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Meta-analysis of the diagnostic value of contrast-enhanced ultrasound for the detection of vascular complications after liver transplantation

Suxian Chen, Xiong Wang, Baoxin Zhang, Baijing Liu and Hui Pan

Department of Ultrasonic. Tianjin Baodi Hospital, No. 8. Tianjin, China

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Correspondence: Suxian Chen. Department of Ultrasonic. Tianjin Baodi Hospital, No. 8. Guangchuan Road. Baodi District. 301800 Tianjin, China

e-mail: suxianchenabc@163.com

ABSTRACT

Background: contrast-enhanced ultrasound (CEUS) is increasingly used to identify vascular complications in patients after liver transplantation. The present study aimed to evaluate the diagnostic accuracy of CEUS using all available data.

Materials and methods: relevant studies published before February 2018 were retrieved from PubMed, EMBASE, ScienceDirect and Web of Science. Pooled sensitivity and specificity, diagnostic odds ratio (DOR) and summary receiver operating characteristic curve (SROC) were calculated to estimate the diagnostic performance of CEUS for vascular complications. Sensitivity analysis was performed that stratified studies according to age, study design and sample size in order to determine the influence of these factors on the overall effect. Meta-regression analyses were performed to examine the possible sources of heterogeneity. Quality assessment and publication bias of the included studies were also evaluated.

Results: thirteen studies which consisted of 2,781 CEUS cases were included in the analysis. The pooled weighted estimates of sensitivity and specificity were 0.90 (95% CI, 0.84 to 0.95) and 1.00 (95% CI, 1.00 to 1.00), the diagnostic odds ratio (DOR) was 431.96 (95% CI, 164.60 to 1,133.59) and the area under the curve (AUC) of SROC was

0.9741. According to the sensitivity analysis, age, study design and sample size had an insignificant influence on the diagnostic performance of CEUS. The meta-regression analyses did not reveal a strong correlation between CEUS accuracy and study design, treatment time of patients and experience of the radiologists.

Conclusion: the results of our meta-analysis showed a high sensitivity, specificity and accuracy of the CEUS modality for the identification of vascular complications in patients after liver transplantation. Since this is the first meta-analysis investigating in this aspect, more evidence is required to validate the clinical utility of CEUS for the identification of vascular complications in patients with a transplanted liver.

Key words: Contrast-enhanced ultrasound. Vascular complications. Liver transplantation. Diagnosis.

INTRODUCTION

Liver transplantation is the most acceptable treatment for patients with end-stage liver diseases. However, despite a rapid development in surgical technology and postoperative therapy, vascular complications are still significant problems that threaten survival after liver transplantation (1-3). The overall incidence of vascular complications is reported at around 7% in patients who receive deceased donor liver transplantation and approximately 13% in patients with a living donor liver transplantation (4-6). Complications that affect the hepatic artery and portal vein are the most common after transplantation (7,8). Hepatic artery thrombosis (HAT) is the most severe and fatal hepatic artery complication, the incidence is 3-5% and the fatality rate is 20-60% (9,10). Portal vein thrombosis (PVT) and portal vein stenosis (PVS) are also adverse vascular complications that damage liver function and threaten the survival of recipients, the incidence is 1-12.5% (10,11). Thus, early diagnosis of vascular complications is crucial for the management of disease and patients survival.

Clinical signs and proof of vascular complications are always non-specific and ambiguous and diagnosis frequently relies on imaging findings. Angiography is still regarded as the gold standard for the assessment of vascular complications.

Computed tomography (CT) is another effective method to diagnose complications. These techniques are not ideal for routine screening after liver transplantation due to the disadvantages of the use of ionizing radiation or nephrotoxic contrast media, high costs and the difficulty to perform this technique at the bedside. Ultrasound (US) is preferred for the detection of vascular complications in the early postoperative period and long-term follow-up as it is a non-invasive, non-radioactive and cost-effective technique that can be performed at the bedside (12,13). Previous studies have shown the good sensitivity of doppler US (75-100%) for the detection of vascular complications (14-16). However, the aliasing or overwriting artifacts and other limiting factors of US examination may result in a misdiagnosis or inconclusive diagnosis. Thus, contrast-enhanced ultrasound (CEUS) has been established as a routine clinical measurement for liver transplant recipients as it overcomes the limitations of angiography, CT and US imaging. CEUS can be applied to evaluate microcirculation of the liver graft and to facilitate visualization of blood vessels, providing real-time angiographic-like images with a high diagnostic efficiency (17). Moreover, CEUS seldom causes adverse reactions and can be used in patients with renal insufficiency. This is due to the fact that ultrasound contrast agents have a low incidence of allergic reactions which only occurs in one out of ten thousand cases, according to previous studies (18,19). Prior studies have revealed a relatively high accuracy (> 90%) of CEUS for the diagnosis of postoperative vascular complications including HAT, HAS, PVT and PVS (10,20,21). However, these individual studies only involved a limited number of patients and therefore, the actual diagnostic value of CEUS could not be determined.

