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Ultrasound radiomics in the prediction of microvascular invasion in hepatocellular carcinoma: A systematic review and meta-analysis

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ABSTRACT

Purpose: To systematically assess the clinical value of ultrasound radiomics in the prediction of microvascular invasion in hepatocellular carcinoma (HCC).

Methods: Relevant articles were searched in PubMed, Web of Science, Cochrane Library, Embase and Medline and screened according to the eligibility criteria. The quality of the included articles was assessed based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. After article assessment and data extraction, the diagnostic performance of ultrasound radiomics was evaluated based on pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR), and the area under the curve (AUC) was calculated by generating the ROC curve. Meta-analysis was performed using Stata 15.1, and subgroup analysis was conducted to identify the sources of heterogeneity. A Fagan nomogram was generated to assess the clinical utility of ultrasound radiomics.

Results: Five studies involving 1260 patients were included. Meta-analysis showed that ultrasound radiomics had a pooled sensitivity of 79% (95% *CI*: 75–83%), specificity of 70% (95% *CI*: 59–79%), PLR of 2.6 (95% *CI*: 1.9–3.7), NLR of 0.30 (95% *CI*: 0.23–0.39), DOR of 9 (95% *CI*: 5–16), and AUC of 0.81 (95% *CI*: 0.78–0.85). Sensitivity analysis indicated that the results were statistically reliable and stable, and no significant difference was identified during subgroup analysis.

Conclusion: Ultrasound radiomics has favorable predictive performance in the microvascular invasion of HCC and may serve as an auxiliary tool for guiding clinical decision-making.

Abbreviations: HCC, hepatocellular carcinoma; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; PLR, positive likelihood ratio; NLR, likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; MVI, Microvascular invasion; PRIMSA-DTA, Preferred Reporting Items for Systematic reviews and Meta-analysis of Diagnostic Test Accuracy Studies; MeSH, Medical Subject Headings; TP, True positive; TN, true negative; FP, false positive; FN, false negative; CDFI, Color Doppler flow imaging; CEUS, contrast-enhanced ultrasound; TD, training dataset; VD, validation dataset.

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1. Introduction

Primary liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer death. Hepatocellular carcinoma (HCC) accounts for 75%–85% of primary liver cancer [1]. Hepatectomy is an important procedure for ensuring long-term survival in liver cancer patients, but the postoperative 5-year recurrence rate is 50%–70% [2,3]. Cancer recurrence remains a key challenge in clinical practice, and hence early identification of recurrence risk factors before surgery is critical for developing personalized treatment [4].

Microvascular invasion (MVI) is a risk factor for post-hepatectomy recurrence and metastasis and one of the main factors for assessing the risk of liver cancer recurrence and selecting treatments [5,6]. At present, MVI status cannot be adequately confirmed or predicted before surgery and can only be determined by postoperative histopathology. The presence of MVI can affect the selection of treatment approach, and extended resection has been shown to significantly improve the survival of MVI-positive patients by removing micrometastases [7]. Therefore, it is necessary to establish a more accurate MVI prediction model based on preoperative parameters to guide clinicians in the selection of treatment options [8,9]. To this end, several prediction models based on clinical data, preoperative laboratory tests, and HCC images have been established and have shown promising application prospects in clinical practice [10–12].

Radiomics is a noninvasive computational approach that extracts quantitative data from medical images and explores their correlation with clinical outcomes [13]. Previous studies have demonstrated that radiomics is a promising tool for predicting preoperative MVI status in HCC patients [14–16]. Conventional ultrasound is a noninvasive, economical, and radiation-free screening measure for the early identification of liver lesions [17,18]. It has been reported that conventional ultrasound and contrast-enhanced ultrasound can be used for the prediction of MVI in HCC [19]. In addition, the advancement in imaging techniques and their combination with radiomics have also improved predictive and diagnostic accuracy [20,21].

There is currently no systematic review of the predictive accuracy of ultrasound radiomics in HCC MVI. Therefore, this meta-analysis is aimed to assess the predictive accuracy of ultrasound radiomics in MVI before hepatectomy.

2. Materials and methods

This systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis of Diagnostic Test Accuracy Studies (PRIMSA-DTA) statement [22]. This study was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/CRD42022379295).

