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REVIEW

Radiomics and Deep Learning as Important Techniques of Artificial Intelligence — Diagnosing Perspectives in Cytokeratin 19 Positive Hepatocellular Carcinoma

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Background: Currently, there are inconsistencies among different studies on preoperative prediction of Cytokeratin 19 (CK19) expression in HCC using traditional imaging, radiomics, and deep learning. We aimed to systematically analyze and compare the performance of non-invasive methods for predicting CK19-positive HCC, thereby providing insights for the stratified management of HCC patients.

Methods: A comprehensive literature search was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Library from inception to February 2025. Two investigators independently screened and extracted data based on inclusion and exclusion criteria. Eligible studies were included, and key findings were summarized in tables to provide a clear overview.

Results: Ultimately, 22 studies involving 3395 HCC patients were included. 72.7% (16/22) focused on traditional imaging, 36.4% (8/22) on radiomics, 9.1% (2/22) on deep learning, and 54.5% (12/22) on combined models. The magnetic resonance imaging was the most commonly used imaging modality (19/22), and over half of the studies (12/22) were published between 2022 and 2025. Moreover, 27.3% (6/22) were multicenter studies, 36.4% (8/22) included a validation set, and only 13.6% (3/22) were prospective. The area under the curve (AUC) range of using clinical and traditional imaging was 0.560 to 0.917. The AUC ranges of radiomics were 0.648 to 0.951, and the AUC ranges of deep learning were 0.718 to 0.820. Notably, the AUC ranges of combined models of clinical, imaging, radiomics and deep learning were 0.614 to 0.995. Nevertheless, the multicenter external data were limited, with only 13.6% (3/22) incorporating validation.

Conclusion: The combined model integrating traditional imaging, radiomics and deep learning achieves excellent potential and performance for predicting CK19 in HCC. Based on current limitations, future research should focus on building an easy-to-use dynamic online tool, combining multicenter-multimodal imaging and advanced deep learning approaches to enhance the accuracy and robustness of model predictions.

Keywords: hepatocellular carcinoma, cytokeratin 19, radiomics, deep learning, artificial intelligence, systematic review

Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer globally and the third leading cause of cancer-related mortality.[1,2] Despite significant advancements in surgical techniques and imaging modalities, which have improved the prognosis of HCC patients, the high rate of intrahepatic recurrence following hepatectomy remains a major therapeutic challenge, with approximately 70% of patients experiencing recurrence within five years.[3,4] Accumulating evidence has identified cytokeratin 19 (CK19) as an independent risk factor for early recurrence after hepatectomy and liver transplantation.[5,6] CK19, a marker for cholangiocytes and hepatic progenitor cells,[7] was often

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associated with aggressive biological behaviors, including microvascular invasion, capsular disruption, and lymph node metastasis, leading to earlier recurrence and poorer survival outcomes.[8–10] To be more specific, compared with the CK19-negative HCC patients, extended surgical resection combined with targeted therapy (such as the multikinase inhibitor sorafenib) and systemic treatment were strongly required to achieve a better prognosis for CK19-positive HCC patients.[11–13] Currently, the diagnosis of CK19 relies primarily on preoperative biopsy and postoperative pathological examination.[14] However, preoperative biopsy is prone to sampling errors due to tumor heterogeneity,[15] and it carries risks of complications such as intraperitoneal bleeding and needle tract metastasis. Moreover, biopsy is not recommended by clinical guidelines as a routine diagnostic procedure for HCC.[16] Therefore, there is an urgent need to develop reliable, non-invasive preoperative methods for guiding personalized stratified management and prognostic evaluation of CK19-positive HCC patients.

However, there are inconsistencies among different studies on preoperative prediction of CK19 expression in HCC using traditional imaging, radiomics, and deep learning. Medical imaging plays a pivotal role in the preoperative evaluation of HCC by providing non-invasive insights into tumor biology and pathology.[17] Numerous studies have explored the potential of traditional imaging features in predicting CK19-positive HCC. For instance, irregular tumor margins, arterial phase (AP) rim enhancement, diffusion-weighted imaging (DWI) target signs, and lower tumor-to-liver signal intensity ratios in the hepatobiliary phase (HBP) have been identified as significant predictors of CK19-positive HCC.[18–33] However, the performance of these features varies across studies, and no consensus has been reached on their predictive value. For example, while Choi et al[18] and Wang et al[22] identified irregular tumor margins and AP rim enhancement as independent predictors, Chen et al[23] found that DWI target signs were predictive, but AP rim enhancement and HBP target signs were not independent predictors for the CK19-positive HCC. Consequently, these discrepancies highlighted the need for further validation and standardization of traditional imaging features for preoperative prediction of CK19 expression in HCC.