Thus, the present systematic review and meta-analysis aimed to assess the diagnostic performance of CEUS for monitoring postoperative vascular complications in patients after liver transplantation via the analysis of all available data.

MATERIALS AND METHODS

Literature search

PubMed, EMBASE, ScienceDirect and Web of Science databases were used to identify articles that investigated the usefulness of CEUS for the detection of vascular

complications after liver transplantation. The applied search terms included the following: contrast-enhanced, ultrasound or ultrasonography, vascular complications or hepatic artery or portal vein, liver transplantation or postoperative and all the possible combinations. The search was limited to studies published no later than the 28th of February of 2018. Two authors screened all the titles and abstracts of the potential studies for eligibility criteria. Articles relevant to the topic were retrieved and the full-text was reviewed. The reviewers subsequently searched manually all the citations of the retrieved studies and other relevant review articles for additional publication that did not appear in the initial search.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: a) the study population consisted of liver transplantation recipients; b) postoperative vascular complications with regard to all types of hepatic artery or portal vein complications were the measurement target; c) vascular complications were assessed using CEUS postoperatively; d) angiography, CT analysis, surgery or clinical follow-up was eligible as a reference standard; e) all studies must provide sufficient data of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) or sensitivity and specificity findings, either directly or indirectly; f) studies were published in English or Chinese; and g) both prospective and retrospective designed studies were included.

Articles that did not satisfy the above criteria, review studies, letters, case reports, comments, unpublished material, conference abstracts and multiple reports published on the same cohort were excluded. The corresponding author of the articles was contacted for information for relevant studies that did not provide the necessary data for analysis. If we did not receive a response from the author within two weeks, the study was excluded from the meta-analysis.

Data extraction and quality assessment

Two reviewers independently extracted and recorded data according to a predefined form for each report. The following information was collected: first author, year of

publication, number of patients who underwent CEUS evaluation, study design (prospective or retrospective), patient clinical characteristics (age, gender, types of liver transplantation), types of vascular complications, timing of CEUS assessment, contrast material (dose) of CEUS, reference standards, imaging interpretation method (blinded or not) and necessary TP, TN, FP and FN data in order to construct a 2 x 2 contingency table. In the case of any disagreements, a third reviewer assessed all discrepant issues and the majority opinion was used for analysis.

The methodological quality of each included study was assessed via the quality assessment of diagnostic accuracy study form (QUADAS-2), which is a revised quality assessment appliance developed explicitly for a meta-analysis of diagnostic accuracy studies. The quality of primary diagnostic studies was assessed via an estimation of the risk of bias of four domains and clinical applicability of three domains of the study characteristics (22).

Statistical analysis

The Stata version 15.0 (Stata Corporation, College Station, TX, USA) and Meta-DiSc 1.4 (Unit of Clinical Biostatistics, Madrid, Spain) software were used for statistical analysis. A random effect model was used for pooled analysis. Forest plots were constructed to demonstrate the variations in the sensitivity and specificity estimates combined for CEUS in each study. The sensitivity, specificity and diagnostic odds ratio (DOR) values with 95% confidence intervals (CI) were calculated. Summary receiver operating characteristic curves (SROC), which were constructed with true-positive rates against false-positive rates, were used to assess sensitivity and specificity. The area under the curve (AUC) of the SROC was calculated in order to estimate the performance of CEUS. A preferable test should have an AUC close to 1, whereas a poor test has an AUC close to 0.5. The Youden index (*Q) was also assessed, which is the point on the SROC where the sensitivity and specificity are equal. The *Q index is considered to be the best statistical method to reflect the diagnostic value.

Heterogeneity of the individual studies was estimated using the Q statistic of the Chi-square value test and the inconsistency index (I^2). Heterogeneity expressed as an I^2

value was defined as low (25-50%), intermediate (50-75%) or high (> 75%). With regard to diagnostic accuracy analysis, threshold effect is one of the possible sources of heterogeneity. Whether the threshold effect existed or not was defined via the Spearman's correlation coefficients. The absence of a threshold effect was defined as a p value of > 0.05 for the Spearman's correlation coefficients. Single-factor meta-regression analysis was also performed to further evaluate the potential non-threshold effect for the heterogeneity. Three groups of meta-regression analysis were performed based on study performance time, radiologists experience and sample size. Variances were considered as explanatory if their regression coefficients reached statistical significance ($p < 0.05$). Publication bias was analyzed by a Deeks funnel plot and an asymmetry test. The existence of notable publication bias was confirmed if a non-zero slope coefficient ($p < 0.05$) was obtained. Sensitivity analysis based on age (pediatric and adult), study design (prospective and retrospective) and sample size (< 40 and > 40) was performed to explore whether the three factors influenced the overall sensitivity and specificity.

