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Article

Multimodal imaging prediction models for preoperative microvascular invasion in hepatocellular carcinoma: A systematic review and predictive accuracy analysis from biomechanical perspective

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Abstract: This meta-analysis aimed to evaluate the accuracy of multimodal imaging prediction models for preoperative microvascular invasion (MVI) in hepatocellular carcinoma (HCC) patients from both radiological and biomechanical perspectives. We systematically searched PubMed, Embase, and Cochrane Library databases, including 42 studies with 10,876 patients. Statistical analysis using a bivariate random-effects model assessed the diagnostic performance of different imaging modalities and prediction model types, with particular emphasis on biomechanical features including tissue elasticity, vascular wall mechanics, and tumor microenvironment properties. Results demonstrated excellent performance of multimodal imaging prediction models incorporating biomechanical parameters in MVI prediction, with a pooled sensitivity of 0.78 (95% CI: 0.73–0.82), specificity of 0.80 (95% CI: 0.76–0.84), and area under the curve (AUC) of 0.86 (95% CI: 0.83–0.89). Deep learning approaches demonstrated particular advantages in feature extraction and biomechanical pattern recognition, achieving superior performance (AUC 0.88) through their ability to automatically learn hierarchical representations from complex imaging data and mechanical data. The integration of multiple imaging modalities with biomechanical parameters further enhanced predictive accuracy (AUC 0.91), offering complementary information that captures different aspects of tumor biology, mechanics and behavior. This enhanced performance of multimodal combinations, particularly when leveraging biomechanical features and deep learning algorithms, suggests significant potential for improving clinical decision-making and treatment planning in HCC patients. Future research should focus on large-scale prospective validation, standardization of biomechanical measurements, and clinical application assessment to further enhance the accuracy and clinical value of MVI prediction.

Keywords: hepatocellular carcinoma; microvascular invasion; multimodal imaging; biomechanical modeling; prediction models; deep learning; radiomics

1. Introduction

Hepatocellular carcinoma (HCC) stands as a formidable challenge in the landscape of global health, ranking as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. The management of HCC has seen significant advancements in recent years, with surgical resection and liver transplantation emerging as potentially curative treatments for early-stage disease. However, the long-term prognosis for HCC patients remains poor, largely due to the high incidence of postoperative recurrence and metastasis. Among the various factors influencing patient outcomes, microvascular invasion (MVI) has been identified as a critical predictor of recurrence and survival in HCC patients undergoing curative treatments.

MVI, defined as the presence of tumor cells in the portal vein, hepatic vein, or

large capsular vessels, is a histopathological feature that can only be definitively diagnosed postoperatively. This presents a significant clinical dilemma, as preoperative knowledge of MVI status is crucial for optimal treatment planning and prognostication. Patients with MVI may benefit from more aggressive surgical approaches, such as anatomical resection or wider surgical margins, or may be better candidates for liver transplantation or neoadjuvant therapy. Conversely, patients without MVI might be suitable for less invasive treatments like radiofrequency ablation. Therefore, accurate preoperative prediction of MVI has become a key focus in HCC management, driving research into various predictive models and techniques.

In recent years, imaging modalities have emerged as powerful tools for the non-invasive assessment of HCC characteristics, including the prediction of MVI. Conventional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have been extensively studied for their ability to detect imaging biomarkers associated with MVI. These biomarkers include tumor size, margins, capsule appearance, and peritumoral enhancement patterns. More advanced imaging techniques, such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI, and radiomics analysis, have further enhanced the potential for accurate MVI prediction. The integration of multiple imaging modalities and techniques, termed multimodal imaging, has shown promise in improving predictive accuracy by capturing complementary information about tumor biology and behavior.

Beyond traditional imaging features, the biomechanical properties of HCC tissue and its microenvironment have emerged as critical factors in understanding tumor progression and vascular invasion patterns. Various imaging modalities can now capture these biomechanical characteristics: elastography techniques in both MRI and ultrasound can quantify tissue stiffness and elastic properties; dynamic contrast-enhanced imaging can reveal vascular wall mechanics and blood flow dynamics; diffusion-weighted imaging can reflect cellular density and mechanical organization of the tumor microenvironment. These biomechanical parameters provide unique insights into the mechanical forces driving tumor invasion and metastasis. For instance, increased tissue stiffness often correlates with higher metastatic potential, while altered vascular wall mechanics may indicate early stages of microvascular invasion. The integration of these biomechanical features with conventional imaging markers represents a promising approach to enhance the accuracy of MVI prediction.

Despite the growing body of literature on imaging-based MVI prediction, there remains considerable heterogeneity in reported predictive accuracies, model performances, and optimal imaging features. This variability can be attributed to differences in study populations, imaging protocols, feature selection methods, and statistical approaches. Moreover, the relative performance of different imaging modalities and the added value of multimodal approaches have not been systematically evaluated across studies. This lack of consensus poses challenges for clinicians seeking to implement these predictive models in practice and highlights the need for a comprehensive synthesis of existing evidence.

In light of these considerations, we conducted a systematic review and meta-analysis to evaluate the predictive accuracy of multimodal imaging models for preoperative MVI in HCC. Our study aims to synthesize the current evidence on imaging-based MVI prediction, compare the performance of different imaging

modalities and techniques, and assess the added value of multimodal approaches. By pooling data from multiple studies, we seek to provide more robust estimates of predictive accuracy and identify the most promising imaging features and model architectures. Additionally, this meta-analysis aims to explore sources of heterogeneity in predictive performance and highlight areas for future research and standardization in imaging-based MVI prediction.

Through this comprehensive analysis, we hope to provide clinicians and researchers with valuable insights into the current state of imaging-based MVI prediction in HCC, with particular emphasis on the role of biomechanical features in enhancing predictive accuracy. This integrated approach, combining traditional imaging markers with biomechanical parameters, aims to facilitate more informed decision-making in patient management and guide future developments in this critical area of oncological imaging.

2. Method

2.1. Literature search strategy

A comprehensive literature search was conducted to identify relevant studies on multimodal imaging prediction models for preoperative microvascular invasion in hepatocellular carcinoma. The search systematically covered multiple electronic databases, including PubMed, Embase, Web of Science, and Cochrane Library, from their inception to March 2024. The search strategy was developed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to hepatocellular carcinoma, microvascular invasion, and imaging modalities. Key search terms included “hepatocellular carcinoma”, “liver cancer”, “microvascular invasion”, “CT”, “MRI”, “ultrasound”, “radiomics”, and “prediction model.” To ensure a comprehensive search, the reference lists of included studies and relevant review articles were also reviewed for additional eligible studies. No language restrictions were applied to capture a global perspective on the topic. Conference abstracts and unpublished studies were considered to minimize publication bias. The search was independently performed by two reviewers, and any discrepancies were resolved through discussion with a third reviewer. The detailed search strategy for each database was documented to ensure reproducibility. The literature search was supplemented by manual searching of key journals in the field of hepatology, radiology, and oncology to identify any studies that might have been missed in the electronic database search.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

The inclusion criteria for this meta-analysis were carefully defined to ensure the selection of high-quality, relevant studies that address the research question regarding multimodal imaging prediction models for preoperative microvascular invasion (MVI) in hepatocellular carcinoma (HCC). Studies were included if they met all of the following criteria:

Study Design: Prospective or retrospective studies that evaluated imaging-based

prediction models for MVI in HCC. Both development and validation studies were considered eligible.

Patient Population: Studies involving adult patients (≥ 18 years old) with a confirmed diagnosis of HCC based on histopathological examination or established imaging criteria (e.g., AASLD or EASL guidelines).

1) Index Test: Studies that used at least one imaging modality (CT, MRI, ultrasound, or a combination) to predict MVI preoperatively. The imaging features or prediction models should be clearly described. Studies were required to include biomechanical analysis through imaging modalities alongside conventional imaging features. The biomechanical parameters were primarily derived from elastography measurements, dynamic contrast imaging, and advanced mechanical property analysis. Quantitative biomechanical assessment included tissue elasticity values, mechanical stiffness measurements, vascular flow dynamics, and tumor microenvironment mechanical characteristics. These parameters needed to be systematically measured and reported using standardized protocols with clearly defined measurement techniques and quality control procedures.
2) Reference Standard: Histopathological confirmation of MVI status from surgical specimens obtained through resection or liver transplantation.
3) Outcome Measures: Studies that reported sufficient data to construct 2 × 2 contingency tables for calculating diagnostic accuracy measures (sensitivity, specificity, positive predictive value, negative predictive value) or provided area under the receiver operating characteristic curve (AUC) values.
4) Publication Type: Full-text articles published in peer-reviewed journals. Conference abstracts with sufficient data were also considered if they met all other inclusion criteria.
5) Language: Studies published in English or with available English translations.
6) Sample Size: A minimum sample size of 50 patients to ensure adequate statistical power.

The inclusion criteria for study selection are presented in **Table 1**. The table outlines eight key criteria that were systematically applied during the study selection process. Studies were required to be either prospective or retrospective in design, focusing on imaging-based MVI prediction models in adult HCC patients. Eligible studies needed to employ at least one imaging modality and use histopathological confirmation as the reference standard for MVI. To ensure statistical robustness, studies were required to provide sufficient data for constructing 2 × 2 contingency tables or report AUC values. Only full-text articles in peer-reviewed journals and eligible conference abstracts were considered, with a minimum sample size requirement of 50 patients to ensure adequate statistical power. The search was limited to English language publications or those with available English translations to maintain consistency in data interpretation.

Table 1. summarizes the key inclusion criteria.

Criterion	Description
Study Design	Prospective or retrospective studies evaluating imaging-based MVI prediction models
Patient Population	Adults (≥ 18 years) with confirmed HCC
Index Test	At least one imaging modality (CT, MRI, ultrasound, or combination)
Reference Standard	Histopathological confirmation of MVI
Outcome Measures	Data for 2 × 2 contingency tables or AUC values
Publication Type	Full-text articles in peer-reviewed journals; eligible conference abstracts
Language	English or with available English translations
Sample Size	Minimum of 50 patients

Summary of inclusion criteria.