2.1. Literature search strategy

Studies published in English investigating the performance of ultrasound radiomics-based models in the preoperative prediction of MVI in HCC patients were searched in PubMed, Embase, Cochrane Library, Web of Science and Medline from inception to March 26, 2023 using Medical Subject Headings (MeSH) and non-MeSH terms. The specific search strategy is shown in Supplementary Materials. The references of the initially identified articles were screened to identify additional eligible studies.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

(1) Patients who have been assessed by ultrasound prior to hepatectomy or liver transplantation (regardless of whether they have been assessed by other imaging means);
(2) Application of ultrasound radiomics model in the prediction of HCC MVI;
(3) HCC MVI confirmed by pathological examination of surgical specimen;
(4) True positive (TP), true negative (TN), false positive (FP) and false negative (FN) data can be directly or indirectly extracted from the reported results to evaluate the sensitivity and specificity of the prediction model in HCC MVI.

2.2.2. Exclusion criteria

(1) Meeting abstract, review, meta-analysis, letters, editorials, case reports, or guidelines;
(2) Overlapping cohort study;
(3) Insufficient data: Sample size was <20 patients; Lack of detailed data on parameters of interest or lack of groups for comparison;
(4) Study with incomplete data or unextractable data.

2.3. Study selection

Articles initially identified by the search terms and search strategy were imported into EndNote X9. After the removal of duplicate records, the title and abstract of the remaining records were independently screened by two researchers to identify eligible studies. Full texts were subsequently reviewed to confirm eligibility.

2.4. Data extraction

Data were independently extracted from the eligible studies by two researchers, including author, year of publication, number of patients, mean age, and performance of radiomics model. The primary outcome measure was the predictive performance of the ultrasound radiomics model in HCC MVI.

2.5. Quality assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) is currently the most recommended tool for the quality assessment of diagnostic accuracy tests adopted by Cochrane Collaboration. QUADAS-2 is the most updated version of QUADAS (10.1002/jrsm.1080) and consists of 4 domains, namely patient selection, index test, reference standard, and flow and timing. Each domain is scored as low risk, high risk, or unclear risk. The quality assessment diagram was generated using RevMan 5.4 (Nordic Cochrane Center, Cochrane Collaboration, 2014).

Article screening, data extraction, and QUADAS-2 assessment were independently completed by two researchers. Any disagreement was discussed with and resolved by a third researcher.

2.6. Statistical analysis

The sensitivity, specificity, NLR, PLR, and DOR of the included studies were pooled using a random effects model [23]. A ROC curve was generated to calculate the AUC in order to evaluate the predictive value of ultrasound radiomics in MVI [24]. Heterogeneity among studies was determined by Cochran's Q test [25] and I^2 -statistic, with $I^2 > 50\%$ indicates significant heterogeneity. Sensitivity and subgroup analyses were performed to explore the source of heterogeneity [25]. Publication bias was not assessed due to the small number of included studies.

