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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
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Μεταπτυχιακή Διπλωματική Εργασία

" The role of ultrasound with contrast agent (CEUS) compared to multidetector computed tomographic angiography (MD-CTA) in the postoperative follow-up of endovascular aortic repair"

υπό

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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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Contents

1. Abstract

Background: The current study is based on the findings of the implementation of ultrasound with the addition of contrast agent (CEUS) to detect endoleaks after endovascular aortic repair (EVAR).

Method: Literature review was performed by searching in Scopus, Cochrane, and PubMed databases, according to the PRISMA protocol. Weighted Mean Difference, Odds Ratio, and 95% Confidence Interval were calculated, implementing Random-Effects model. Patients undergoing EVAR were observed with the following imaging techniques: CEUS and MD-CTA. CEUS was then compared to MD-CTA for its accuracy. The type of the endoleak, the diameter aneurysm, and the time elapsed after EVAR were the basic features that were analyzed.

Results: The present meta-analysis included twenty six articles, accounting for a total of 3,986 patients. CEUS was found as not different to multidetector computed tomography (MD-CTA), in identifying endoleaks after EVAR ($p < 0.05$). These two modalities showed similar positive predictive value.

Conclusion: CEUS represents a valid non-bloody imaging tool in the context of endoleaks diagnosis after EVAR, as a follow-up tool, and do not differ with MD-CTA. However, our results should be considered cautiously as there is lack of RCTs.

Keywords: CEUS; contrast-enhanced ultrasound; endoleaks; endovascular aortic repair; meta-analysis

1.2 Περίληψη

Εισαγωγή: Η παρούσα μελέτη στοχεύει στην αξιολόγηση του υπερηχογραφήματος με σκιαγραφικό ενίσχυσης (CEUS) σε σύγκριση με την αξονική αγγειογραφία (CTA) στην ανίχνευση διαφυγής μετά από ενδοαγγειακή αποκατάσταση αορτικού ανευρύσματος (EVAR).

Μέθοδος: Πραγματοποιήσαμε συστηματική αναζήτηση βιβλιογραφίας σε τρεις βάσεις δεδομένων (Pubmed, Scopus, CENTRAL) για πρωτότυπες μελέτες (1990-2021). Τα στατιστικά μοντέλα που χρησιμοποιήθηκαν ήταν τα fixed και random effect, ανάλογα με το επίπεδο ετερογένειας, ενώ υπολογίστηκαν τα Q και I^2 statistic για να αξιολογηθεί η ετερογένεια. Το βασικό ερώτημα ήταν η ακρίβεια του CEUS σε σύγκριση με την MD-CTA. Καταγράφηκαν και επεξεργάσθηκαν οι ακόλουθες παράμετροι: η διάμετρος του ανευρύσματος, ο τύπος διαφυγής και ο χρόνος που μεσολάβησε από την EVAR.

Αποτελέσματα: Συμπεριλήφθηκαν είκοσι έξι άρθρα με συνολικά 3.986 ασθενείς. Το CEUS βρέθηκε να μην διαφέρει από την αξονική (MD-CTA), στην ανίχνευση διαφυγών μετά από EVAR ($p<0,05$). Η θετική προγνωστική αξία ήταν παρόμοια μεταξύ των δύο μεθόδων.

Συμπέρασμα: Το CEUS είναι μία ασφαλής και αποτελεσματική μη επεμβατική μέθοδος απεικόνισης στην παρακολούθηση μετά από ενδοαγγειακή αποκατάσταση αορτικού ανευρύσματος EVAR για την ανίχνευση διαφυγών και δε διαφέρει από την MD-CTA.

2. Introduction

Conventional open surgery has been replaced by a minimally invasive alternative method in vascular surgery; endovascular aneurysm repair (EVAR) [1]. In fact, EVAR is connected with a low rate of operative morbidity, mortality, and reduced hospital stay for elective aneurysm of the abdominal aorta (AAA) repair in contrast to conventional open surgery [2-4]. The drawback of EVAR is the importance of a regular follow-up to detect the complications that occur from stent-grafting. [5].

Endoleak is a quiet common complication, that occurs in 20%–50% of patients after EVAR [6]. In most cases, endoleaks are asymptomatic, thus highlighting the importance of early detection of an endoleak, which may allow its treatment in a minimally invasive manner [7]. Nevertheless, there is not a general agreement referring to the ideal diagnostic imaging modalities for the follow-up after EVAR. Contrast-enhanced ultrasonography (CEUS) along with Magnetic resonance angiography (MRA) may be more accurate than MD-CTA [10].

The ideal imaging technique in the follow-up should be of low-cost, safe, repeatable, accurate and non-invasive. Contrast-enhanced ultrasound (CEUS) represents a higher sensitivity than Duplex Ultrasound (DUS), and compared to MD-CTA it has certain advantages, such as no radiation exposure and contrast-induced nephropathy (CIN) [8-9]. Microbubble-based ultrasound contrast agents can act as echo-enhancers giving the opportunity to visualize endoleaks after EVAR with more accuracy than conventional ultrasound [10].

Several studies that evaluated CEUS in the detection of endoleaks suggested that its sensitivity is comparable with MD-CTA. Furthermore, CEUS has the ability to provide precise details for the classification of endoleak, as it permits the diffusion of the contrast agent in the region where we are interested in and in real time [7]. Moreover, measurements such as contrast's flow velocity, the flow of the blood into the aneurysm, and its direction can be taken, unlike the MD-CTA which gives static images, leading to false-negative results. [10]

In spite of its satisfactory cost–effective ratio, effectiveness, and safety in contrast to the rest of the imaging modalities CEUS has not been implemented into the clinical practice of most diagnostic imaging services and vascular surgery.

