Contrast-enhanced ultrasound versus conventional ultrasound in guided liver puncture biopsy: a systematic review and meta-analysis

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Abstract

Aim: To evaluate the contrast-enhanced ultrasound (CEUS) versus conventional ultrasound (US) in guided liver puncture biopsy through a systematic review and meta-analysis. Material and methods: Comparative studies on CEUS and US in liver puncture biopsy were systematically searched from PubMed, Embase, Cochrane library, Chinese Biomedical Literature Database. Two researchers independently screened and extracted data, and RevMan 5.3 software was used for data analysis. Results: The area under the curve (AUC) for CEUS and US in diagnosing liver biopsy was 0.98 (95%CI 0.99-0.97) and 0.95 (95%CI 0.97-0.93), respectively. CEUS demonstrated significantly higher single puncture success rate (38.0% vs 36.4%) [OR=2.67; 95% CI 1.38-5.17; p=0.003] and pathological diagnosis rate (95.6% vs 90.5%) [OR =4.35; 95%CI 2.25-8.39; p<0.001] compared to the US group. The diagnostic accuracy of the CEUS group was 95.6% (1964/2054), while that of the US group was 90.5% (1729/1909). The combined analysis indicated significant advantages for CEUS over US [(OR = 2.36). 95%CI 1.81-3.09, p<0.001]. Conclusions: CEUS is superior to US in the diagnostic performance, single puncture success rate, pathological diagnosis rate and diagnostic accuracy of liver biopsy in patients with liver lesions.

Keywords: contrast-enhanced ultrasound; ultrasound; liver biopsy; meta-analysis

Introduction

The pathological types of biopsy for focal liver lesions are diverse, encompassing malignant tumors (primary hepatic carcinoma, metastatic hepatic carcinoma), benign neoplasms (hepatic adenoma, hemangioma), or sclerotic nodules [1]. Given the significant variation in prognosis among different pathological types, obtaining accurate pathology is essential for guiding treatment decisions and prognostic assessments [2,3]. Percutaneous liver biopsy with ultrasound guidance provides histopathological results that serve as the gold standard for clinical diagnosis of liver lesions [4]. This minimally invasive diagnostic method allows real-time ultrasound-guided sampling of liver lesions and subsequent histopathological examination [5], making it a crucial tool in obtaining pathological results for space-occupying lesions in the liver.

Conventional ultrasound (US) has inherent limitations in guiding percutaneous liver biopsy due to factors such as tumor type, size, and location [6]. For lesions with poor visualization and large tumors exhibiting necrosis, the positive rate of conventional ultrasound-guided biopsy is low. Contrast-enhanced ultrasound (CEUS), on the other hand, utilizes contrast agents to enhance backscattered echo and significantly improves the resolution, sensitivity, and specificity of US diagnosis [7]. It has been reported that compared to US, CEUS enables real-time observation of blood perfusion within liver lesions and accurate evaluation of active versus necrotic areas within masses. This capability helps avoid sampling failure caused by tissue necrosis while enhancing diagnostic accuracy for needle biopsies [8,9]. However, there is currently a lack of comparative studies assessing the application and diagnostic value between US
and CEUS in liver biopsy. Therefore, our objective is to conduct a systematic review and meta-analysis aiming to evaluate the value of CEUS while providing evidence-based support for its application in liver biopsy.

Materials and methods

Literature search strategy

The present study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [10] and AMSTAR (Methodological Quality Assessment of Systematic Reviews) [11] guidelines and has been registered on Prospero (https://www.crd.york.ac.uk/PROSPERO) as CRD42023389161.

A comprehensive computerized search was conducted in PubMed, Web of Science, Medline, Cochrane Library, Wanfang, and CNKI databases from their inception until December 01, 2023. The search strategy included combinations of keywords such as “ultrasound” or “contrast-enhanced ultrasound” or “enhanced ultrasound” with terms like “liver mass,” “liver lesion,” “liver tumor,” or “focal liver,” along with either “biopsy” or “puncture.” Furthermore, a thorough examination of the references included in this study was performed to expand the search scope and identify potentially relevant studies. Only articles published in Chinese or English were considered.