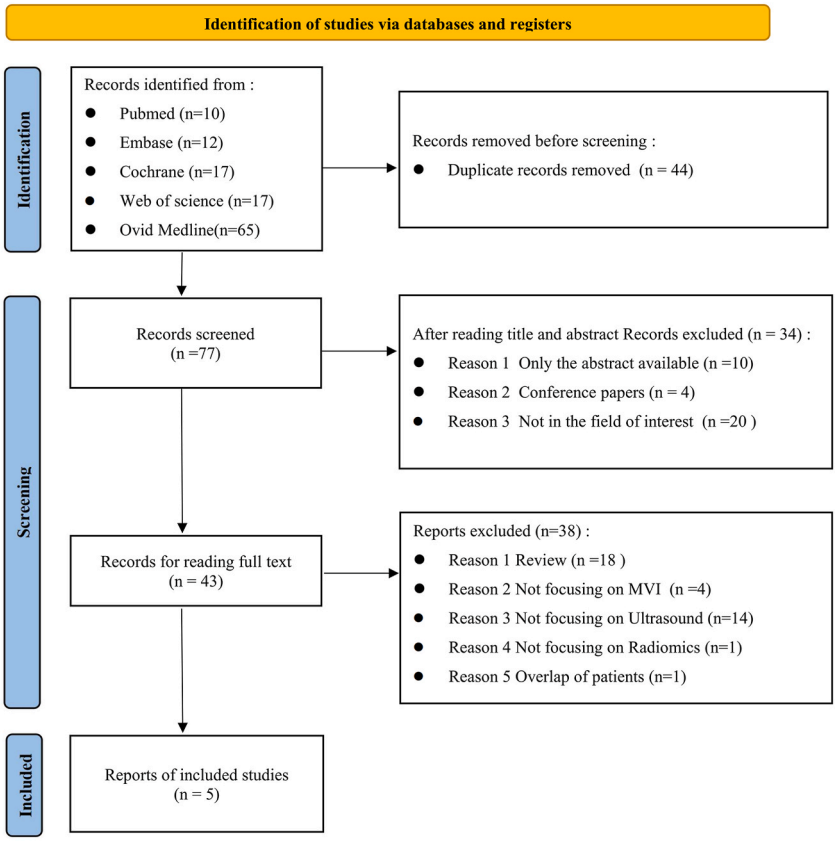

Fig. 1. Flow diagram of the study selection process for this meta-analysis.

Table 1
Characteristics of included articles.

First author	Year	Investigative type	N	MVI-	MVI+	Mean age (SD) / range	Male/ Female	Gold standard	Ultrasonic machine type	Ultrasonic probe	TP	FP	FN	TN
Dong	2020	Retrospective study	322 TD:221 VD:101	178 TD:141 VD:37	144 TD:80 VD:64	MVI+: 58 ± 11 (20–81) MVI-: 58 ± 11 (29–74)	272/50	Pathological analyses	Multi-parameter and multi-model	Multiple probe frequencies	50 48 54 52	17 15 16 17	14 16 10 12	20 22 21 20
Yao	2018	Prospective study	43	22	21	MVI+:53.9 ± 8.0 MVI-:56.0 ± 8.9	37/6	Pathological analyses	Toshiba Aplio i900 ultrasound equipment	PV1-475BX convex array probe (1–8 MHz)	18 19 19	4 1 0	3 2 2	18 21 22
Zhang	2021	Retrospective study	313 TD:192 VD:121	185 TD:113 VD:72	128 TD:79 VD:49	TD:55.1 ± 11.1 (27–83) VD:55.37 ± 12.1 (21–83)	TD:166/ 26 VD:99/22	Pathological analyses	Aloka ARIETTA 70	C251, Abdominal probe	37	21	12	51
Dong	2022	Prospective study	100	68	32	59.05 ± 10.59	78/22	Pathological analyses	Siemens Acuson Sequoia machine	5C-1 convex array transducer	25 22 27 27	33 19 37 18	7 10 5 5	35 49 31 50
Hu	2018	Retrospective study	482 TD:341 VD:141	287 TD:205 VD:82	195 TD:136 VD:59	TD:53.5 ± 10.7 (26–84) VD:53.4 ± 11.8 (18–83)	TD:301/ 40 VD:116/ 25	Pathological analyses	Multi-parameter and multi-model	Multiple probe frequencies	40	23	19	59

TD, training dataset; VD, validation dataset; MVI, microvascular invasion.

3. Results

3.1. Literature search

Of the 121 initially identified articles, 44 duplications were removed, 14 were excluded due to the inaccessibility of the full texts, and 20 were excluded due to irrelevance. The full texts of the remaining 43 studies were reviewed and 38 records were further excluded, which included reviews, meeting abstracts, meta-analyses, and studies that did not focus on the topic of this study. A final total of 5 original eligible studies were included in the systematic review and meta-analysis [26–30]. The flow chart of the article screening and selection processes is shown in Fig. 1.

3.2. Characteristics of included studies

Table 1 summarizes the characteristics of the included studies. Of the 5 included studies, 3 were retrospective studies [26–28] and 2 were prospective studies [29,30]. All studies indicated postoperative pathological examination of biopsy as the gold standard for HCC diagnosis. In addition, all studies reported sample size, number of MVI-positive and -negative patients, mean age, and male-to-female ratio. Imaging parameters are summarized in Table 2.

3.3. Quality assessment

The quality assessment results are shown in Figs. 2 and 3. The risk of bias for "index test" was unclear in all 5 studies [26–30] due to the lack of a predefined threshold. One study [30] had a high risk of bias for "flow and timing" due to the lack of analysis of all included patients. However, aside from these biases, all other parameters were of low risk of bias for all studies.