This article was performed to evaluate the existing evidence in the available studies on the efficacy of CEUS as an imaging modality which has the potential to detect endoleaks after EVAR.

3. Materials and Methods

3.1. Search method and articles inclusion

The current research was completed in agreement with a protocol accepted by all authors who participated and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [11]. A careful search in the available studies was completed in Scopus (ELSEVIER), Cochrane Central Register of Controlled Studies (CENTRAL) and Pubmed (Medline) (last search: November 10, 2021). The below terms were employed in every potential combination: "ultrasound with contrast agent", "CEUS", "endovascular aortic repair", "EVAR", "aortic aneurysm repair", "aneurysm".

The present study included only the articles that were in accordance with the following criteria: (i) conducted on human subjects, (ii) primary studies with $\geqslant$ 10 patients, (iii) written in the English language, (iv) issued between 1990 to 2021 and (v) reporting outcomes of CEUS in patients who undergo endovascular aortic repair. In the event of multiple studies that where based on the same population group, only the study that presented the longest follow-up or the study with the larger population group, was selected in this meta-analysis.

The data from the included studies were selected by two independent investigators (MPF, DEM). Any disagreement between the two reviewers concerning the included or excluded studies were discussed with the senior author (GA) to choose articles that best fitted in the protocol until agreement was accomplished. Moreover, the lists of all the studies, that were included in the present review, were further evaluated for the possibility of entitled articles. Furthermore, to assess the rate of accordance between the reviewers kappa coefficient test was applied

3.2. Data extraction

Data relative to demographics (size of the sample, scan pairs, follow-up, time interval between CEUS and MD-CTA) was extracted for each study that was included in this review along with the primary endpoints (sensitivity, specificity, the positive and negative predictive value (PPV and NPV) of CEUS as compared with MD-CTA. Two researchers (MPF, DEM) conducted the data extraction and made the comparison of the strength of the data until agreement was completed.

3.3. Statistical Analysis

Referring to the categorical variables, the Odds Ratio (ORs) and 95% confidence interval (95% CI) were calculated by the use of Random-Effects model (Mantel-Haenszel statistical method). OR<1 result was noticed to be more frequent in the CEUS group. Weighted mean difference (WMD) with its 95 % CI was used to calculate continuous outcomes, by Random-Effects (Inverse Variance statistical method) models. When WMD < 0, values in the CEUS group were elevated . The Random-Effects model was selected as we did not anticipate that all the studies that were included would present a similar effect size. Cochran Q statistic and estimated I2 were used to asses study heterogeneity. [12]. Moreover, we implemented a bivariate meta-analytic approach, based on 2x2 tables, in order to pool the weighted summary rates of sensitivity and specificity for CEUS and MD-CTA modalities, and a hierarchical summary receiver operating characteristic (HSROC) model was applied to form the summary receiver operating characteristic (SROC) curves with 95% confidence intervals (CIs) and prediction regions [11]. Forest plots were constructed concerning the variables that were analyzed. Analysis of the data was done using the Cochrane Collaboration RevMan version 5.4.

3.4.Quality and Publication Bias Assessment

Assessment of non-Randomized Controlled Trials (non-RCTs) was done by the use of the Newcastle-Ottawa Quality Assessment Scale (NOS) [13]. The scale varies from zero to nine stars. Studies that were characterized with a score equal to or higher than five were reflected to have enough methodological quality and were included. In the present meta-analysis no RCTs were included. The studies included in the current review were rated separately by two investigators (MPF, DEM) and ultimate decision was made by agreement. Evaluation of the hazard of publication bias was done by the visual inspection of funnel plots.

4. Results

4.1. Article Selection And Patient Demographics

Systematic literature search flow diagram is demonstrated in *Figure 1* and the *Prisma Checklist*. Altough 180 studies were retrieved in Pubmed, Scopus, and CENTRAL , only 26 studies were included in the quantitative and qualitative synthesis [13-38]. The degree of consensus between the two reviewers was "almost perfect" (kappa=0.936; 95% CI: 0.863, 1.000). There were no randomized-controlled studies incorporated in the present meta-analysis. A number of 3,986 patients was incorporated in the present study. In *Table 1* there are the baseline characteristics of the included studies represented, as well as, the Newcastle-Ottawa rating scale assessment for all studies. In most of the studies SonoVue was injected as a contrast agent.

