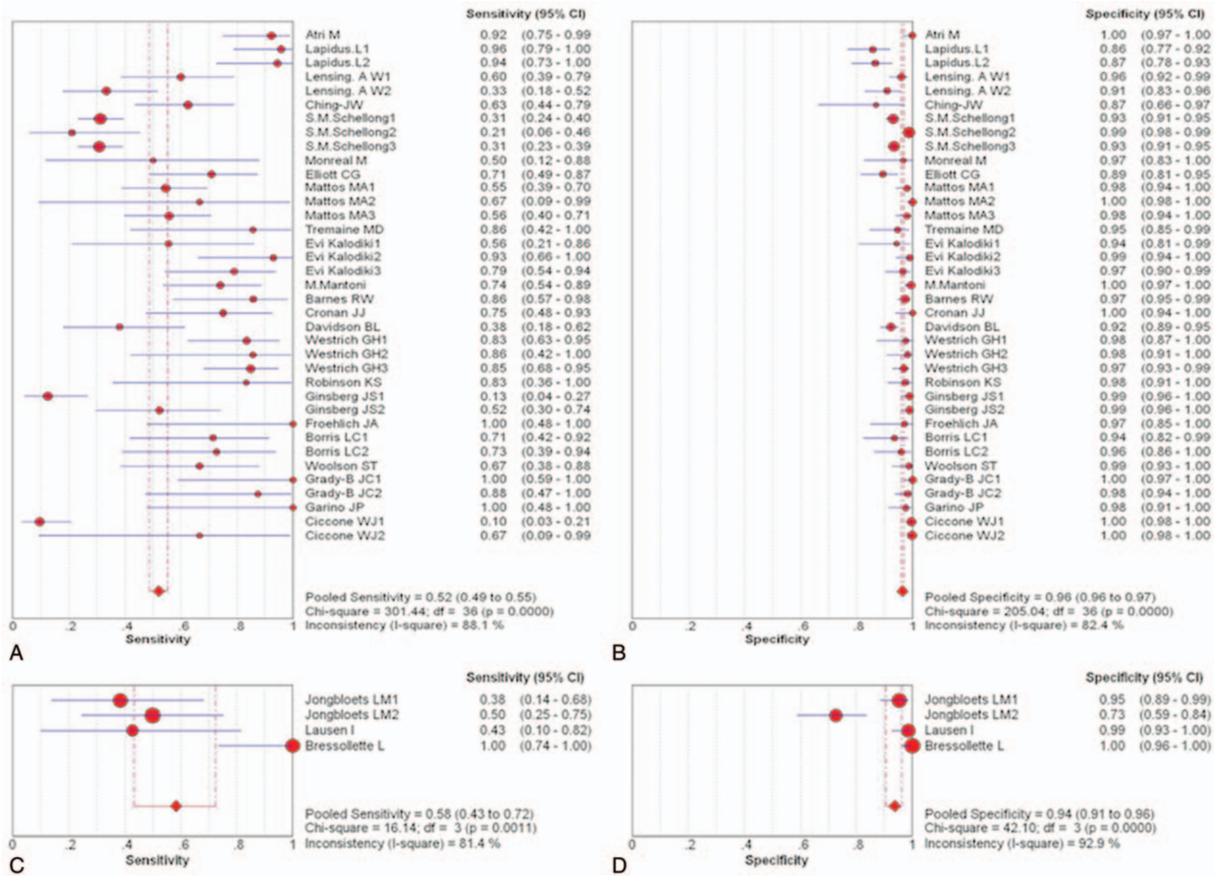

Figure 4. Pooled sensitivity and specificity of ultrasound for the diagnosis of asymptomatic lower limbs deep-vein thrombosis. (A) Post-major orthopedic surgery patients pooled sensitivity. (B) Post-major orthopedic surgery patients pooled specificity. (C) Other types of patients pooled sensitivity. (D) Other types of patients pooled specificity.