3.4. Meta-analysis

The overall incidence of HCC MVI of the 5 included studies was 41.27% (520/1260) based on the postoperative pathological diagnostic criteria. The pooled sensitivity and specificity of ultrasound radiomics for the diagnosis of HCC MVI were 79% (95% *CI*: 75–83%) and 70% (95% *CI*: 59–79%), respectively. The pooled PLR, NLR and DOR of all eligible studies were 2.6 (95% *CI*: 1.9–3.7), 0.30 (95% *CI*: 0.23–0.39), and 9 (95% *CI*: 5–16), respectively (Fig. 4). The AUC of ROC was 0.81 (95% *CI*: 0.78–0.85) (Fig. 5), which suggested that ultrasound radiomics had favorable diagnostic performance in HCC MVI.

3.5. Heterogeneity assessment

Heterogeneity among the included studies was assessed using the Cochran Q test and I^2 statistic (Fig. 4). For the pooled sensitivity analysis, I^2 was 28.44 (95% *CI*: 0.00–75.59), with a $p > 0.05$ for the Cochran Q test. For the pooled specificity analysis, I^2 was 78.94 (95% *CI*: 68.01–89.88), with a $p < 0.001$ for the Cochran Q test, which indicated significant heterogeneity. Therefore, the source of

Table 2
Radiomics characteristics of included articles.

First author	Year	Type of features	Feature extraction software	Feature selection method	Feature extracted/ selected	Model algorithms	Cross validation
Dong	2020	Morphological, first-order, texture	R software3.5.2	mRMR	1595/100	RF	10-fold Cross validation
Yao	2018	Texture	NA	SR	GM:512/NA GEM:1536/NA GEVM:2560/NA	SVM	LOOCV
Zhang	2021	Morphology, intensity, laws, wavelet, texture	ITK-SNAP3.8.0	LASSO	BM:479/6 AP:479/2 PVP:479/8 DP:479/9	Logistic regression	5-fold Cross validation
Dong	2022	Shape, histogram, texture	3D Slicer	LASSO	GrayTR:1010/813 GrayPT:1010/856 KupfferTR:1010/628 KupfferPT:1010/771	Logistic regression	LOOCV
Hu	2018	Histogram, wavelet, filter, texture	A.K.software	LASSO	1044/6	Logistic regression	10-fold Cross validation

SR, Sparse representation; LASSO, Least absolute shrinkage and selection operator; mRMR, Minimum redundancy maximum relevance; GM, MVI prediction model based on ultrasound grayscale; GEM, Gray-scale and shear wave elastography modality; GEVM, Gray-scale, shear wave elastography and viscosity modality; BM, B-mode; AP, arterial phase; PVP, portal venous phase; DP, delay phase; GrayTR, Grayscale tumoral; GrayPT, Grayscale peritumoral; KupfferTR, Kupffer phased tumoral; KupfferPT, Kupffer phase peritumoral regions; SVM, Support vector machine; RF, Random forest; LOOCV, leave one out cross validation.

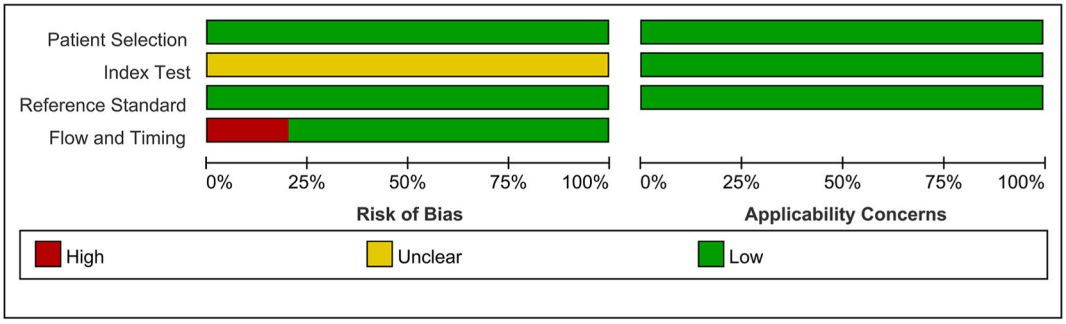

Fig. 2. Results of the QUADAS-2 quality assessment of included studies.