RESULTS

Study selection

Three hundred and seventy potential citations were identified for inclusion into the study via multiple database searches and cross-checking of reference lists. Thirty-five articles were potentially relevant according to their titles and abstracts. After reviewing the full text, 12 were further excluded due to duplication (n = 2), non-assessment of vascular complications (n = 3) and insufficient data to create the 2 x 2 contingency table (n = 7). Eventually, 13 studies that consisted of 2,781 cases of CEUS evaluations were enrolled into the meta-analysis. A flow chart of published study selection is presented in figure 1.

Study characteristics

Relevant data extracted from all 13 studies are summarized in table 1 (23-35). Only two studies involved more than 100 cases for CEUS evaluation. The study size of the other eleven trials ranged from 8 to 99 cases. The gender and age distribution of

study cohorts are shown in table 1. Seven of the included studies assessed more than one type of vascular complication and provided separate results or combined outcomes. Six studies focused on one particular complication. The most investigated complications were HAT, HAS, PVT and PVS. Other less common complications studies included hepatic artery pseudoaneurysm (HAP) and splenic artery steal syndrome (SASS). Reference standards varied from study to study and for different complications. A study might use different reference standards according to disease types and patients characteristics. Conventional angiography, CT, computed tomographic angiography (CTA), clinical follow-up and surgery served as reference standards among the 13 included studies. Furthermore, six studies enrolled patients prospectively and seven studies were retrospective. Only three studies reported that the interpreters were blinded to the results of CEUS when performing and reading the reference standard examinations. The CEUS examinations were carried out by radiologists with more than four years of experience in CEUS evaluations of the liver. All the enrolled studies used a SonoVue (Bracco, Milan, Italy) contrast agent. Information about the local contrast protocol including timing of CUES evaluation, the ultrasound devices used and dose of CEUS contrast agent are presented in table 1.

Quality assessment

The quality assessment of the 13 studies was moderate based on the QUADAS-2 items. The detailed information of each included study and the results of the distribution are presented in figure 2.

Diagnostic accuracy

The sensitivity and specificity with 95% CI of each study are displayed as forest plots in figure 3A. The pooled weighted values of CEUS were a sensitivity of 0.90 (95% CI, 0.84 to 0.95), a specificity of 1.00 (95% CI, 1.00 to 1.00) and a DOR of 431.96 (95% CI, 164.60 to 1,133.59) (Fig. 3B). The AUC of SROC was 0.9741 ± 0.0136, which was very close to a perfect performance and the *Q index was 0.9267 ± 0.0232 (Fig. 3C). There was no evidence of a publication bias among the included studies according to the

Deeks funnel plot asymmetry analysis (p = 0.11).

The sensitivity analysis stratified subgroups into different ages, study design and sample sizes as the present meta-analysis included studies with varied characteristics. Only the study by Bonini (23) enrolled pediatric patients; all the others studies included patients > 18 years old. After removing the study result by Bonini, subgroup analysis revealed a sensitivity of 0.91 (95% CI, 0.84 to 0.95) and a specificity of 1.00 (95% CI, 1.00 to 1.00) of CEUS for the evaluation of vascular complications in adult patients. Sensitivity analysis based on study design showed a high sensitivity and specificity in both prospective (sensitivity: 0.93 [0.84-0.98] and specificity: 0.99 [0.95-1.00]) and retrospective (sensitivity: 0.88 [0.79-0.94] and specificity: 1.00 [1.00-1.00]) subgroups. Sample size did not significantly affect the overall analysis as both small (< 40) and large (> 40) sample cohort studies had a high sensitivity and specificity of CEUS performance (Table 2).

Heterogeneity text

The statistical analysis resulted in an I^2 of 40.3% for sensitivity analysis and I^2 of 32.6% for specificity. Although heterogeneity was not significant, it was still considered as moderate among the studies. Thus, threshold effect testing was also performed. The Spearman's correlation coefficients of CEUS were 0.195 (p = 0.523), which indicated the absence of a threshold effect in the CEUS assessment. Three pairs of meta-regression analyses, with regard to study design (prospective or retrospective), treatment time of patients (before 2012 or after 2012) and CEUS experience of radiologists (more than four years or more than ten years) were performed in order to assess the non-threshold effect. The results of meta-regression indicated that study design, treatment time of patients and experience of radiologists had no strong association with CEUS accuracy (Table 3).