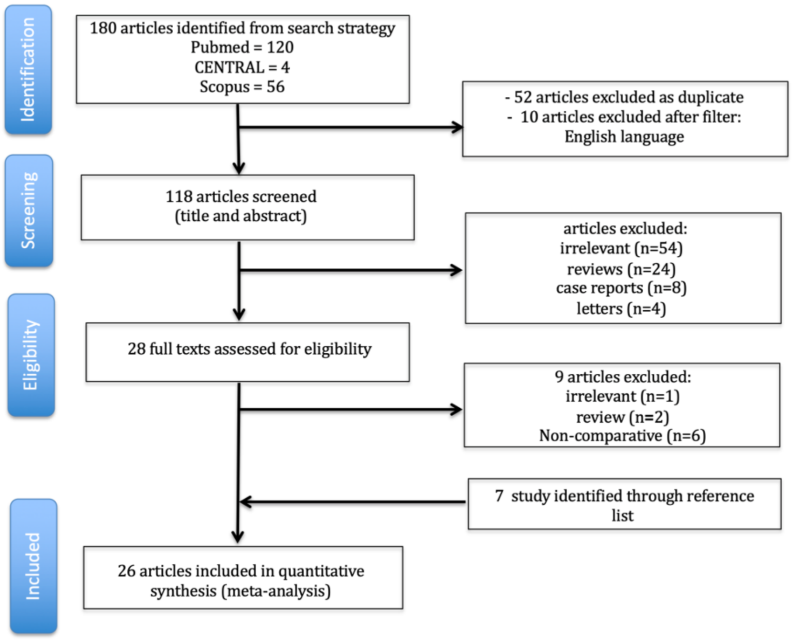


Figure 1. Evaluation of CEUS after EVAR flow diagram.

4.2. Endoleaks

Fourteen studies compared CEUS with MD-CTA regarding all types of endoleaks. As stated in our analysis both imaging modalities were related to similar outcomes in diagnosing all types of endoleaks (OR:1.06 [95% CI: 0.77, 1.46]; p=0.71) (Figure 2).

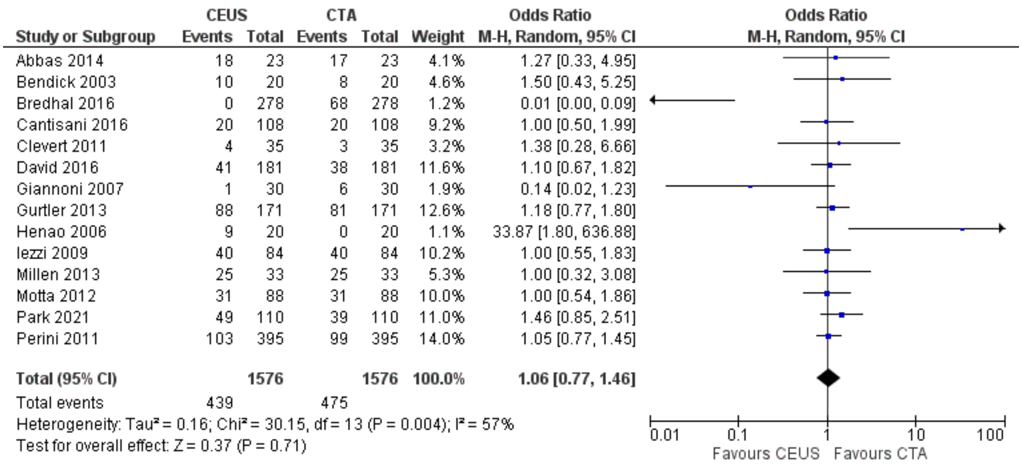


Figure 2. Forest plot for endoleaks

4.3. Type I and III endoleaks

Endoleaks characterized as type I were diagnosed equally by both CEUS and MD-CTA (OR:1.16 [95% CI: 0.74, 1.81]; *p*=0.52) (Figure 3). In addition, based on our analysis both imaging modalities were represented similar outcomes in detecting type III endoleaks (OR:0.84 [95% CI: 0.42, 1.70]; *p*=0.63) (Figure 4).

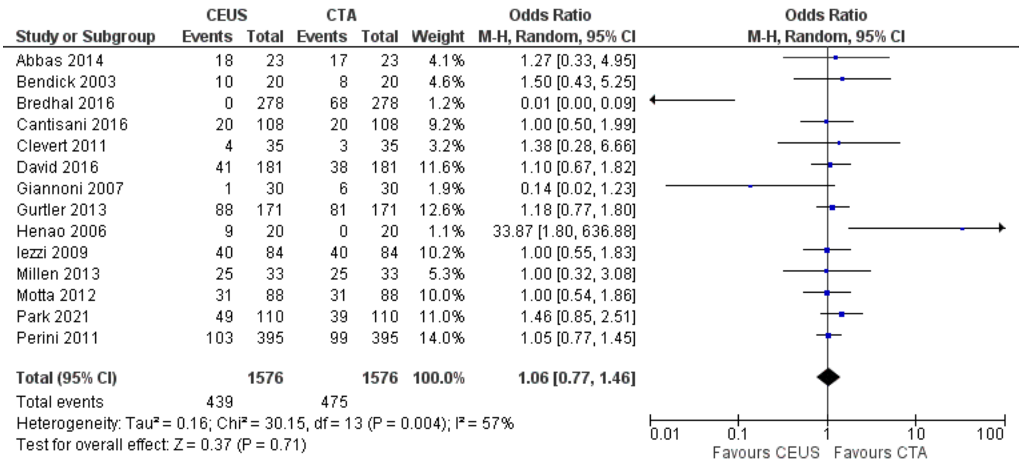


Figure 3. Forest plot for type I endoleaks

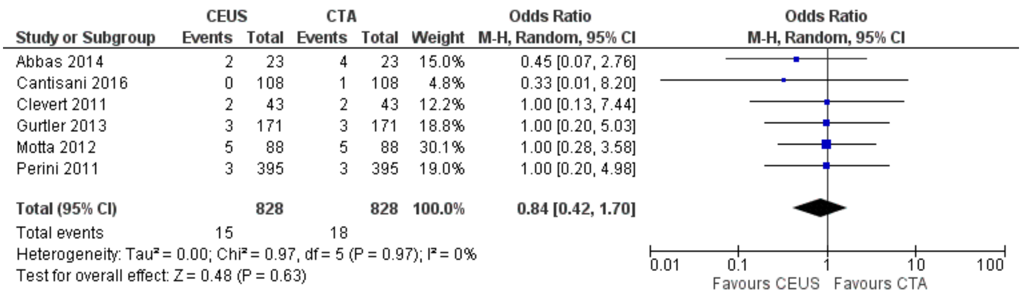


Figure 4. Forest plot for type III endoleaks

4.4. *Type II endoleaks*

Fourteen studies compared CEUS with MD-CTA regarding type II endoleaks. As referred to our analysis, both modalities represented similar outcomes in detecting type II endoleaks (OR:0.99 [95% CI: 0.59, 1.68]; *p*=0.98) (Figure 5).