In recent years, radiomics has emerged as a promising field, enabling the extraction of high-dimensional quantitative features from routine clinical images and their transformation into mineable data.[34,35] By leveraging machine learning algorithms, radiomics facilitates the development of models for preoperative diagnosis, prognosis prediction, and treatment response assessment.[36–38] Several studies have explored the diagnostic potential of radiomics in predicting CK19 expression in HCC,[22,28,39–44] demonstrating promising results within their respective datasets. However, due to differences and inconsistencies in variable selection, dimensionality reduction methods, and model construction algorithms, there were significant differences in diagnostic performance among different studies. For instance, Wang et al[22] reported that a fusion radiomics model combining AP and HBP images, constructed using the least absolute shrinkage and selection operator (LASSO) and logistic regression (LR), achieved optimal diagnostic performance. Similarly, Yang et al[41] found that a fusion model based on DWI and T2-weighted imaging (T_2WI), built using an artificial neural network (ANN) classifier, yielded superior results. Additionally, Hu et al[42] demonstrated that a three-phase fusion radiomics model utilizing a recursive feature elimination (RFE) algorithm and LR algorithm exhibited the highest diagnostic accuracy. Consequently, these inconsistencies underscore the challenges and ongoing debates regarding the role of radiomics in preoperative prediction of CK19 expression in HCC.

Unlike radiomics, deep learning—a machine learning technique based on deep neural networks—focuses on the automated extraction of imaging features. This approach eliminates the need for manual feature extraction and screening, enabling the direct learning of rich, high-level image features while minimizing human error and reducing labor-intensive processes.

To the best of our knowledge, no comprehensive review has systematically evaluated the roles of traditional imaging, radiomics, and deep learning in the preoperative prediction of CK19 expression in HCC. Therefore, this study aims to conduct a systematic review to compare and clarify the diagnostic value of these approaches, focusing on differences in image analysis methods, variable selection, and model construction algorithms. By synthesizing current evidence, this review seeks to provide a reference for future research in artificial intelligence-driven techniques, such as radiomics and deep learning, for predicting CK19-positive HCC, and provide key insights for the clinical stratified management and prognostic evaluation of CK19-positive HCC patients.

Materials and Methods

Search Methods

This systematic review adheres to the PRISMA guidelines, and a systematic evaluation was conducted based on these guidelines. Two researchers independently searched PubMed, EMBASE, Web of Science, and Cochrane Library databases for relevant articles published from inception to February 2025. The following search strategies were used.

(a) "Computed Tomography" OR "CT" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".
(b) "Ultrasound" OR "US" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".
(c) "Magnetic Resonance Imaging" OR "MRI" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".
(d) "Positron-Emission Tomography" OR "PET" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".
(e) "radiomics" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".
(f) "deep learning" AND "hepatocellular carcinoma" OR "HCC" AND "Cytokeratin-19" OR "CK-19".

Eligibility Criteria

Inclusion Criteria

(1) The original study that used imagine feature, radiomics or deep learning of the computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) or positron emission tomography (PET) for predicting CK-19 expression in HCC.
(2) The diagnosis of HCC was clear.
(3) Studies that provided a clear description of CK-19 expression status (positive or negative).
(4) Articles included in radiomics and deep learning studies need to explicitly include the model's diagnostic performance of the area under the curve (AUC) or sensitivity and specificity.

Exclusion Criteria

(1) Studies with controversial diagnostic criteria for HCC.
(2) Studies that lacked a clear description of CK-19 expression status.
(3) Review, meta-analysis, case report, expert comment, letter and conference abstract should be excluded.
(4) Lack of diagnostic value description for predicting HCC CK-19 expression.
(5) Non-English publications should be excluded.

Study Selection and Data Extraction

All identified studies were managed by using Zotero and EndNote X9 softwares. FW (nine years in abdominal radiological diagnosis), XLH (two years in abdominal radiological diagnosis) and CYY (five years in abdominal diagnosis) independently extracted the basic characteristics of the studies according to the predefined inclusion and exclusion criteria, and MY (27 years in abdominal radiological diagnosis) and DQX (25 years in preventive medicine) reviewed and validated the obtained data.

Duplicated studies were removed, and the full text of the articles was searched manually and by Zotero software. After screening the titles and abstracts, the full texts of potentially eligible studies were downloaded for further assessment, according to the inclusion and exclusion criteria. Data were extracted into a standard data extraction table, including author, year, country, sample size, object, imagine source (eg US, MRI, PET), research direction, study type, sample source, date group. Additionally, segmentation methods, feature screening and dimensionality reduction methods, and model construction algorithms were extracted. The area under the receiver operating characteristic curve (ROC) or C index, sensitivity, specificity and accuracy were also extracted for preliminary comparison of the diagnostic value of the models.

