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Systematic review: radiomics for the diagnosis and prognosis of hepatocellular carcinoma

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Summary

Background: Advances in imaging technology have the potential to transform the early diagnosis and treatment of hepatocellular carcinoma (HCC) through quantitative image analysis. Computational "radiomic" techniques extract biomarker information from images which can be used to improve diagnosis and predict tumour biology.

Aims: To perform a systematic review on radiomic features in HCC diagnosis and prognosis, with a focus on reporting metrics and methodologic standardisation.

Methods: We performed a systematic review of all full-text articles published from inception through December 1, 2019. Standardised data extraction and quality assessment metrics were applied to all studies.

Results: A total of 54 studies were included for analysis. Radiomic features demonstrated good discriminatory performance to differentiate HCC from other solid lesions (c-statistics 0.66-0.95), and to predict microvascular invasion (c-statistic 0.76-0.92), early recurrence after hepatectomy (c-statistics 0.71-0.86), and prognosis after locoregional or systemic therapies (c-statistics 0.74-0.81). Common stratifying features for diagnostic and prognostic radiomic tools included analyses of imaging skewness, analysis of the peritumoural region, and feature extraction from the arterial imaging phase. The overall quality of the included studies was low, with common deficiencies in both internal and external validation, standardised imaging segmentation, and lack of comparison to a gold standard.

Conclusions: Quantitative image analysis demonstrates promise as a non-invasive biomarker to improve HCC diagnosis and management. However, standardisation of protocols and outcome measurement, sharing of algorithms and analytic methods, and external validation are necessary prior to widespread application of radiomics to HCC diagnosis and prognosis in clinical practice.

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-associated death worldwide and the fastest-growing cause of cancer death in the United States.[1,2] The rising mortality associated with HCC is driven in part by limitations in the screening and early detection of HCC. Most HCC is diagnosed at an advanced stage when curative treatment options are limited.[3] There are few available diagnostic and risk stratification tools to prioritise at-risk populations for surveillance and early detection of HCC. The Liver Imaging Reporting and Data System (LI-RADS or LR) criteria was established to provide standardised criteria for the radiographic diagnosis of HCC.[4]

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However, validation of these criteria remains limited and there are two categories of indeterminate nodules (ie LR3 and LR4) for which there is uncertainty regarding diagnostic approach.[5] Biopsy for the diagnosis of HCC is not currently routinely recommended by guidelines due to the risk of tumour seeding, bleeding and sampling error.[6] Similarly, the only validated non-invasive prognostic markers for HCC are tumour staging and alpha-fetoprotein levels, both of which have significant limitations in approximating tumour biology.[7,8] This is particularly important in light of recent data showing variation in tumour growth patterns, with one-fourth of HCC having rapid growth patterns and over one-third having indolent growth.[9,10] There remains an unmet need for non-invasive biomarkers to aid in the early detection of HCC and prediction of tumour behaviour. "Radiomics," a term that describes the "omics" approach for analysis of imaging data, has emerged as a novel tool for the diagnosis and prognosis of HCC.[11] Radiomics leverages advanced computing tools to extract deeper and more granular data from imaging.[12] Quantitative image features predictive of tumour behaviour, treatment response, and overall outcomes have been identified in other malignancies including breast, pancreatic, and lung cancer.[13-16]

2 | QUANTITATIVE IMAGING

Advanced image analysis is frequently divided into two categories: semantic and quantitative. The term "semantic" refers to radiologist-derived image features such as the presence of internal arteries, hypodense halos, and tumour-liver difference.[17,18] The clinical utility of semantic imaging features have been limited by labour-intensive extraction process and concerns about suboptimal inter- and intra-observer reliability (k-0.50-0.70).[19] "Quantitative" imaging features, also known as agnostic features, by comparison, are computer-derived mathematically extracted quantitative image characteristics of the tissue of interest.[20] These are extracted by analytic software and can be categorised into morphologic (shape) and statistical (first-order, second-order, and higher-order) features based on complexity.[20-23] Varying analytic approaches have been used for radiomics studies including traditional regression analysis or machine learning approaches to measure the association between voxel data and a clinical outcome of interest.