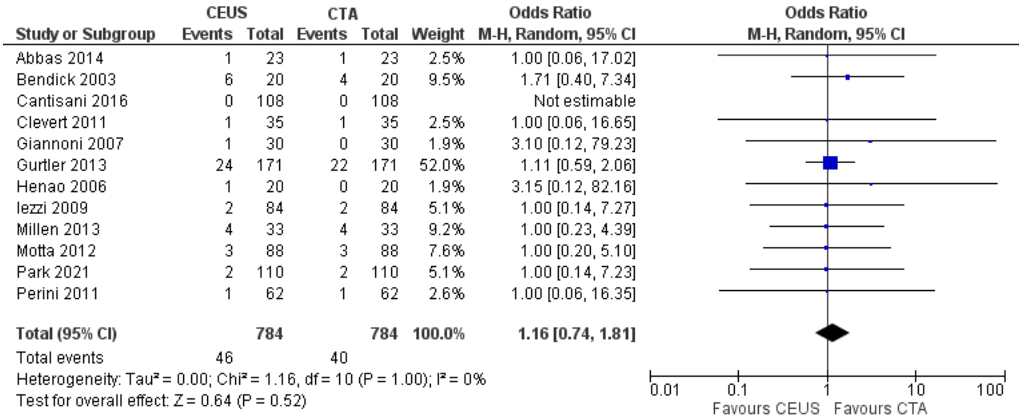
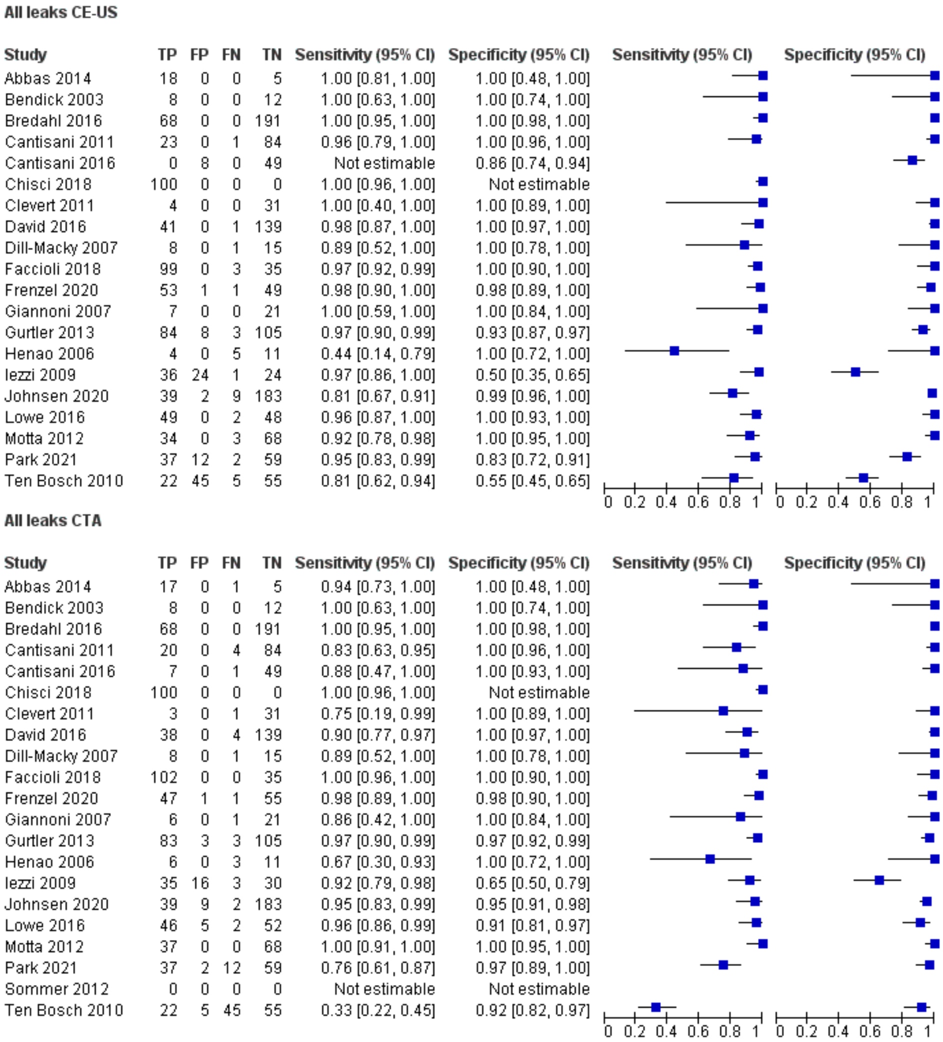


Figure 5. Forest plot for type II endoleaks

4.5. SROC curve for CEUS and MD-CTA

The SROC curves of CEUS and MD-CTA were constructed by stratifying sensitivity against specificity for the diagnosis of post-EVAR endoleaks and the Forest Plot is provided in *Figure 6*. The curves the total performance test of all the studies that were included. Moreover, they represented that the 95% confidence and prediction regions were related to impressing heterogeneity that appeared among the studies. The total weighted area under the SROC curve (AUC) was similar for both modalities as demonstrated in *Figure 7*.



