

Review

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Integrating artificial intelligence into multidisciplinary evaluations of HCC: opportunities and challenges

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and a leading cause of cancer-related mortality globally. The heterogeneity of HCC complicates prognostic, management, and predictive strategies across different patient populations. Recent advancements in artificial intelligence (AI) and machine learning (ML) offer transformative opportunities to improve HCC management. This review consolidates findings from various studies regarding integrating AI in detecting, diagnosing, and treating HCC, leveraging diverse data sources such as radiological imaging, genomics, and clinical records. AI-based approaches have shown potential to improve the accuracy and efficiency of HCC screening, early detection, tumor characterization, and treatment response evaluation, surpassing traditional methods. However, the deployment of AI technologies is hindered by challenges, including data standardization, validation across multiple centers, and ethical considerations regarding AI applications. This review emphasizes the need to establish comprehensive multimodal datasets and collaborative research efforts to validate AI applications in HCC management. By addressing these challenges, the integration of AI technology has the potential to revolutionize HCC care, ultimately leading to improved patient outcomes and a more personalized approach to treatment strategies.

Keywords: Hepatocellular carcinoma (HCC), artificial intelligence (AI), machine learning (ML), validation, convolutional neural network (CNN)



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INTRODUCTION

Liver cancer was the sixth most commonly diagnosed cancer type and the third leading cause of cancer-related mortality globally in 2020, with over 900,000 new cases and over 830,000 deaths^[1]. Hepatocellular carcinoma (HCC) constitutes over 80% of liver cancer cases and is among the top three causes of cancer-related deaths in 46 countries, as well as ranking in the top five in 90 countries^[2]. Over recent decades, the incidence of HCC has shown a decline in various countries, while certain regions have experienced an increase^[3]. Notably, the Americas, Europe, and the Middle East report lower HCC rates compared to Asia and Africa^[1,4].

Most patients with HCC also have cirrhosis, which is frequently associated with known risk factors such as hepatitis B (HBV) or hepatitis C virus infections, alcohol-related liver disease (ALD), and steatotic liver disease (MASLD) related to metabolic dysfunction^[5]. Current guidelines from the European Association for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and American Association for the Study of Liver Diseases (AASLD) recommend biannual ultrasound surveillance for high-risk groups^[6]. Additionally, professional organizations widely endorse the Barcelona Clinic Liver Cancer (BCLC) staging system to guide treatment allocation^[6,7].

Over the last two decades, there have been significant advancements in HCC treatment^[8]. However, effective treatment decisions for individual patients are best made through multidisciplinary teams of healthcare professionals, including transplant hepatologists, surgeons, interventional radiologists, and medical oncologists^[6,9]. There is currently no reliable radiomic-based model to assess TIME status, predict clinical outcomes, or forecast immune checkpoint inhibitor (ICI) response in HCC, despite the emergence of several noninvasive techniques for cancer diagnosis and prognosis^[10]. The concept of intelligence, particularly in medical imaging, remains a subject of debate. In this context, artificial intelligence (AI) involves machine learning (ML) algorithms aimed at enhancing medical image analysis and identifying novel biomarkers^[11]. The emergence of advanced multi-layered neural network (NN) algorithms, including convolutional neural networks (CNNs), has given rise to deep learning (DL)^[12], a complex subset of ML that has been effectively applied to the analysis of endoscopic^[13], radiological^[14], ophthalmological^[15], and histological samples^[16]. **Figure 1** illustrates the definitions of AI, ML, and DL, demonstrating the evolution of these technologies. CNNs are a class of artificial NNs that have been a dominant method in computer vision tasks since the astonishing results were shared in the object recognition competition known as the ImageNet Large Scale Visual Recognition Competition (ILSVRC) in 2012^[17]. Random forest (RF) and eXtreme gradient boosting (XGB) are ML algorithms, and CNNs and ensemble [CNN + recurrent neural networks (RNNs)] are DL tools^[18]. Recently, AI has positioned itself as a vital tool in improving clinical practices related to HCC, especially in diagnosis, prognostication, and treatment response evaluation. This review focuses on recent advancements in AI within the context of HCC, elucidating both its advantages and the challenges it faces.