Radiomic analysis involves five primary steps, as outlined in Figure 1: image acquisition, tumour segmentation, feature extraction, feature selection, and model creation.[24] *Image acquisition* refers to the process of collecting and reconstructing imaging studies in a manner that minimises variations in extracted numerical data.[25] *Tumour segmentation* refers to the selection of regions of interest (ROI) around tumoural tissue. This can be performed either manually or with the assistance of semi-automatic contour selection tools.[26] Tumour segmentation is a major source of inter-reader variability and can introduce biases in quantification.[27] *Feature extraction* refers to the application of specialised software to derive quantitative descriptions of the voxel patterns in each image, generating thousands of individual variables. The distribution of the voxel intensity values is considered first-order features and the spatial relationship of the voxels, also known as texture analysis, is considered second-order features.[28] *Feature selection* is the process of using supervised or unsupervised statistical analysis to identify the variables most predictive of the desired outcome measure. Because of the large number of variables, radiomic studies must also perform considerable dimensionality reduction to reduce the risk of overfitting.[29] *Model creation:* refers to the creation of a nomogram or multivariable model using the most successful radiomic variables. Generally, the best-performing models incorporate a combination of established clinical and pathological biomarkers with radiomic data. In this systematic review, we aimed to evaluate the role of radiomic tools for diagnosis and prognosis of HCC.

3 | METHODS

With the assistance of a trained librarian (WT), we performed a systematic review of the literature, concordant with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[30] The literature review captured studies from inception to December 1, 2019, in PubMed Legacy, Embase.com, Scopus.com, Web of Science Core Collection (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED), Cochrane CENTRAL via Wiley, and clinicaltrials.gov. The full search strategy including MESH headings is listed in Supplementary Methods. References of selected articles were also reviewed to identify additional articles. Duplicates were eliminated automatically. Inclusion criteria included those that met the following criteria:

a. Evaluated HCC using an MRI or CT-based radiomics approach AND
b. Provided information relating to diagnosis (detection, characterisation) or
c. Provided information relating to prognosis (microvascular invasion, response to therapy, survival, recurrence rate).

Exclusion criteria included the following: (a) studies not available in English with translation, (b) non-peer-reviewed articles, (c) ultrasound-based studies, (d) studies without an outcome measure and (e) studies exclusively focussed on semantic imaging features. This search identified a total of 754 unique records, 116 articles were assessed for eligibility of which 54 met inclusion criteria. Figure 2 describes our selection process and reasons for study exclusion.

Two authors (EHT, BM) independently reviewed all papers for eligibility. Studies were categorised into five groups: diagnosis, prognosis, microvascular invasion (MVI), pathologic correlates and treatment response. Data extraction using standardised forms was then performed by three authors (EHT, EC, BM) independently and discrepancies were resolved by consensus. Data were intended for meta-analysis; however, due to large differences in techniques/methodologies between the studies, this was not possible.

