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Original Article

A meta-analysis of ultrasound imaging in diagnosis of endoleak among patients after endovascular abdominal aortic aneurysm repair

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Abstract: Background: Due to the high expenditure and the harmfulness of ion radiation of tradition computed tomography (CT) in endoleak diagnosis with patients after endovascular abdominal aortic aneurysm repair (EVAR), the alternative diagnostic methods with lower cost and more safety were being investigated. Although ultrasound (US) imaging had great prospect, its clinical sensitivity and specificity remained uncertain. Methods: All the relative publications were searched through PubMed and Embase, irrespective of the language restriction. And studies, that compared one or more US with CT in diagnosis of endoleak among patients after EVAR, were included. The data of true positive, false positive, true negative and false negative in each study were extracted, based on which, the sensitivity and specificity with their 95% confidence intervals (CI) were figured out as outcome. Then a meta-analysis was performed, in view of the significant heterogeneity among different types of US, we also performed the subgroup analysis of color-Doppler ultrasound (CDUS), power color-Doppler ultrasound (PDUS) and contrast enhanced ultrasonography (CEUS). Besides, the summary receiver operating characteristic (SROC) curve was plotted and its area under the curve (AUC) was calculated, which was convenient for latter comparison. Results: Based on results of meta-analysis, CEUS seemed the optimal choice with the largest AUC of 0.936, and its sensitivity was 0.889 with 95% CI from 0.813 to 0.936. And the secondary was CDUS, AUC of which was 0.822, but had the best performance in specificity of 0.887 with 95% CI from 0.826 to 0.929. No overlap in 95% CI of sensitivity indicated the significant difference between CDUS and CEUS, while there was less discrepancy in specificity. In terms of PDUS, it was insufficient in both items with AUC of 0.803. Besides, CEUS had higher positive ratio in general, when compared with CTA. Conclusion: CEUS with good comprehensive performance in sensitivity and specificity of diagnosing endoleak was recommended to be an alternate of CT. Because of the good performance, especially in specificity, CDUS also can be popularized as a primary or assisted diagnosis. The efficacy of PDUS remained uncertain. And more high-quality studies should be conducted for further research to reach a more powerful conclusion, so the present clinical diagnosis selection needed to take an adequate consideration of patients' situation.

Keywords: Ultrasound, color-Doppler ultrasound, power color-Doppler ultrasound, contrast enhanced ultrasonography, endovascular abdominal aortic aneurysm repair, endoleak, meta-analysis

Introduction

Abdominal aortic aneurysms (AAA) is an enlargement of abdominal artery with the diameter more than 50% larger than normal, which is a relatively common disease, especially in elderly male [1]. Usually, AAA is asymptomatic, difficult to detect on physical examination, and silent until discovered during radiologic testing for other reasons, like abdominal, back or leg pain [2]. One of the therapeutic approaches is endovascular aneurysm repair (EVAR) which was first described in 1991 and has been widely used to replace old open aneurysm repair [3]. EVAR avoids aneurysm rupture caused by AAA and relieve general pressure by exclusion of the aneurysmic sac from the systemic circulation [4]. Besides, EVAR has been demonstrated to achieve low perioperative mortality during treatment of AAA [5]. The patients taking EVAR require a shorter hospital stay. However, there are still unknown questions surrounding the long-term durability of EVAR [6, 7]. Many potential complications, including endoleak, graft

Table 1. Studies included in comparison of US, with contingency tables of diagnostic accuracy