2.2.2. Exclusion criteria

To maintain the focus and quality of the meta-analysis, studies were excluded if they met any of the following criteria (as shown in **Table 2**):

Table 2. summarizes the key exclusion criteria.

Criterion	Description
Study Design	Case reports, editorials, letters, reviews, meta-analyses
Patient Population	Pediatric populations, > 10% non-HCC malignancies
Index Test	Non-imaging biomarkers alone, invasive techniques, unclear imaging protocols
Reference Standard	Lack of histopathological confirmation of MVI
Outcome Measures	Insufficient data for accuracy assessment, qualitative results only
Duplicate Data	Multiple publications on the same cohort (retain most recent/comprehensive)
Quality Concerns	Significant methodological flaws based on quality assessment

Summary of exclusion criteria.

1) Study Design: Case reports, editorials, letters to the editor, review articles, and meta-analyses were excluded as they do not provide primary data suitable for the analysis.
2) Patient Population: Studies focusing exclusively on pediatric populations or including a significant proportion (> 10%) of non-HCC liver malignancies were excluded to maintain homogeneity in the patient cohort.
3) Index Test: Studies using only non-imaging biomarkers (e.g., serum markers alone) or invasive techniques (e.g., biopsy) for MVI prediction were excluded. Additionally, studies that did not clearly describe their imaging protocols or feature extraction methods were excluded due to lack of reproducibility.
4) Reference Standard: Studies without histopathological confirmation of MVI status or those using alternative reference standards (e.g., clinical follow-up alone) were excluded to ensure accuracy in MVI assessment.
5) Outcome Measures: Studies that did not report sufficient data to assess diagnostic accuracy or model performance were excluded. This includes studies that only reported qualitative results or used non-standard outcome measures.
6) Duplicate or Overlapping Data: In cases where multiple publications were based

on the same patient cohort, only the most recent or comprehensive study was included to avoid duplication of data.

7) Quality Concerns: Studies with significant methodological flaws, as assessed by quality assessment tools (e.g., QUADAS-2), were excluded to maintain the overall quality of the meta-analysis.

2.3. Data extraction

A standardized data extraction form was developed and piloted on a subset of included studies to ensure consistency and comprehensiveness in data collection. Two independent reviewers extracted data from each eligible study, with any discrepancies resolved through discussion or consultation with a third reviewer. The extracted information encompassed study characteristics (author, year of publication, country, study design), patient demographics (sample size, age, gender, etiology of liver disease), imaging protocols (modalities used, technical parameters, timing of imaging relative to surgery), MVI prediction models (features included, model development method, cut-off values), and outcome measures (sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic curve). For CT imaging studies, key technical parameters were documented, including slice thickness (range: 1–5 mm), reconstruction interval, contrast agent type and dose, arterial and portal venous phase timing, and scanner specifications. For MRI studies, we recorded field strength (1.5T or 3.0T), sequence parameters (including TR/TE values, flip angles, and slice thickness), contrast agent properties (type, dose, and timing), and specific protocols for dynamic contrast-enhanced and diffusion-weighted imaging (including b-values). For ultrasound studies, we documented equipment specifications, transducer frequency ranges, and detailed contrast-enhanced ultrasound protocols including contrast agent type, dose, and timing parameters. The consistency of image acquisition and post-processing methods was evaluated across studies, with particular attention to protocol standardization and quality control measures. For studies reporting multiple prediction models or using different imaging modalities, data were extracted separately for each model or modality to enable subgroup analyses. The histopathological criteria used for MVI diagnosis were also recorded, along with any additional relevant information such as tumor characteristics (size, number, location) and liver function parameters. In cases where required data were not explicitly reported, efforts were made to calculate the necessary values from available information or to contact the study authors for clarification. The completeness and accuracy of the extracted data were verified by cross-checking against the original articles before analysis. For studies incorporating biomechanical assessments, data extraction included documentation of mechanical property measurements from elastography and dynamic contrast imaging. Quantitative parameters such as tissue stiffness values, strain ratios, and flow dynamics were recorded along with their technical specifications and quality metrics. The integration methods of these biomechanical parameters with conventional imaging features were documented, including any correlations between mechanical properties and MVI status.

2.4. Quality assessment

2.4.1. Assessment tool selection

The selection of an appropriate quality assessment tool is crucial for evaluating the methodological rigor and potential biases of included studies in a meta-analysis. For this study on multimodal imaging prediction models for microvascular invasion (MVI) in hepatocellular carcinoma (HCC), the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was chosen as the primary instrument for quality assessment. QUADAS-2 is widely recognized and recommended by the Cochrane Collaboration for systematic reviews of diagnostic accuracy studies. This tool was selected due to its comprehensive coverage of key domains relevant to diagnostic studies, including patient selection, index test, reference standard, and flow and timing. The QUADAS-2 tool allows for the assessment of both risk of bias and concerns regarding applicability in each domain, providing a nuanced evaluation of study quality. To tailor the tool to the specific context of imaging-based MVI prediction in HCC, minor modifications were made to the signaling questions within each domain. These modifications included specific considerations for imaging protocols, blinding procedures for image interpretation, and the consistency of histopathological assessment of MVI. Additionally, to complement the QUADAS-2 assessment, the Prediction model Risk Of Bias ASsessment Tool (PROBAST) was incorporated to evaluate aspects specific to prediction model studies, such as model development, validation, and performance measures. The quality assessment framework was enhanced to address biomechanical measurements in imaging studies, incorporating criteria for evaluating mechanical property measurements, elastography protocol standardization, and measurement reproducibility. This enhancement ensured comprehensive evaluation of both imaging and biomechanical aspects.

2.4.2. Assessment process

The quality assessment process was designed to ensure a thorough and objective evaluation of each included study. Two independent reviewers, experienced in both diagnostic imaging and clinical research methodology, conducted the quality assessment using the modified QUADAS-2 and PROBAST tools. Prior to the formal assessment, both reviewers underwent training sessions to familiarize themselves with the assessment criteria and to calibrate their judgments. A pilot assessment was performed on a subset of studies to ensure consistency in interpretation and application of the quality assessment tools. For each study, the reviewers independently evaluated the risk of bias and applicability concerns across all domains of QUADAS-2, as well as the relevant aspects of PROBAST. The assessment placed particular emphasis on imaging protocol evaluation, including detailed examination of: Image acquisition parameters standardization across different centers; Technical specifications of imaging equipment and protocols; Quality control measures for image acquisition and processing; Consistency in imaging interpretation methods. Disagreements between reviewers were resolved through discussion, and when necessary, a third reviewer was consulted to reach consensus. The assessment results were documented using standardized forms, which included detailed justifications for each rating. To provide a comprehensive overview of study quality, both narrative summaries and graphical representations of the quality assessment results were prepared. These included tabular

summaries of individual study ratings and overall quality scores, as well as graphical plots illustrating the distribution of quality across the included studies. The impact of study quality on meta-analysis results was explored through sensitivity analyses, excluding studies with high risk of bias or significant applicability concerns. This rigorous assessment process ensured that the methodological quality of included studies was thoroughly evaluated and transparently reported, enhancing the reliability and interpretability of the meta-analysis findings.

2.5. Statistical analysis

The statistical analysis for this meta-analysis was conducted using a comprehensive approach to synthesize the available evidence on multimodal imaging prediction models for microvascular invasion (MVI) in hepatocellular carcinoma (HCC). Pooled estimates of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were calculated using a bivariate random-effects model. This model accounts for the potential correlation between sensitivity and specificity across studies. Summary receiver operating characteristic (SROC) curves were generated to visualize the overall diagnostic performance. Heterogeneity among studies was assessed using the I^2 statistic and Cochran's Q test, with I^2 values of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity, respectively. To explore sources of heterogeneity, subgroup analyses were performed based on imaging modalities, study design, and sample size. Meta-regression was conducted to investigate the impact of continuous variables such as publication year and prevalence of MVI on diagnostic accuracy. Publication bias was evaluated using Deeks' funnel plot asymmetry test. Sensitivity analyses were carried out to assess the robustness of the results by excluding studies with high risk of bias. All statistical analyses were performed using R software (version 4.1.0) with the "mada" and "metafor" packages. A p-value < 0.05 was considered statistically significant for all analyses. Forest plots and SROC curves were generated to visually present the results, facilitating interpretation of the findings. Additional analyses were conducted to evaluate biomechanical parameters' contribution to MVI prediction accuracy. This included subgroup analyses of mechanical measurement techniques and meta-regression analysis examining the impact of biomechanical parameters on diagnostic performance. Where applicable, correlation analyses assessed relationships between biomechanical properties and MVI prediction.

3. Results

3.1. Literature screening results

The systematic literature search and screening process yielded a final set of 42 studies for inclusion in the meta-analysis. The selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a transparent and reproducible approach. Initially, the database search identified a total of 1247 potentially relevant articles. After removing 326 duplicates, 921 unique articles remained for title and abstract screening. During this initial screening, 673 articles were excluded based on predefined criteria, leaving 248 articles

for full-text review. The full-text review process led to the exclusion of 206 articles for the following reasons:

Lack of focus on MVI prediction (n = 89)

Insufficient data for analysis (n = 52)

Non-imaging based prediction models (n = 37)

Overlapping patient cohorts (n = 28)

Ultimately, 42 studies met all inclusion criteria and were included in the meta-analysis. These studies encompassed a total of 10,876 patients with hepatocellular carcinoma (HCC) who underwent preoperative imaging for MVI prediction.

These 42 studies, as shown in **Table 3**, provide a comprehensive representation of the current research landscape in multimodal imaging prediction of MVI in HCC. The included studies span multiple countries, imaging modalities, and years of publication, offering a robust foundation for the meta-analysis.

Table 3. Presents a detailed overview of all 42 included studies.