ROLE OF AI IN PREDICTION OF HCC

Numerous studies have established predictive models for early HCC detection by identifying relevant laboratory, clinical, and demographic risk factors through accepted statistical methodologies^[19]. The risk of developing HCC can vary significantly over time for each individual, making it challenging to capture these non-linear changes using traditional regression models, which often suffer from limited generalizability, moderate accuracy, and insufficient external validity^[19].

However, HCC risk prediction has recently improved due to the rapid growth in the use of electronic health record (EHR) data. It allows for the utilization of extensive, longitudinal datasets that facilitate automatic

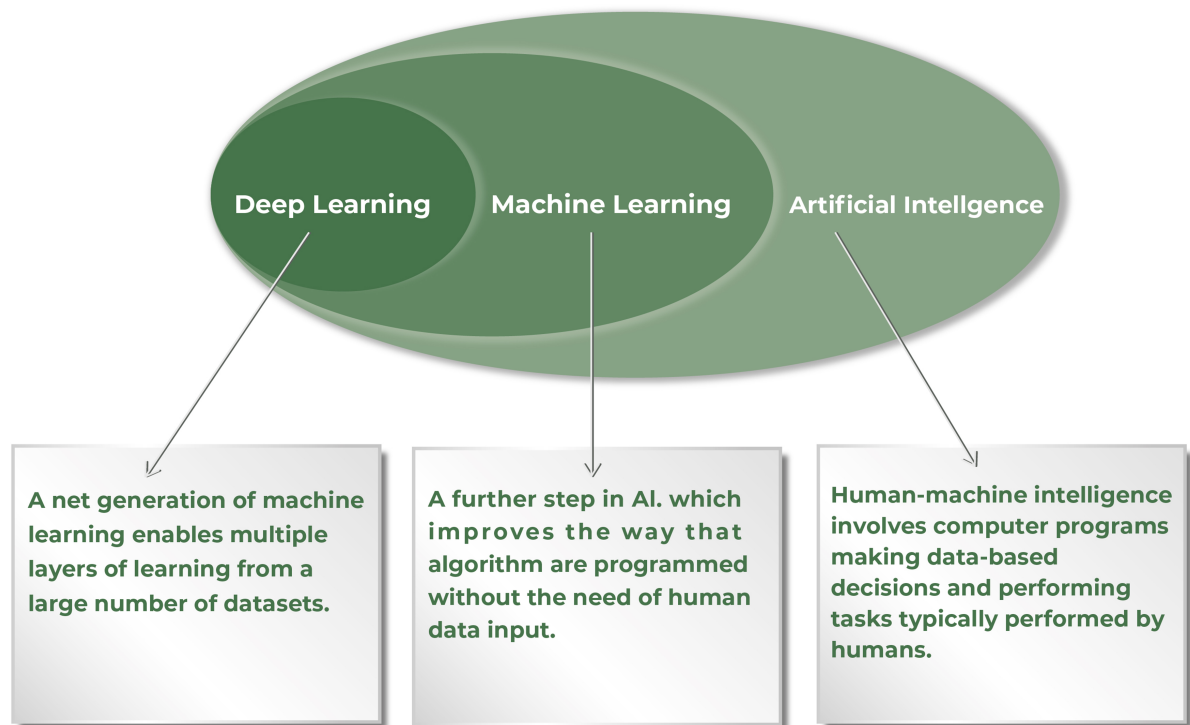


Figure 1. Definitions of AI, ML, and DL. AI: Artificial intelligence; ML: machine learning; DL: deep learning.

feature selection throughout an extended monitoring period^[20]. One model demonstrated an area under the receiver operating characteristic curve (AUROC) of 0.759 for predicting incident HCC in patients with chronic hepatitis C infection^[21]. Additionally, Ioannou *et al.* discovered that subjects falling within the highest 51% of their NN-derived HCC risk score were categorized as a target group, in which 80% were expected to develop HCC within the following three years^[21]. Nonetheless, the practical applicability of such AI-based scoring systems for estimating HCC remains uncertain, particularly due to their limited generalizability, which is affected by the training data sets' quantity and variety^[22].