US imaging	Study information	Country	Sample	TP	FP	FN	TN
CDUS	Bendick et al, 2003	USA	20	6	0	2	12
	Bendick et al, 2003	USA	20	8	2	0	10
	Cantisani et al, 2011	Italy	108	14	6	10	78
	Iezzi et al, 2009	Italy	84	25	16	15	28
	Collins et al, 2007	USA	31	10	14	3	4
	Sandford et al, 2006	UK	244	15	18	12	199
	Henao et al, 2006	USA	20	3	1	3	13
	AbuRahma et al, 2005	USA	367	23	4	11	329
	Raman et al, 2003	USA	494	21	18	28	427
	Giannoni et al, 2003	UK	26	2	0	2	22
	Parent et al, 2002	USA	151	18	18	10	105
	McWilliams et al, 2002	UK	84	2	4	15	63
	Greenfield et al, 2002	USA	11	6	1	1	3
	Pages et al, 2001	France	109	14	5	15	75
	Zannetti et al, 2000	Italy	198	11	3	1	183
	Wolf et al, 2000	USA	163	51	3	11	98
	Sato et al, 1998	USA	100	33	17	1	49
	Clevert et al, 2008	Germany	43	5	2	10	26
	Golzarian et al, 2002	Belgium	53	17	3	5	28
	Nagre et al, 2011	USA	561	54	19	100	388
	Schmieder et al, 2009	USA	472	48	62	27	335
	Jung et al, 2010	Germany	29	10	8	0	11
	Pfister et al, 2009	Germany	30	6	0	15	9
	Manning et al, 2009	Ireland	115	24	33	6	52
	Elkouri et al, 2004	USA	281	9	27	27	218
CEUS	Cantisani et al, 2011	Italy	108	23	0	1	84
	Iezzi et al, 2009	Italy	84	39	8	1	36
	Iezzi et al, 2009	Italy	84	37	9	3	35
	Giannoni et al, 2003	UK	26	4	3	0	19
	Abbas et al, 2014	UK	30	17	1	0	12
	Abbas et al, 2014	UK	30	17	1	0	12
	Gurtler et al, 2013	Germany	200	84	8	3	105
	Ten Bosch et al, 2010	Netherlands	127	22	45	5	55
	Perini et al, 2011	France	395	83	20	16	276
	Clevert et al, 2008	Germany	43	15	2	0	26
	McWilliams et al, 1999	UK	20	3	6	0	11
	Perini et al, 2012	France	62	5	1	2	54
	Jung et al, 2010	Germany	31	14	3	1	13
	Pfister et al, 2009	Germany	30	12	1	9	8
PDUS	McWilliams et al, 2002	UK	86	2	6	15	63
	Jung et al, 2010	Germany	29	11	7	0	11
	Pfister et al, 2009	Germany	30	6	0	15	9

Color-Doppler ultrasound, CDUS; power color-Doppler ultrasound, PDUS; contrast enhanced ultrasonography, CEUS; true positive, TP; false positive, FP; true negative, TN; false negative, FN.

migration, graft thrombosis [8], occur in one quarter or more of all patients, and what's worse, the rate of complications does not diminish with time [9]. Therefore, patients after EVAR have no choice but to take a lifelong surveillance for possible potential complications. If any complications occur, re-intervention need to be applied to prevent aortic rupture [10].

Among the clinically complications mentioned after EVAR, a common and important complication is the occurrence of endoleak which is defined as the flow of blood within the aneurysm sac but outside the endovascular graft. Half of all patients who need re-intervention after EVAR to detect endoleak [7]. It may result in continued aneurysm growth and, rupture eventually.

According to the report of EUROSTAR registry, among different diagnosis methods of endoleak during post-operation follow-ups, contrast enhanced computed tomography (CT) was in 84%, angiography was in 4%, magnetic residence angiography was in 3%, and 8% was Doppler ultrasound examination [11]. Therefore, at present, CT is widely accepted as the most appropriate method for detection of endoleak, which is also considered as the gold standard in the efficacy analysis of endoleak diagnosis. However, given the policy of lifelong surveillance of endoleak, CT carries considerable cost. About 65% of postoperative EVAR costs