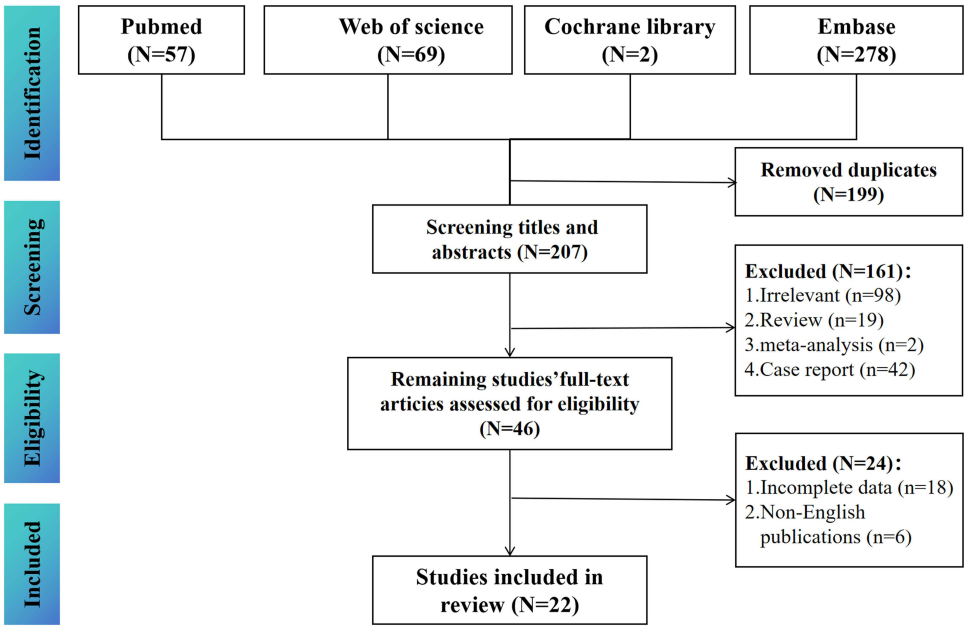

Figure 1 A flowchart of the literature screening process.

Results

Study Selection

Ultimately, a total of 22 studies were included in our systematic review,[18–33,39–44] encompassing a sample size of 3395 HCCs. The literature screening process is illustrated in Figure 1.

Study Baseline Characteristic

The basic characteristics of the included studies are summarized in Table 1. Among the 22 included studies, 59.1% (13/22) involved clinical parameters (eg, alpha-fetoprotein [AFP]), 72.7% (16/22) involved traditional imaging features,

Table 1 The Basic Characteristics of the Included Studies

Study/First Author	Year	Nation	Sample Sizes	Reference Standard	Image Source	Direction	Study Type	Data Sources	Data sets
Seo-Youn Choi[18]	2018	Korea	242	CK19	MRI	I	Retrospective	Single-center	TR
Xin-Xing Hu[19]	2019	China	201	CK19	MRI	I	Retrospective	Single-center	TR
He-Qing Wang[20]	2019	China	78	CK19	MRI	I	Retrospective	Single-center	TR
Jie Chen[21]	2020	China	115	CK19, EpCAM	MRI	I	Retrospective	Single-center	TR
Wentao Wang[22]	2020	China	227	CK19	MRI	I&R	Retrospective	Single-center	TR&TE
Yuying Chen[23]	2021	China	141	CK19	MRI	I&DL	Retrospective	Multi-center	TR, TE&V
Yixian GUO[24]	2022	China	61	CK19	MRI	I	Prospective	Single-center	TR
Jiejun Chen[25]	2023	China	73	CK19	MRI	I	Prospective	Single-center	TR
Mengtian Lu[26]	2023	China	147	CK19	MRI	I	Retrospective	Single-center	TR
Yue Zhao[27]	2023	China	158	CK19	MRI	I	Retrospective	Multi-center	TR&V
Liqing Zhang[28]	2023	China	311	CK19	MRI	I&R	Retrospective	Multi-center	TR, TE&V
Yidi Chen[29]	2023	China	334	CK19, CK7	MRI	I	Retrospective	Single-center	TR&TE
Weiyang Fang[30]	2024	China	116	CK19	MRI	I&DL	Retrospective	Multi-center	TR
Yanan Gu[31]	2025	China	159	CK19	MRI	I	Retrospective	Single-center	TR
Takayuki Kawai[32]	2017	Japan	98	CK19	PET	I	Retrospective	Single-center	TR
Jing Lv[33]	2023	China	66	CK19	PET	I	Retrospective	Single-center	TR

(*Continued*)

Table 1 (Continued).