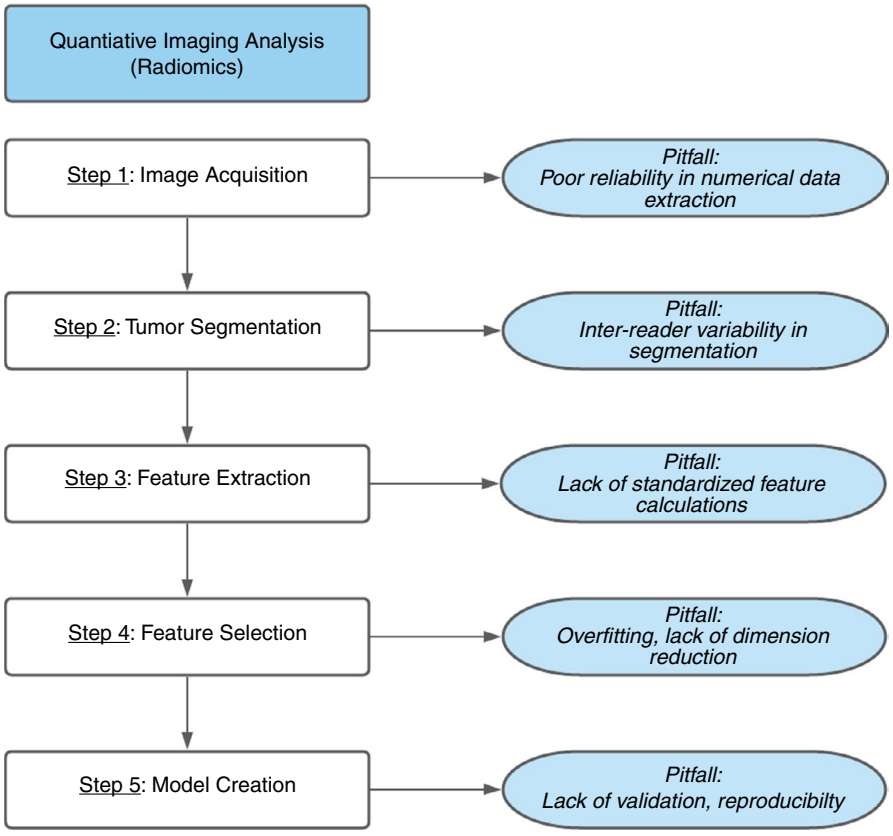

FIGURE 1 Radiomics analysis workflow with common pitfalls

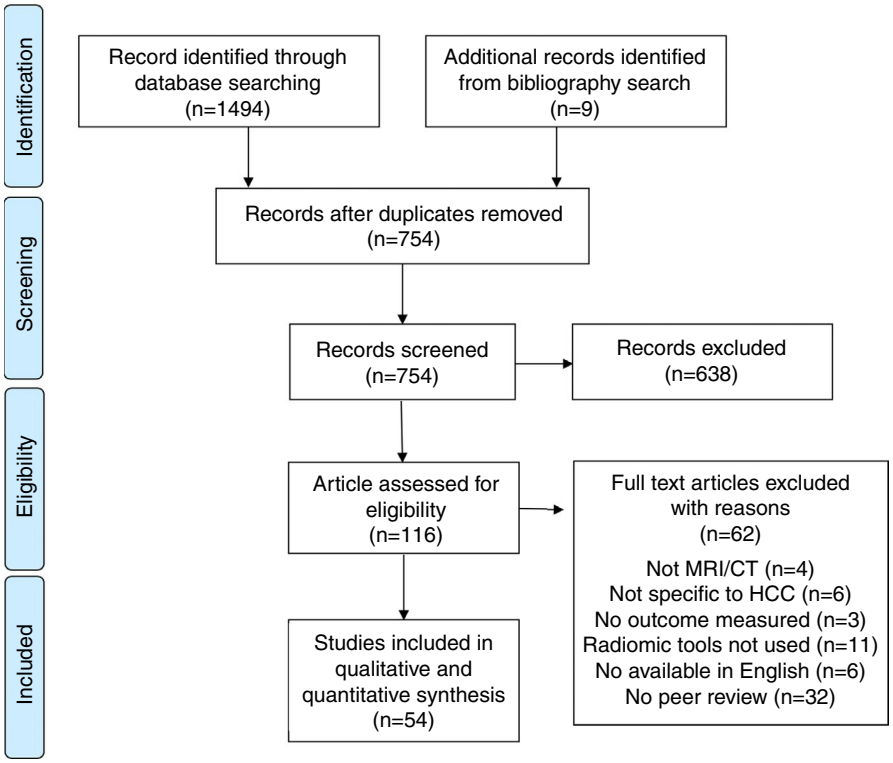

FIGURE 2 Literature search algorithm for generation of MRI and CT-based radiomic studies

4 | QUALITY ASSESSMENT

Two reviewers (EHT and BM) applied the radiomics quality score (RQS) to assess radiomic studies on the basis of 16 components (score range 0-36). Each reviewer individually scored studies and discrepant results were adjudicated by consensus. The score is based on clinical utility, feature reduction, image protocol quality, multivariable analysis, gold standard comparison, cut-off analysis, discrimination statistics, multiple segmentations, biological correlates, calibration

statistics, validation, prospective study, multiple timepoints, phantom studies, open science data, and cost-effectiveness analysis.[31]

5 | RESULTS

5.1 | HCC diagnosis

Of the 54 studies met eligibility criteria, nine evaluated aspects of HCC diagnosis (Table 1). Four studies primarily focussed on distinguishing hepatic haemangiomas from HCC.[32-35] Mokrane et al evaluated 178 patients with indeterminate nodules and sought to categorise the nodules as high- or low-risk for HCC. They demonstrated an AUC of 0.74 in a training cohort and 0.66 in a validation cohort using CT scans.[36] Dankerl et al demonstrated that radiomic tools could outperform radiologists at predicting lesion histology (benign vs malignant) with an accuracy of 75.1% compared with a range of 52%-74% for radiologists depending on level of experience.[37] Stocker et al also compared radiomic features against human radiologists, and demonstrated that a combination of 13 arterial phase features outperformed radiologists at distinguishing HCC from non-malignant tumours.[38] The majority of diagnostic studies have relied on textural features alone, however, even simple textural features have not been directly comparable between protocols. Asayama et al demonstrated that the non-cancerous hepatic parenchyma of livers with HCC exhibits a consistent pattern of high kurtosis and low skewness on MRI, compared to patients without HCC, indicating that patients with HCC have features in the background parenchyma that can predict the risk of HCC.[39] Rosenkrantz et al found that high MRI skewness (a measure of lateral histogram distortion) in an indeterminate liver lesion was associated with the progression of indeterminate lesions to malignant HCC.[40]