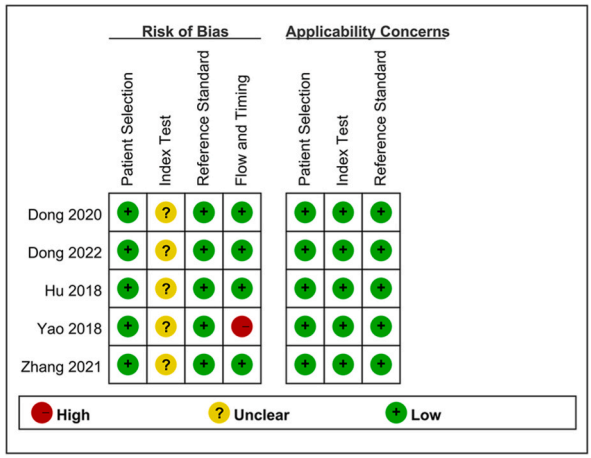

Fig. 3. Results of the QUADAS-2 quality assessment of included studies.

heterogeneity was further assessed by sensitivity and subgroup analyses.

3.6. Sensitivity analysis

Sensitivity analysis showed that the bivariate model had moderate robustness in the goodness-of-fit analysis and bivariate normal distribution (Fig. 6a and b). Three outliers were identified by influence analysis and outlier detection (Fig. 6c and d). The removal of the outlier did not significantly alter the overall results (Supplement 2), indicating that the study results were statistically reliable and stable.

3.7. Subgroup analyses

Subgroup analyses were performed to further identify the source of heterogeneity (Table 3). Pooled sensitivity was slightly higher and pooled specificity was higher in subgroups of other characteristics [26,30] than in the LASSO-based feature selection subgroup [27–29] (0.809 vs. 0.749 and 0.673 vs. 0.647, respectively). Furthermore, pooled sensitivity and specificity were slightly higher in the Leave-One-Out Cross-Validation subgroup [29,30]than in subgroups of other validation methods [26–28] (0.811vs. 0.769 and 0.715 vs. 0.627, respectively). On the other hand, pooled sensitivity and specificity were slightly lower in the logistic regression subgroup [27–29] than in subgroups of other algorithms [26,30] (0.749 vs. 0.809 and 0.647 vs 0.673, respectively).

3.8. Clinical application

The clinical application of ultrasound radiomics can be assessed using a Fagan nomogram constructed based on likelihood ratios (Fig. 7). When the pre-test probability for HCC MVI was 20%, the post-test probability of a given positive and negative ultrasound radiomics analysis was 40% and 7%, respectively. The Fagan nomogram showed that the post-test probability was increased by 20% in patients with positive pre-test and decreased by 13% in patients with negative pre-test, which indicated that ultrasound radiomics has good clinical applicability.