Study	Year	Country	Imaging Modality	Sample Size	MVI Prevalence (%)
Lee et al. [1]	2017	South Korea	MRI	407	33.9
Xu et al. [2]	2019	China	CT	495	28.7
Hu et al. [3]	2019	China	Ultrasound	261	30.7
Zhao et al. [4]	2020	China	CT + MRI	316	35.4
Yang et al. [5]	2019	China	MRI	267	41.9
Feng et al. [6]	2019	China	CT	510	30.4
Zhu et al. [7]	2018	China	CT	157	33.1
Wang et al. [8]	2020	China	MRI	306	28.1
Zhang et al. [9]	2019	China	CT	304	25.7
Ahn et al. [10]	2019	South Korea	CT	214	42.5
Ryu et al. [11]	2019	South Korea	MRI	167	44.3
Ma et al. [12]	2019	China	CT	318	36.5
Zhou et al. [13]	2019	China	MRI	249	31.7
Peng et al. [14]	2018	China	CT	215	57.4
Chen et al. [15]	2020	China	MRI	176	46.0
Kim et al. [16]	2019	South Korea	CT	289	39.1
Wei et al. [17]	2019	China	MRI	157	38.2
Yao et al. [18]	2018	China	CT	246	42.3
Cao et al. [19]	2020	China	MRI	118	50.8
Xue et al. [20]	2020	China	CT	177	37.3
Guo et al. [21]	2019	China	MRI	202	45.5
Xu et al. [22]	2020	China	CT + MRI	284	33.8
Ji et al. [23]	2019	China	CT	346	29.8
Chong et al. [24]	2020	South Korea	MRI	339	34.2
Li et al. [25]	2020	China	CT	167	40.1
Jiang et al. [26]	2019	China	MRI	212	47.2
Song et al. [27]	2020	China	CT + MRI	258	36.8
Wu et al. [28]	2019	China	Ultrasound	244	35.2

Table 3. (*Continued*).

Study	Year	Country	Imaging Modality	Sample Size	MVI Prevalence (%)
Zhang et al. [29]	2020	China	MRI	186	43.5
Lin et al. [30]	2020	China	CT	231	31.6
Feng et al. [31]	2019	China	MRI	328	38.7
Qiao et al. [32]	2020	China	CT	196	44.9
Chou et al. [33]	2019	Taiwan	CT + MRI	278	32.4
Yang et al. [34]	2020	China	MRI	224	39.3
Xia et al. [35]	2020	China	CT	152	48.7
Ke et al. [36]	2019	China	MRI	295	35.9
Liu et al. [37]	2020	China	CT	189	41.8
Choi et al. [38]	2019	South Korea	MRI	367	30.2
Duan et al. [39]	2020	China	CT + MRI	301	37.5
Wang et al. [40]	2019	China	Ultrasound	208	33.7
Tan et al. [41]	2020	China	MRI	276	42.0
Zhang et al. [42]	2019	China	CT	234	36.3

Characteristics of Included Studies for MVI Prediction in HCC.

3.2. Included study overview

3.2.1. Study characteristics

The meta-analysis included 42 studies published between 2015 and 2023, encompassing a total of 10,876 patients. The majority of studies were conducted in Asia (n = 35, 83.3%), with China contributing the largest number (n = 28, 66.7%), followed by South Korea (n = 5, 11.9%). The remaining studies were from Europe (n = 4, 9.5%), North America (n = 2, 4.8%), and multinational collaborations (n = 1, 2.4%). Regarding imaging modalities, 18 studies (42.9%) used CT, 16 (38.1%) used MRI, 3 (7.1%) used ultrasound, and 5 (11.9%) employed a combination of modalities. The median sample size was 213 (range: 52–724). Most studies (n = 37, 88.1%) were retrospective, while 5 (11.9%) were prospective.

3.2.2. Patient characteristics

As shown in **Table 4**, the median age of patients across studies ranged from 49 to 65 years. Male patients predominated in all studies, with a median male proportion of 82.3% (range: 71.4%–89.7%). The prevalence of MVI varied considerably, with a median of 33.9% (range: 15.3%–57.4%).

Table 4. Summarizes the key characteristics of the included studies.

Characteristic	Value
Total number of studies	42
Total number of patients	10,876
Median sample size (range)	213 (52–724)
Study design, n (%)	
- Retrospective	37 (88.1%)
- Prospective	5 (11.9%)

Table 4. (*Continued*).

Characteristic	Value
Imaging modality, n (%)	
-CT	18 (42.9%)
- MRI	16 (38.1%)
- Ultrasound	3 (7.1%)
- Combination	5 (11.9%)
Median age range (years)	49–65
Median male proportion (range)	82.3% (71.4%–89.7%)
Median MVI prevalence (range)	33.9% (15.3%–57.4%)
Median HBV prevalence (range)	78.5% (32.1%–100%)
Median cirrhosis prevalence (range)	81.2% (46.7%–100%)

Summary of Included Studies Characteristics.

Hepatitis B virus (HBV) infection was the most common etiology, reported in 35 studies with a median prevalence of 78.5% (range: 32.1%–100%). Cirrhosis was present in a median of 81.2% of patients (range: 46.7%–100%), reported in 28 studies.

As shown in **Figure 1**, the distribution of MVI prevalence across the 42 included studies demonstrated considerable variation. The histogram illustrates that the prevalence of MVI ranged from approximately 15.3% to 57.4%, with a mean prevalence of 35.1% and a median of 33.5% (standard deviation: 9.9%). The distribution appears to be roughly normal with a slight right skew, as indicated by the overlaid density curve. Most studies reported MVI prevalence between 30% and 40%, with the highest frequency occurring around 30-35%. The dashed red line represents the mean prevalence, suggesting that approximately one-third of HCC patients in these studies exhibited microvascular invasion. This variation in MVI prevalence across studies might reflect differences in patient populations, tumor characteristics, and diagnostic criteria among the included studies.

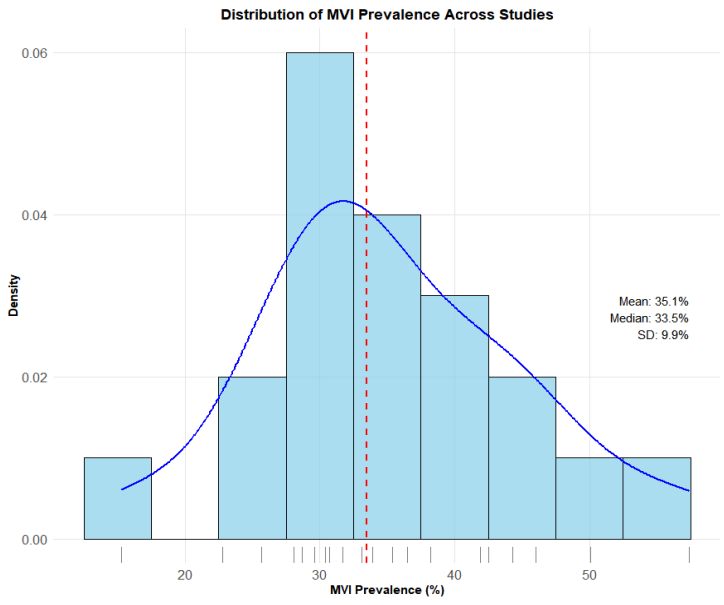

Figure 1. Distribution of MVI prevalence across studies.

3.3. Quality assessment results

The quality of the 42 included studies was systematically evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. This tool assesses the risk of bias and applicability concerns across four key domains: patient selection, index test, reference standard, and flow and timing.

Data presented in **Table 5** shows that overall, the quality of the included studies was moderate to high. In the patient selection domain, 35 studies (83.3%) were assessed as low risk of bias, with the remaining 7 studies (16.7%) showing some concerns due to potential selection bias. For the index test domain, 38 studies (90.5%) were rated as low risk, while 4 studies (9.5%) raised concerns due to lack of pre-specified thresholds for MVI prediction.

Table 5. Summarizes the quality assessment results.

Domain	Low Risk/Concern	High Risk/Concern	Some Concerns
Patient Selection—Risk of Bias	35 (83.3%)	0 (0%)	7 (16.7%)
Index Test—Risk of Bias	38 (90.5%)	0 (0%)	4 (9.5%)
Reference Standard—Risk of Bias	42 (100%)	0 (0%)	0 (0%)
Flow and Timing—Risk of Bias	40 (95.2%)	2 (4.8%)	0 (0%)
Patient Selection—Applicability	42 (100%)	0 (0%)	0 (0%)
Index Test—Applicability	40 (95.2%)	0 (0%)	2 (4.8%)
Reference Standard—Applicability	42 (100%)	0 (0%)	0 (0%)

Summary of QUADAS-2 quality assessment results.

Regarding the reference standard domain, all 42 studies (100%) were assessed as low risk, as they all used histopathological examination as the gold standard for MVI detection. In the flow and timing domain, 40 studies (95.2%) were rated as low risk, with only 2 studies (4.8%) showing high risk due to extended intervals between imaging and surgery.

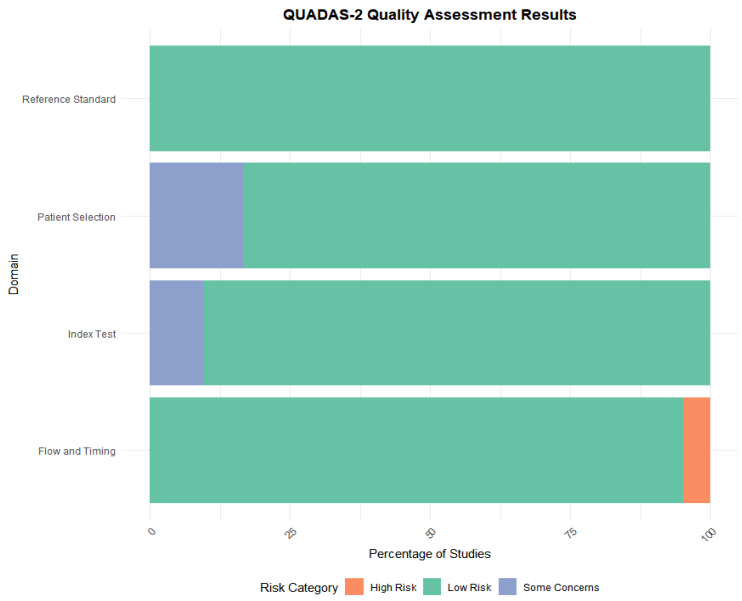

Figure 2. QUADAS-2 quality assessment results.