Study/First Author	Year	Nation	Sample Sizes	Reference Standard	Image Source	Direction	Study Type	Data Sources	Data sets
Xialing Huang[39]	2019	China	100	CK19, CK7	MRI	R	Retrospective	Single-center	TR
Zhijun Geng[40]	2021	China	53	CK19	MRI	R	Retrospective	Single-center	TR
Fan Yang[41]	2021	China	257	CK19	MRI	R	Retrospective	Multi-center	TR&V
Xiaojun Hu[42]	2023	China	110	CK19	MRI	R	Retrospective	Single-center	TR
Jun-Qi Liu[43]	2023	China	134	CK19, CK7	MRI	R	Retrospective	Single-center	TR
Linlin Zhang[44]	2022	China	214	CK19	US	R	Retrospective	Multi-center	TR, TE&V

Abbreviations: I, traditional image feature; R, radiomics; DL, deep learning; TR, training set; TE, test set; V, validation set; EpCAM, epithelial cell adhesion molecule; CK19, cytokeratin 19; CK7, cytokeratin 7; MRI, magnetic resonance imaging; US, ultrasound; PET, positron emission tomography; HCC, hepatocellular carcinoma.

36.4% (8/22) utilized radiomics, 9.1% (2/22) employed deep learning, and 54.5% (12/22) involved a combined model of each of the above techniques. More than 90% of the studies (20/22) were conducted in China, with more than half published between 2022 and 2025 (12/22). Regarding image sources, 86.4% (19/22) of the studies utilized MRI, 9.1% (2/22) used PET, and 4.5% (1/22) employed US. In terms of study design, 27.3% (6/22) were multicenter studies, 36.4% (8/22) had a test set or external validation set, and only 13.6% (3/22) were prospective studies. All studies employed manual segmentation for radiomics image segmentation, with half constructing 3D models. For feature selection and dimensionality reduction, 50% (4/8) of the studies used LASSO, while the remaining studies utilized the maximum relevance minimum redundancy algorithm (MRMR), recursive feature elimination (RFE), and eXtreme Gradient Boosting (XGBoost). In terms of model construction, 62.5% (5/8) of the studies employed the logistic regression (LR) algorithm, with the rest using artificial neural networks (ANN), support vector machines (SVM), K-nearest neighbors (KNN), or XGBoost. In terms of the diagnostic performance, approximately 31.8% (7/22) of the studies demonstrated high diagnostic efficacy (AUC > 0.9) in the training set; however, due to limited validation set data, only 13.6% (3/22) of the studies conducted multicenter external validation.

Clinical Imaging Features for Predicting CK19-Positive HCC

Eighteen studies, involving 2998 hCC patients, explored the value of clinical parameters and traditional imaging features in predicting CK19-positive HCC (Supplementary Table 1). Among these, 13 studies included clinical parameters, and 16 studies incorporated traditional imaging features, and the AUC range was 0.560 to 0.917.

Clinical Parameters

Thirteen studies involving 2197 HCC patients evaluated clinical parameters. In 10 studies, AFP was identified as an independent risk factor for predicting CK19-positive HCC. One study found that an increase in the NLR value was an independent risk factor. Three studies established clinical multiparameter models. Additionally, seven studies demonstrated the diagnostic efficacy of clinical parameters in predicting CK19-positive HCC, with AUC ranges of 0.650–0.711 for AFP and 0.718–0.917 for the clinical combination models.

Traditional Imaging Features

Among the 16 traditional imaging studies involving 2527 HCC patients, 14 studies focused on MRI imaging features and two studies focused on PET. The results indicated that the overall AUC range for MRI images was 0.635–0.881, with AUC ranges of 0.644–0.881 for MRI quantitative parameters and 0.635–0.765 for MRI qualitative features. Additionally, four studies constructed combined models based on MRI imaging features, with AUC ranges of 0.713–0.881 for the combined models and 0.635–0.845 for single image features.

Radiomics for Predicting CK19-Positive HCC

Eight studies involving 1406 HCC patients explored the value of radiomics models in the preoperative prediction of CK19-positive HCC and were summarized in Supplementary Table 2. Seven studies investigated MRI radiomics, while one study explored ultrasonic radiomics. Among the seven MRI radiomics studies, six studies were based on enhanced

MRI radiomics, and one study was based on SWI radiomics. All studies were retrospective, with 37.5% (3/8) being multicenter studies with external validation sets. For feature selection and dimensionality reduction, 50% (4/8) of the studies used the LASSO, while the remaining studies employed algorithms such as MRMR, RFE, and XGBoost. Only one study compared the diagnostic performance of various classifiers, and no study combined and compared different feature selection methods and classifiers.

The performance of MRI radiomics showed AUC ranges of 0.648–0.951, 0.665–0.824, and 0.605–0.790 in the training set, test set, and external validation set, respectively. Furthermore, the AUC ranges for single-phase radiomics models were 0.700–0.905, 0.665–0.777, and 0.605–0.734 in the three cohorts. Moreover, it is worth noting that the AUC ranges for fusion radiomics models were 0.648–0.951, 0.822–0.824, and 0.726–0.790 in the three cohorts. Additionally, the AUC of the ultrasonic model were 0.949, 0.789, and 0.787 in the three cohorts, respectively. However, there was only one study.

