

# INPLASY PROTOCOL

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None declared.

## LR-5 by LI-RADS under contrast enhanced ultrasonography manifests satisfactory diagnostic performance for hepatocellular carcinoma: A systematic review and meta-analysis

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**Review question / Objective:** To evaluate the relative diagnostic sensitivity, specificity, and accuracy of LR-5 under contrast-enhanced ultrasonography (CEUS) LI-RADS system in the differential diagnosis of hepatocellular carcinoma (HCC).

**Information sources:** A comprehensive and thorough search of literature was carried out through internationally acknowledged medical literature resources database, including PubMed/MEDLINE, EMBASE, Ovid, and Web of Science along with regional databases with key research words of (“hepatocellular carcinoma” OR “liver cancer” OR “liver tumor” OR “liver nodule” OR “liver mass” OR “liver lesion”) AND (“contrast-enhanced US” OR “contrast-enhanced ultrasonography” OR “contrast-enhanced ultrasound” OR “CEUS”) AND (“LI-RADS” OR “liver reporting and data system”) for studies published between January 2017 and June 2021. We limited the language used in the literature as English only.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 October 2022 and was last updated on 03 October 2022 (registration number INPLASY2022100011).

### INTRODUCTION

**Review question / Objective:** To evaluate the relative diagnostic sensitivity, specificity, and accuracy of LR-5 under contrast-enhanced ultrasonography (CEUS) LI-RADS system in the differential

diagnosis of hepatocellular carcinoma (HCC).

**Rationale:** Hepatocellular carcinoma ranks the third among all malignancies with increasingly high morbidity and mortality, which contributes to heavy disease related economic and social burden. Moreover,

disease progress is frequently witnessed after the tumor enters mid- and late stages. Thus, early diagnosis followed by radical surgery is regarded as the best and most crucial way of HCC containment. Because of typical features under several imaging techniques, most of HCC cases are diagnosed merely based on imaging features without pathological observation which involves invasive procedures, regardless of biopsy and surgery. Considering the large population who are vulnerable for HCC, including patients with long duration of hepatitis B virus (HBV) infection, liver cirrhosis, etc, liver ultrasonography has been widely applied as the primary diagnostic and screening tool for potentially underlying liver nodules.

**Condition being studied:** In recent years, with the development of microbubble contrast agent in ultrasonography, as well as advantages of zero radiation, convenience, and inexpensiveness, contrast-enhanced ultrasonography has gained increasingly dominant role in defining the essence of discovered liver nodules. In 2016 and 2017, the American College of Radiology (ACR) released an original and updated version of LI-RADS for CEUS, which facilitated more standardized reporting process and precise determination of liver nodules. Based on specific guidelines, focal liver lesions can be categorized into 5 grades (category 1-5). Among them, classification of LR-5 is of critical significance since radical surgery may be arranged followed by such diagnosis. In addition, since LR-5 is HCC specific, such diagnosis might help clinicians differentiate HCC from other malignant liver nodules, which greatly influences the choice of subsequent treatment. However, despite the ever widely appliance of LI-RADS and standardized performance of CEUS based on LI-RADS protocols, the sensitivity, specificity, and accuracy varied enormously, with sensitivity of LR-5 ranging from 33% to 86% and specificity from 58% to 100% according to different clinical studies, which has hindered further promotion of LI-RADS. Meanwhile, the number of included lesions, patients, the

sizes of included lesions also varied greatly from study to study, which might contribute to potential bias while generally analyzing the clinical significance of LI-RADS.

## METHODS

**Search strategy:** A comprehensive and thorough search of literature was carried out through internationally acknowledged medical literature resources database, including PubMed/MEDLINE, EMBASE, Ovid, and Web of Science along with regional databases with key research words of (“hepatocellular carcinoma” OR “liver cancer” OR “liver tumor” OR “liver nodule” OR “liver mass” OR “liver lesion”) AND (“contrast-enhanced US” OR “contrast-enhanced ultrasonography” OR “contrast-enhanced ultrasound” OR “CEUS”) AND (“LI-RADS” OR “liver reporting and data system”) for studies published between January 2017 and June 2021. We limited the language used in the literature as English only.

**Participant or population:** Patients with focal liver lesions.

**Intervention:** The patients went through CEUS examination.

**Comparator:** Pathological findings of the liver nodules were regarded as the golden standard.

**Study designs to be included:** The primary inclusion criterion was having reported the diagnostic efficacy of LR-5 of CEUS LI-RADS for identifying HCC in patients with high vulnerability.

**Eligibility criteria:** The primary inclusion criterion was having reported the diagnostic efficacy of LR-5 of CEUS LI-RADS for identifying HCC in patients with high vulnerability. The exclusion criteria included: (a) studies that did not report the diagnostic performance for HCC specifically; (b) studies that used modified or reformative version of CEUS LI-RADS rather than the standard version; (c) studies that was not able to clearly state the reference standard, or the reference

standard did not include pathological determination; (d) studies that were case reports, report of case series, letters, editorials, comments, animal studies, conference abstracts.

**Information sources:** A comprehensive and thorough search of literature was carried out through internationally acknowledged medical literature resources database, including PubMed/MEDLINE, EMBASE, Ovid, and Web of Science along with regional databases with key research words of (“hepatocellular carcinoma” OR “liver cancer” OR “liver tumor” OR “liver nodule” OR “liver mass” OR “liver lesion”) AND (“contrast-enhanced US” OR “contrast-enhanced ultrasonography” OR “contrast-enhanced ultrasound” OR “CEUS”) AND (“LI-RADS” OR “liver reporting and data system”) for studies published between January 2017 and June 2021. We limited the language used in the literature as English only.

**Main outcome(s):** Pooled diagnostic sensitivity, specificity, and accuracy.

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

**Data management:** Pooled estimates (sensitivity and specificity) with their 95% CIs were calculated using the bivariate model as well as the hierarchical summary receiver operating characteristic (HSROC) model and a fixed- or random-effects model. In the meantime, diagnostic odds ratio (DOR) was simultaneously calculated to display the general diagnostic accuracy. Specifically, if one article invited more than one expert to categorize the lesion, we would display the stratification of all experts in order to fully demonstrate the diagnostic effectiveness. To evaluate the potential heterogeneity between studies, a meta regression analysis was performed. All the aforementioned statistical analysis was done with Review Manager (Cochrane Collaboration, Copenhagen, Denmark) and Meta-Disc version 1.4 (Clinical Biostatistics Unit, UK).

**Quality assessment / Risk of bias analysis:** Quality assessment was strictly launched

by 2 independent reviewers in accordance with Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) evaluation system, in which the risk of bias as well as applicability were rigorously weighed. A third reviewer would be assigned to re-evaluate the outcomes of the 2 reviewers if inconsistency came into being.

**Strategy of data synthesis:** Pooled estimates (sensitivity and specificity) with their 95% CIs were calculated using the bivariate model as well as the hierarchical summary receiver operating characteristic (HSROC) model and a fixed- or random-effects model.

**Subgroup analysis:** We did not intend to perform subgroup analysis in this study.

**Sensitivity analysis:** Pooled estimates (sensitivity and specificity) with their 95% CIs were calculated using the bivariate model as well as the hierarchical summary receiver operating characteristic (HSROC) model and a fixed- or random-effects model.

**Language restriction:** English.

**Country(ies) involved:** China.

**Other relevant information:** None.

**Keywords:** Hepatocellular carcinoma; LR-5; CEUS LI-RADS; sensitivity; specificity.

**Dissemination plans:** Lecture or conferences.

**Contributions of each author:**

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