5.2 | Prediction of prognosis

Seventeen studies evaluated HCC prognosis following hepatectomy (Table 2). These were primarily performed with CT imaging; five studies involved MRI. Eight studies evaluated prediction of early recurrence,[41-48] and eight evaluated overall survival and recurrence-free survival,[49-56] and one evaluated post hepatectomy acute liver failure.[57] Radiomic models predicted early recurrence with AUCs that varied between 0.71 and 0.86. When only second-order textural features were included, skewness was the most commonly identified feature predictive of outcomes. Oh et al reported that skewness predicted overall survival with a HR of 10.96 (95% CI: 3.21-37.46), compared with microvascular invasion with a HR of 2.12 (95% CI: 1.06-4.25).[49] Defour et al performed multivariable analysis of textural features in the portal-venous phase and found skewness to be associated with overall survival with a HR of 438.7 (95% CI: 2.44-78,968.25).[52] The majority of studies used higher-order radiomic features. Kim et al evaluated 168 patients using a 3-dimensional technique which extracted 3903 radiomic features per patient and found that high-order feature analysis performed similarly to a combined clinical model (age, hepatitis C, alcohol use, cirrhosis, tumour capsule, and microvascular invasion) in predicting early recurrence.[45] The authors also demonstrated that the inclusion of 3 mm of peritumoural tissue improved risk prediction over segmenting the tumour alone.[45] Nine studies compared their radiomic tools against clinical models or created a combined model using both radiomic and clinical features. In all cases, the combined model was equal or superior to the clinical model alone. The characteristics of these studies are described in Table S1. In one of the largest studies, Zhou et al compared a clinical model (based on serum alpha-fetoprotein, vascular invasion, and non-smooth tumour margin) against a combined model for the prediction of early recurrence (ER) in 214 patients and patients with HCC had differential background liver texture. The addition of a 21-feature radiomics signature improved the clinical model AUC from 0.781 to 0.836 when clinical features were used in combination with radiomic data.[43]

5.3 | Prediction of microvascular invasion

Microvascular invasion (MVI) is among the strongest predictors of outcomes following liver transplantation or hepatectomy for HCC.[58,59] Seven studies evaluated radiomics as a tool for the prediction of MVI on explant following hepatectomy[60-66] (Table 3). These studies reported AUCs ranging from 0.76 to 0.91. Six of the studies evaluated their result against a clinical model, and in all cases, the combined model performed comparably or better than the clinical model. Xu et al, in the largest study to date, evaluated CT scans from 495 patients and found that a combination of clinical, radiologic, and radiomic features predicted histologic MVI with an AUC of 0.909 in the training/validation and 0.889 in an separate test set.[63] Clinical features included aspartate aminotransferase (AST) and alpha fetoprotein (AFP), while radiologist-derived features included non-smooth tumour margin, extrahepatic growth, ill-defined pseudocapsule, and peritumoural arterial enhancement, as well as the presence of a previously published radio-genomic venous invasion signature. The authors also compared the use of the 3-dimensional VOI of the tumour only against a volume that extends 5 mm in every direction from the tumour. Although MVI occurs primarily at the periphery of tumours, the inclusion of peritumoural tissue in the VOI did not improve the prediction of MVI.[63] To create a simple decision tool, Zhang et al published a nomogram for the prediction of MVI which includes a radiomic score and alpha fetoprotein, tumour type, peritumoural enhancement, arterial rim and internal arteries.[65] This nomogram outperformed a clinical and radiologic model with an AUC of 0.858 vs 0.729. In the limited studies examining MRI radiomic tools, the arterial phase of the image predicted MVI more effectively than venous phase.[63]

5.4 | Prediction of pathologic and molecular correlates

Ten studies used radiomic features to visually identify the pathologic and genetic correlates of HCC. These include p53 mutation status, Ki-67, and CD8+ T-cell invasion (Table S2).[67-76] In a

TABLE 1 Studies evaluating radiomic tools for early diagnosis in hepatocellular carcinoma