Deep Learning for Predicting CK19-Positive HCC

Currently, there are only two studies based on deep learning models, both of which utilized Gd-EOB-DTPA-enhanced MRI images, with AUC ranges of 0.718–0.820. To be more specific, two studies of deep learning for predicting CK19-positive HCC was summarized in Supplementary Table 3.

Combined Models for Predicting CK19-Positive HCC

Twelve studies explored the value of combined models of clinical, imaging, radiomics, and deep learning for predicting CK19-positive in HCC and were summarized in Supplementary Table 4. Among these, 11 studies were based on MRI combined models, and one study was based on a US combined model. Two studies were prospective, and four studies established external validation sets. 81.8% (9/11) of the studies constructed clinical-imaging models, with a few involving clinical-radiomics models, clinical-imaging-radiomics models, or clinical-imaging-deep learning models. Importantly, the diagnostic performance of the combination models showed AUC ranges of 0.614–0.995. Furthermore, the AUC ranges for the clinical-imaging models were 0.714–0.857, 0.676–0.753, and 0.719–0.778 in the training set, test set, and validation set, respectively. Moreover, the AUC ranges for the clinical-imaging-radiomics models were 0.914–0.959, 0.846–0.855, and 0.731–0.819 in the three cohorts. The AUC ranges for the deep learning combined models were 0.648–0.842. In the clinical-ultrasonic model, the AUC values were 0.995, 0.867, and 0.862 in the three cohorts.

Main Steps of Development Model for Predicting CK19-Positive HCC

Figure 2 illustrates an end-to-end pipeline operating on different data types for building CK19-positive HCC modelling. The workflow comprises five main steps.

Step 1 – Data processing and Acquisition. Clinical data and/or radiomics data and/or images were appropriately collected and stored, integrated and pre-processed. The processed data were divided into a training and a test set. And multimodal data integration could be performed in different stages of the pipeline.

Step 2 – Tumor Segmentation and Feature Extraction. Currently, the commonly used semi-automatic segmentation tools are ITK-SNAP (https://www.itksnap.org/) or 3D Slicer (https://www.slicer.org/). The common segmentation methods included intratumoral, peritumoral, and whole tumor of 3D volume of interest (VOI). Moreover, the traditional feature extraction was based on PyRadiomics (https://pyradiomics.readthedocs.io/en/latest/) and scientific deep learning algorithms.

Step 3 – Model Training. Different techniques could be applied for the model to learn from the training set. The Deep learning approach (supervised, semi-supervised, unsupervised) was steered by the end goals and the availability of labelled data.

Step 4 – Model Analysis. The AUC, sensitivity and specificity were used to assess the model's diagnostic performance. Calibration curve, decision curve analysis (DCA) and clinical impact curves (CIC) were used to evaluate the calibration capability and clinical applicability.

Step 5 – Clinical Practice of Model. The trained model's performance was evaluated on the internal and external validation sets, which holds the "ground truth". Importantly, how the model yields the prediction was explained. The