DISCUSSION

Although US is still the routine clinical modality for the measurement of vascular complications after liver transplantation and angiography is still the gold standard for definition, the inaccurate diagnoses of US and the invasiveness and high cost of

angiography mean that they are imperfect for evaluation. CEUS is non-invasive, non-radiative and easy to perform at the bedside and can improve visualization in both the hepatic artery and portal vein characteristics. It is recommended as a useful alternative for the detection of postoperative vascular complications. Thus, the current meta-analysis aimed to estimate the diagnostic accuracy of CEUS for the assessment of vascular complications during the postoperative period. Pooled statistics of 13 studies revealed a sensitivity of 90%, a specificity of 100% and an AUC of 0.9741 ± 0.0136 for CEUS evaluation. Thus, indicating an ideal diagnostic performance. Sensitivity analysis showed that patient age, study design and sample size did not highly influence the performance of CEUS. On the other hand, sensitivity analysis further confirmed that the results of our meta-analysis were robust, which verified the high accuracy of CEUS for the diagnosis of vascular complications after liver transplantation. Since this is the first meta-analysis to assess the diagnostic value of CEUS for postoperative vascular complications, we could not find other reports to compare with or support our findings. The main reason is that CEUS is a novel imaging method for monitoring liver transplantation recipients and the real effects still require further investigation. However, the use of CEUS for the diagnosis of other liver-related diseases has already shown promising results. A study showed that CEUS had a high sensitivity (85%) and specificity (91%) for the identification of hepatocellular carcinoma (36). Other studies also revealed a high sensitivity and specificity (more than 90%) for the diagnosis of focal liver lesions (37,38). Our study further expanded the use of CEUS for the assessment of vascular complications in patients after liver transplantation.

Although high diagnostic performance of CEUS was found for measuring vascular complications after liver transplantation, it did not imply that CEUS should replace the use of US postoperatively. Virtually all of the included studies enrolled patients with suspected vascular complications, an absence of hepatic artery signal or abnormal liver function after US evaluation. CEUS was only performed when conventional US could not sufficiently diagnose whether a patient had developed vascular complications (39). Berstad et al. demonstrated that CEUS could successfully visualize the doubtful cases based on doppler US, whilst avoiding other

more expensive imaging procedures (40). Hom et al. reported that CEUS could potentially decrease the number of false-negative examinations assessed by US, which aids to decrease the need for angiography (26). Therefore, instead of denying the effectiveness of US in postoperative evaluations, researchers should combine the use of CEUS and US to achieve the highest efficiency. US should remain as the routine modality for patients after liver transplantation. CEUS can be performed immediately in patients with abnormal or indeterminate US in order to confirm whether or not patients have vascular complications.

Furthermore, CEUS has been accepted as a reliable technique for the identification of certain vascular complications. Therefore, it has been suggested by several studies that for the detection of HAT, a negative CEUS would avoid unnecessary invasive angiography (16,28,41). However, this approach cannot be applied to all cases. In the study of Ren, three patients with negative CEUS were confirmed as having PVT by further investigations (42). Moreover, a review of long-term outcomes after liver transplantation reported that vascular complications might occur early (< 3 months) or late (> 3 months) after transplantation (43). Patients without symptoms at an early stage still have a chance to develop vascular complications during long-term follow up. Thus, patients with a negative CEUS still need to undergo further investigations such as US, conventional angiography, CT, CTA or interventional treatment according to the patients' condition. Garcacriado et al. performed daily US plus CEUS if necessary for patients with a negative CEUS (25). Lu et al. proceeded with a monthly clinical follow-up and doppler US in patients with negative findings (28). However, with regard to the types of diagnostic tests that should be performed on patients with a negative CEUS, a definite conclusion cannot be drawn according to the current information and further clinical trials in this field are required. Researchers have also proposed the performance of CEUS may vary according to the different types of complications. While some believe that CEUS had a high diagnostic accuracy for the identification of HAT and PVT, some claimed the diagnostic value of CEUS was limited for HAS diagnosis (10). Many of the enrolled studies provided combined results of CEUS for different vascular complications. Therefore, it is difficult to perform a subgroup analysis to compare the efficiency of CEUS for

different types of vascular complications or to define whether CEUS is useful in particular complications. More evidence is required to confirm the diagnostic performance of CEUS in certain kinds of vascular complications such as HAT, HAS, PVT or PVS. Moreover, we assumed that the experience of radiologists who are responsible for performing CEUS and reading CEUS imaging may also affect the diagnostic accuracy. As CEUS examination is operator-dependent and requires specific skills and training (24), misreading may occur sometimes. Some included studies restricted the interpretation protocol in order to reduce the chance of a misdiagnosis. CEUS was not performed if there were no available trained radiology staff in the study of Garcacriado (25). More than one experienced examiner was involved in analyzing the CEUS scan in order to avoid misreading in the study performed by Rennert and Zheng (32,34). However, most of the studies did not apply the same protocol as above. Thus, we assessed the influence of the radiologists' experience on the diagnostic performance of CEUS. Although meta-regression analysis in our study revealed that radiologists' experience has no strong correlation with CEUS accuracy, future studies should not ignore this factor.