All leaks CE-US

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abbas 2014	18	0	0	5	1.00 [0.81, 1.00]	1.00 [0.48, 1.00]
Bendick 2003	8	0	0	12	1.00 [0.63, 1.00]	1.00 [0.74, 1.00]
Bredahl 2016	68	0	0	191	1.00 [0.95, 1.00]	1.00 [0.98, 1.00]
Cantisani 2011	23	0	1	84	0.96 [0.79, 1.00]	1.00 [0.96, 1.00]
Cantisani 2016	0	8	0	49	Not estimable	0.86 [0.74, 0.94]
Chisci 2018	100	0	0	0	1.00 [0.96, 1.00]	Not estimable
Clevert 2011	4	0	0	31	1.00 [0.40, 1.00]	1.00 [0.89, 1.00]
David 2016	41	0	1	139	0.98 [0.87, 1.00]	1.00 [0.97, 1.00]
Dill-Macky 2007	8	0	1	15	0.89 [0.52, 1.00]	1.00 [0.78, 1.00]
Faccioli 2018	99	0	3	35	0.97 [0.92, 0.99]	1.00 [0.90, 1.00]
Frenzel 2020	53	1	1	49	0.98 [0.90, 1.00]	0.98 [0.89, 1.00]
Giannoni 2007	7	0	0	21	1.00 [0.59, 1.00]	1.00 [0.84, 1.00]
Gurtler 2013	84	8	3	105	0.97 [0.90, 0.99]	0.93 [0.87, 0.97]
Henao 2006	4	0	5	11	0.44 [0.14, 0.79]	1.00 [0.72, 1.00]
Iezzi 2009	36	24	1	24	0.97 [0.86, 1.00]	0.50 [0.35, 0.65]
Johnsen 2020	39	2	9	183	0.81 [0.67, 0.91]	0.99 [0.96, 1.00]
Lowe 2016	49	0	2	48	0.96 [0.87, 1.00]	1.00 [0.93, 1.00]
Motta 2012	34	0	3	68	0.92 [0.78, 0.98]	1.00 [0.95, 1.00]
Park 2021	37	12	2	59	0.95 [0.83, 0.99]	0.83 [0.72, 0.91]
Ten Bosch 2010	22	45	5	55	0.81 [0.62, 0.94]	0.55 [0.45, 0.65]

All leaks CTA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abbas 2014	17	0	1	5	0.94 [0.73, 1.00]	1.00 [0.48, 1.00]
Bendick 2003	8	0	0	12	1.00 [0.63, 1.00]	1.00 [0.74, 1.00]
Bredahl 2016	68	0	0	191	1.00 [0.95, 1.00]	1.00 [0.98, 1.00]
Cantisani 2011	20	0	4	84	0.83 [0.63, 0.95]	1.00 [0.96, 1.00]
Cantisani 2016	7	0	1	49	0.88 [0.47, 1.00]	1.00 [0.93, 1.00]
Chisci 2018	100	0	0	0	1.00 [0.96, 1.00]	Not estimable
Clevert 2011	3	0	1	31	0.75 [0.19, 0.99]	1.00 [0.89, 1.00]
David 2016	38	0	4	139	0.90 [0.77, 0.97]	1.00 [0.97, 1.00]
Dill-Macky 2007	8	0	1	15	0.89 [0.52, 1.00]	1.00 [0.78, 1.00]
Faccioli 2018	102	0	0	35	1.00 [0.96, 1.00]	1.00 [0.90, 1.00]
Frenzel 2020	47	1	1	55	0.98 [0.89, 1.00]	0.98 [0.90, 1.00]
Giannoni 2007	6	0	1	21	0.86 [0.42, 1.00]	1.00 [0.84, 1.00]
Gurtler 2013	83	3	3	105	0.97 [0.90, 0.99]	0.97 [0.92, 0.99]
Henao 2006	6	0	3	11	0.67 [0.30, 0.93]	1.00 [0.72, 1.00]
Iezzi 2009	35	16	3	30	0.92 [0.79, 0.98]	0.65 [0.50, 0.79]
Johnsen 2020	39	9	2	183	0.95 [0.83, 0.99]	0.95 [0.91, 0.98]
Lowe 2016	46	5	2	52	0.96 [0.86, 0.99]	0.91 [0.81, 0.97]
Motta 2012	37	0	0	68	1.00 [0.91, 1.00]	1.00 [0.95, 1.00]
Park 2021	37	2	12	59	0.76 [0.61, 0.87]	0.97 [0.89, 1.00]
Sommer 2012	0	0	0	0	Not estimable	Not estimable
Ten Bosch 2010	22	5	45	55	0.33 [0.22, 0.45]	0.92 [0.82, 0.97]

Figure 6. Forest plot for sensitivity and specificity of CEUS and MD-CTA for endoleaks