Inclusion and exclusion criteria

The studies included in this meta-analysis consisted of randomized controlled trials (RCTs) or non-randomized comparative trials (N-RCTs) published in full text, which fulfilled the following inclusion criteria: (a) Patients: individuals requiring ultrasound-guided percutaneous liver biopsy; (b) Intervention: puncture guided by CEUS; (c) Comparator: puncture guided by US; and (d) Outcomes: the primary outcome encompassed diagnostic performance measures such as sensitivity, specificity, and accuracy, while secondary outcomes comprised rates of pathological diagnosis and single puncture success. Safety data were also subjected to analysis.

The exclusion criteria were as follows: (1) absence of a control group; (2) inclusion of case reports, abstracts, conference reports, or animal experiments; and (3) inability to obtain outcome data from the articles or author despite attempts.

Study selections and extraction

Literature selection and data extraction were independently conducted by two researchers (LZ and TZ) based on predefined inclusion and exclusion criteria. In case of disagreement between the two researchers regarding article inclusion or exclusion, consultation with a third researcher (HZ) was sought. Following completion of data extraction, the extracted information was reviewed by HZ, who resolved any discrepancies through discussion and re-extraction if necessary.

The extracted data encompassed: (1) Study details such as author, publication year, country, and study design; (2) Subject characteristics including patient number, age distribution, gender distribution, and number of lumps; (3) Outcome measures comprising final diagnosis accuracy indicators such as diagnostic sensitivity, specificity, accuracy rate along with pathological diagnosis rate and single puncture success rate. In cases where data was incomplete or missing information existed, corresponding authors were contacted via phone or email to obtain the required information.

Definitions

The following definitions were employed in this study:

a. Final diagnosis: The ultimate pathological diagnosis of liver biopsy primarily relies on the pathological findings post-surgical resection of the tumor or based on the clinical course of disease (clinical progression or malignant death) after a minimum follow-up period of 6 months.

b. Diagnostic sensitivity: Also known as the true positive rate, it is calculated as the proportion of true positive samples (TP) among actual positive samples (TP + false negative (FN)). If the biopsy result indicates a benign tumor while the final diagnosis confirms a malignant tumor, it is considered as FN. Additionally, if there is uncertainty in the pathological result or insufficient material for analysis, it is also regarded as FN.

c. Diagnostic specificity: Also referred to as the true negative rate, it is calculated by determining the proportion of true negative samples (TN) among actual negative samples (TN + false positives (FP)). Since malignant pathological results from biopsies will correspond to final pathological results being malignant too, FP equals zero and thus diagnostic specificity becomes 1.

d. Diagnostic accuracy: Proportion of samples with biopsy pathological results consistent with final pathological results out of all total samples.

e. Pathological diagnosis rate: Proportion of samples with sufficient puncture materials and obtained pathological results out of all total samples.

f. Single puncture success rate: Proportion of satisfactory tissue specimens obtained after a single puncture out of all total samples.

Quality assessment

The evaluation of treatment efficacy was conducted using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which comprises four key components: patient selection, index test, reference
standard, and flow and timing. The risk level for each study, categorized as low, high or unclear risk, was determined based on the specific circumstances of the included research. Any discrepancies were resolved through discussion.

**Statistical analysis**

Statistical analysis was conducted using RevMan 5.3 and R-Studio software. Odds ratio (OR) and 95% confidence interval (CI) were utilized as effect size statistics for dichotomous data, while the Q test and I² statistics were employed to assess heterogeneity. When p ≥0.1 and I² ≤50%, indicating low heterogeneity among studies, a fixed effects model was used for analysis; when p<0.1 or I² >50%, suggesting high heterogeneity among included studies, a random effects model was applied instead. Diagnostic performance was evaluated by calculating pooled sensitivity, specificity, and their corresponding 95% CIs through forest plot visualization and summary receiver operating characteristic (SROC) curve generation. The “mada” package [12] in R-Studio software was utilized to compute the area under the receiver operating characteristic curve (AUC). A significance level of p<0.05 was considered statistically significant.