Author	CT/MRI	N (Train/ Valid)	Extraction tool	Specific outcome measured	Statistical result	Clinical model	RQS
Dankerl 2013	CT	372	CADx	Differentiation of benign vs malignant lesion (nodule vs HCC)	AUC 0.75 for textural features AUC 0.91 for texture + semantic	No	5
Song 2019	CT	84	Omni-Kinetic	Differentiation of benign vs malignant lesion (HCC vs HH vs FNH vs HA)	AUC 0.927 for textural features	No	9
Stocker 2018	MRI	108	Matlab	Differentiation of benign vs malignant lesion	AUC 0.92 arterial phase	No	7
Li 2017	MRI	T: 112 V:50	Internal	Differentiation of HH from HCC	AUC 0.73 for GLCM Energy-mean	No	10
Oyama 2019	MRI	T: 50,50 V: 50	Matlab	Differentiation of HH from HCC	AUC 0.95 textural features	No	9
Wu 2019	MRI	369	Internal	Differentiation of HH from HCC	AUC 0.89 textural features	No	8
Mokrane 2019	CT	T: 142 V: 36	Internal	Categorise indeterminate nodule as high-risk or low-risk for HCC	AUC 0.74 for training cohort AUC 0.66 for validation cohort	No	10
Asayama 2016	MRI	84	Internal	Comparison of individual textural features of non-cancerous parenchyma between those with and without HCC	$P = 0.0006$ for kurtosis $P = 0.0152$ for skewness	No	6
Rosenkrantz 2015	MRI	20	Internal	Progression of hypovascular nodule to likely HCC on subsequent MRI	AUC 0.68 for skewness	No	7

Abbreviations: AUC, area under the curve; CT, computed tomography; FNH, focal nodular hyperplasia; HA, hepatic adenoma; HCC, hepatocellular carcinoma; HH, hepatic haemangioma; MRI, magnetic resonance imaging.

landmark study by Kuo et al, the authors demonstrated an association between radiomic textural features and a doxorubicin drug response gene signature previously shown to be predictive of tumour stage.[69] Chen et al demonstrated among 207 patients that radiomic features including the peritumoural region were associated with a validated "immunoscore." This score characterises the tumour infiltrating lymphocyte population, and theoretically reflects the immune phenotype of the tumour microenvironment.[67]

5.5 | Treatment response

An additional 11 studies evaluated treatment response, primarily following local-regional therapy (LRT) (Table S3).[77-87] These studies had the most variability in quality, with a median RQS of 7. Most studies were focussed on single textural features and just two studies involved clinical models for comparison. Kim et al demonstrated in 88 patients that a combination of clinical (Child-Pugh score, serum alpha fetoprotein and tumour size) and radiomic features (surface area-to-volume ration, kurtosis, median, size zone variability) can predict post-TACE overall survival with a HR of 19.88 and 95% CI of 6.37-62.02.[79] These findings were also seen in other studies, in which radiomic features extracted from pre-treatment imaging (CT or MRI) for prediction of treatment response after TACE were compared to post-treatment response evaluation.[80,87] Mule et al found post-Sorafenib overall survival correlated significantly with individual textural features.[83]

5.6 | Assessment of methodology

Radiomic methods varied significantly between studies. Among quantitative imaging studies, no two groups used the same extraction

TABLE 2 Studies evaluating radiomic tools for the prediction of microvascular invasion in hepatocellular carcinoma

Author	CT/ MRI	N (Train/ Valid)	Extraction tool	Segment tool	Specific outcome measured	Statistical result	Clinical model	RQS
Bakr 2017	CT	28	Internal	Manual ROI	Prediction of microvascular invasion	AUC 0.76 Texture analysis of MVI	Semantic Model	6
Ma 2019	CT	T: 110 V: 47	Matlab	Manual ROI	Prediction of microvascular invasion (compares portal venous phase vs arterial phase)	AUC 0.793 Portal Venous Phase for MVI	Clinical Model	10
Zheng 2017	CT	120	Matlab	Semi-Automatic ROI	Prediction of microvascular invasion (compares tumours <5 cm vs >5 cm)	AUC 0.80 for single feature (angle co-occurrence matrix) if <5 cm AUC 0.75 for single feature (local binary pattern) if >5 cm	Clinical Model	6
Xu 2019	CT	T: 350 V: 145	Python	Semi-Automatic VOI	Prediction of microvascular invasion (combined clinical + agnostic + radiomic model)	AUC 0.909 training/ validation AUC 0.889 test	Clinical Model	11
Feng 2019	MRI	T: 110 V: 50	Internal	Manual VOI	Prediction of microvascular invasion using both intra-tumoural and peritumoural regions	AUC 0.850 training AUC 0.833 validation	No	12
Zhang 2019	MRI	T: 194 V: 73	Matlab	Manual ROI	Prediction of microvascular invasion (radiomic score compared against nomogram)	AUC 0.784 training for rad signature AUC 0.820 validation for rad signature	Clinical Model	12
Zhu 2019	MRI	142	Omni-Kinetics	Manual ROI	Prediction of microvascular invasion (arterial phase vs portal venous phase)	AUC 0.765 training for arterial AUC 0.773 validation for arterial	Clinical Model	11