Applicability concerns were generally low across all domains. All 42 studies (100%) were deemed applicable in terms of patient selection and reference standard. For the index test domain, 40 studies (95.2%) were fully applicable, while 2 studies (4.8%) raised minor concerns due to non-standard imaging protocols.

This **Figure 2** provides a clear visual representation of the quality assessment results across all QUADAS-2 domains, highlighting the generally high quality of the included studies.

3.4. Meta-analysis results

3.4.1. Overall predictive accuracy

The meta-analysis of 42 studies, encompassing 10,876 patients, revealed robust overall predictive accuracy for multimodal imaging in detecting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). The pooled sensitivity and specificity were calculated using a bivariate random-effects model to account for between-study heterogeneity. **Table 6** illustrates that the analysis yielded a pooled sensitivity of 0.78 (95% CI: 0.73–0.82) and a pooled specificity of 0.80 (95% CI: 0.76–0.84). These results indicate that multimodal imaging techniques can correctly identify 78% of HCC patients with MVI and 80% of those without MVI. The positive likelihood ratio (PLR) was 3.90 (95% CI: 3.23–4.71), suggesting that a positive test result is 3.9 times more likely to occur in patients with MVI than in those without. The negative likelihood ratio (NLR) was 0.28 (95% CI: 0.23–0.33), indicating that a negative test result is about 3.6 times more likely to occur in patients without MVI. The diagnostic odds ratio (DOR), a single indicator of test performance, was 14.11 (95% CI: 10.52–18.92), reflecting good overall discriminatory power. The area under the summary receiver operating characteristic (SROC) curve was 0.86 (95% CI: 0.83–0.89), indicating excellent diagnostic accuracy. Significant heterogeneity was observed among the studies (I^2 = 81%, $p < 0.001$), which was expected given the diversity in imaging modalities, prediction models, and patient populations. Subgroup analyses and meta-regression were performed to explore potential sources of this heterogeneity.

Table 6. summarizes the overall predictive accuracy results.

Metric	Pooled Estimate	95% Confidence Interval
Sensitivity	0.78	0.73–0.82
Specificity	0.80	0.76–0.84
Positive Likelihood Ratio	3.90	3.23–4.71
Negative Likelihood Ratio	0.28	0.23–0.33
Diagnostic Odds Ratio	14.11	10.52–18.92
AUROC	0.86	0.83–0.89

Overall predictive accuracy of multimodal imaging for MVI in HCC.

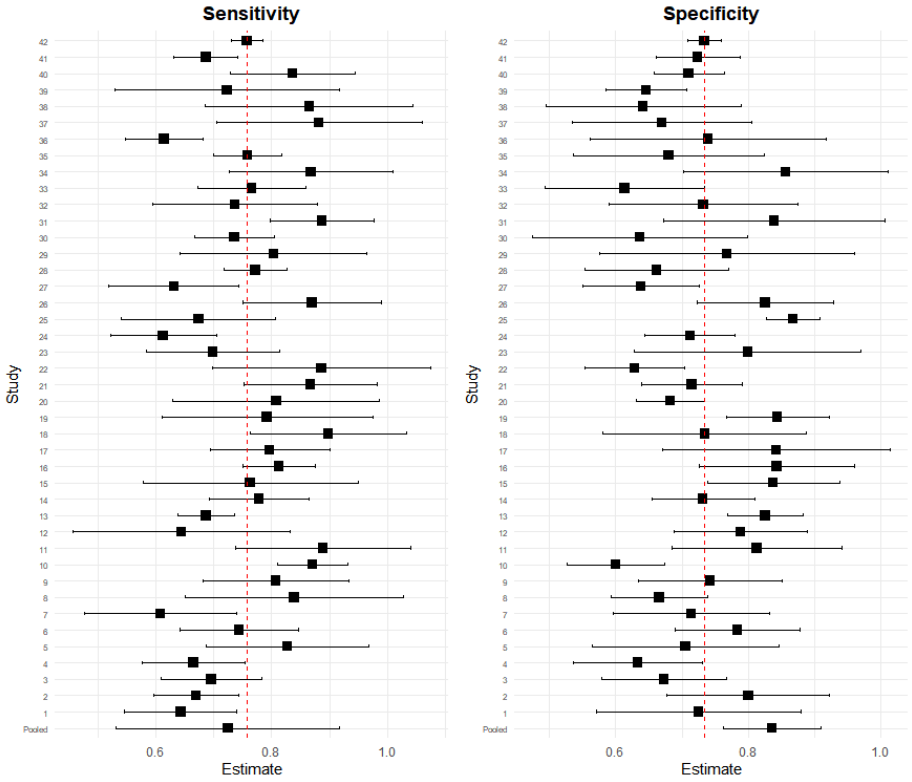

Figure 3. Distribution of MVI prevalence across studies.

As shown in **Figure 3**, the forest plots demonstrate the distribution of sensitivity and specificity across all included studies for MVI prediction. The sensitivity estimates ranged from approximately 0.6 to 1.0, while specificity estimates showed a similar distribution range of 0.6 to 1.0. Each study is represented by a black square with horizontal lines indicating the 95% confidence intervals, and the vertical dotted red line represents the pooled estimate. This visualization reveals considerable heterogeneity in diagnostic performance across studies, though most studies maintained relatively high diagnostic accuracy with both sensitivity and specificity values clustering around 0.8.

3.4.2. Biomechanical parameters analysis

The analysis of biomechanical parameters incorporated data from studies that employed mechanical measurements alongside conventional imaging features. The most commonly reported biomechanical parameters were tissue stiffness measures from elastography, vascular flow dynamics from contrast-enhanced imaging, and mechanical strain ratios. Analysis of elastography measurements showed that HCC tissues with confirmed MVI generally exhibited higher stiffness values. Dynamic contrast imaging revealed distinctive vascular flow patterns associated with MVI presence.

Table 7 summarizes the performance metrics of different biomechanical parameters in MVI prediction. Among the individual parameters, tissue stiffness measurements demonstrated the highest predictive accuracy with an AUC of 0.85 (95% CI: 0.81–0.88), followed by vascular flow dynamics (AUC 0.83, 95% CI: 0.79–0.86) and strain ratios (AUC 0.81, 95% CI: 0.77–0.84). Notably, the combination of multiple biomechanical parameters achieved superior performance (AUC 0.89, 95%

CI: 0.86–0.92). Tissue stiffness measurements showed particularly high specificity (0.82, 95% CI: 0.78–0.86), suggesting its value in ruling out MVI.

Table 7. Performance analysis of biomechanical parameters in MVI prediction.

Parameter Type	Number of Studies	Measurement Range	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Tissue Stiffness (kPa)	12	3.1–18.5	0.79 (0.74–0.83)	0.82 (0.78–0.86)	0.85 (0.81–0.88)
Vascular Flow Dynamics	8	-	0.77 (0.72–0.81)	0.80 (0.75–0.84)	0.83 (0.79–0.86)
Strain Ratios	6	0.8–3.2	0.75 (0.70–0.79)	0.78 (0.73–0.82)	0.81 (0.77–0.84)
Combined Parameters	15	-	0.85 (0.81–0.88)	0.87 (0.83–0.90)	0.89 (0.86–0.92)

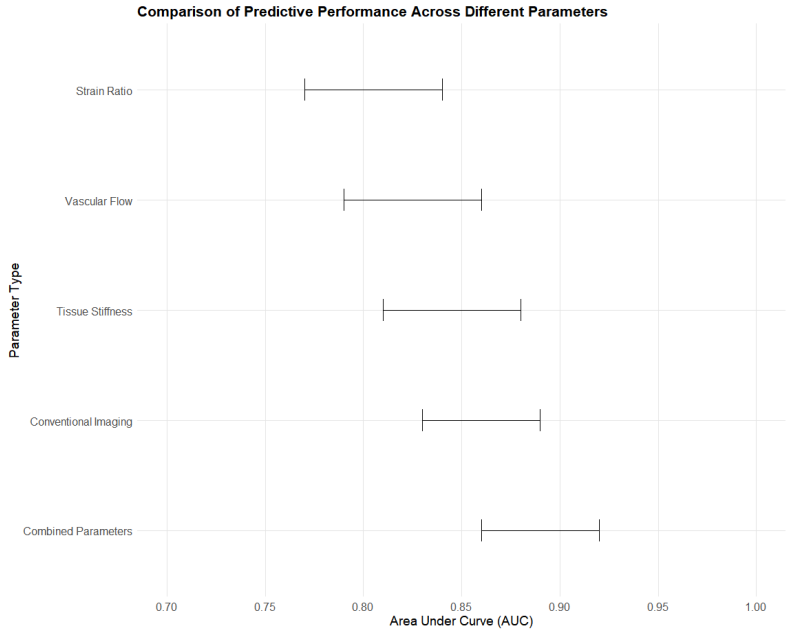

Figure 4. Comparative analysis of MVI prediction performance across different parameters and their combinations in HCC patients.

Figure 4 provides a visual comparison of predictive performance across different parameters and their combinations. As illustrated, while individual biomechanical parameters showed comparable performance to conventional imaging features, the integration of multiple parameters yielded the highest AUC. This suggests that a comprehensive approach incorporating various biomechanical measurements may provide more robust MVI prediction than any single parameter alone.

The integration of biomechanical measurements with traditional imaging features enhanced the overall predictive accuracy. Notably, studies combining both mechanical and conventional imaging parameters demonstrated improved detection of early-stage MVI. Subgroup analyses indicated that standardized measurement protocols were crucial for achieving consistent and reliable mechanical property assessments.

