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Liu, QY<sup>1</sup>; Liu, T<sup>2</sup>; Yang, Q<sup>3</sup>.**ADMINISTRATIVE INFORMATION****Support** - Henan Provincial Young Talent Support Project.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202380044**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 August 2023 and was last updated on 10 August 2023.**INTRODUCTION**

**Review question / Objective** The unique Kupffer phase (KP) of Sonazoid may improve the sensitivity of HCC diagnosis. So some scholars proposed the modified CEUS LI-RADS. It changed mild and late ( $\geq 60$  seconds) washout as the main criteria in CEUS LI-RADS LR-5 to KP ( $> 10$  minutes) defects as the main criteria, and related original studies were conducted. The aim of this study was to assess the efficacy of the modified CEUS LI-RADS proposed for Sonazoid for the diagnosis of HCC.

**Condition being studied** HCC has a poor prognosis, so early diagnosis is important in patients with HCC. Puncture biopsy may present with uncontrollable bleeding and the size of the nodule may lead to false-negative results. These limit its value in the diagnosis of HCC. HCC is the only cancer that can be diagnosed by imaging. Ultrasonography plays an increasingly important role in the diagnosis of intrahepatic nodules. In 2016 and 2017, the American College of Radiology

(ACR) released the original and updated versions of the LI-RADS for liver ultrasonography, which provides a more standardized evidence base for the diagnosis of ultrasonography of liver nodules. However, it is only applicable to blood pool contrast agents (e.g., SonoVue). With the application of blood pool and Kupffer cell combined contrast agent (Sonazoid) in the clinic, some scholars found that its characteristic KP phase may help to improve the sensitivity of HCC diagnosis. A modified version of CEUS LI-RADS that replaces the KP ( $> 10$  minutes) defects with mild and late ( $\geq 60$  seconds) washout has been proposed. Some original studies on this modified CEUS LI-RADS are currently performed and we will evaluate the diagnostic performance of this algorithm.

**METHODS**

**Search strategy** A comprehensive and systematic search was conducted in PubMed, Embase, the Cochrane Library and Web of Science up to July 13, 2023, with no language restrictions. The

literature search strategy used MeSH and free word search. Search terms included "liver neoplasms", "LI-RADS", "CEUS" and "sulfur hexafluoride".

**Participant or population** Patients aged >18 years at high risk of HCC were included according to CEUS LI-RADS (v2017). Patients were also categorized and evaluated for intrahepatic nodules using the modified CEUS LI-RADS.

**Intervention** Blood pools and Kupffer cells combined contrast agent (Sonazoid) were applied to evaluate intrahepatic nodules in patients at high risk of HCC. A modified version of CEUS LI-RADS was applied to classify intrahepatic nodules.

**Comparator** Not applicable.

**Study designs to be included** The main inclusion criteria were prospective or retrospective studies that had reported the diagnostic efficacy of LR-5 with modified CEUS LI-RADS in patients at high risk for HCC.

**Eligibility criteria** The main inclusion criteria were prospective or retrospective studies that had reported the diagnostic efficacy of LR-5 with modified CEUS LI-RADS in patients at high risk for HCC. Exclusion criteria include: 1. meta-analysis, reviews, case reports, letters, comments, and abstracts of meetings; 2. Research that does not belong to the focus area of this study; 3. Studies with overlapping patient data; 4. Insufficient information, unable to extract diagnostic performance 2x2 data table research.

**Information sources** A comprehensive and systematic search was conducted in PubMed, Embase, the Cochrane Library and Web of Science up to July 13, 2023, with no language restrictions.

**Main outcome(s)** The sensitivity, specificity and SROC curve of modified CEUS LI-RADS for diagnosis HCC.

**Additional outcome(s)** PLR, NLR, DOR, etc.

**Quality assessment / Risk of bias analysis** The quality of the included diagnostic accuracy studies was critically assessed for risk of bias and applicability using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. Included primary studies were assessed independently by two reviewers, and discrepancies were negotiated with a third reviewer until agreement was reached. The included studies were tested for publication bias.

**Strategy of data synthesis** Statistical analysis was performed using STATA, RevMan, and Meta-DiSc software. A bivariate mixed-effects model was used to synthesize the diagnostic performance of modified CEUS LI-RADS. Spearman's correlation coefficient was used to assess threshold effects. Heterogeneity was assessed using Q-test and I<sup>2</sup> statistic. Meta-regression was used to find the source of heterogeneity.

**Subgroup analysis** None.

**Sensitivity analysis** A bivariate mixed-effects model was used to synthesize the diagnostic performance of modified CEUS LI-RADS. Spearman's correlation coefficient was used to assess threshold effects. Heterogeneity was assessed using Q-test and I<sup>2</sup> statistic. Meta-regression was used to find the source of heterogeneity.

**Language restriction** Without restrictions.

**Country(ies) involved** China.

**Keywords** Hepatocellular carcinoma (HCC); contrast-enhanced ultrasonography (CEUS); Liver Imaging Reporting and Data System (LI-RADS); Perfluorobutane.

#### **Contributions of each author**

Author 1 - Qianyu Liu - The author drafted the manuscript, searched of articles, extraction of data, and provided statistical analysis.

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Author 2 - Ting Liu - The author searched of articles, extraction of data, and provided statistical analysis.

Author 3 - Qing Yang - The author designed the whole study.

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