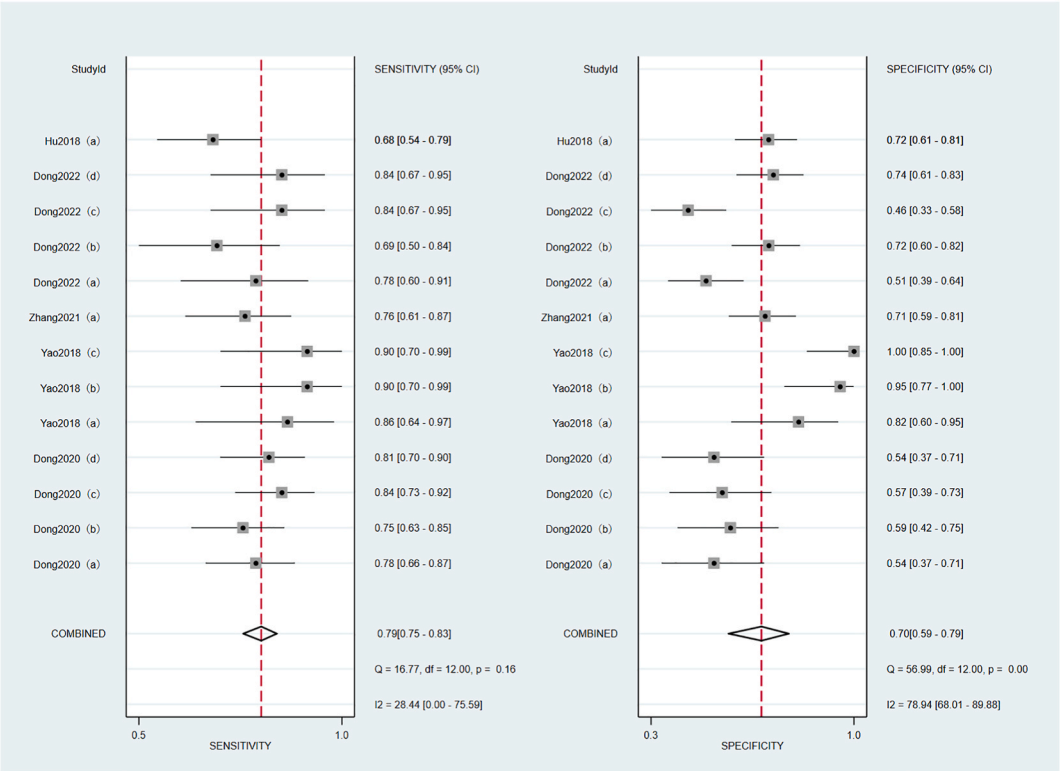

Fig. 4. Coupled forest plot of sensitivity and specificity of radiomics based-ultrasound for preoperative prediction of microvascular invasion.

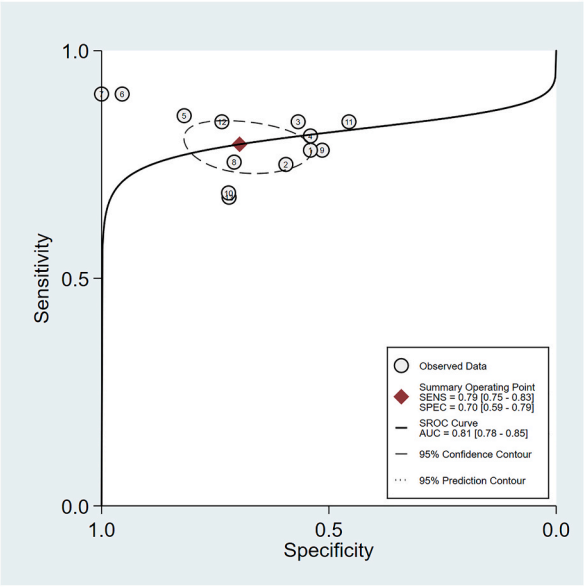

Fig. 5. Summary receiver operating characteristics (SROC) curve of radiomics based-ultrasound for preoperative prediction of microvascular invasion. AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

4. Discussion

In the present study, we evaluated the diagnostic performance of ultrasound radiomics in identifying MVI in HCC by conducting a more comprehensive literature search and using more stringent selection criteria. Our results showed that the 5 included studies had a