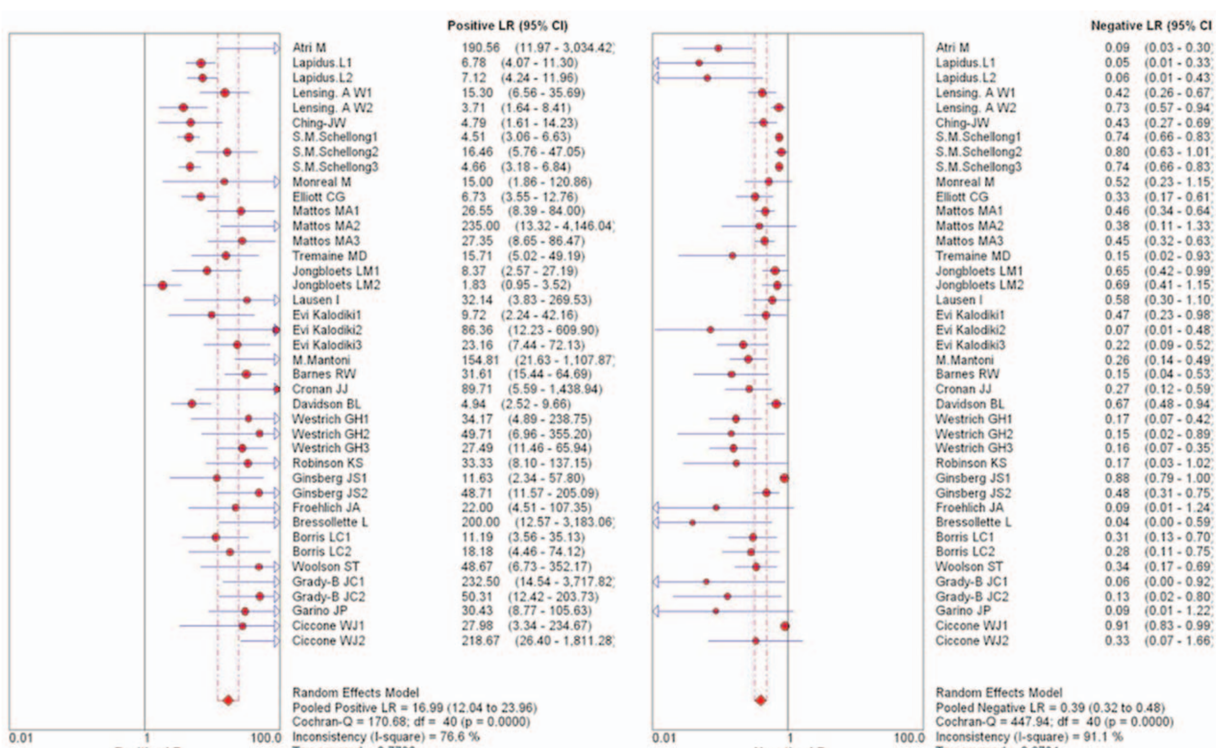

Figure 5. Positive likelihood and negative likelihood ratios of ultrasound for the diagnosis of asymptomatic lower limbs deep-vein thrombosis.