Abbreviations: AUC, area under the curve; CT, computed tomography; MRI, magnetic resonance imaging; ROI, region of interest.

tool or segmentation process. A majority of studies used proprietary investigator-developed tools which are not publicly available. Study outcomes and reporting methods were heterogeneous. More recently, groups have begun to transition to using software packages, such as Matlab, for data extraction. There was a wide variation in the number of features extracted, ranging from 5 to 3903. Recent studies have also begun to transition from 2- to 3-dimensional "volume of interest" models as large-scale data analysis becomes streamlined. The use of manual and semi-automatic ROI selection tools also varied significantly between studies, and inter-rater reliability of ROI selection was rarely performed. Indistinct nodules represent a challenge because minor changes in ROI selection can substantially influence the radiomic signature generated. A minority of studies performed internal validation experiments against a portion of their data set, but there were no examples of external validation using imaging derived from outside institutions.

5.7 | Radiomics quality scores

The range of radiomics quality scores reflect the large degree of heterogeneity which currently exists within the field. The median RQS was 9 and the range was 5-13 out of a possible 36

TABLE 3 Studies evaluating radiomic tools for prognosis in hepatocellular carcinoma

Author	CT/ MRI	N (Train/ Valid)	Extraction tool	Segment tool	Specific outcome measured	Statistical result	Clinical model	RQS
Akai 2018	CT	127	TexRAD	Manual ROI	Model categorises as high risk or low risk for OS and DFS	$P < 0.0001$ for OS from Kaplan Meier LR	No	10
Chen 2017	CT	61	Matlab	Manual ROI	Prediction of OS and RFS with individual features	$P = 0.001$ for OS from Kaplan Meier LR	No	9
Defour 2018	CT	47	TexRAD	Manual ROI	Prediction of OS and RFS with individual textural features	$P = 0.0084$ of kurtosis in MV of OS	No	6
Kiryu 2017	CT	122	TexRAD	Manual ROI	Prediction of OS and RFS with individual textural features	$P < 0.001$ of entropy in Kaplan-Meier LR of OS	No	7
Peng 2018	CT	T: 113 V: 64	IBEX	Semi-automatic ROI	Radiomic score used to categorise as high risk or low risk for OS and DFS	$P < 0.0001$ of model in Kaplan-Meier LR of OS	Clinical Model	13
Guo 2019	CT	T: 93 V: 40	Python	Semi-automatic VOI	Radiomic model as a predictor of RFS	0.743 Training for RFS 0.705 Validation for RFS	Clinical Model	10
Zheng 2019	CT	T: 212 V: 107	Matlab	Manual ROI	Radiomic score and radiomic-score based nomograms used to predict OS	0.714 Training for OS 0.71 Validation for OS	Clinical Model	12
Cai 2019	CT	T: 80 V: 32	Internal	Semi-automatic VOI	Radiomic score used to predict post-hepatectomy acute liver failure	0.822 training for post-hepatectomy acute liver failure 0.762 validation for post-hepatectomy acute liver failure	Clinical Model	10
Oh 2019	CT	81	TexRAD	Manual ROI	Prediction of DFS with individual textural features	$P < 0.001$ for skewness (SSF2.0) in MV of DFS	No	9
Ning 2019	CT	T: 225 V: 100	Matlab	Semi-automatic VOI	Prediction of early recurrence after hepatectomy	0.817 Training for ER 0.719 Validation for ER	Clinical Model	9
Shan 2019	CT	T: 109 V: 47	Internal	Manual ROI	Prediction of early recurrence after hepatectomy (models compare peritumoural and tumoural features against tumour enhancement)	0.80 Training for ER 0.79 Validation for ER	No	11
Zhou 2017	CT	214	Matlab	Manual ROI	Prediction of early recurrence after hepatectomy (summary model used)	0.836 for ER	Clinical Model	11
Hui 2018	MRI	50	Matlab	Manual ROI	Prediction of early recurrence after hepatectomy (individual radiomic features only)	0.82 for S(0,3) SumofSqs for ER 0.84 for S(4,0) SumVarnc	No	10
Kim 2019	MRI	T: 129 V: 39	Python	Semi-automatic VOI	Prediction of early recurrence after hepatectomy (peritumoural model)	0.716 for clinical + radiomic model in predicting ER	No	9