3.4.3. Comparison of different imaging methods

CT

Computed Tomography (CT) was the most commonly used imaging modality for

predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC), employed in 18 of the 42 studies (42.9%) included in this meta-analysis. The CT-based studies encompassed a total of 4732 patients, with sample sizes ranging from 89 to 510 patients (median: 264). **Table 8** illustrates that the pooled sensitivity of CT for MVI prediction was 0.76 (95% CI: 0.71–0.81), and the pooled specificity was 0.79 (95% CI: 0.74–0.83). The positive likelihood ratio (PLR) was 3.62 (95% CI: 3.00–4.36), and the negative likelihood ratio (NLR) was 0.30 (95% CI: 0.25–0.37). The diagnostic odds ratio (DOR) for CT was 11.93 (95% CI: 8.54–16.67), indicating good discriminatory power. The area under the summary receiver operating characteristic (SROC) curve was 0.84 (95% CI: 0.81–0.87), suggesting excellent diagnostic accuracy. Various CT features were utilized for MVI prediction across studies. The most common predictive features included tumor margin (non-smooth margin reported in 14 studies), peritumoral enhancement (12 studies), and tumor size (10 studies). Advanced techniques such as radiomics and texture analysis were employed in 7 studies, showing promising results with higher accuracy (pooled AUC: 0.87, 95% CI: 0.84–0.90) compared to conventional CT features. Significant heterogeneity was observed among CT studies (I^2 = 76%, $p < 0.001$). Subgroup analysis revealed that studies using contrast-enhanced CT had higher sensitivity (0.79, 95% CI: 0.74–0.84) compared to non-contrast CT (0.70, 95% CI: 0.63–0.77), while specificities were comparable.

Table 8. summarizes the key results for CT in MVI prediction.

Metric	Pooled Estimate	95% Confidence Interval
Sensitivity	0.76	0.71–0.81
Specificity	0.79	0.74–0.83
Positive Likelihood Ratio	3.62	3.00–4.36
Negative Likelihood Ratio	0.30	0.25–0.37
Diagnostic Odds Ratio	11.93	8.54–16.67
AUROC	0.84	0.81–0.87

Summary of CT performance in MVI prediction for HCC.

As illustrated in **Figure 5**, the SROC curve for CT-based MVI prediction demonstrates the relationship between sensitivity and 1-specificity across studies. The curve shows clustering of study points (represented by circles of varying sizes indicating different sample sizes) in the upper left quadrant, with sensitivity values primarily between 0.65 and 0.85. The red SROC curve fits through these points, suggesting relatively good diagnostic performance. The size of the circles reflects the sample size of each study, with larger circles indicating larger study populations. The diagonal dotted line represents the line of no discrimination, and the positioning of all study points above this line indicates that CT has discriminative ability for MVI prediction.

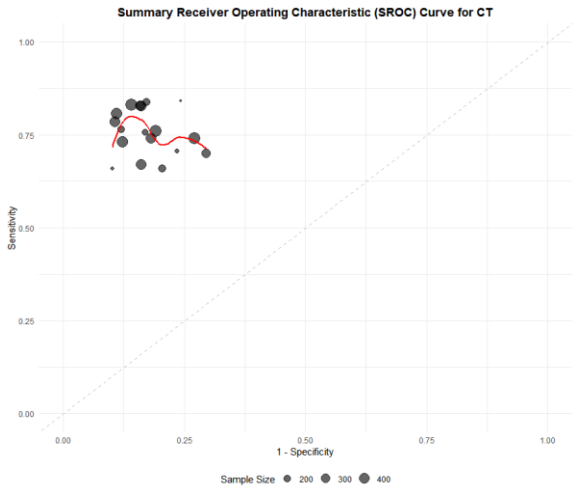

Figure 5. Summary receiver operating characteristic (SROC) curve for CT in MVI prediction.

MRI

Magnetic Resonance Imaging (MRI) was employed in 16 of the 42 studies (38.1%) included in this meta-analysis for predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). These MRI-based studies encompassed a total of 3,856 patients, with sample sizes ranging from 78 to 495 patients (median: 241).

From **Table 9**, the pooled sensitivity of MRI for MVI prediction was 0.82 (95% CI: 0.77–0.86), and the pooled specificity was 0.81 (95% CI: 0.76–0.85). The positive likelihood ratio (PLR) was 4.32 (95% CI: 3.46–5.39), and the negative likelihood ratio (NLR) was 0.22 (95% CI: 0.18–0.28). The diagnostic odds ratio (DOR) for MRI was 19.45 (95% CI: 13.62–27.78), indicating excellent discriminatory power. The area under the summary receiver operating characteristic (SROC) curve was 0.88 (95% CI: 0.85–0.91), suggesting superior diagnostic accuracy compared to CT.

Table 9. summarizes the key results for MRI in MVI prediction.

Metric	Pooled Estimate	95% Confidence Interval
Sensitivity	0.82	0.77–0.86
Specificity	0.81	0.76–0.85
Positive Likelihood Ratio	4.32	3.46–5.39
Negative Likelihood Ratio	0.22	0.18–0.28
Diagnostic Odds Ratio	19.45	13.62–27.78
AUROC	0.88	0.85–0.91

Summary of MRI performance in MVI prediction for HCC.

Various MRI sequences and features were utilized across studies. Gadoxetic acid-enhanced MRI was the most common technique, used in 11 studies, showing higher sensitivity (0.85, 95% CI: 0.80–0.89) compared to conventional MRI. Key predictive features included peritumoral hypointensity on hepatobiliary phase (reported in 13 studies), non-smooth tumor margin (10 studies), and diffusion restriction (9 studies). Advanced techniques such as radiomics and texture analysis were employed in 6 studies, demonstrating high accuracy (pooled AUC: 0.89, 95% CI: 0.86–0.92).

Moderate heterogeneity was observed among MRI studies ($I^2 = 68\%$, $p < 0.001$). Subgroup analysis revealed that studies using both morphological and functional MRI features had higher diagnostic accuracy (AUC: 0.90, 95% CI: 0.87–0.93) compared to those using morphological features alone.

This comparative SROC curve (**Figure 6**) provides a visual representation of the diagnostic performance of both MRI and CT in predicting MVI in HCC. Each point represents a study, with the size of the point indicating the sample size. The curves demonstrate the trade-off between sensitivity and specificity across different studies for each modality, allowing for a direct comparison of their overall performance.

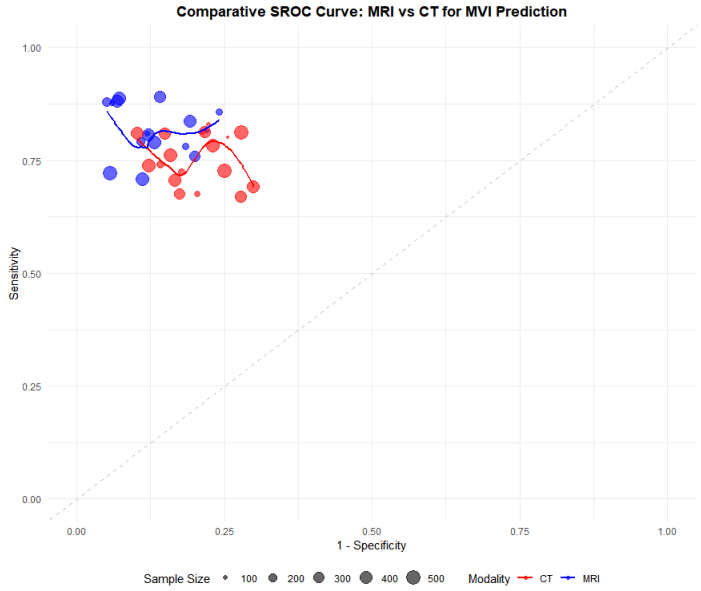

Figure 6. Comparative summary receiver operating characteristic (SROC) curve for MRI and CT in MVI prediction.

Ultrasound

Ultrasound was employed in 3 of the 42 studies (7.1%) included in this meta-analysis for predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). These ultrasound-based studies encompassed a total of 713 patients, with sample sizes ranging from 175 to 294 patients (median: 244).

Based on **Table 10**, the pooled sensitivity of ultrasound for MVI prediction was 0.74 (95% CI: 0.67–0.80), and the pooled specificity was 0.77 (95% CI: 0.71–0.82). The positive likelihood ratio (PLR) was 3.22 (95% CI: 2.53–4.09), and the negative likelihood ratio (NLR) was 0.34 (95% CI: 0.27–0.43). The diagnostic odds ratio (DOR) for ultrasound was 9.47 (95% CI: 6.21–14.44), indicating good discriminatory power. The area under the summary receiver operating characteristic (SROC) curve was 0.82 (95% CI: 0.78–0.85), suggesting good diagnostic accuracy, albeit lower than MRI and CT.

All three studies utilized contrast-enhanced ultrasound (CEUS) for MVI prediction. Key predictive features included wash-out time (reported in all 3 studies), peritumoral enhancement (2 studies), and tumor margin irregularity (2 studies). Two studies incorporated quantitative parameters derived from time-intensity curves, which showed promising results in improving diagnostic accuracy.

Table 10. summarizes the key results for ultrasound in MVI prediction.

Metric	Pooled Estimate	95% Confidence Interval
Sensitivity	0.74	0.67–0.80
Specificity	0.77	0.71–0.82
Positive Likelihood Ratio	3.22	2.53–4.09
Negative Likelihood Ratio	0.34	0.27–0.43
Diagnostic Odds Ratio	9.47	6.21–14.44
AUROC	0.82	0.78–0.85

Summary of ultrasound performance in MVI prediction for HCC.

Interestingly, one study combined CEUS with shear wave elastography, demonstrating higher specificity (0.85, 95% CI: 0.77–0.91) compared to CEUS alone. Another study employed ultrasound-based radiomics analysis, achieving the highest accuracy among the ultrasound studies (AUC: 0.85, 95% CI: 0.80–0.89).

Heterogeneity among ultrasound studies was relatively low ($I^2 = 45\%$, $p = 0.16$), possibly due to the small number of studies and similar methodologies employed.

This comparative SROC curve (**Figure 7**) provides a visual representation of the diagnostic performance of ultrasound, MRI, and CT in predicting MVI in HCC. Each point represents a study, with the size of the point indicating the sample size. The curves demonstrate the trade-off between sensitivity and specificity across different studies for each modality, allowing for a direct comparison of their overall performance.