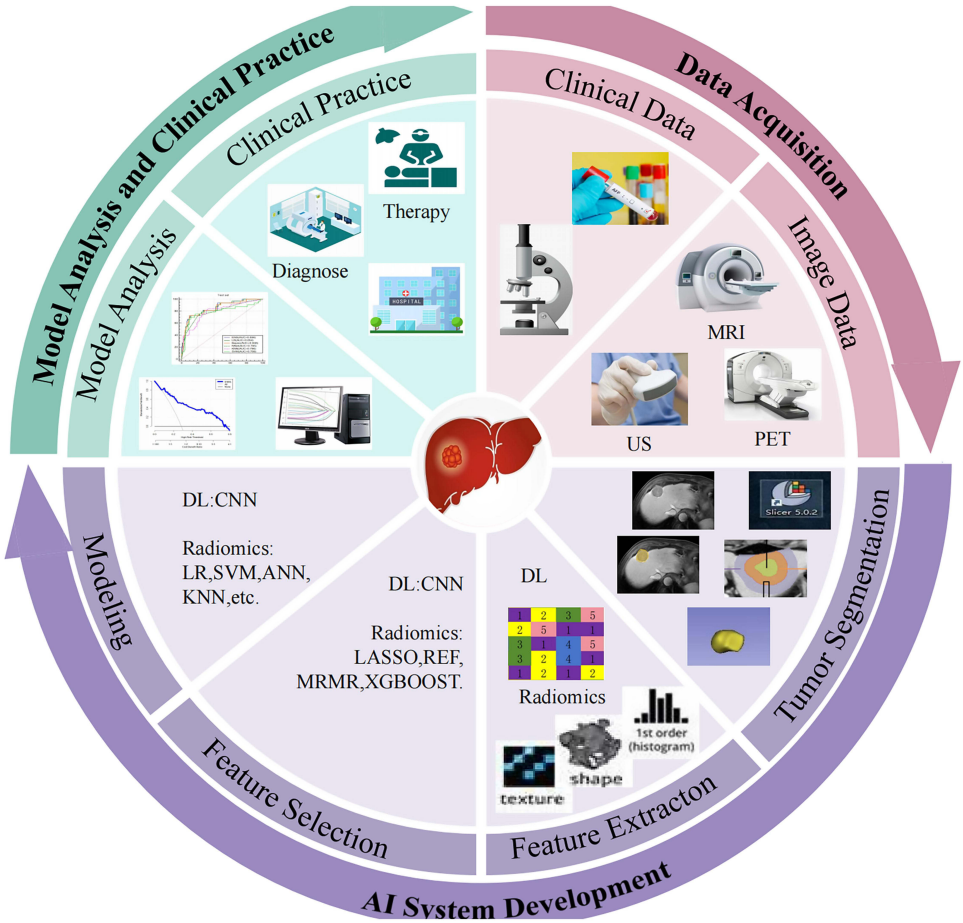

Figure 2 The workflow and main steps for development of CK19-positive HCC prediction model.

predictive power and explainability of the model were validated on external datasets to assess its robustness and generalizability on unseen data (eg, data from a different medical centre).

Discussion

CK19 has emerged as an independent prognostic biomarker associated with poor outcomes following HCC hepatectomy and liver transplantation.[5,6] Consequently, noninvasive preoperative prediction of CK19 status has become a critical focus in HCC management. The integration of advanced imaging technologies with modern artificial intelligence, particularly radiomics and deep learning, has shown great potential in enhancing the accuracy of CK19 expression prediction in HCC. However, diagnostic performance varies across traditional imaging, radiomics, and deep learning approaches due to differences in variable selection, image analysis methodologies, and model construction algorithms. Therefore, this systematic review correctly evaluates 22 original studies to objectively assess the diagnostic value of these approaches in CK19-positive HCC.

Main Findings of Clinical Risk Factors for CK19-Positive HCC

Alpha-fetoprotein (AFP) has been established as the most clinically relevant risk factor with optimal diagnostic efficacy for CK19-positive HCC. Substantial evidence indicates that AFP serves as a crucial tumor marker in HCC, demonstrating significant correlation with CK19 expression. Elevated serum AFP levels in HCC patients exhibit positive associations with poor differentiation, microvascular invasion, and tumor recurrence,[45,46] aligning with the aggressive biological behavior characteristic of CK19-positive HCC. These findings underscore the clinical utility of AFP in preoperative prediction of CK19 expression.

Main Findings of Imaging Risk Factors for CK19-Positive HCC

Analysis of 14 studies revealed that both MRI qualitative features and quantitative parameters serve as independent risk factors for preoperative prediction of CK19-positive HCC. For instance, Chen et al[25] reported that while qualitative MRI features showed no significant differentiation between CK19-positive and negative HCC, decreased mean diffusivity (MD) emerged as an independent risk factor for predicting CK19-positive HCC, with an AUC of 0.823. Hence, quantitative diffusion parameters were demonstrated to be a better tool for identifying CK19-positive HCC compared to traditional qualitative image features. Similarly, Zhao[27] observed that MRI semantic features exhibited limited accuracy and sensitivity relative to MRI quantitative parameters in predicting CK19 expression. Notably, integrated models combining multiple imaging features demonstrated enhanced predictive performance in comparison to single imaging features. For instance, Choi et al[18] reported improved specificity in combined models. Similarly, Guo et al[24] achieved an AUC of 0.881 through the integration of β, AD, and Dp parameters, demonstrating higher predictive efficacy in comparison to individual parameters.

In ^{18}F-FDG PET studies, both tumor maximum standardized uptake value (T-SUVmax) and tumor-to-non-tumor ratio (SUVmax-TNR) demonstrated statistical significance in predicting CK19-positive HCC. Jing et al[33] identified T-SUVmax as an independent predictive factor, while Takayuki et al[32] established SUV-TNR as the most sensitive indicator. Furthermore, fluorescence-activated cell sorting (FACS) analysis revealed significantly higher ^{18}F-FDG uptake in CK19-positive HCC cells compared to their CK19-negative counterparts.