**Results**

**Study identification and selection**

The search results process is illustrated in figure 1. A total of 763 potentially relevant articles were identified based on the implemented search strategy. After reviewing the titles and abstracts, 23 studies with potential relevance were selected for further analysis. Of the remaining 23 studies, 16 were excluded after full text analysis for reasons such as center or patient cohort overlap (1 study), lack of interesting results (10 studies), or meeting one of the exclusion criteria (5 studies). Ultimately, a total of 7 articles [8,9,13–17] that met the inclusion criteria were included for subsequent analysis.

**Study characteristics and quality assessment**

The main baseline characteristics of all included studies are presented in Table I. Among the seven included studies, three were RCTs [8,15,17] while four were N-RCT studies [9,13,14,16]. Five of the studies were conducted in China and two in Romania. A total of 3823 patients participated in the analysis, with 1965 patients assigned to the CEUS group and 1858 patients assigned to the US group. Table II provides data on diagnostic performance using a four-fold table approach as well as success rate for single puncture and pathological diagnosis rate.

Overall, no significant risk of bias was identified for each item. However, an unclear risk of bias was observed in the item of ‘patient selection’, primarily due to insuffi-
### Table I. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study period</th>
<th>Study design</th>
<th>Patients</th>
<th>Age (mean±SD)</th>
<th>Gender (F/M)</th>
<th>Biopsied lesions</th>
<th>Size (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu 2006</td>
<td>China</td>
<td>2002-2005</td>
<td>N-RCT</td>
<td>96</td>
<td>53.4±16.2</td>
<td>129/82</td>
<td>CEUS</td>
<td>149</td>
</tr>
<tr>
<td>Spârchez 2015</td>
<td>Romania</td>
<td>2009-2013</td>
<td>RCT</td>
<td>86</td>
<td>62.1±14.7</td>
<td>30/56</td>
<td>CEUS</td>
<td>86</td>
</tr>
<tr>
<td>Lin 2017</td>
<td>China</td>
<td>2013-2016</td>
<td>N-RCT</td>
<td>27</td>
<td>58.0±8.4</td>
<td>11/16</td>
<td>CEUS</td>
<td>28</td>
</tr>
<tr>
<td>Spârchez 2019</td>
<td>Romania</td>
<td>2011-2019</td>
<td>RCT</td>
<td>79</td>
<td>64.1±9.9</td>
<td>19/60</td>
<td>CEUS</td>
<td>149</td>
</tr>
<tr>
<td>Wen 2022</td>
<td>China</td>
<td>2017-2020</td>
<td>N-RCT</td>
<td>289</td>
<td>59.8±11.3</td>
<td>192/97</td>
<td>CEUS</td>
<td>324</td>
</tr>
<tr>
<td>Huang 2022</td>
<td>China</td>
<td>2017-2019</td>
<td>N-RCT</td>
<td>362</td>
<td>53.5±11.3</td>
<td>210/152</td>
<td>CEUS</td>
<td>362</td>
</tr>
<tr>
<td>Wu 2022</td>
<td>China</td>
<td>2016-2019</td>
<td>RCT</td>
<td>1026</td>
<td>58±11</td>
<td>643/377</td>
<td>CEUS</td>
<td>1026</td>
</tr>
</tbody>
</table>

RCT, Randomized-Controlled Trial; N-RCT, Non-randomized controlled study; CEUS, contrast-enhanced ultrasound; US, conventional ultrasound; M: male; F: female; NR: not report

### Table II. Four-fold table data for diagnostic performance

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>US</th>
<th>CEUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TP</td>
<td>FN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu 2006</td>
<td>153</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>Spârchez 2015</td>
<td>81</td>
<td>61</td>
<td>15</td>
</tr>
<tr>
<td>Lin 2017</td>
<td>45</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Spârchez 2019</td>
<td>65</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>Wen 2022</td>
<td>77</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Huang 2022</td>
<td>458</td>
<td>417</td>
<td>34</td>
</tr>
<tr>
<td>Wu 2022</td>
<td>1030</td>
<td>851</td>
<td>77</td>
</tr>
</tbody>
</table>

TP, True Positive; FP, False Positive; TN, True Negative; FN, False Negative
ties (I²=61%), random-effect models were employed for pooled analysis of the data. Meta-analysis demonstrated a significantly higher single puncture success rate in the CEUS group compared to the US group (OR=2.67; 95%CI 1.38-5.17, p=0.003) (fig 5).