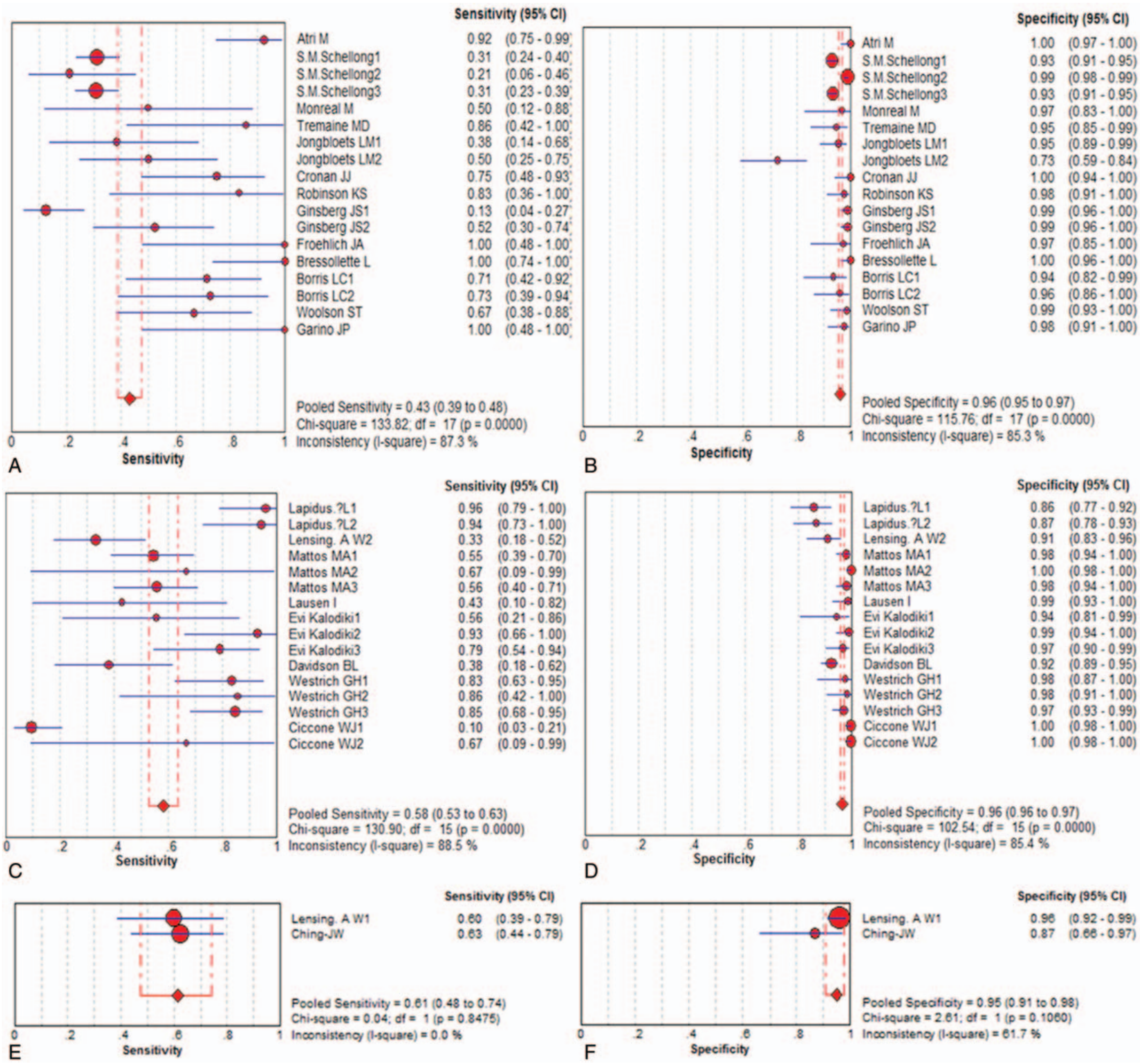

Figure 6. Pooled sensitivity and specificity of ultrasound for the diagnosis of asymptomatic lower limbs deep-vein thrombosis. (A) Pure compression sensitivity. (B) Pure compression specificity. (C) Pure color/doppler sensitivity. (D) Pure color/doppler specificity. (E) Compression and color/doppler sensitivity. (F) Compression and color/doppler specificity.

has a low sensitivity and high specificity as a screening method for asymptomatic patients.

One study[50] showed that emergency physicians can attain a reasonably high initial accuracy when applying US to various clinical problems after a 10-hour training period. There were also some differences in the US power and frequency among the included studies. Different authors take different language expression ways in their original studies. Various types and names of US were used. Subgroup analysis showed that pure compression technique for DVT had a poor sensitivity of 43%. Pour color/doppler technique for DVT had a moderate sensitivity of 58%. Mixing compression and color/doppler technique for DVT had a moderate sensitivity of 61%. Therefore, the color/doppler technique should be the preferred approach in patients without symptoms of DVT. The different qualifications of the individuals performing the US investigations and interpreting venography results in the studies may be considered potential sources of bias. Our use of meta-regression analysis searching for heterogeneous sources revealed that heterogeneity was not related to the 4 main factors of the examined part, the type of US, the type of patient, the year of publication or the experience of the operator. Moreover, subgroup analyses based on the 5 main factors did not exhibit significantly different diagnostic accuracies relative to using the overall pooled data and did not increase the statistical heterogeneity.

Some shortcomings of the present meta-analysis should be mentioned. The most recent study within the meta-analysis was reported a decade ago and studies date back to 1988. Improving technology, operator skill and development of triplex techniques render our pooled diagnostic test characteristics subject to bias here. But We would like to emphasize that the conclusions that high sensitivity of US for proximal DVT and distal DVT have emerged from these ancient articles. However, there are no relevant studies after 2007 indicates that US is reliable for the detection of