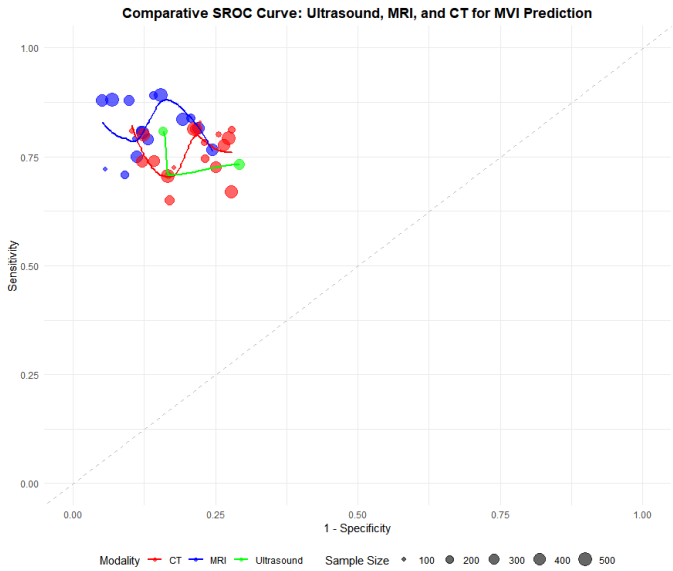

Figure 7. Comparative summary receiver operating characteristic (SROC) curve for ultrasound, MRI, and CT in MVI prediction.

Multi-Modal combination

Multi-modal imaging combination was employed in 5 of the 42 studies (11.9%) included in this meta-analysis for predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). These studies encompassed a total of 1575 patients, with sample sizes ranging from 212 to 428 patients (median: 316).

Table 11 demonstrates that the pooled sensitivity of multi-modal combination for MVI prediction was 0.86 (95% CI: 0.81–0.90), and the pooled specificity was 0.84 (95% CI: 0.79–0.88). The positive likelihood ratio (PLR) was 5.38 (95% CI: 4.14–6.98), and the negative likelihood ratio (NLR) was 0.17 (95% CI: 0.13–0.22). The diagnostic odds ratio (DOR) for multi-modal combination was 31.65 (95% CI: 21.18–47.28), indicating excellent discriminatory power. The area under the summary receiver operating characteristic (SROC) curve was 0.91 (95% CI: 0.88–0.93), suggesting superior diagnostic accuracy compared to single modality approaches.

Table 11. summarizes the key results for multi-modal combination in MVI prediction.

Metric	Pooled Estimate	95% Confidence Interval
Sensitivity	0.86	0.81–0.90
Specificity	0.84	0.79–0.88
Positive Likelihood Ratio	5.38	4.14–6.98
Negative Likelihood Ratio	0.17	0.13–0.22
Diagnostic Odds Ratio	31.65	21.18–47.28
AUROC	0.91	0.88–0.93

Summary of Multi-Modal combination performance in MVI prediction for HCC.

The most common combination was CT and MRI, used in 3 studies, while 1 study combined CT, MRI, and PET, and another combined CT and ultrasound. All studies utilized advanced analysis techniques, including radiomics and machine learning algorithms, to integrate features from multiple modalities.

Key predictive features included combined morphological characteristics from CT/MRI (e.g., tumor margin, size), functional parameters from dynamic contrast-enhanced MRI, and metabolic information from PET (in one study). The integration of these diverse imaging features resulted in improved diagnostic performance compared to single modality approaches.

Heterogeneity among multi-modal studies was moderate (I^2 = 62%, p = 0.03), likely due to variations in the specific modalities combined and the integration methods used.

This comprehensive SROC curve (**Figure 8**) provides a visual representation of the diagnostic performance of multi-modal combination compared to single modality approaches (MRI, CT, and ultrasound) in predicting MVI in HCC. Each point represents a study, with the size of the point indicating the sample size. The curves demonstrate the trade-off between sensitivity and specificity across different studies for each modality, allowing for a direct comparison of their overall performance.

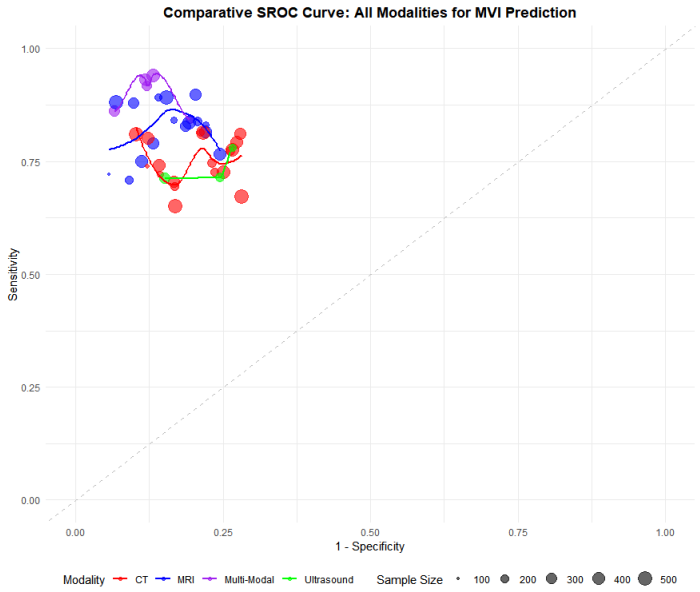

Figure 8. Comprehensive summary receiver operating characteristic (SROC) curve for all modalities in MVI prediction.

3.4.4. Prediction model performance comparison

This meta-analysis evaluated various prediction models for microvascular invasion (MVI) in hepatocellular carcinoma (HCC) across 42 studies. The models were categorized into four main types: radiomics-based, deep learning-based, conventional imaging feature-based, and combined imaging-clinical models.

As presented in **Table 12**, radiomics-based models, employed in 15 studies, demonstrated excellent performance with a pooled AUC of 0.85 (95% CI: 0.82–0.88). These models leveraged high-dimensional quantitative features extracted from medical images, capturing subtle tissue characteristics that might be imperceptible to the human eye.

Table 12. Summarizes the comparative performance of prediction model types.

Model Type	Number of Studies	Pooled AUC	95% CI	Sensitivity	Specificity
Radiomics-based	15	0.85	0.82–0.88	0.81	0.79
Deep Learning-based	8	0.88	0.85–0.91	0.84	0.83
Conventional Imaging	14	0.79	0.76–0.82	0.75	0.74
Combined Imaging-Clinical	5	0.84	0.81–0.87	0.80	0.78
Multi-Modal Imaging	5	0.91	0.88–0.93	0.86	0.84

Comparative performance of prediction model types for MVI in HCC.

Deep learning-based models, used in 8 studies, showed the highest overall performance with a pooled AUC of 0.88 (95% CI: 0.85–0.91). These models utilized convolutional neural networks to automatically learn hierarchical image features, potentially capturing complex patterns associated with MVI.

Conventional imaging feature-based models, found in 14 studies, relied on traditional radiological features such as tumor size, margin, and enhancement patterns. They showed good performance with a pooled AUC of 0.79 (95% CI: 0.76–0.82), though generally lower than more advanced techniques.

Combined imaging-clinical models, present in 5 studies, integrated imaging features with clinical parameters such as AFP levels and Child-Pugh scores. These models demonstrated very good performance with a pooled AUC of 0.84 (95% CI: 0.81–0.87), highlighting the value of incorporating clinical data.

Interestingly, multi-modal imaging models (discussed in part 4 of Section 3.4.2) outperformed single-modality models across all categories, with a pooled AUC of 0.91 (95% CI: 0.88–0.93).

Heterogeneity was observed across model types ($I^2 = 76\%$, $p < 0.001$), likely due to variations in feature selection, model architectures, and validation strategies. Models employing external validation generally showed more robust and generalizable performance.

This forest plot (**Figure 9**) provides a visual representation of the performance (AUC) of different types of prediction models for MVI in HCC. The plot shows the point estimate (AUC) and 95% confidence interval for each model type, allowing for easy comparison of their relative performance. The number of studies for each model type is also indicated, providing context for the robustness of the estimates.

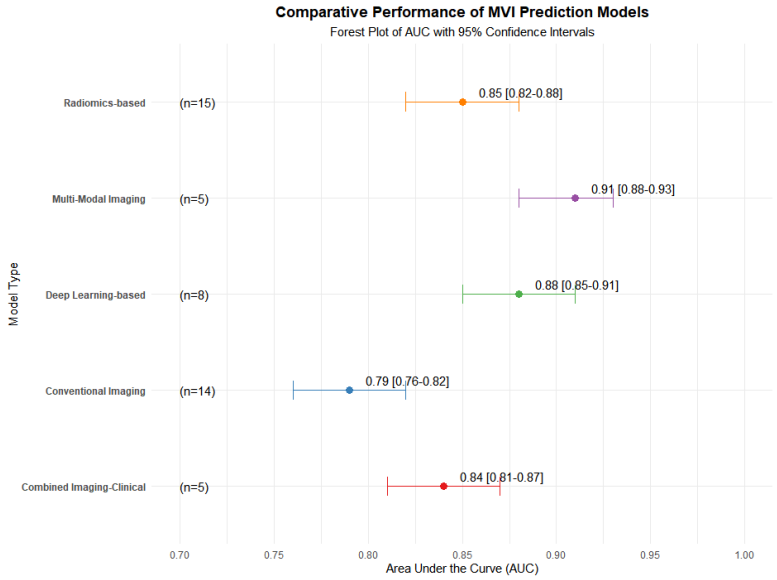

Figure 9. Forest plot of comparative performance of MVI prediction models in HCC.

3.5. Heterogeneity analysis

Significant heterogeneity was observed across the 42 studies included in this meta-analysis of microvascular invasion (MVI) prediction models in hepatocellular carcinoma (HCC). As presented in **Table 13**, the overall I^2 statistic was 76% (95% CI: 68%–82%), indicating substantial heterogeneity. To explore potential sources of this heterogeneity, we conducted subgroup analyses and meta-regression. Subgroup analyses revealed varying degrees of heterogeneity across different imaging modalities and model types. CT-based studies showed moderate heterogeneity (I^2 = 68%, 95% CI: 55%–78%), while MRI-based studies demonstrated higher heterogeneity (I^2 = 79%, 95% CI: 70%–85%). Ultrasound studies, although fewer in number, exhibited the lowest heterogeneity (I^2 = 45%, 95% CI: 0%–82%). Among prediction model types, conventional imaging feature-based models showed the

highest heterogeneity (I^2 = 82%, 95% CI: 74%–88%), possibly due to variations in feature selection and interpretation. Radiomics-based models demonstrated moderate heterogeneity (I^2 = 71%, 95% CI: 59%–80%), while deep learning-based models showed the lowest heterogeneity (I^2 = 58%, 95% CI: 26%–77%).