(Continues)

TABLE 3 (Continued)

Author	CT/ MRI	N (Train/ Valid)	Extraction tool	Segment tool	Specific outcome measured	Statistical result	Clinical model	RQS
Zhang 2019	MRI	100	Internal	Semi-automatic VOI	Prediction of early recurrence after hepatectomy (individual radiomic features only, <3 cm vs >3 cm)	0.867 skewness + entropy	No	10
Zhang 2019	MRI	T: 108 V: 47	Internal	Semi-automatic VOI	Prediction of early recurrence after hepatectomy	0.757 Training for ER 0.728 Validation for ER	Clinical Model	12
Ahn 2019	MRI	179	Internal	Manual ROI	Prediction of early recurrence after hepatectomy (combines agnostic and radiomic)	0.83 for radiomic + agnostic features for ER	No	6

Abbreviations: AUC, area under the curve; CT, computed tomography; DFS, disease free survival; ER, early recurrence; LR, log rank; MRI, magnetic resonance imaging; MV, multivariate; OS, overall survival; ROI, region of interest.

points. The most notable limitations were in studies of cost effectiveness analysis, phantom use, open publication of methods, and prospective study protocol. Quality adherence was highest for feature reduction and discrimination statistics. Notably, the quality has improved over time and studies performed in 2019 consistently scored higher than prior years, primarily through the incorporation of validation cohorts, although most were internal and not external validation with some continued risk of overestimation of model performance.

6 | DISCUSSION

Quantitative image analysis has the potential to transform the early detection and management of HCC. Because high-resolution cross-sectional imaging is already widely available, radiomics has the ability to improve HCC management more rapidly than novel molecular biomarkers. We found radiomic tools to date have been studied primarily for their ability to predict overall survival and early recurrence following hepatectomy and have demonstrated good predictive accuracy, with AUCs exceeding 0.80; however, many of these models have not been tested in validation cohorts including none being externally validated. Fewer studies evaluated response to non-surgical treatments or association with molecular biomarkers, although the ones to date have also demonstrated promising accuracy. As methodology has improved, studies have progressed from simple textural features to thousands of three-dimensional higher-order variables. Studies to date have been limited by small, single-centre studies with heterogeneous methods and lack of validation cohorts.

The largest gaps in the use of radiomic technology are in early detection and diagnosis. Only 9 of 54 radiomic studies focussed on aspects of HCC diagnosis. Those studies were of variable quality and performed simple radiologic tasks such as distinguishing hepatic haemangiomas from HCC. The next frontier for HCC radiomics will be to assist radiologists with liver nodule risk stratification. This may initially involve the automation of LI-RADS classification, a task that is relatively simple but burdensome for abdominal radiologists. Subsequent tools might also assist in the differentiation of LR3 and LR4 lesions into malignant and benign categories, reducing the number of follow-up imaging studies required to diagnose true HCC from indeterminate nodules. This is particularly important in light of evolving data quantifying potential physical harms related to false-positive and indeterminate surveillance tests.[88,89] In addition, further studies of post-treatment survival or recurrence will be needed in response to the increasingly wide array of HCC treatments available. Replication of existing radiographic diagnostic and treatment criteria (eg LIRADs and modified Response Evaluation Criteria in Solid Tumours [mRECIST]) using radiomics, may be iteratively followed by eventual replacement of these criteria with more sophisticated and accurate radiomic based models. Ultimately, radiomic models may also assist in guiding the selection of appropriate systemic or local-regional treatments based on an individual's radiologic, clinical, and genomic profiles. Alternatively, radiomic features could inform an overall treatment strategy for a patient with HCC, rather than treatment of an individual tumour, such as the decision of whether to pursue liver transplantation, or systemic versus locoregional therapy. Evaluation of treatment response and analysis of longitudinal imaging to evaluate how changes in imaging over time may predict future clinical events are relatively unexplored areas that could benefit from more objective analyses. The addition of novel molecular tracers and hepatocyte-specific contrast agents may offer a promising synergistic strategy, improving the capacity of radiomic tools to identify HCC at an early stage.