There are some limitations in the present meta-analysis. First, the small sample size might influence the statistical power of the individual study and lead to inconclusive and imprecise results. Furthermore, our study assessed the usefulness of CEUS for the detection of all types of vascular complications. Whether CEUS has a high accuracy for the diagnosis of a particular kind of complications is yet to be established. Moreover, the included studies only performed CEUS in cases of suspicious US findings, instead of conducting it in every patient. Thus, the diagnostic yield may be overestimated. This condition further suggested that CEUS should be used in conjunction with US. Many other factors including patient demographics (obesity), types and doses of contrast agents and timing of CEUS evaluation should be taken into consideration. However, no consensus has been reached with regard to these factors, making it impossible to conduct a subgroup analysis in this meta-analysis.

CONCLUSION

Our meta-analysis revealed that CEUS had a high sensitivity and specificity for the detection of vascular complications. CEUS is a non-invasive, non-radiative and liable imaging modality, which can accurately diagnose vascular complications in patients after liver transplantation. Nonetheless, as a relatively new technique, CEUS should be applied cautiously and may be used in conjunction with other modalities. Further clinical studies with large cohorts and better designed trials are necessary in order to prove its clinical value.

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Table 1. Basic characteristic of the included studies

Study	Year	No. of CEUS cases	Gender (Male/ Female)	Age	Target diseases	Reference standards	Study design	Radiologists experience	Interpretation	Timing of CEUS	CEUS devices	CEUS dose
Bonini	2007	44	M: 21; F: 19	2 months to 10 years	HAT, HVT, PVT	Angiography, CT	Prospective	-	-	After US evaluation	ATL HDI 5000, Technos Esaote and Sequoia Siemens	Intravenous bolus at a dose of 0.5 ml (up to three injections)
Clevert	2009	36	M: 21; F: 15	57	HAT, HAS, PVT, PVS	CTA, MAR	Prospective	-	Blinded	After US evaluation	Multi-frequency transducer (2.5-4 MHz, Logic 9; GE Healthcare)	Intravenous bolus injection of 1.6-2.4 cc
Garcacrido	2014	34	-	52.9 (18-76)	HAT, HAS, SASS	Arteriograph, surgery	Prospective	More than 9 years	-	Within 8 days post-transplant	Sequoia 512 (Acuson, Mountain View, CA, USA)	A bolus of 2.4 ml (concentration of 8 µl/ml)
Hom	2006	8	-	52.3 (30.5-68.2)	HAT	Arteriograph, clinical follow-up	Prospective	13 years	Blinded	Within 24 hours of conventional US	Sequoia 512 (Acuson, Mountain View, CA, USA)	Intravenous bolus at a dose of 0.5 ml (maximum of 3 ml)
Huang	2008	11	-	30 to 63 years	HAT, HAS, PVT, PVS	Clinical follow-up	Prospective	-	-	After US evaluation	Real-time sector scanner and pulse doppler procedures (GE Logiq 9)	-

Lu	2012	45	M: 36; F: 9	45.6 (30-69)	HAT	Angiography, surgery and clinical follow-up	Retrospective	More than 5 years	-	After US evaluation	Sequoia 512 (Acuson, Mountain View, CA, USA)	1.2 ml bolus
Lyu	2015	99	M: 85; F: 14	48 ± 10.8	Collateral transformation of the hepatic artery	Angiography, CTA	Retrospective	More than 5 years	Blinded	After US evaluation	MPX DU8 machine (Esaote Biomedica, Genoa, Italy), Sequoia 512 (Acuson, Mountain View, CA, USA)	Intravenous bolus at a dose of 0.5 to 1 ml (maximum of 3 ml)
Rbenthaler	2016	60	-	52 ± 12.8	Vascular complications	CT	Retrospective	More than 15 years	-	Mean of 30.4 months after transplantation	Siemens Acuson Sequoia and Siemens S2000, EPIQ 7, Philips Ultrasound	1.4 to 2.0 ml (min 1.0 ml; max 4.8 ml)

Study	Year	No. of CEUS cases	Gender (Male/ Female)	Age	Target diseases	Reference standards	Study design	Radiologists experience	Interpretation	Timing of CEUS	CEUS devices	CEUS dose
Ren	2016	2,085	M:1617; F: 468	-	HAP	CTA, emergency operation	Retrospective	-	-	1-2 weeks after the operation	Sequoia 512 (Acuson, Mountain View, CA, USA)	A single dose of 0.5-2.4 ml/time
Rennert	2012	23	M: 10; F: 13	39.8 (18-72)	HAT, HAS, PVT, PVS	CECT, CE-MRI	Retrospective	More than 10 years	-	After US evaluation	Multi-frequency convex transducer (1–5 MHz, LOGIQ	A maximum dose of 5 ml