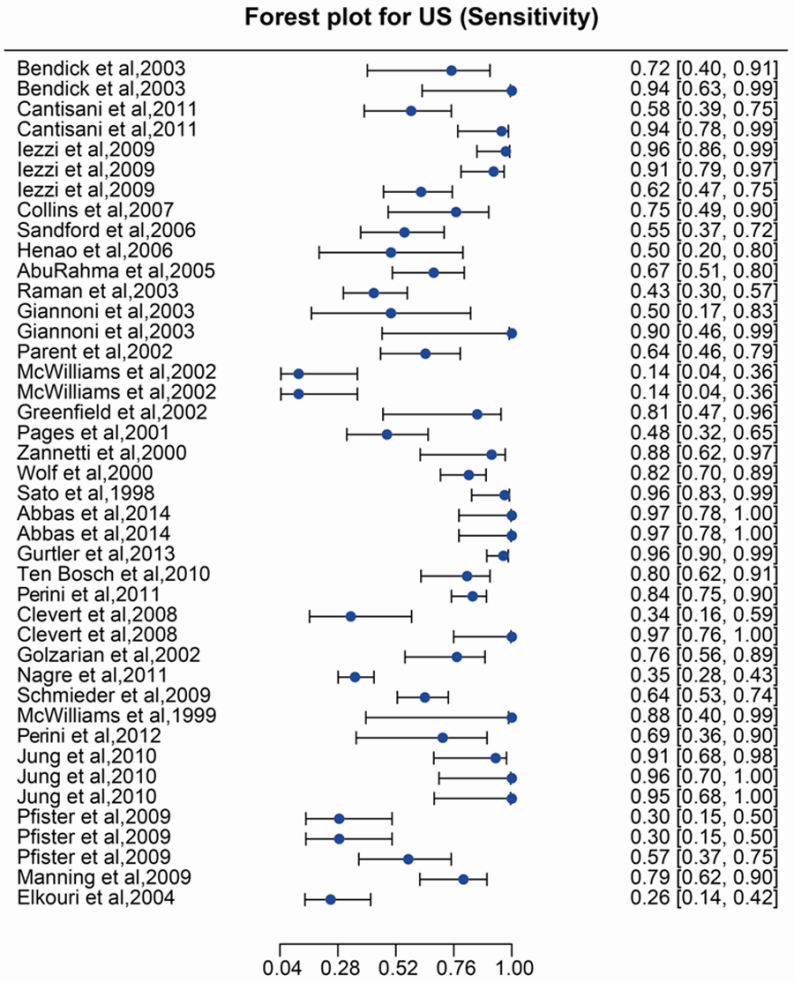

Figure 1. The sensitivity forest plots of US in endoleak diagnosis with patients after EVAR. The sensitivity from each study are represented by roundness, and the 95% confidence interval (CI) is indicated by error bars. The pooled sensitivity: 0.719 (95% CI: 0.626, 0.797).

are due to CT [12]. Also it is known that CT sometimes fails to detect the presence of endoleak [13]. Therefore, other endoleak detection methods are required to be as an assist or an alternative if possible. US methods have been investigated for many years as a potential alternative to CT for the follow-up of EVAR patients, since it usually carries less cost and lowers the risk of ionizing radiation.

Although lots of studies had compared usefulness of a certain single US method in endoleak detection to that with CT, many discrepancies in existing studies made it difficult to reach a powerful conclusion. With the same method, computed tomographic angiography (CTA), as the gold standard, the conclusion of Ten Bosch et al. indicates that contrast enhanced ultrasonography (CEUS) had higher rate in detecting endoleak as 67 versus 27 [14], but the data shown in the study of Pfister et al. was 13 positive using CEUS, while 21 using CTA [15]. Besides, no any specific meta-analysis had been done on the overall comparison of diagnostic value among US methods to solve these contradictions. Consequently, it is necessary to perform a meta-analysis to assess the efficacy of US imaging method. And this study will focus on diagnostic value of three common US methods which are CEUS, color Doppler ultrasound (CDUS), and power Doppler ultrasound (PDUS) in order to do a systematic comparison and provide reference for the clinical treatment.

Materials and methods

Literatures identification

Relative literatures were identified through electronic searching from database of PubMed, Embase and Cochrane Library, regardless of language restriction. The following searching terms as “ultrasonic imaging diagnosis”, “endovascular abdominal aortic aneurysm repair”, “endoleak” and their synonyms were jointly used. Additionally, all the reference lists of relative literatures were searched and examined manually, for fear of any omission. Then, two reviewers retrieved all the potential literatures respectively.

Inclusion criteria

The eligible study need to meet the following criteria: (i) study subjects must have undergone the EVAR surgery, without limitation of aneurysm type, and were clinical suspected endoleak patients; (ii) study must involve at least one