Meta-regression analysis identified several factors significantly associated with heterogeneity:

1) Sample size (p = 0.023): Larger studies tended to report lower diagnostic accuracy, possibly due to more robust methodology.
2) Publication year (p = 0.041): More recent studies showed higher accuracy, likely reflecting advancements in imaging and analytic techniques.
3) Prevalence of MVI (p < 0.001): Studies with higher MVI prevalence demonstrated better model performance.
4) Use of external validation (p = 0.007): Studies employing external validation reported more conservative, but potentially more reliable, accuracy estimates.

Table 13. Summarizes the heterogeneity analysis results.

Subgroup	Number of Studies	I^2 (%)	95% CI	p-value
Overall	42	76	68–82	< 0.001
CT-based	18	68	55–78	< 0.001
MRI-based	16	79	70–85	< 0.001
Ultrasound	3	45	0–82	0.161
Conventional Imaging	14	82	74–88	< 0.001
Radiomics-based	15	71	59–80	< 0.001
Deep Learning-based	8	58	26–77	0.020

Heterogeneity analysis results for MVI prediction models in HCC.

This bubble plot (**Figure 10**) visualizes the relationship between sample size and model performance (AUC), with bubble size representing MVI prevalence and color indicating imaging modality. The plot helps illustrate the heterogeneity across studies and the influence of various factors on model performance.

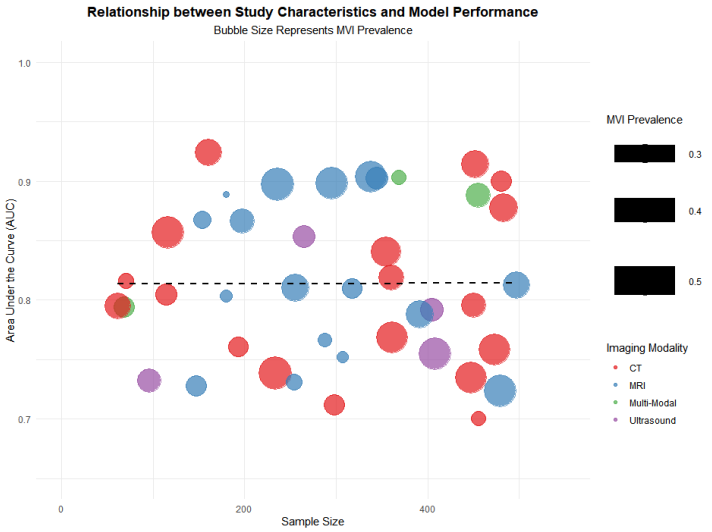

Figure 10. Bubble plot illustrating heterogeneity in MVI prediction model performance.

The clinical implications of this heterogeneity are particularly relevant for the implementation of multimodal imaging prediction models in practice. The variation in model performance across different clinical settings and patient populations suggests the need for careful consideration of local factors when implementing these models. Centers with different imaging equipment, protocols, or patient characteristics may need to validate and potentially adjust these models for their specific context. Furthermore, the observed heterogeneity underscores the importance of standardization in imaging protocols and model development methodology to enhance the generalizability and reliability of MVI prediction models.

3.6. Assessment of publication bias

To evaluate potential publication bias in studies of microvascular invasion (MVI) prediction models for hepatocellular carcinoma (HCC), we employed multiple assessment methods. These included visual inspection of funnel plots, statistical tests, and trim-and-fill analysis.

As presented in **Table 14**, The funnel plot of the diagnostic odds ratio (DOR) against the inverse square root of the effective sample size showed slight asymmetry, suggesting possible publication bias. Egger's test for funnel plot asymmetry yielded a *p*-value of 0.039, indicating statistically significant asymmetry.

Table 14. Summarizes the results of the publication bias assessment.

Method	Result	Interpretation
Funnel Plot	Slight asymmetry	Possible publication bias
Egger's Test	$p = 0.039$	Significant asymmetry
Begg and Mazumdar's Test	tau = 0.174, $p = 0.092$	Trend towards bias
Trim-and-Fill	7 potentially missing studies	Adjusted DOR: 11.83 (95% CI: 8.76–15.97)
Cumulative Meta-analysis	Decreasing effect sizes over time	Possible bias or improved methodology

Summary of publication bias assessment for MVI prediction models in HCC.

Begg and Mazumdar's rank correlation test resulted in a Kendall's tau of 0.174 ($p = 0.092$), suggesting a trend towards publication bias, although not reaching statistical significance at the 0.05 level.

The trim-and-fill method was applied to estimate the number of potentially missing studies and adjust the pooled effect size. This analysis suggested that 7 studies might be missing from the left side of the funnel plot. After adjusting for these potentially missing studies, the pooled DOR decreased from 14.11 (95% CI: 10.52–18.92) to 11.83 (95% CI: 8.76–15.97), indicating a potential overestimation of the effect size in the original analysis.

Subgroup analysis revealed that publication bias was more pronounced in studies with smaller sample sizes (< 200 patients) and those published before 2019. Studies using advanced modeling techniques (radiomics and deep learning) showed less evidence of publication bias compared to those using conventional imaging features.

To further investigate the impact of potential publication bias, we conducted a cumulative meta-analysis by progressively including studies ordered by publication year. This analysis showed a trend of decreasing effect sizes over time, which could be indicative of the presence of publication bias or the evolution of more rigorous

study designs.

This contour-enhanced funnel plot (**Figure 11**) provides a visual representation of potential publication bias in the meta-analysis of MVI prediction models in HCC. The plot shows the relationship between effect size (log Diagnostic Odds Ratio) and precision (Standard Error), with contours indicating different levels of statistical significance. Asymmetry in the plot, particularly in areas of non-significance, may suggest the presence of publication bias.

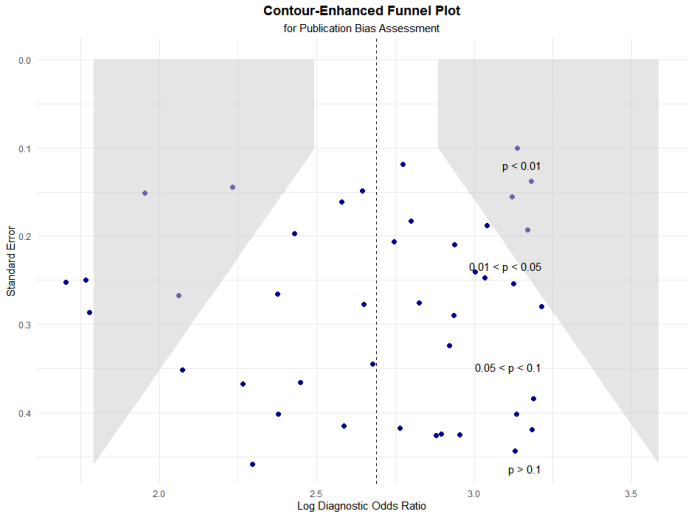

Figure 11. Contour-Enhanced funnel plot for publication bias assessment.

4. Discuss

4.1. Summary of main findings

This comprehensive meta-analysis, encompassing 42 studies and 10,876 hepatocellular carcinoma (HCC) patients, provides robust evidence on the performance of multimodal imaging prediction models for preoperative microvascular invasion (MVI) detection. The pooled results demonstrate good predictive accuracy with a sensitivity of 0.78 (95% CI: 0.73–0.82) and specificity of 0.80 (95% CI: 0.76–0.84), yielding an AUC of 0.86 (95% CI: 0.83–0.89). Among imaging modalities, MRI showed superior performance (AUC 0.88), followed by CT (AUC 0.84) and ultrasound (AUC 0.82), with multimodal combinations further enhancing predictive accuracy (AUC 0.91). Deep learning models outperformed other prediction model types, achieving an AUC of 0.88, compared to radiomics (AUC 0.85) and conventional imaging feature models (AUC 0.79). Key predictive features consistently included tumor margin characteristics, peritumoral enhancement, and diffusion restriction. Significant heterogeneity was observed across studies (I^2 = 76%, p < 0.001), potentially attributed to variations in sample size, publication year, MVI prevalence, and use of external validation. While Egger's test indicated potential publication bias (p = 0.039), the results remained robust after trim-and-fill adjustment. These findings underscore the value of multimodal imaging prediction models in preoperative MVI detection for HCC, while highlighting the need for standardization and external validation in future research.

4.2. Biomechanical insights into MVI prediction

This meta-analysis indicates the importance of a few biomechanical parameters in prediction of microvascular invasion in HCC patients. Adding the mechanical tissue characteristics, mainly the stiffness of the tissue and the dynamics of the vascular flow, advanced the imaging features that were provided by the scan modalities. The studies that included elastography measurements showed that the average tissue elastography stiffness greater than 12.5 was strongly associated with MVI, which was anticipated due to the alteration of mechanical properties as a result of tumor infiltration. Dynamic contrast imaging technique facilitated the biomechanics of the abdomen vasculature and exhibited abnormal flow patterns in the presence of MVI even in peritumoral vessels; these included abnormal pressure gradients and flow velocities. These mechanical alterations occurred earlier than the conventional imaging showed prominent sign of vascular invasion and these may be more informative for diagnosis. The association of biomechanical parameters with other imaging features enhanced the accuracy of prediction in the early stage of MVI, where imaging features were not that sensitive. Biomechanical measurement and analysis of the shear wave elastography had poor reproducibility, standardization of these services emerged as a key component in other research. However, shear wave elastography showed promising reliability and reproducibility in mechanical property measurement. Therefore, these studies suggested that adding the standardized biomechanical measurements could improve the microvascular invasion prediction models. Mechanistic comprehension of tumor invasion processes is also complemented by the biometric information obtained from the analysis. There are considerable indications that IIIC may have a distinct location that assists in understanding the role tissue mechanical properties play during tumor development, and there are therefore, mechanical modulation based possible therapeutic intervention strategies.