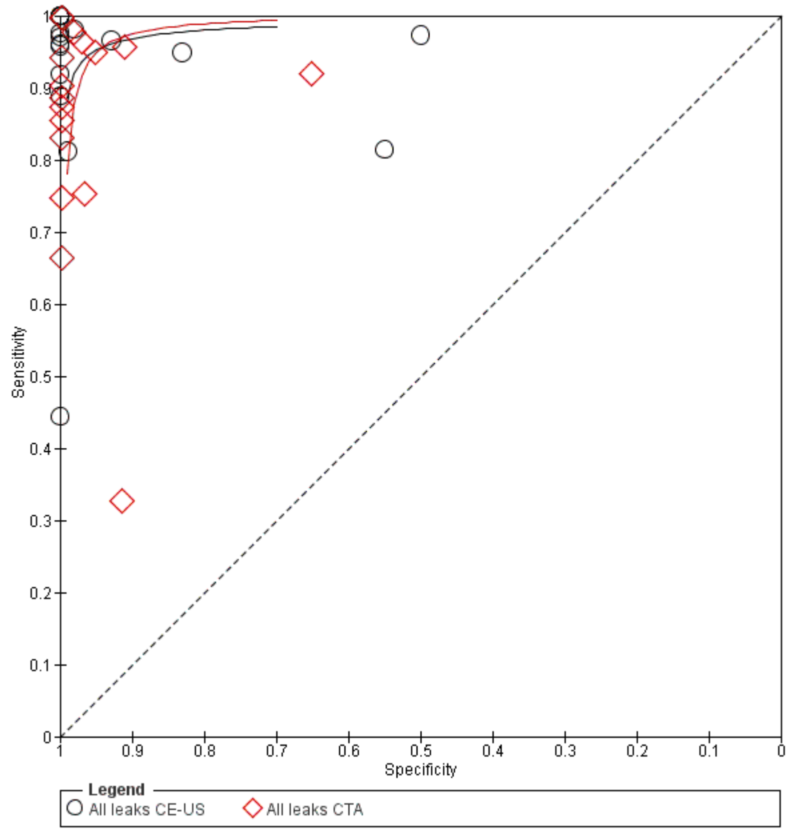


Figure 7. SROC curve demonstrating CEUS and MD-CTA sensitivity and specificity for endoleaks

4.6. Publication Bias

High heterogeneity was denoted regarding all type and type I endoleaks. Furthermore, low heterogeneity was noticed in type II and type III endoleaks. Funnel plots (*Figures 8-11*) showed asymmetry, as long as there were no studies being either to top or bottom of the graph, thus creating an important publication bias. The short list of the included studies, the different protocols among different centers, along with the different inclusion/exclusion criteria were the most important reason for the reported asymmetry.