**CEUS enhance pathological diagnosis rate**

The included literature from six studies [8,9,13–16] reported on the rates of pathological diagnosis, which were found to be at a level of 98.7% (805/816) for the CEUS group and at a slightly lower level of 94.6% (853/902) for the US group respectively. With low heterogeneity observed among these studies (I²=9%), we applied a fixed-effect model for our pooled analysis. Our meta-analysis findings revealed that there is significant evidence supporting higher rates of pathological diagnosis within the CEUS group when compared to those within the US group (OR=4.35; 95%CI 2.25-8.39, p<0.001) (fig 6).

**CEUS increased diagnostic accuracy rate**

All seven studies [8,9,13–17] reported the diagnostic accuracy of CEUS and US guided biopsy. The CEUS group demonstrated a diagnostic accuracy of 95.6% (1964/2054), while the US group showed a diagnostic accuracy of 90.5% (1729/1909). Due to low heterogeneity (I²=31%), a fixed effect model was employed for pooled analysis. Meta-analysis revealed that the diagnostic accuracy of the CEUS group was significantly superior to that of the US group (OR=2.36; 95%CI 1.81-3.09, p<0.001), as depicted in figure 7.

Furthermore, we conducted subgroup analyses on the diagnostic accuracy of CEUS and US-guided biopsy.

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**Fig 3.** The pooled sensitivity and specificity on CEUS and US in guided liver puncture biopsy

**Fig 4.** The summary receiver operating characteristic curve on CEUS and US in guided liver puncture biopsy

**Fig 5.** Forest plot compares the single puncture success rate of CEUS and US in guiding liver biopsy
based on different lesion sizes. The results indicated that CEUS exhibited significantly higher diagnostic accuracy than US for lesions with diameters <2 cm (OR=3.57; 95%CI 2.04-6.26, p<0.001), between 2-5cm (OR=1.56; CI95% 1.02-2.38, p=0.04), and >5 cm (OR=2.77; CI95% 1.69-4.52, p<0.001) (fig 8).

Fig 6. Forest plot compares the pathological diagnosis rate of CEUS and US in guiding liver biopsy

Fig 7. Forest plot comparing the diagnostic accuracy rate of CEUS and US in guiding liver biopsy

Fig 8. Forest plot comparing CEUS and US for diagnostic accuracy based on different lesion sizes
Adverse events of clinical significance

We also conducted an analysis on the clinical safety of both CEUS and US guidance methods. Pain at the puncture site was reported in three studies [13,15,16], while bleeding at the puncture site was reported in five studies [8,13–15,17]. Meta-analysis results indicated that there were no significant differences in these adverse events between CEUS and US (OR=0.75; 95%CI 0.48-1.18, p=0.21) and (OR=1.24; 95%CI 0.28-5.49, p=0.78), as depicted in figure 9. None of the seven studies reported any deaths related to puncture or needle transfer during follow-up period either. Spârchez et al [15] documented one patient who required surgical intervention due to bleeding at the puncture site, whereas Wu et al [13] described a case where pneumothorax occurred after puncturing due to the close proximity of the liver tumor to the diaphragm muscle.

Discussion

Although non-invasive diagnostic methods, such as CT or MRI, play a crucial role in the diagnosis of hepatic space-occupying lesions, histopathological findings remain the cornerstone for treatment formulation and disease prognosis prediction [18,19]. Ultrasound-guided percutaneous liver biopsy is widely utilized in clinical practice due to its simplicity, absence of radiation exposure, and low complication rate [5]. However, distinguishing necrotic tissue by ultrasound can be challenging for large liver lesions often leading to biopsy failure or false negatives [20]. Additionally, conventional ultrasound may result in false negative results for smaller liver lesions due to difficulties in accurate targeting during puncture procedures [17]. Different pathological types exhibit distinct tissue blood perfusion patterns [21], thus CEUS provides valuable insights into lesion nature assessment and facilitates precise selection of puncture sites. CEUS enables easy differentiation of necrotic tissue with no contrast filling observed at any stage while active regions display visible radiographic agent filling. Consequently, CEUS has been successfully employed in the puncture biopsy of various tumors [22,23].