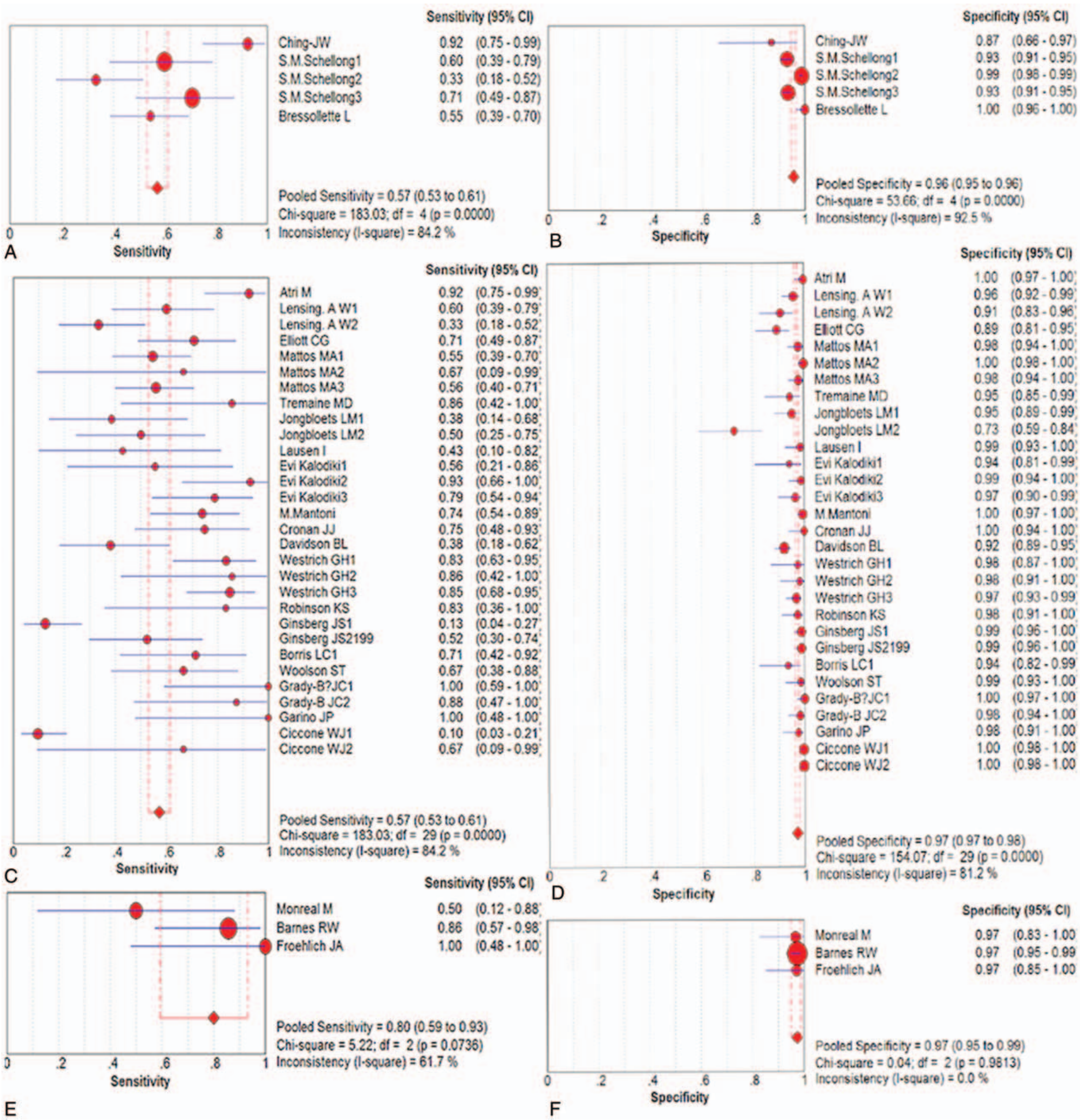

Figure 7. Pooled sensitivity and specificity of ultrasound for the diagnosis of asymptomatic lower limbs deep-vein thrombosis. (A) 2000s sensitivity. (B) 2000s specificity. (C)1990s sensitivity. (D)1990s specificity. (E) 1980s sensitivity. (F) 1980s specificity.

asymptomatic DVT due to the progress in US-methods and technology. The presence of significant statistical heterogeneity limits the ability to summarize the pooled diagnostic statistics.

5. Conclusions

US could be a useful tool for diagnosing DVT, but it has a lower positive rate and a higher false negative rate. The rate of missed diagnosis of lower-limb DVT by US amounts to 50% or so in the patients without symptoms of DVT. The negative results do not preclude the possibility of DVT and if appropriate heightened surveillance and continued monitoring or try a more accurate inspection method is warranted. The whole leg evaluation and color/doppler technique should be the preferred approach.

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