											E9, GE, USA)	
Rübenthaler	2017	45	-	49.56 ± 13.05	Vascular complications	Histopathological result	Retrospective	More than 9 years	-	-	Siemens Acuson Sequoia and Siemens S2000 with C4-1 and C6-1 HD probes, EPIQ 7, Philips Ultrasound) with C9-2 probe	1.4 to 2.0 ml (min 1.0 ml; max 4.8 ml)
Zheng	2010	47	M: 40; F: 7	46.2 (28-68)	HAS	Conventional angiography, CTA	Prospective	More than 5 years	Blinded	6 days to 49 months after transplantation	MPX DU8 machine (Esaote Biomedica, Genoa, Italy), Sequoia 512 (Acuson, Mountain View, CA, USA)	Intravenous bolus at a dose of 0.5 to 1 ml (maximum of 3 ml)
Zhu	2012	244	M: 221; F: 26	48.6 ± 5.7	SASS	Celiac trunk angiography	Retrospective	More than 10 years	-	-	Sequoia 512 (Acuson, Mountain View, CA, USA)	A bolus injection of 2.0 ml

CEUS: contrast-enhanced ultrasound; HAT: hepatic artery thrombosis; HVT: hepatic vein thrombosis; HAS: hepatic artery stenosis; PVT: portal vein thrombosis; PVS: portal vein stenosis; SASS: splenic artery steal syndrome; HAP: hepatic artery pseudoaneurysm; CT: computed tomography; CTA: computed tomography angiography; MAR: magnetic resonance angiography; CECT: contrast-enhanced computed tomography; CE-MRI: contrast-enhanced magnetic resonance imaging.

Table 2. Sensitivity analyses based on patient age (pediatric and adult), study design (prospective and retrospective) and sample size (< 40 and > 40)

Factor	*Subgroup*	*n*	*Article*	*Sensitivity*	*Specificity*
Age	Adult	12	Clevert DA	1.00 (0.16-1.00)	1.00 (0.90-1.00)
			Garcacriado	1.00 (0.72-1.00)	1.00 (0.85-1.00)
			Hom	1.00 (0.16-1.00)	1.00 (0.54-1.00)
			Huang	1.00 (0.16-1.00)	1.00 (0.66-1.00)
			Lu	1.00 (0.75-1.00)	0.97 (0.84-1.00)
			Lyu	1.00 (0.69-1.00)	1.00 (0.96-1.00)
			Rbenthaler	0.89 (0.72-0.98)	1.00 (0.89-1.00)
			Ren	0.75 (0.35-0.97)	1.00 (1.00-1.00)
			Rennert J	1.00 (0.16-1.00)	1.00 (0.84-1.00)
			Rübenthaler	0.62 (0.32-0.86)	1.00 (0.89-1.00)
			Zheng	0.92 (0.79-0.98)	0.88 (0.47-1.00)
			Zhu	1.00 (0.63-1.00)	1.00 (0.98-1.00)
			Pooled outcome	0.91 (0.84-0.95)	1.00 (1.00-1.00)
Study design	Prospective	6	Bonini	0.80 (0.28-0.99)	1.00 (0.91-1.00)
			Clevert DA	1.00 (0.16-1.00)	1.00 (0.90-1.00)
			Garcacriado	1.00 (0.72-1.00)	1.00 (0.85-1.00)
			Hom	1.00 (0.16-1.00)	1.00 (0.54-1.00)
			Huang	1.00 (0.16-1.00)	1.00 (0.66-1.00)
			Zheng	0.92 (0.79-0.98)	0.88 (0.47-1.00)
			Pooled outcome	0.93 (0.84-0.98)	0.99 (0.95-1.00)
	Retrospective	7	Lu	1.00 (0.75-1.00)	0.97 (0.84-1.00)
			Lyu	1.00 (0.69-1.00)	1.00 (0.96-1.00)
			Rbenthaler	0.89 (0.72-0.98)	1.00 (0.89-1.00)
			Ren	0.75 (0.35-0.97)	1.00 (1.00-1.00)
			Rennert J	1.00 (0.16-1.00)	1.00 (0.84-1.00)
			Rübenthaler	0.62 (0.32-0.86)	1.00 (0.89-1.00)
			Zhu	1.00 (0.63-1.00)	1.00 (0.98-1.00)