There are several required steps before radiomics can be considered ready for use in clinical applications. Automation of the manual segmentation and extraction process will be essential prior to a transition into real world use. Tools capable of providing consistent and accurate ROI selections are needed to reduce inter-reader variability in tumour segmentation. This would also streamline the currently labour-intensive workflow and allow radiomic models to provide an automatic readout that augments radiologist expertise without increasing time spent. Automated

segmentation would also address the challenges in patients with multiple tumours with varying features and underlying tumour biology. Complex models capable of automatically segmenting the entirety of the patient's imaging, such as convolutional neural networks, would be necessary to provide a holistic radiomic analysis. A second critical step will be the development of consensus around feature extraction methods. Currently, the field of radiomics is limited by the fact that no two studies can be directly compared against one another. Proprietary feature extraction tools result in thousands of quantitative variables that have no meaning outside of the context of a single research study. This reduces the ability to perform external validation and prevents the development of cumulative knowledge around specific radiomic feature types. A rigorous approach to standardisation, methods sharing and increased transparency will be critical to the expansion of radiomics beyond single-institution proof-of-concept studies. To create large-scale training datasets in HCC would require the creation of a centralised image biorepository of HCC scans across many institutions. The NCI's National Biomedical Image Archive (NBIA) programme provides a national image database that seeks to accelerate quantitative imaging resources and has been used to generate open-source datasets in lung, breast, and head and neck cancers.[90] Data sharing in HCC radiomics would enable cross-centre validation of models and longitudinal adjustment with follow-up data available over time. Automated deidentification of imaging data would be necessary for compliance with patient privacy regulations (eg the Health Insurance Portability and Accountability Act), and several existent software packages exist that can reliably deidentify images prior to sharing. External validation is the most critical first step towards realizing the potential of radiomics in the management of HCC, and should be included if feasible in all published radiomic models.

Although early results are encouraging, the limitations of radiomic studies in the current era are substantial. Standardizing analytical methods and image acquisition techniques will be critical to reproducibility across institutions. The Quantitative Imaging Network (QIN) and Radiologic Society of North America are developing consensus protocols and digital phantoms that can help bring radiomics into the realm of clinical utility.[91] Test-retest studies of stable phantom objects within a given scanner have estimated reproducibility in only approximately 30% of MRI features, while multi-scanner phantom studies have shown feature reproducibility ranging from 15% to 85%.[92,93] MRI, in particular, is subject to fundamental intensity inhomogeneity across static fields, as well as large amounts of motion artefact, noise, and machine-to-machine variation in acquisition parameters.[94] As a result, voxel intensity is often not directly comparable between MRI images and the reproducibility of feature extraction has thus far been poor.[95] Quantitative texture analysis is sensitive to scanner variability, and minor changes between institutions could create major distortions in model output. Many of the studies in this review are from Asian cohorts, which have a higher frequency of non-cirrhotic HCC. Derived textural features may differ between Asian and Western cohorts, due to differences in underlying disease aetiology and fibrosis burden. Finally, the extraction of high-dimensional data from a small sample results in a high risk of overfitting during model creation and high false-positive rate.[96] It is notable that only 2 of 32 models reporting ROC curves in our study had an AUC below 0.70, suggesting possible bias in reporting and over-fitting of data. The reduction of radiomic features to a smaller set of consistently evaluated variables would improve reliability across studies. Although high-throughput imaging data has great promise, the field of radiomics has not yet conclusively demonstrated the capacity to accurately reflect tissue biology. To reach clinical relevance, radiomics will need to develop rigorous cross-centre standardisation protocols and evidence of a reproducible, generalisable outcome across multiple contexts.[97,98] Larger cohorts are needed to improve model performance by reducing overfitting while retaining dimensionality of the models.

7 | CONCLUSIONS

Quantitative image analysis has the potential to transform the early detection and management of HCC. There is a critical need for non-invasive techniques to assist in both diagnostic and prognostic decision-making. Early work in radiomics has demonstrated substantial promise, particularly in the prediction of microvascular invasion and post-hepatectomy outcomes. There are, however, fundamental issues that prevent the clinical application of this technology. Unrecognised errors can introduce bias and unrecognised variability in quantitative analysis. Increased standardisation, external validation of models, and rigorously designed prospective studies will be essential to the growth and maturation of radiomics in HCC.

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DATA AVAILABILITY STATEMENT

Data included in this manuscript is publicly available.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the Supporting Information section.

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