APPLICATION OF AI FOR HCC SCREENING IN HIGH-RISK POPULATIONS

The conventional surveillance approach involves liver ultrasonography or alpha-fetoprotein (AFP) testing conducted every six months; however, the sensitivity of ultrasound for detecting small or early-stage tumors is limited^[23]. To enhance HCC surveillance among high-risk populations, the integration of AI tools is currently being explored and implemented^[24]. Comparing AI analysis of ultrasound images to human interpretation alone, several studies have shown that AI can enhance the detection of early-stage HCCs^[22]. It is possible to train ML algorithms to recognize subtle sonographic characteristics of malignant lesions that might be challenging to detect visually^[22]. Using both clinical data and ultrasound images, a DL model outperformed experienced radiologists for HCC screening in patients with hepatitis B cirrhosis and has achieved 97% accuracy^[24]. AI integration into ultrasound screening procedures may greatly increase the early detection of HCC and decrease missed diagnoses^[22,24].

ROLE OF AI IN DIAGNOSIS OF HCC

Radiological diagnosis

According to current clinical guidelines, patients with cirrhosis should have routine B-mode abdominal ultrasound surveillance to detect HCC^[25,26]. However, regarding the identification of focal liver lesions, ultrasound has a number of well-documented limitations, such as a significant reliance on the operator's experience, the caliber of the equipment, and the patient's body habitus, further to the fact that B-mode ultrasound's sensitivity for detecting HCC is only 46%-63%^[27]. Using 367 ultrasound pictures and the related radiological reports as a training dataset, Schmauch and associates developed a supervised DL model. This model achieved mean AUROC values of 0.93 and 0.92, respectively, demonstrating its ability to distinguish between benign and malignant liver lesions^[28]. Yang *et al.* used a large multicenter ultrasound image library from 13 hospital systems to create and externally assess a deep convolutional neural network (DCNN). The resulting model's AUROC of 0.92 for distinguishing between benign and malignant hepatic lesions fell only short of MRI accuracy (87.9%), comparable to the diagnostic accuracy of skilled radiologists (both at 76.0%), and was marginally lower than contrast-enhanced CT (84.7%)^[29]. Furthermore, Guo and associates demonstrated that the implementation of a DL system on hepatic focal lesions (HFLs) detected using contrast-enhanced ultrasonography (CEUS) improved the sensitivity, specificity, and overall accuracy in identifying HCC^[30]. Other researchers have applied AI to integrate pattern recognition classifiers within CEUS DCNN algorithms, which improved the detection of indeterminate HFLs^[31]. Current guidelines for diagnosing HFLs, which frequently exhibit indeterminate characteristics on CT or MRI, recommend either biopsy or close monitoring through serial imaging^[27]. However, this practice is deemed suboptimal, leading to unnecessary imaging, increased patient anxiety, and risks of delayed liver cancer diagnosis. AI-based approaches have been investigated to enhance risk stratification of suspicious HFLs, allowing for more precise HCC detection at early stages^[30].

Preis *et al.* merged patient demographics and clinical data from 98 patients to evaluate HFLs identified by 18F-FDG-PET/CT (fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography) examinations using a NN. Their model achieved an AUROC of 0.896 for the identification of HFLs, exceeding the accuracy of blinded radiologists^[32]. Mokrane and associates conducted a brief retrospective review on 178 patients who had diagnostic liver biopsies and cirrhosis with unclear HFLs. Using DL approaches, they developed a radiomics signature that included 13,920 CT imaging classifiers and effectively distinguished between HCC and non-HCC HFLs, achieving an AUROC of 0.70^[33].