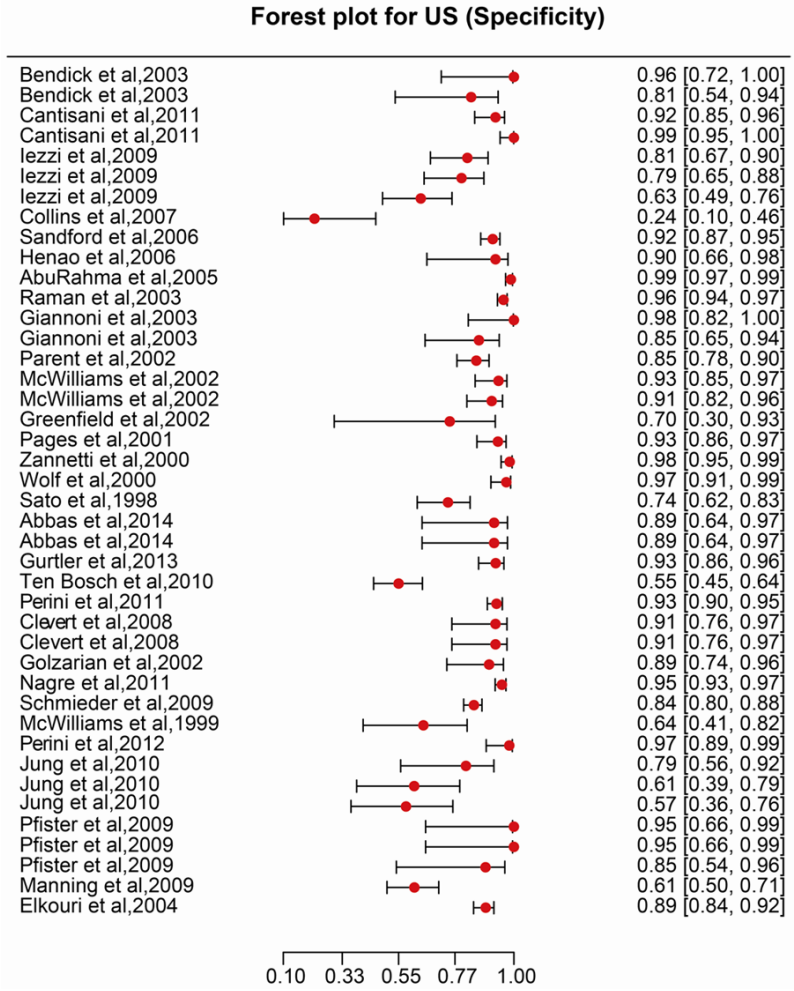

Figure 2. The specificity forest plots of US in endoleak diagnosis with patients after EVAR. The specificity from each study are represented by roundness, and the 95% confidence interval (CI) is indicated by error bars. The pooled specificity: 0.877 (95% CI: 0.833, 0.911).

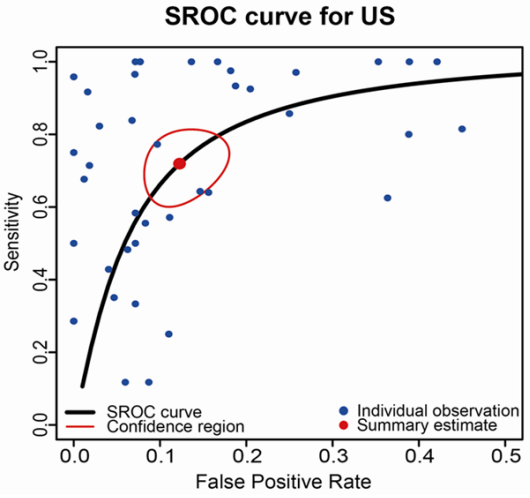

Figure 3. The SROC curve for US with AUC value of 0.884.

ultrasonic imaging diagnosis; (iii) the gold standard must be CT, irrespective of modality; (iv) a comparison must be performed in the study between ultrasonic imaging diagnosis and gold standard.

Data extraction

The titles and abstracts of the retrieved literatures were screened by two reviewers independently, and if necessary, full text was examined for more details to make the final list of eligible studies. And any disagreements were solved under discussion. For each selected studies, the study characteristics were extracted, including author, year, country, sample size, gold reference, imaging modality of ultrasonic diagnosis method and outcome of each method. In terms of the outcome of gold standard and index test, the data of true positive, false positive, true negative and false negative can be obtained to fulfill the 2×2 contingency table.

Statistical analysis

According to the data in both true- and false-positives and -negatives contingency tables, sensibility and specificity of each index test was calculated as percentages. To test if the data can be pooled together, the heterogeneity among selected studies was tested through Cochran's Q. Usually, when $P < 0.01$, there was significant heterogeneity, and subgroup analyses were necessary.

Next, meta-analysis model involved total ultrasonic imaging methods and subgroup meta-analyses were fitted for sensibility and specificity, with the help of R® version 3.2.1 (MathSoft, Cambridge, Massachusetts). The sensibility and the specificity of each diagnosis method