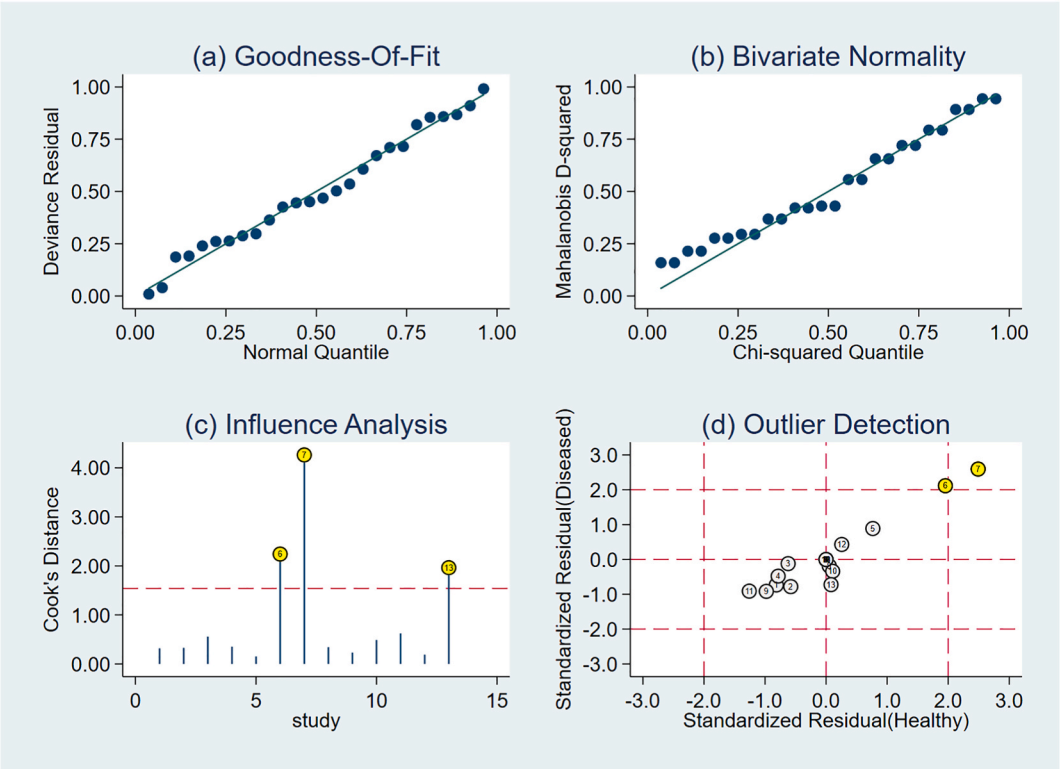

Fig. 6. Sensitivity analysis of studies. (a)Goodness-of-fit (b)Bivariate normality (c)Influence analysis (d)Outlier detection.

Table 3
Subgroup analysis of radiomics based-ultrasound in the diagnosis of microvascular invasion of hepatocellular carcinom

Subgroup	Study Number (Sample)	Sen [95%CI]	Spe [95%CI]	PLR [95%CI]	NLR [95%CI]	DOR [95%CI]
Feature selection method						
LASSO	3 (895)	0.749 [0.686,0.803]	0.647 [0.543,0.738]	2.158 [1.693,2.750]	0.360 [0.295,0.439]	6.065 [4.192,8.775]
The other	2 (365)	0.809 [0.761,0.849]	0.673 [0.535,0.786]	2.232 [1.584,3.143]	0.334 [0.269,0.416]	10.343 [4.550,23.508]
Cross Validation						
LOOCV	2 (143)	0.811 [0.747,0.862]	0.715 [0.568,0.827]	2.631 [1.744,3.969]	0.315 [0.238,0.418]	12.978 [5.196,32.416]
The other	3 (1117)	0.769 [0.719,0.812]	0.627 [0.554,0.695]	2.011 [1.718,2.355]	0.368 [0.314,0.430]	5.478 [3.875,7.742]
Model algorithms						
Logistic regression	3 (895)	0.749 [0.686,0.803]	0.647 [0.543,0.738]	2.158 [1.693,2.750]	0.360 [0.295,0.439]	6.065 [4.192,8.775]
The other	2 (365)	0.809 [0.761,0.849]	0.673 [0.535,0.786]	2.232 [1.584,3.143]	0.334 [0.269,0.416]	10.343 [4.550,23.508]

Sen, sensitivity; Spe, specificity; PLR, positive likely ratio; NLR, negative likely ratio; DOR, diagnostic odds ratio; LASSO, Least absolute shrinkage and selection operator; LOOCV,Leave-One-Out cross-validation.

pooled sensitivity of 0.79, pooled specificity of 0.70, and an overall diagnostic accuracy rate (AUC) of 81%. These findings indicated that ultrasound radiomics can provide essential information for identifying HCC MVI.

Postoperative HCC recurrence is associated with multiple factors, among which MVI is considered to be a key contributing factor [31]. Therefore, accurate preoperative prediction of MVI in HCC patients is vital for the selection and modification of treatment regimens and assessment of patient prognosis by medical staff [32,33].