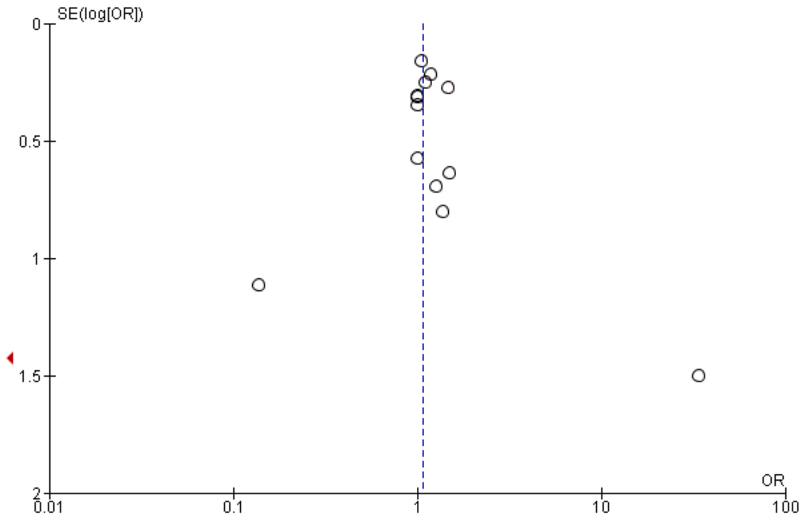


Figure 8. Funnel plot for total endoleaks

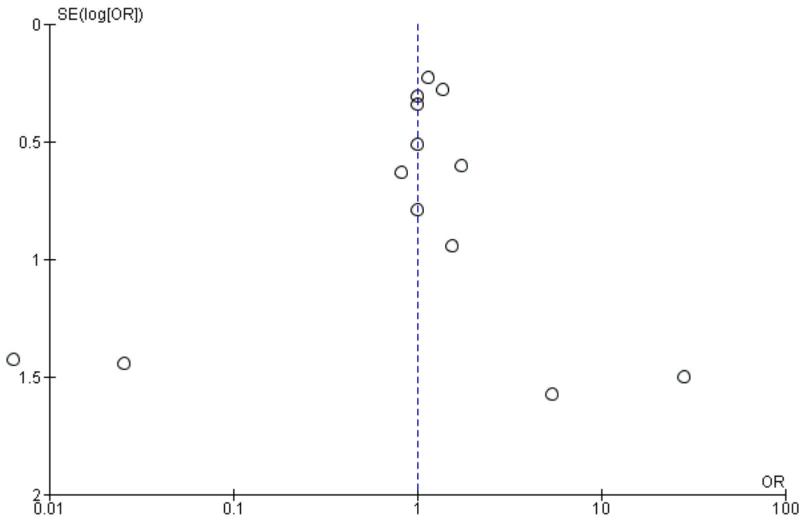


Figure 9. Funnel plot for total type I endoleaks

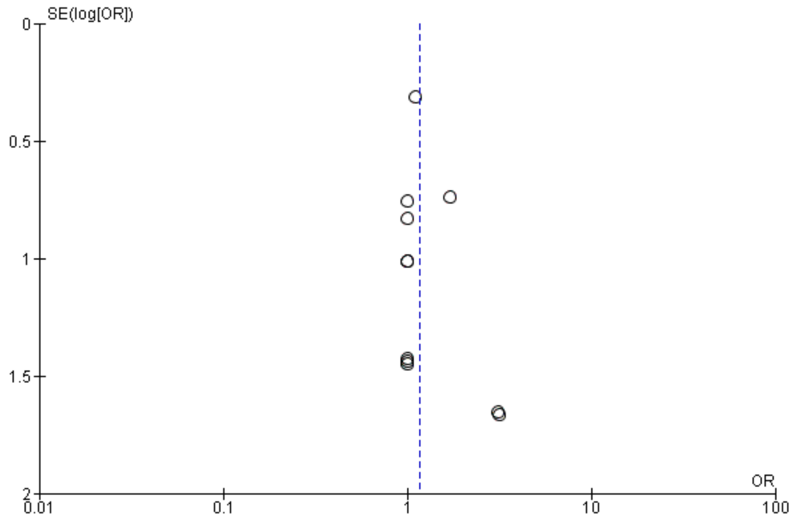


Figure 10. Funnel plot for total type III endoleaks

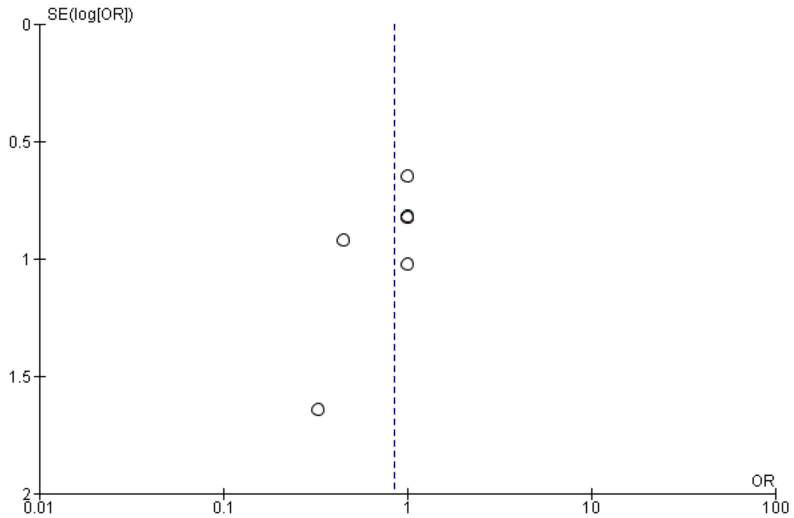


Figure 11. Funnel plot for total type II endoleaks

5.Discussion

Aneurysm repair of the Abdominal aorta with endovascular grafting approach (EVAR) has been proposed as an alternative technique to conventional surgery, as it combines a low rate of early mortality, importantly fewer adverse effects and a low incidence of aneurysm rupture [1, 2].

Endoleaks have an occurence between 2.4 and 45.5% and the treatment should be early to avoid a potential rupture. Patients who have been treated with EVAR should be approached with an appropriate follow-up surveillance to assess the adjustment of the graft, its integrity, and any potential complication, such as endoleaks. [41,42].

There are five categories of endoleaks [40, 41]. Type I endoleaks are happening because of insufficient proximal (Ia) or distal (Ib) sealing of the grafting and need immediate repair. Type II endoleaks caused by the existence of collateral flow from lumbar arteries and the inferior mesenteric artery. Type III endoleaks present structural defects or disconnections of parts of the graft and need immediate repair. Type IV endoleaks are not very common and are attributed to graft porosity. Type V endoleak, which cannot be detected by any imaging modality due to its low flow and quick thrombosis [43]. Type I and II endoleaks are the most common in the literature [43,44].

MD-CTA is the most usually employed modality as it is available to any hospital, with high diagnostic value and rapid acquisition [45,46] . Nonetheless, MD-CTA has some drawbacks such as increased cost, the risk of nephrotoxicity which is induced by the contrast agent, and exposure to radiation. There is no a generally accepted agreement on the MD-CTA protocol for endoleak diagnosis, and some researchers support the need of the arterial or delayed phase [47,48]. On the other hand, MRA has benefits such as no radiation exposure and a lower nephrotoxicity risk. Nevertheless, it remains a coslty, and time-consuming imaging method, that is not available in every hospital 24 hours a day [49].

On the other hand, CEUS is a non-invasive imaging tool with additive diagnostic accuracy to that of color duplex ultrasound (CDUS) in the diagnosis of endoleaks after EVAR [47]. CEUS combines the benefits of the ultrasound modality (low-cost, no radiation, safe, non-invasive) . Furthermore, contrast-enhanced ultrasound (CEUS) has certain advantages compared to MD-CTA. For example, it does not cause contrast-induced nephropathy (CIN) [8-9]. Microbubble-based ultrasound contrast agents act as echo-enhancers, and thus, the diagnosis of endoleaks becomes more accurate compared to conventional ultrasound [10]. CEUS offers direct visualizing of blood flow, providing hemodynamic information and allows better definition of the type of endoleak compared to MD-CTA, that provides static images. The disadvantage of CEUS is that it is operator-dependent and thus it varies according to the operators expertise while the anatomical and anthropometric conditions can make more difficult the exam [21]. Complications associated with CEUS are very rare and they are attributed to the micobubble-based contrast agent, which can cause allergic reaction, dizziness, nausea, flushing, temperature elevation chest pain, dyspnea or back pain. All these side effects are resolved spontaneously without treatment [50].