In another retrospective analysis, Yasaka *et al.* built a three-layer CNN using CT imaging classifiers from three phases (delayed, arterial, and non-contrast-enhanced) to differentiate between cases of HCC, non-HCC liver tumors, indeterminate HFLs, hemangiomas, and cysts. Their CNN achieved a median AUROC of 0.92 and a diagnostic accuracy of 0.84^[34]. Shi and associates compared the effectiveness of a four-phase CT approach with a triple-phase contrast-enhanced CT procedure using a DL model in order to differentiate HCC from other HFLs^[35]. In a collaborative effort in 2017 known as the Liver Tumor Segmentation (LiTS) Challenge, researchers created AI algorithms proficient at autonomously segmenting HFLs utilizing a global dataset comprising 200 CT scans (130 for training and 70 for validation). The top-performing algorithm attained a Dice score of 0.96, while the most successful segmentation technique attained Dice scores between 0.67 and 0.70^[36].

Despite these advancements, a previous study that applied MRI-based classifiers to clinical data showed a sensitivity of 0.73 for identifying HCC and a specificity of only 0.56 for distinguishing HCC from metastases, liver adenomas, cysts, or hemangiomas^[37]. With a NN method developed by Hamm *et al.*, MRI HFLs can be classified with 92% sensitivity, 98% specificity, and 92% overall accuracy^[38]. Zhang *et al.*

demonstrated the feasibility of using an automated method for segmenting multi-parameter MR images in 20 patients with HCC, thereby avoiding the time-consuming manual creation of MRI-based^[39]. Recently, Zhen *et al.* used CNNs to create a novel DL system that utilized structured and unstructured clinical data, an external validation set of 201 patients from 1,210 liver tumor cases, and enhanced and unenhanced magnetic resonance imaging^[40]. A DL model was created by Wang *et al.* to improve the interpretability of AI-driven radiomics assessments^[41]. Therefore, analysis of radiological images using AI models involves several training radiomics models that have been extensively described in literature and can be summarized into five steps: image requisition and preprocessing, segmentation, feature extraction, model training, and model validation.

Histopathology

Using two large data sets of digital slides stained with H&E, Liao *et al.* applied a CNN to distinguish HCC from adjacent normal tissues; the Area under the curves (AUCs) were higher than 0.90^[42]. Kiani *et al.* developed a technique that could differentiate between cholangiocarcinoma and HCC in image patches. With an accuracy of 0.88 for the validation set, the scientists noted that the pathologist and model worked better together than they did separately. The implication is that AI technologies should be used to enhance traditional histology diagnosis rather than replace it^[43]. They also highlighted the need for caution when using AI models to automate diagnosis by demonstrating how a wrong prediction could harm the pathologists' final diagnosis^[43]. Numerous studies have shown that the histopathological characteristics of human malignancies, including HCC, can provide significant insights into the underlying molecular alterations and potential prognostic outcomes for patients^[44,45].

Furthermore, Wang *et al.* created a multitask DL NN for the automated segmentation and categorization of individual cells on digital slides. This method facilitated the extraction of spatial correlations between neoplastic cells and infiltrating lymphocytes, as well as the quantification of picture attributes linked to individual cells^[46]. Another study reported that the AUC for the DL model's capacity to predict specific genetic defects associated with recurrent HCC ranged from 0.71 to 0.89^[47]. Consequently, recent innovative research has sought to identify molecular signatures or alterations that may predict responses to systemic treatments by analyzing digital histopathological images using NNs^[48]. For example, this was employed in gastrointestinal cancers to predict microsatellite instability, a trait strongly associated with immunomodulating treatment sensitivity^[48]. A different pan-cancer study showed that NN models could foretell a variety of molecular changes or signatures, some of which are connected to how a patient would react to specific systemic treatments^[49,50]. Although no molecular feature of HCC can predict how well a patient would respond to systemic treatments, Sangro *et al.* found that patients with cancers that showed elevation of particular immune gene profiles were more likely to respond to the anti-PD1 antibody nivolumab^[51]. Haber *et al.* further supported this by showing that HCCs with upregulated interferon-gamma and antigen presentation gene sets were more sensitive to immunotherapy^[52].