			Pooled outcome	0.88 (0.79-0.94)	1.00 (1.00-1.00)
Sample size	< 40	5	Clevert DA	1.00 (0.16-1.00)	1.00 (0.90-1.00)
			Garcacriado	1.00 (0.72-1.00)	1.00 (0.85-1.00)
			Hom	1.00 (0.16-1.00)	1.00 (0.54-1.00)
			Huang	1.00 (0.16-1.00)	1.00 (0.66-1.00)
			Rennert J	1.00 (0.16-1.00)	1.00 (0.84-1.00)
			Pooled outcome	1.00 (0.82-1.00)	1.00 (0.96-1.00)
	> 40	6	Bonini	0.80 (0.28-0.99)	1.00 (0.91-1.00)
			Lu	1.00 (0.75-1.00)	0.97 (0.84-1.00)
			Lyu	1.00 (0.69-1.00)	1.00 (0.96-1.00)
			Rbenthaler	0.89 (0.72-0.98)	1.00 (0.89-1.00)
			Rübenthaler	0.62 (0.32-0.86)	1.00 (0.89-1.00)
			Zheng	0.92 (0.79-0.98)	0.88 (0.47-1.00)
			Pooled outcome	0.89 (0.81-0.94)	0.99 (0.97-1.00)

Table 3. Results of the regression meta-analysis

	Study design	Treatment time of patients	Experience of radiologists
Coefficient	0.003	0.868	1.064
Standard error	1.248	1.059	1.815
p-value	0.997	0.436	0.396
RDOR	1.00	2.38	2.90
(95% CI)	0.06, 17.82	0.21, 27.43	0.19, 44.55

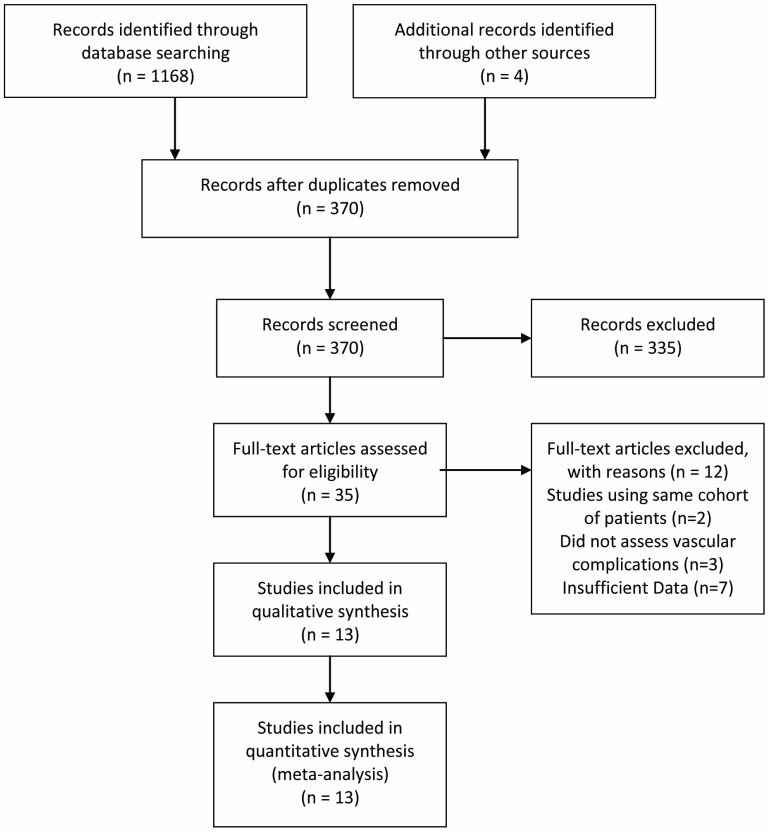

Fig. 1. Flow diagram of the literature search.