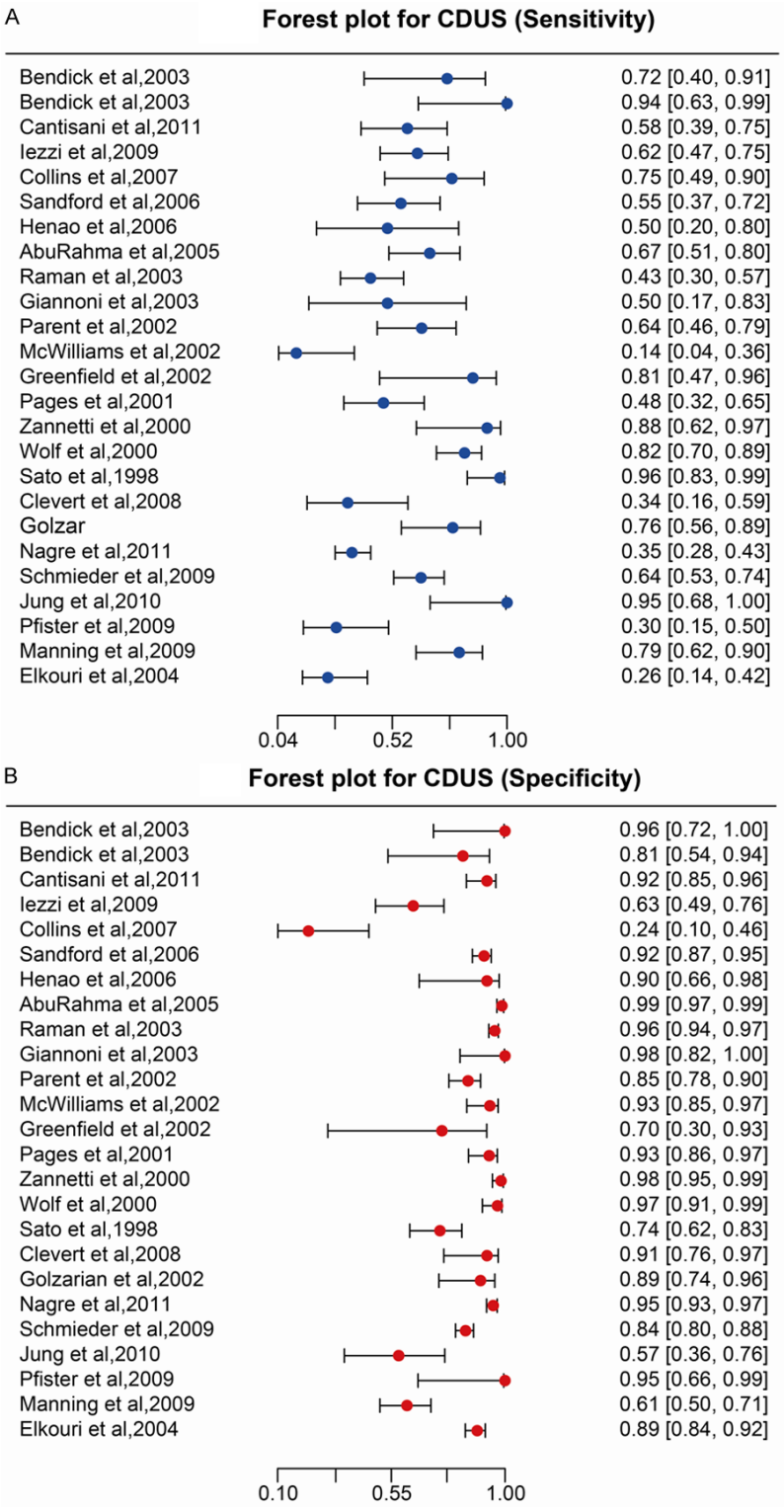

Figure 4. The sensitivity (A) and specificity (B) forest plots of CDUS. The pooled sensitivity: 0.613 (95% CI: 0.513, 0.705), the pooled specificity: 0.887 (95% CI: 0.826, 0.929).

compared with gold standard were expressed in forest plots as pooled point estimates with 95% confidence intervals (CI). Based on these data, a summary receiver operating characteristic (SROC) curve was performed, and the area under the SROC curve (AUC) was computed through the relative integral formula to reflect the sensibility and specificity of different imaging diagnosis methods. The AUC values were in the range of 0 to 1, and if a diagnosis method is certainly the best, its AUC would be 1; contrarily, AUC of the worst was 0. Besides, to make our SROC curves more visible, we used false positive rate (FPR), instead of specificity, as abscissa. And the conversion between them is: *FPR=1-SPE*.

Results

Included studies

A total of 42 studies from 30 articles [14-43] with 5,229 subjects were included (**Table 1**), as they met the criteria mentioned above, out of 105 initial retrieved articles. 34 full texts were reviewed, which included 58 studies. Among them, 16 studies were excluded, since they tested non-ultrasound methods, or one study embodied three sub-studies with different follow-ups, in which cases final sub-study with the longest follow-up was included.