Molecular biology and biomarkers

Extensive, intricate data sets comprising genetic and molecular information derived from bulk tissues and individual cells have become incredibly accessible in recent years. AI algorithms that use integrative multi-omics techniques have been developed to enhance HCC tumor detection, characterization, disease diagnosis, staging, recurrence prediction, and treatment response^[53,54]. Integrated multi-omics analyses, for instance, are increasingly being employed to evaluate individual variability in significant patterns of hepatic gene expression and to characterize intertumoral heterogeneity^[55]. Using these classified features, Zeng *et al.* developed gene expression signatures for cancer using RNA sequencing (RNA-seq)-defined samples as the foundation for their DL model^[56]. Chaudhary *et al.* employed supervised and unsupervised DL methodologies on DNA methylation data, miRNA-seq, and RNA-seq to discern two distinct HCC

subpopulations exhibiting differential survival outcomes. The C-statistic for the training dataset was 0.68, whereas the C-statistics for the five external validation sets varied from 0.67 to 0.82^[57]. The consensus driver genes associated with HCC survival have been discovered through the subsequent application of this algorithm to external HCC cohorts ($n = 1,494$)^[58]. The ability to profile thousands of single cells at once and objectively is now possible thanks to single-cell RNA-seq technologies, which have enormous potential for effective DL strategies^[59]. Single-cell RNA-seq enables the identification of distinct cellular subpopulations and their transcriptome, in addition to complex gene regulation networks^[59]. In the liver, single-cell RNA-seq has been used to clarify the cellular transcriptomes linked to cirrhosis and nonalcoholic steatohepatitis, as well as to discover new cell types and cell-cell interactions^[60,61]. This has made it easier to identify novel tumor-infiltrating lymphocyte populations in HCC, such as regulatory T cells, clonally enhanced tired CD8⁺ T cells, and tumor-associated macrophages^[62]. The noise and incompleteness of generated data, as well as the variation in data quality and sensitivity between methods, are some of the major challenges still facing the emerging field of single-cell RNA-seq^[63]. The phenomenon known as “dropout” refers to the frequent loss of low-abundance data, which makes an expressed transcript undetectable^[64]. Conversely, over-amplification of noise may unnecessarily highlight the importance of less important pathways^[65]. There are currently many DL-based techniques available to tackle challenges in single-cell RNA-seq datasets. These include node-gene interaction-based Deep Impute and SAUCIE, as well as variants of generative adversarial networks that can produce single-cell RNA-seq data and identify different cell types using NNs^[66]. It is anticipated that future advancements in DL algorithms would use methods like imputation and “denoising” via autoencoders to increase the dependability of single-cell RNA-seq datasets. By predicting the mean, standard deviation, and likelihood of gene dropout, these autoencoders make it easier to analyze data later on^[67]. Other DL-based technologies have also been developed to integrate epigenetic and proteomic assays with single-cell RNA-seq profiling, enabling more comprehensive profiling of individual cells^[68].

AI in specific HCC subtypes

AI is also crucial for analyzing how HCC behaves in patients with and without cirrhosis, differentiating between primary and metastatic liver cancers^[69], and most importantly, making the distinction between cholangiocarcinoma and HCC, which can be challenging to diagnose using current methods and have totally different prognoses and management strategies^[69].

AI TOOLS IN PROGNOSTICATION OF HCC PATIENTS

Age, PIVKA-II serum levels (prothrombin induced by vitamin K absence or antagonist-II), tumor size, and AFP are key characteristics used in prognostication. An external validation cohort demonstrated the effectiveness of a model known as MoRAL-AI, evaluated through C-indices compared to other advanced predictive models, such as the Milan criteria^[70]. A multitude of DL applications have been devised to improve the prediction of survival or recurrence in patients with HCC, utilizing CT, MRI, or histopathological images, as the morphological features of HCC significantly influence patient prognosis^[71]. Saillard *et al.* created a model using digital HCC slides to predict the survival of patients undergoing surgical resection. This model showed enhanced accuracy when scores included all pertinent clinical, biochemical, and pathological characteristics^[71]. Furthermore, Yamashita *et al.* validated the fact that AI applications can effectively anticipate outcomes using image processing of histology^[72].