According to our results, both MD-CTA and CEUS were associated with similar outcomes in detecting all types of endoleaks. In fact, this result is harmonious with a previously published meta-analysis [51].

The limitations of the present systematic review are inherent to the restrictions of the studies included in the analysis. The lack of RCTs weakens the strength of the current study. Additionally, certain patients' inclusion criteria and publication biases cannot be excluded based on the asymmetry of funnel plots. Finally, CEUS protocol and operator differences may consist additional potential sources of bias.

6. Conclusion

The present systematic review on 26 studies evaluating CEUS versus MD-CTA, in the diagnosis of endoleak after EVAR demonstrated that both modalities do not differ in terms of our primary and secondary endpoints. Nevertheless, these results should be interpreted carefully in the absence of RCTs and to the fact that the included studies in the analysis may be inherent to several biases. Taking into consideration the importance of having access to a valid, safe, easily-available, low-cost, and friendly-to-use imaging tool during the post-EVAR period, new evidence is necessary to further support our findings. Finally, our study provides the best currently available evidence on the postoperative EVAR imaging follow-up.

Conflicts of interest

Nothing to disclose.

Acknowledgements

Does not apply.

7. References

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Study, year	No. of patients	Scan pairs	Range of follow up	Interval between CEUS and CTA	CEUS+ CT+	CEUS+ CT-	CEUS- CT+	CEUS- CT-	Sensitivity, %	Specificity, %	NOS
Abbas et al, 2014 [14]	23	30	Not stated	3.9 +/- 2.7 weeks	17	1	0	12	94	92	6
Bendick et al, 2003 [15]	69	20	1-12 months	2 weeks	20	0	49	0	100	N/A	7
Bredhal et al, 2016 [16]	359	278	3-12 months	7 days	278	0	7	74	85	95	7
Cantisani et al, 2011 [17]	108	108	1-24 months	Max 1 week	20	3	0	85	100	97	6
Cantisani et al, 2016 [18]	57	57	1-12 months	Same day ? (unclear)	7	1	0	49	100	98	6
Chisci et al, 2018 [19]	880	100	24-84 months	Within 30 days	100	124	562	686	100	100	7
Clevert et al, 2011 [20]	43	43	No follow-up or protocol	Within 1 day	15	2	0	26	100	93	7

			given								
David et al, 2016 [21]	181	181	1-48 months	Max 6 days	37	4	1	139	97	97	7
Dill Macky et al, 2007 [22]	24	24	2 days – 32 weeks	Same day or within a month	6	2	2	14	75	88	6
Faccioli et al, 2018 [23]	157	137	6 years	2-7 days	137	0	20	0	96	100	7
Frenzel et al, 2021 [24]	76	76	1-12 months	1-3 days	55	0	21	0	98.1	97.7	7
Gargiulo et al, 2014 [25]	22	22	1 – 35 months	Within 30 days	2	0	1	19	67	100	7
Giannoni et al, 2007 [26]	29	29	1 month – 1 year	Within 15 days	7	1	0	21	100	95	7
Gilabert et al, 2012 [27]	35	126	6-38 months	Within 30 days	33	0	1	92	97	100	7
Gurtler et al, 2013 [28]	132	200	Not started	Within 30 days	84	8	3	105	97	93	7

Henao et al, 2006 [29]	**20**	**20**	**1-36 months**	**Same day**	**6**	**3**	**0**	**11**	**100**	**79**	**7**
Iezzi et al , 2009 [30]	**84**	**84**	**1- 24 months**	**Same day**	**39**	**8**	**1**	**36**	**98**	**82**	**7**
Jiang et al, 2015 [31]	**16**	**16**	**2 years**	**More than 2 weeks**	**16**	**0**	**0**	**0**	**Equal to CT**	**N/A**	**6**
Johnsen et al, 2020 [32]	**92**	**233**	**1- 24 months**	**Same day**	**92**	**0**	**0**	**0**	**81.3**	**98.9**	**6**
Lowe et al, 2016 [33]	**99**	**100**	**Not stated**	**Max 4 weeks**	**44**	**5**	**2**	**49**	**96**	**91**	**7**
Millen et al, 2013 [34]	**539**	**33**	**0 – 132 months**		**33**	**0**	**506**	**0**	**N/A**	**N/A**	**6**
Motta et al, 2012 [35]	**88**	**142**	**1 month – 100 years**	**Same day**	**34**	**0**	**3**	**105**	**89**	**100**	**7**
Park et al, 2021 [36]	**110**	**110**	**1- 65**	**Max 3 months**	**110**	**0**	**0**	**0**	**75.5**	**96.7**	**7**
Perini et al, 2011 [37]	**614**	**431**	**35 days – 9 years**	**Max 15 days**	**395**	**0**	**1**	**0**	**Same efficacy**		**7**
Sommer et al, 2012 [38]	**46**	**46**	**32 (+/- 16) months**	**1 day**	**17**	**1**	**2**	**26**	**89**	**96**	**6**

Ten Bosch et al, 2010 [39]	**83**	**127**	**1- 77 months**	**Within 30 days**	**22**	**45**	**5**	**55**	**98**	**91**	**6**