Characteristics of included studies

The ultrasonic imaging methods of these 42 studies involved CDUS, CEUS, high/low-dose contrast-enhanced ultrasound (HLCE/LDCE), three-dimensional CEUS (3D-

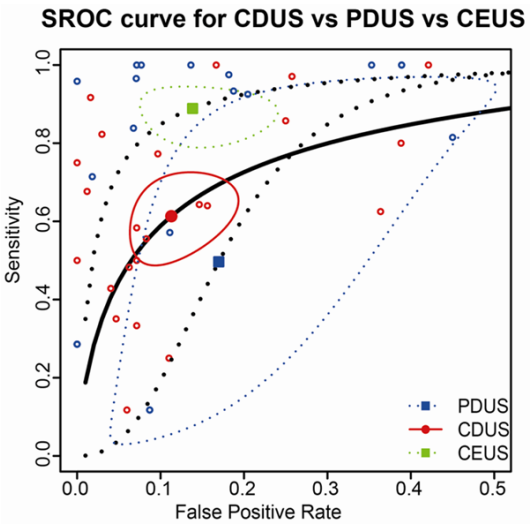

Figure 5. The SROC curves for CDUS, PDUS and CEUS with AUC values of 0.822, 0.936, and 0.803, respectively.

CEUS) and PDUS. And all the selected studies compared the diagnosis outcome of these ultrasonic methods with traditional CT, some cases were supplement by magnetic resonance imaging (MRI), as gold standard, in patients after EVAR.

Total ultrasound imaging

All the 42 studies were aimed to make a comparison between different US imaging and CT. Pooling the whole data together, it can be statistic that the its sensitivity was 0.719 with 95% CI ranged from 0.626 to 0.797 (see **Figure 1**), while its specificity was 0.877 with 95% CI from 0.911 to 0.833 (see **Figure 2**). Both values were lower than 1.000, which accounted for its less insufficient to traditional CT with normal sensitivity and good specificity. Additionally, based on the SROC curve for US shown in **Figure 3**, we can attain its AUC was 0.884.

Meanwhile, heterogeneity among all the ultrasonic diagnosis methods was calculated individually, as to sensibility and specificity. And both *P* values were less than 0.01, which could be deemed as existing significant heterogeneity. In consideration of the probable differences generated by the various imaging modality, the subgroup analysis was performed. All the ultrasonic diagnosis methods were divided into three subgroups, as CDUS, CEUS and PDUS, which means HDCE, LDCE and 3D-CEUS were all categorized in CEUS.

Color-Doppler ultrasound (CDUS)

The subgroup analysis of CDUS was involved 25 studies with 3,814 patients (see **Figure 4**). In terms of sensitivity, except one case was 0.95 with 95% CI from 0.68 to 1.00 [37], which suggested there was no apparent difference between CDUS and CT, nearly all the data indicated its low-sensitivity. And the merged data of sensitivity was 0.613 and 95% CI was 0.513 to 0.705, revealing the existing difference. Besides, 23 of 25 studies showed distinctive specificity, and its pooled outcome was 0.887 with 95% CI from 0.826 to 0.929. And the AUC of SROC curve was 0.822, as **Figure 5** displayed.

Power color-Doppler ultrasound (PDUS)

There are just three studies, relative to PDUS, were included, shown in **Figure 6**. Among these three studies, the sensitivity existed obvious difference, since the outcome of McWilliams et al. was 0.14 with 95% CI from 0.04 to 0.36 [23], while Jung et al.'s data were 0.96 and 95% CI included 1.00 [37]. The summarized outcome of sensitivity was 0.497 with wide 95% CI from 0.057 to 0.941 and of specificity was 0.830 with 95% CI from 0.576 to 0.946. Moreover, the AUC of SROC curve for PDUS (see **Figure 5**) was 0.803.

Contrast enhanced ultrasonography (CEUS)

In this subgroup, contained 14 studies illustrated in **Figure 7**, two- or three-dimensional, normal dose, low dose and high dose contrast enhanced ultrasonography were pooled together, under the assumption that no heterogeneity was among different types. As to sensitivity, the pooled data was 0.889 with 95% CI between 0.813 and 0.936, showing good diagnosis capacity. While the summarized specificity outcome was 0.862 with 95% CI ranged from 0.783 to 0.915. In addition, these methods seemed to have the best performance, as its AUC was 0.936 in SROC curve for CEUS (see **Figure 5**).

Discussion

This meta-analysis gathered data from 42 studies involved 30 articles with 5,229 patients, who were suspected to endoleak after EVAR and assessed the sensitivity and specificity of US imaging compared with tradition CT. Six