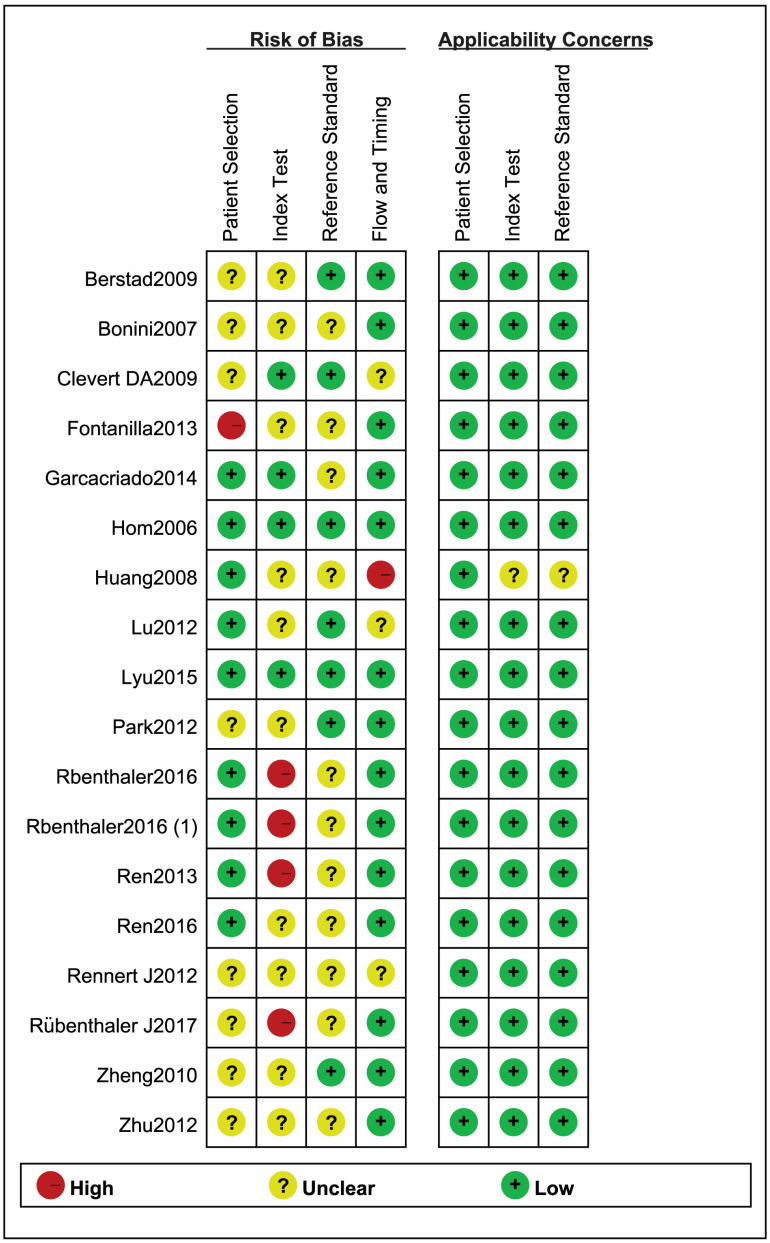

Fig. 2. Methodological quality summary of the 13 included studies. (green+ = yes; red- = no; yellow? = unclear).

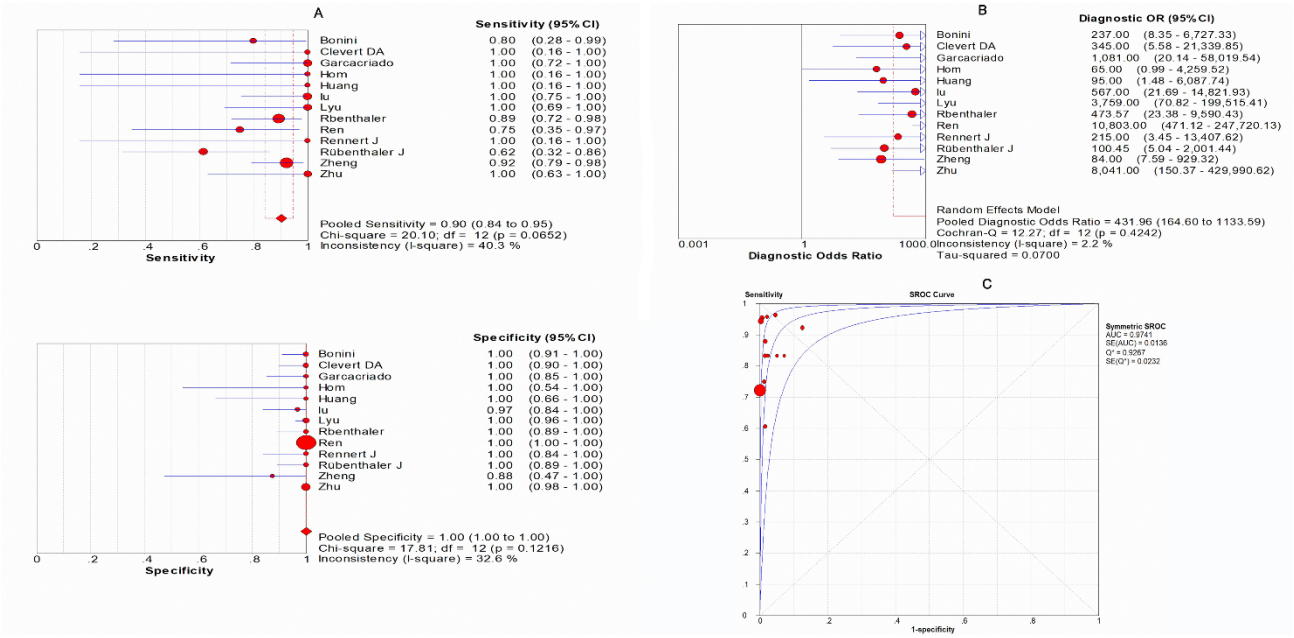

Fig. 3. A. Forest plot of CEUS sensitivity and specificity to assess vascular complications after liver transplantation. B. Forest plot of the diagnostic odds ratio of CEUS for the identification of vascular complications after liver transplantation. C. Summary receiver operating characteristic curve of CEUS evaluation.