Main Findings of Radiomics Models for CK19-Positive HCC

In the studies of MRI radiomics, gadoxetic acid disodium-enhanced MRI, a hepatocyte-specific contrast agent, is most commonly utilized. A comprehensive analysis revealed that fusion radiomics models incorporating multi-phase or multi-sequence consistently demonstrated superior predictive efficacy compared to single-phase or single-sequence models across various studies. For instance, Hu et al[42] demonstrated the AUCs of the AP-LR, PVP-LR, and HBP-LR radiomics models were 0.70, 0.83, and 0.89, respectively. Subsequently, the three-phase radiomics features were integrated, resulting in a fused radiomics model with an AUC of 0.92. This model exhibited a sensitivity of 0.84, an accuracy of 0.88, and a specificity of 0.89, demonstrating significantly enhanced diagnostic performance. Ultrasonomics also demonstrated promising diagnostic performance, as evidenced by Zhang et al,[28] where an XGBoost-constructed model achieved AUC values of 0.949, 0.789, and 0.787 in training, test, and external validation sets, respectively. It demonstrated that ultrasonomics was able to predict the expression of CK19 in HCC, indicating that grayscale ultrasound images have enormous potential for predicting tumor heterogeneity.

Main Findings of Deep Learning Models for CK19-Positive HCC

Currently, the difficulty of manually outlining ROIs for radiomics can be overcome by deep learning (DL) models. DL can extract image features directly from deep neural networks with higher reproducibility. And the fully automatic analysis of images can be realized after constructing the training model.[47,48] Comparative studies have demonstrated superior performance of DL models over conventional clinical parameters and imaging features in predicting CK19 expression status. For instance, Chen et al[23] reported that a DL model based on Gd-EOB-DTPA-enhanced MRI HBP images significantly outperformed both clinical (AUC 0.820 vs 0.656) and traditional MRI imaging models (AUC 0.820 vs 0.669), with a sensitivity of 0.800. These findings suggest that DL algorithms effectively utilize both intra- and peri-tumoral image information, establishing DL as a promising noninvasive approach for CK19-positive HCC prediction.

Main Findings of Combined Models for CK19-Positive HCC

Integration of preoperative AFP levels with imaging features consistently enhanced performance across traditional imaging, radiomics, and deep learning approaches. Clinical-imaging-radiomics models constructed using LR algorithms demonstrated optimal performance in predicting CK19-positive HCC, which is significantly superior to the diagnostic efficacy of the clinical-imaging model and the clinical-radiomics model. For instance, Zhang's[28] combined clinical-imaging-radiomics model (AFP $\geq$ 400 ng/mL, arterial-phase edge enhancement, fused radiomics labels) C-indexes of 0.914, 0.855, and 0.795 in the three cohorts, all demonstrated excellent diagnostic performance. It is indicated that there is

a synergy between clinical, traditional imaging, radiomics and deep learning, which not only improves the diagnostic efficacy of the combined model in clinical practice but also further enhances the generalisation capability.

Comparison of Traditional Image Feature, Radiomics and Deep Learning

Traditional imaging features (eg, MRI, CT, etc) are able to provide crucial non-invasive alternative biological and pathological information that can serve as an independent risk factor for preoperative prediction of CK19-positive HCC. But traditional imaging has some limitations such as subjectivity and limited predictive efficacy. It is mainly extracted visually by experienced radiologists, restricting its application in clinical practice. However, radiomics can extract a large number of macro-unidentifiable high-dimensional features through advanced data mining techniques.[49] In cancer research, radiomics has been demonstrated to identify tumour pathology information such as tumour grade, disease progression and gene expression in medical imaging features without the need for tumour biopsy. This allows non-invasive detection of tumour pathology at multiple time-points,[34] assisting clinicians to further improve the accuracy of diagnosing disease and predicting prognosis. Nevertheless, there are still some problems in radiomics-related research, such as insufficient biological interpretation of radiomics features and radiomics models and inconsistent methods and tools for radiomics feature screening and model construction. Thus, a consensus should be established on the normalisation of radiomics research. In addition, ROIs for radiomics are largely dependent on manual outlining by radiologists, resulting in a considerable waste of time and manpower. Fortunately, deep learning, as an advanced algorithm in machine learning, can make up for some of the shortcomings of radiomics. It can automatically identify the best features for a specific task, omitting the steps of manually extracting and screening image features. It directly extracts and learns richer deep image features while reducing human mistakes and saving manpower. For example, it can automatically identify the optimal features for a specific task, omitting the steps of manually extracting and selecting image features. Moreover, it can directly extract and learn richer deep image features while reducing human mistakes and saving manpower. However, deep learning models are very complex like a black box and it is difficult to interpret the results. And there is a lack of research based on deep learning methods in predicting the CK19 expression of HCC, so more deep learning algorithms should be added in the future to verify their feasibility.