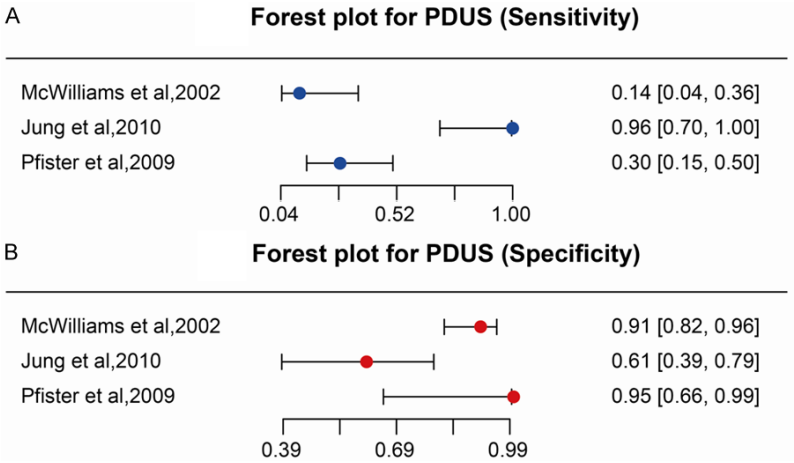

Figure 6. The sensitivity (A) and specificity (B) forest plots of PDUS. The pooled sensitivity: 0.497 (95% CI: 0.057, 0.941), the pooled specificity: 0.83 (95% CI: 0.576, 0.946).

modalities of US imaging were tested and they were categorized into three subgroups as CDUS, PDUS and CEUS, in consideration of the significant heterogeneity among them. Due to the safety of ultrasound, this analysis was designed to investigate if the widely used CT can be replaced by US imaging in post-EVAR endoleak diagnosis.

According to the AUC of SROC curve for US, CDUS, PDUS and CEUS, CEUS would be the best with the AUC of 0.936, which was the most approached to 1.000, and it was the only type over US. Besides, CDUS seemed better than PDUS, with lager AUC. When sensitivity was evaluated alone, CEUS was superiority and CDUS (0.889 vs 0.613) was secondary. Although CEUS (0.862, 95% CI=0.783-0.915) did not have very good performance in specificity, which was next to CDUS (0.887, 95% CI=0.826-0.929) as second place, there was no significant difference existing between two methods. And PDUS (sensitivity: 0.497, 95% CI=0.057-0.941; specificity: 0.830, 95% CI=0.576-0.946) was the worst in both items.

The working principle of CDUS is based on the difference of frequency between the receiving signal reflected or scattered by the moving target and the sending signal, which is so-called Doppler Effect. The detected Doppler shift can be transformed into color signal and superimposes on the traditional B mode ultrasound image [44]. Therefore, we could know the characteristics of blood flow and diagnosis endoleak after EVAR with the help of CDUS image. However, with the influence of pulse repetition frequency on the manifested scope of blood velocity, when the high speed blood flow is manifested, color overlap and mosaic pattern can mislead the diagnosis [45], since artery flow is usually high pressure with high velocity. On the whole, CDUS was widespread in clinical, since it is noninvasive and rapid with high specificity.

Furthermore, PDUS was developed from CDUS and had a great improvement on sensitivity to detect low velocity flow, imaging tortuous vessel and accuracy of grading stenosis, which are less help to endoleak diagnosis, except its good motion sensitivity can be applied to continuous scanning [46]. Nevertheless, the outcome of PDUS did not show any advantage over CDUS on both sensitivity and specificity. Undeniably, the limited studies with significant heterogeneity among them played an important role in the poor analysis results.

With the application of US contrast agent, a kind of intravenous administration gas-filled microbubble, on tradition US imaging technology [47], CEUS are much more sensitive and specific, due to its high resolution ratio. Because of the plenty of water in human body, blood and its surrounding tissue have some similar echogenicities, which is so-called acoustically homogeneous. However, the microbubbles in contrast medium vibrate under ultrasound, which can enhance the US backscatter and make blood flow image clearer [48]. Through the mechanism of CEUS, we can easily explain its good performance in sensibility. As far as specificity, we can found the positive rate of CEUS seemed higher than that of gold standard, which was demonstrated in 11 of 14 studies with the evidence that 483 subjects were diagnosed as endoleak using CEUS, but just 416 were confirmed by CTA. The reason could be accounted as CEUS is a continuous real-time contrast enhanced scanning, while