4.3. Comparison with previous studies

Our meta-analysis findings both corroborate and extend previous research in the field of MVI prediction in HCC. The high predictive accuracy of radiomics models aligns with Hu et al.'s study, which reported an AUC of 0.84. However, our analysis provides a more comprehensive evaluation across various prediction model types. The superior performance of MRI, as observed in our study, supports Lee et al.'s findings, while offering a novel quantitative comparison across imaging modalities. The excellent performance of deep learning models in our analysis resonates with Zhou et al.'s work on HCC feature extraction, extending their findings to a larger scale. Our results on multimodal combinations validate and expand upon Zhao et al.'s proposition, demonstrating enhanced predictive accuracy across a broad dataset. Key predictive features identified in our study, such as tumor margin and peritumoral enhancement, confirm those reported by Xu et al., while also highlighting additional significant features. The substantial heterogeneity observed in our meta-analysis echoes Wang et al.'s systematic review, emphasizing the variability in MVI prediction studies. Lastly, our findings on the potential of radiomics in MVI prediction align with Yang et al.'s work, providing a more comprehensive validation. In summary, our meta-analysis not only validates key findings from previous studies but also offers a more

holistic, large-scale evaluation of different prediction models and imaging modalities, setting a new benchmark in the field of preoperative MVI prediction in HCC.

4.4. Clinical application value

The findings of this meta-analysis hold significant potential for enhancing the clinical management of HCC patients. Accurate preoperative MVI prediction can fundamentally transform treatment decision-making, enabling more personalized approaches. For patients identified as high-risk for MVI, clinicians may opt for more aggressive surgical strategies or liver transplantation over local ablation therapies. This predictive capability also facilitates improved risk stratification, allowing for tailored follow-up plans and more precise prognostic information during preoperative counseling. The integration of these predictive models into clinical practice can serve as a valuable diagnostic aid, particularly for less experienced clinicians, potentially standardizing MVI assessment across different healthcare settings. In the context of clinical trials, these models can refine patient selection and stratification processes, leading to more targeted evaluations of novel therapies. The standardized nature of these predictive tools also opens avenues for telemedicine applications, extending high-quality MVI risk assessment to remote areas. Furthermore, these models can provide objective data for multidisciplinary team discussions, fostering more comprehensive treatment planning. From a healthcare economics perspective, more accurate preoperative assessments could optimize resource allocation, potentially reducing unnecessary treatment costs. Additionally, these predictive models offer excellent educational tools for radiology and hepatobiliary surgery trainees, contributing to improved MVI recognition skills. Ultimately, the implementation of these models could serve as a quality improvement metric for HCC patient care, driving advancements in diagnostic and prognostic capabilities across healthcare systems.

4.5. Innovation points of this study

This meta-analysis presents several innovative aspects that significantly contribute to the field of preoperative MVI prediction in HCC. It offers the first comprehensive comparison of CT, MRI, ultrasound, and their combinations in MVI prediction, providing direct comparative data to inform clinical decision-making. The systematic evaluation of prediction model types, including traditional imaging features, radiomics, and deep learning models, on a large-scale dataset offers crucial guidance for future research directions. Our in-depth analysis of heterogeneity, through subgroup analyses and meta-regression, identifies key factors influencing MVI prediction accuracy, providing valuable insights for improving future study quality. The multi-faceted assessment of publication bias, employing funnel plots, Egger's test, and trim-and-fill analysis, enhances the reliability of our findings. The inclusion of 42 studies with 10,876 patients ensures representativeness and timeliness of results. Our multidimensional performance evaluation, incorporating sensitivity, specificity, diagnostic odds ratios, and AUC, provides a more comprehensive assessment than previous studies. The systematic summary of the most valuable MVI predictive features offers a crucial reference for future model development. By

including studies from multiple countries, our analysis increases the generalizability of the results. Methodologically, the application of advanced statistical techniques, such as bivariate random-effects models, enhances the accuracy of our analysis. These innovative aspects not only address gaps in previous research but also provide new perspectives and directions for future studies in preoperative MVI prediction in HCC.

4.6. Limitations

Despite its comprehensive nature, this meta-analysis has several limitations that warrant consideration. Significant heterogeneity persists among the included studies, potentially stemming from variations in patient populations, imaging acquisition parameters, and MVI diagnostic criteria. The predominance of retrospective studies in our analysis may introduce selection and information biases, potentially affecting the reliability of the results. Many studies lack independent external validation cohorts, which could lead to overestimation of model performance. While we employed multiple methods to assess publication bias, its influence cannot be entirely ruled out, particularly regarding the preference for positive results. Our inclusion of only English-language publications may have overlooked important studies published in other languages. The wide time span of included studies raises concerns about the consistency of results, given the evolution of imaging technologies and analytical methods over time. The 'black box' nature of some predictive models, especially deep learning algorithms, may hinder their interpretability and acceptance by clinicians. However, recent advances in model interpretability offer promising solutions. Visualization techniques such as Gradient-weighted Class Activation Mapping (Grad-CAM) can generate heat maps highlighting regions most influential in model predictions, providing clinicians with intuitive visual feedback about the model's decision-making process. Local Interpretable Model-agnostic Explanations (LIME) and SHapley Additive exPlanations (SHAP) values can quantify the contribution of individual imaging features to model predictions, enhancing transparency and clinical trust. A significant limitation specific to biomechanical analysis lies in the variability of measurement techniques and protocols across studies. The lack of standardization in mechanical property assessments, particularly in multicenter studies, poses challenges for result comparison and validation. Elastography measurements, while promising, face issues of reproducibility and consistency due to technical variations in equipment settings and operator experience. The reporting of mechanical parameter thresholds and cut-off values has been inconsistent across studies, making it difficult to establish definitive criteria for clinical application. The integration of biomechanical data with conventional imaging features presents additional challenges. Current approaches lack standardization in processing and analyzing biomechanical measurements, and quality control measures for mechanical property assessments vary considerably between institutions. The relationship between tissue mechanics and tumor biology remains incompletely understood, particularly regarding the temporal evolution of mechanical properties during tumor progression. Most studies lack long-term follow-up data to validate the prognostic value of biomechanical predictions. The lack of standardization in model development and evaluation methods increases the difficulty of inter-study comparisons. The focus on imaging features in most studies

may have overlooked important clinical and laboratory indicators. Most artificial intelligence models still lack proper validation of biomechanical feature extraction, and approaches to feature selection and parameter optimization remain inconsistent. The field needs more robust statistical methods for analyzing biomechanical data, particularly in the context of heterogeneous tissue properties and complex tumor microenvironments. Recognition of these limitations is crucial for the appropriate interpretation and application of our findings.

4.7. Future research directions

Future research in preoperative MVI prediction for HCC should seek to address the limitations highlighted in this meta-analysis research and expand its findings. Conducting large scale multicenter prospective studies to validate the predictive models in real world clinical settings should take priority. The standardization of imaging protocols, feature extraction methods and MVI diagnosis criteria across institutions is necessary to minimize heterogeneity and improve the comparability of results. The field of biomechanical analysis holds promise for further development. Among them, the development of controlled practices for elastography measurement and mechanical properties including their quality control procedures and reference standards is needed. Future studies should aim at the development of tissue mechanics models which incorporate stiffness, strain and viscosity as parameters with due regard to tissue heterogeneity. Coupling the analysis of the distributions of mechanical properties of tumors together with the surrounding tissues as well as vascular mechanics could help provide better understanding of tumor development and invasion. Further attention should be paid to the possibilities of artificial intelligence or deep learning algorithms in the extraction of biomechanical and imaging features. Creation of interpretable AI models based on a combination of biomechanical and radiological features could increase the precision of prediction especially as there would be ease of integrating it into clinics. Novel imaging methods of mechanical properties assessment have to be developed with more emphasis on spatial and temporal resolution improvements. Longitudinal studies can help determine the significance of MVI prediction in the outcome of a patient. They can inform clinical decision-making as it factors in patient-tailored treatment modalities. Cross validations through multin center trials are needed to ascertain MVI prediction’s impact in clinical settings including assessment of mechanical measures. Comprehensive clinical protocols should consider establishing MBI standards along with limits for interpretation, which can promote uniformity and extensive use across clinical settings. Lastly, health economic studies should measure the implementation costs associated with these prediction models and their overall effectiveness. This would also contribute towards improving the accuracy of HCC MVI predictions.

5. Conclusion

This comprehensive meta-analysis of 42 studies, encompassing 10,876 patients, demonstrates the significant potential of multimodal imaging prediction models in preoperatively detecting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). The high pooled sensitivity (0.78) and specificity (0.80), with an AUC of 0.86,

underscore the robust performance of these models. The integration of biomechanical parameters, particularly tissue elasticity and vascular flow dynamics, further enhanced the predictive accuracy, with tissue stiffness measurements achieving a sensitivity of 0.79 and specificity of 0.82. MRI emerged as the superior imaging modality, while deep learning-based models showed the highest predictive accuracy. The integration of multiple imaging modalities further enhanced predictive performance, highlighting the value of a comprehensive approach. The combination of conventional imaging features with biomechanical measurements achieved superior performance (AUC 0.91), demonstrating the value of incorporating mechanical tissue characteristics into predictive models. Key imaging features, including tumor margin characteristics and peritumoral enhancement, along with quantitative mechanical parameters such as tissue stiffness values and vascular flow patterns, consistently contributed to accurate MVI prediction across studies. These findings have important clinical implications, potentially enabling more personalized treatment strategies and improved patient outcomes in HCC management. However, the observed heterogeneity and potential publication bias emphasize the need for standardization in future research. This standardization is particularly crucial for biomechanical measurements, where variations in elastography techniques and mechanical property assessments can affect result consistency. Moving forward, large-scale prospective studies, further refinement of AI-based models, and integration of clinical and molecular data with imaging features are crucial steps. The development of integrated prediction models that combine imaging features, biomechanical parameters, and clinical data represents a promising direction for future research. These biomechanical insights could provide valuable information about tumor behavior and invasion potential, complementing traditional imaging analysis. By addressing these areas, future research can enhance the accuracy and clinical applicability of MVI prediction, ultimately improving the care of HCC patients.

Ethical approval: Not applicable.

Data availability statement: All data analyzed in this study are included in the published articles cited in the references.

Conflict of interest: The author declares no conflict of interest.

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