Radiomics involves the extraction and analysis of imaging features from medical images and the identification of omics features that are undetectable by the naked eyes in order to reveal microscopic pathological changes in disease and thereby assist in clinical decision-making [34,35]. MVI has been shown to be closely associated with the biological heterogeneity and invasiveness of HCC cells, and hence the pathological state of tumor lesions and tissues can be effectively predicted using imaging techniques. Several recent

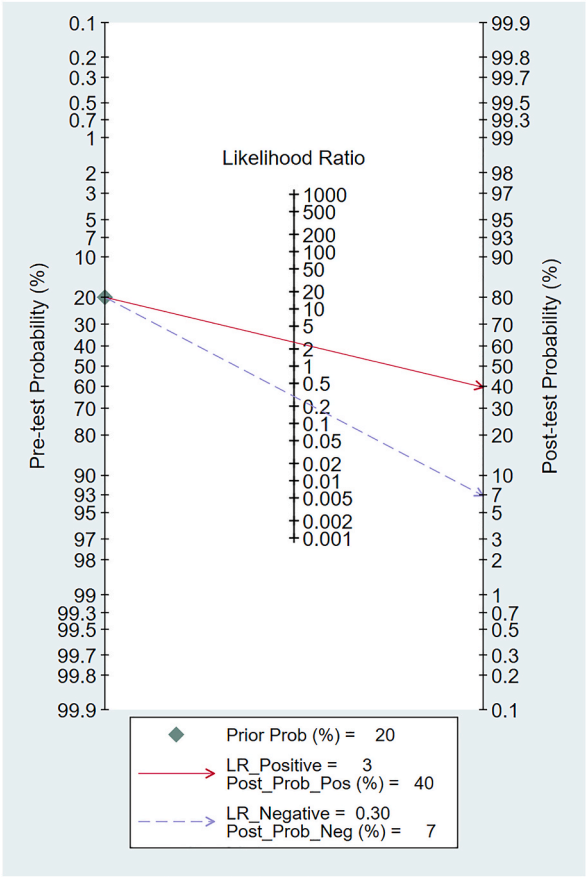

Fig. 7. Fagan nomogram for the elucidation of post-test probabilities with a pre-test probability of 20%. LR, likelihood ratio; Prob, probability.

studies have reported the use of CT and MRI in the prediction of MVI in HCC [36–39]. A meta-analysis by Zhong et al. [19]. Investigating the predictive performance of CT, MRI and ultrasound radiomics in preoperative MVI in HCC showed that the pooled sensitivity and specificity were 84% and 79% for the CT-based model, and both 82% for the MRI-based model, respectively. Their pooled sensitivity and specificity of the CT- and MRI-based models were slightly higher than those in this study, which could be attributed to the higher definition of CT/MRI compared with ultrasound. Similar results were also reported by Meng et al. [40] and Liu et al. [15].

Conventional ultrasound has been an important method for the early identification of liver lesions due to its noninvasive and economic advantages [41,42]. Color Doppler flow imaging (CDFI) and contrast-enhanced ultrasound (CEUS) are widely used to measure the quantity and features of vessels in liver lesions [43,44]. The predictive and diagnostic accuracy of ultrasound is greatly improved when used in combination with radiomics. However, very few studies have investigated the predictive performance of ultrasound radiomics. Zhong et al. [19] showed that the ultrasound radiomics-based model had a pooled specificity and sensitivity of 78% and 60%, respectively, which were lower than those in our study. This difference may be attributed to the low number of ultrasound radiomics studies included in the meta-analysis by Zhong et al. [19], which can ultimately impact the reliability of the results.

There are several limitations in this study. First, our sample size was small as only 5 studies involving 1260 patients were included, therefore our results should be considered preliminary. Second, there was some heterogeneity among the included studies, despite no bias in the subgroup and sensitivity analyses. These variations may be attributed to differences in ultrasound technician experience, equipment, sensitivity to contrast agents, case selection，patient selection, size and clinical staging of HCC, and tumor differentiation. Third, among the articles we included, two were written by the same author and had the same patient sources, which may have a potential impact on the results and may lead to certain analytical biases. Last, we only searched for studies published in English and may have missed studies in other languages.

5. Conclusions

Ultrasound radiomics has relatively high sensitivity, specificity, and accuracy in the diagnosis of MVI in HCC, and is hence a promising auxiliary tool for predicting and diagnosing MVI in HCC.

Statements and declarations

Ethics approval

Not applicable.

Author contribution statement

Qinyu Xiao: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Wenjun Zhu: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Huanliang Tang: Contributed reagents, materials, analysis tools or data.

Lijie Zhou: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16997.

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