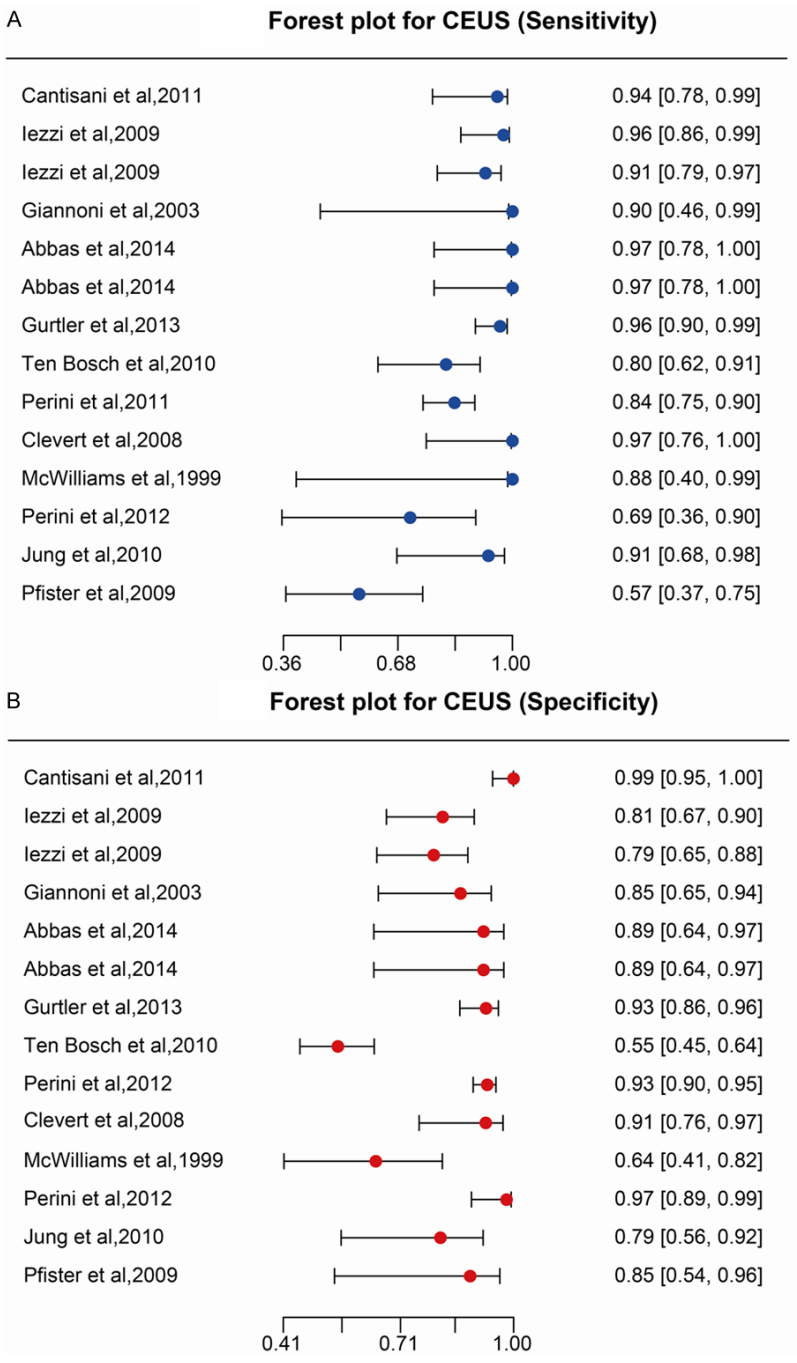

Figure 7. The sensitivity (a) and specificity (b) forest plots of CEUS. The pooled sensitivity: 0.889 (95% CI: 0.813, 0.936), the pooled specificity: 0.862 (95% CI: 0.783, 0.915).

the CTA just shows the temporal angiographic images of arterial phase and delayed phase [14].

This meta-analysis compared ultrasonic imaging technology with traditional CT and indicated the sensitivity and specificity of three common US diagnostic methods, CDUS, PDUS and CEUS, to endoleak in patient after EVAR. But there were still some limitations: (i) to some extent, the poor performance of PDUS on both aspects generated by the few included studies and their significant heterogeneity, so more clinical studies should be conducted for further perfecting this meta-analysis; (ii) as some studies did not differentiate the types of endoleak, the endoleak types were not extracted either. However, through some literature, we knew the endoleak types did have influences on the outcome of diagnosis and usually type II was more detectable [37]; (iii) different equipments also had differences in sensitivity and specificity, which were not taken into consideration; (iv) based on the widespread application of CT, it was chosen as gold reference. Occasionally, some branch endoleak cannot be detected in CT, but shown in a US image [49], and in a reexamination of videotape study, endoleak in US shown absence in CTs were defined [16], which means CT was not an absolute reference.

According to present studies, CEUS seemed the optimal endoleak diagnostic method in varieties of US imaging technology with satisfactory sensitivity and can took place of traditional CT in some cases. Meanwhile, due to the good performance, especially in specificity, CDUS also can be popularized as a primary or assisted diagnosis. As to PDUS, the efficacy remained further study. More important, the clinical selection of endoleak diagnosis methods in patients after EVAR should combine with patients' situation.

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Disclosure of conflict of interest

None.

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