In 2004, Schlottmann et al [24] reported the application of CEUS in liver biopsy, suggesting its potential to identify target areas of liver lesions and reduce false negative results by avoiding liquefied necrotic regions. CEUS is a convenient method that does not significantly prolong the duration of liver biopsy surgery and has already become a routine diagnostic tool for patients with liver masses in several large medical centers [17]. Utilizing CEUS guidance for liver biopsy could be an ideal strategy to enhance diagnostic sensitivity and accuracy in these patients [25]. However, there is limited evidence available comparing the efficacy of CEUS and US in guiding liver tumor biopsies. Therefore, we conducted this meta-analysis as the first systematic review comparing CEUS and US guidance for liver biopsy, further confirming the clinical value of CEUS.

Our analysis of the diagnostic performance of ultrasound-guided liver biopsy revealed that CEUS-guided liver biopsy exhibited superior efficacy compared to US, with areas under the curve (AUC) of 0.99 and 0.95, respectively. This finding further substantiates the effectiveness of ultrasound-guided liver biopsy and highlights the superior diagnostic efficiency of CEUS guidance over US guidance. Moreover, our analysis on clinical adverse
events demonstrated excellent safety profiles for both CEUS and US techniques. None of the included studies reported any puncture-related fatalities, while only one study [15] documented a complication necessitating surgical intervention due to post-biopsy bleeding at the puncture site. Other adverse events such as puncture pain did not require specific interventions.

CEUS has been reported to improve the success rate of a single puncture liver biopsy [13], a finding that is further supported by our meta-analysis, demonstrating a significantly higher success rate of CEUS-guided liver biopsy compared to conventional ultrasound. However, relying solely on visual assessment may introduce subjectivity in evaluating sample quality [26]. Therefore, we evaluated the histopathological diagnostic rate of liver biopsies as an indicator of successful acquisition of sufficient and viable tissue specimens rather than necrotic samples [4]. Our results revealed a significantly higher histopathological diagnostic rate in the CEUS-guided group compared to the US group, confirming the utility of CEUS in distinguishing liquefied necrotic tissue and facilitating accurate target selection.

CEUS, enhanced CT, and enhanced MRI are considered equally crucial for the diagnosis of liver tumors, and these three methods serve as the standard examination techniques [27]. Utilizing CEUS guidance in a liver biopsy enables operators to preliminarily differentiate between benign and malignant lesions, facilitating accurate puncture without the need for repeated attempts [9,15]. During needle biopsies of malignant tumors, CEUS can clearly visualize necrotic areas within the tumor, allowing avoidance during puncture while targeting arterial phase-enhanced regions to obtain precise samples of malignant tissue [28]. In cases of liver metastases requiring needle biopsies, active lesions exhibit more significant enhancement than inactive ones during the arterial phase. This distinction guides piercers towards selecting active lesions for puncture and thereby improves accuracy [29]. Additionally, CEUS excels at displaying smaller tumor locations and depths with precision compared to US, thus further enhancing puncture accuracy. Our meta-analysis results also demonstrate a significantly higher diagnostic accuracy for CEUS-guided liver biopsies compared to US.

Our study has certain limitations that require further elucidation. Firstly, the scope of our manuscript was limited to China and Romania, necessitating additional multi-center randomized controlled trials to validate the generalizability of our meta-analysis findings on a global scale. Secondly, due to the challenges in data collection, we only conducted a subgroup analysis on liver lesions of different diameters, without considering factors such as liquefaction and necrosis of the mass or visibility under US. Furthermore, it is important to acknowledge that the proficiency of clinical piercers can inevitably impact the accuracy of puncture diagnosis.

**Conclusion**

In conclusion, CEUS demonstrates superiority over US in guiding liver lesion biopsies by significantly enhancing the quality and accuracy of pathological diagnosis. Therefore, we recommend the routine implementation of CEUS-guided liver biopsy.

**Conflict of interest:** none

**References**