Lu and Daigle applied multivariable Cox regression analysis to determine survival-related features by using three advanced CNNs - VGG-16, Inception v3, and ResNet50 - that had been pre-trained on ImageNet for feature extraction from TCGA-LIHC cohort histopathology slides^[73]. Saito *et al.* developed an integrated model that obtained an accuracy of 89% in predicting HCC recurrence post-resection by manually extracting image features from whole-slide images of a smaller cohort of 158 HCC individuals using

traditional ML techniques^[74].

Ji *et al.* assessed the likelihood of recurrence after hepatectomy by employing radiomics signatures along with various clinical and biological factors, such as albumin-bilirubin (ALBI) grade, tumor margin status, and serum AFP^[75]. Other researchers have also investigated the use of CT or MRI images to predict microvascular invasion (MVI), cytokeratin 19 expression (associated with a progenitor phenotype), or early tumor recurrence^[76,77].

Abajian *et al.* evaluated the response to transarterial chemoembolization (TACE) using logistic regression and RF models based on manually generated radiomics characteristics from MRI images^[78]. In order to determine predictive risk factors for overall survival based on AI employing CT image radiomics characteristics, Liu *et al.* used both DL and traditional ML algorithms. However, the lack of external validation and the straightforward train-validate-test split methodology may restrict the generalizability of their findings^[79]. Similarly, Zhang *et al.* used CT scans of HCC patients undergoing TACE plus sorafenib to create a DL score based on a DenseNet-121 feature extraction framework^[80]. Peng *et al.* created an algorithm based on residual CNNs, which achieved AUC values of at least 0.94 for predicting complete or partial responses to TACE therapy, validating the model externally with 562 patients and additional cohorts of 89 and 138 patients^[81]. In one study involving ultrasound, Oezdemir *et al.* predicted the response to TACE by analyzing HCC microvascular features derived from contrast-enhanced ultrasound (CEUS) images. While this study reported an accuracy rate of 86%, further analysis was warranted due to the limited sample size of 36^[82]. Table 1 provides an overview of some studies assessing AI methods based on imaging for HCC diagnosis and treatment.

AI APPROACHES REGARDING MANAGEMENT PLANS AND TREATMENT OPTIONS IN HCC PATIENTS

AI can enable healthcare systems to achieve their “quadruple aim” by democratizing and standardizing a future of connected, AI-augmented care, precision diagnostics, precision therapeutics and, ultimately, precision medicine^[88]. Despite more than a decade of significant focus, the use and adoption of AI in clinical practice remains limited, with many AI products for healthcare still at the design and development stage^[89,90]. Assigning treatments more precisely and molecularly may be possible by incorporating genetic and radiomic data. By linking MRI characteristics to gene expression patterns, a radio genomics technique was able to predict the chemotherapeutic response^[91,92]. As pharmacogenomic knowledge advances, AI is poised to significantly contribute to the integration of genetic data into predictive models for treatment plans^[91-95]. AI-guided interventions may enhance training and procedural accuracy. Comprehensive validation will be necessary to be integrated into clinical systems to guarantee safety and efficacy^[96,97]. The graphical abstract shows different AI contributions for HCC patients.

Liver transplantation

In a study by Guo *et al.*, an AI model utilizing CT imaging was employed to evaluate the HCC recurrence risk following liver transplantation^[98]. By combining radiomics signatures with other risk indicators, the study created a radiomics nomogram that showed excellent predictive performance for recurrence-free survival. In both the training and validation datasets, the model’s C-index was 0.785 and 0.789, respectively^[98]. Eight factors - target lesion diameter, number of nodules, AFP, waiting time duration, radiological response, model for end-stage liver disease (MELD), living donor liver transplantation, and center volume - were identified in another study as having a significant correlation with the risk of HCC recurrence following liver transplantation and were utilized in the development of the TRAIN-AI model^[10].