Comparison of Different Image Sources

MR, as a non radiative, multi sequence, multi directional, and high tissue resolution imaging technique, has the ability to combine morphological and functional imaging techniques. It has become the preferred imaging technique for clinical detection, diagnosis, staging, and efficacy evaluation of liver cancer. But MRI is expensive and takes a long time to examine, so it is not suitable for some metal implant patients. US examination has the advantages of relatively low cost, repeatable observation, shorter examination time, and is not affected by the metal in the patient's body. However, US examination is more subjective and are easily limited by the operator's skills and experience. It is difficult for both US and MRI to link tumor metabolic differences with gene expression in HCC. The ^{18}F-FDG PET can reflect abnormal metabolic activity of tumors through glucose uptake,[50] and can also detect distant metastasis of hepatocellular carcinoma.[51] Its imaging features can also be used to predict the CK19 status of HCC. However, due to the relatively high cost and radiation of PET examination, it cannot be promoted as a census at present. At present, there is no research on using radiomics models based on CT images to predict the expression status of HCC CK19. However, CT images have the advantages of easy acquisition and strong reproducibility. Perhaps, CT related research can also provide some value for predicting the expression status of HCC CK19. It is speculated that combining the radiomics features of CT and MRI may provide greater reference for judging the expression status of HCC CK19.

Comparison with Previous Studies

As far as we know, this study is the first systematic review to date that evaluates the use of traditional imaging, radiomics, and deep learning for preoperative prediction of HCC CK-19 expression. Covering all routine examination images, including CT, US, MRI, and PET images. Compare and analyze the performance of clinical parameters, traditional imaging features, radiomics models, deep learning models, and combination models. A meta-analysis of including 11 studies (1278 HCCs from 1264 patients) by Qin et al[52] investigated the value of preoperative MRI in predicting CK19

expression in HCC. Similarly, another meta-analysis by Lu Zhou et al[53] investigated the value of radiomics in diagnosing CK19 expression in HCC. Unfortunately, the meta-analysis did not analyze or compare other imaging devices such as CT, US, and PET, and there is also no analysis of clinical risk factors, the value of combined models of clinical, imaging, radiomics, and deep learning for predicting CK19-positive in HCC. Moreover, some related studies were not included in the aforementioned meta-analysis. By comparison, although this review did not conduct a meta-analysis, this study is the most comprehensive in predicting CK19 positive HCC.

Strengths and Limitations

Currently, this is the first systematic review of traditional imaging, radiomics, and deep learning in predicting the expression of CK19 in HCC. This review is expected to provide reference value for future research on the prediction of CK19 expression in HCC using artificial intelligence technologies such as radiomics and deep learning. This also provides key clues for the clinical application of imaging in preoperative diagnosis of CK19-positive HCC.

However, several limitations must be taken into account. Firstly, most of the included studies were single-center retrospective studies. Furthermore, some radiomics studies did not specify whether standardization and image registration were performed during data preprocessing, which poses a certain risk of overfitting. The difference in image standardization might be the main reason for the inconsistency in the diagnostic performance of different studies. Moreover, a large number of studies lacked prospective and multi-center external validation. Therefore, more prospective, multi-center studies are needed to fully validate the generalization ability of imaging. Secondly, the interpretability of radiomics and deep learning models is a major challenge, and most of the included studies have not been conducted. Perhaps in future research, through additional model explanations such as SHAP (Shapley Additive exPlanations) and Grad-CAM (Gradient-weighted Class Activation Mapping) analysis, it can be visually demonstrated which features the model focuses on when making decisions. In addition, there are few studies on PET and US, and the sample size is not large enough. Finally, as most studies come from Asia, our results may have geographical bias. Moreover, in future studies, researchers may try the organic combination of multiple imaging radiomics, pathomics, metabolomics and genomics.

Conclusion and Future Work

Based on the above research, we found that traditional imaging, radiomics, and deep learning can indeed serve as a promising non-invasive diagnostic tool for preoperative prediction of CK19-positive in HCC. However, due to the lack of unified norms, standardization and image registration, there are differences in variable selection, research design, feature screening, dimensionality reduction, and model construction. It mainly relies on the subjective experience of researchers, leading to significant heterogeneity in various research results. Therefore, there are still some challenges in conducting and implementing imaging diagnosis of CK19 positive HCC in clinical practice. In view of this, this review proposes potential directions for future research. Firstly, summarize the independent risk factors that have been confirmed by a large number of researchers using scientific regression analysis, and then integrate them together to establish an easy to use dynamic web online tool. Thus, a standardized open-source dataset of CK19 hCC will be established for multi-center external validation. Secondly, in radiomics and deep learning design, standardized preprocessing of images and data is performed to compare the performance of various feature and dimensionality reduction methods, determine the optimal combination model, and perform interpretability analysis on the model. Moreover, in deep learning research, the differences between different deep learning algorithms, such as VGG, Resnet, Densenet, Inception, Mobilenet, Vit, etc. are compared to determine the optimal deep learning model.

Data Sharing Statement

All datasets generated for this study are included in the article.

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Disclosure

The authors report no conflicts of interest in this work.

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