Table 1. Summary of studies assessing AI applications in imaging for prediction and treatment of HCC

Author, year	HCC cases (n)	Validation method	AI algorithm	Test outcome
Aujay <i>et al.</i> , 2022 ^[83]	22 HCC patients	No model development	Four characteristics of radiomics correlated with early reaction	AUC for all four features: 0.86-1
Wang <i>et al.</i> , 2021 ^[84]	100 patients with HCC (TRS, 60 subjects/TS, 40 subjects)	IV and Testing	CNN	Accuracy: 66.81-77.50, AUC: 0.6865-0.7969
Zhang <i>et al.</i> , 2021 ^[77]	237 patients IV set: 79 subjects TRS: 158 subjects	IV	RF	AUC for training: 0.81 Validation: AUC: 0.72
Song <i>et al.</i> , 2021 ^[85]	601 subjects with HCC (TRS 461 subjects/TS 140 subjects)	IV and testing	CNN	Training: accuracy: 0.727-0.871 AUC: 0.764-0.934 Testing results: accuracy: 0.671-0.886, AUC: 0.731-0.931
Oezdemir <i>et al.</i> , 2020 ^[82]	36 patients	IV	Distance weighted discrimination method	Accuracy: 86%
Liu <i>et al.</i> , 2020 ^[86]	130 subjects (TRS 89/VS 41)	IV	Radiomics CNN	Training: accuracy: 78%-98%, AUC: 0.82-0.98 Validation: accuracy: 80%-90%, AUC: 0.80-0.93
Peng <i>et al.</i> , 2020 ^[81]	TRS: 562 subjects Two EV sets of 89 + 138 subjects	IV and EV	Residual CNN	AUCs for external validation sets are > 0.94, and accuracy is 82.8%-85.1%
Jiang <i>et al.</i> , 2021 ^[76]	405 patients (validation set 81/TRS 324)	IV	Radiomics, clinical parameters gradient boosting CNN (4 models)	AUC for training: 0.900-0.980 Validation: accuracy: 80.2%-85.2%, AUC: 0.875-0.906
Zhang <i>et al.</i> , 2020 ^[80]	201 subjects (EV set 81/TRS 120)	EV	CNN	Training range: 0.664-0.739 External validation: 0.679-0.730
Shan <i>et al.</i> , 2019 ^[87]	156 patients (EV set 47/TRS 109)	IV and EV	Least absolute shrinkage and selection operator logistic regression	Validation: AUC: 0.61-0.79

AI: Artificial intelligence; HCC: hepatocellular carcinoma; AUC: area under the curve; TRS: training set; TS: test set; IV: internal validation; CNN: convolutional neural network; RF: random forest; EV: external validation.

Surgical resection

The existence of micrometastatic HCC emboli within the liver's arteries, or MVI, is a critical factor in predicting early recurrence and survival^[99]. Using CT images, three distinct groups created radiomics-based models that performed well in predicting preoperative MVI, particularly when paired with clinical factors^[76]. Three teams created CNN-based models for MRI that were also capable of accurately predicting MVI; one of these models used diffusion-weighted MRI^[77,84]. Lastly, a grayscale ultrasound image-based radiomics model also demonstrated encouraging outcomes for MVI prediction^[100]. Ji *et al.* integrated various preoperative clinical and laboratory factors, along with radiomics features, to evaluate the HCC recurrence risk following hepatectomy^[75]. This approach showed that both preoperative and postoperative models, which incorporated pathological findings, outperformed standard outcome prediction scores such as the BCLC scoring system^[75]. Furthermore, a patient-tailored algorithm for the optimal possible therapy allocation was created using data from a Japanese and another Italian cohort of patients who had recurrent HCC following a first surgical procedure, and this algorithm was externally validated^[101].

Transarterial therapies

TACE

The BCLC classification designates TACE as the preferred treatment for patients with intermediate-stage B HCC^[25,102]. The potential of AI techniques to forecast TACE response in patients with advanced HCC has been evaluated in several studies^[103]. Morshid *et al.* employed two CNNs to extract features from CT images, which were then processed through radiomics and utilized as inputs for a RF model. The prediction accuracy rate was 74.2% when the BCLC stage was combined with quantitative image characteristics,

compared to 62.9% when using the BCLC stage only^[103]. To predict complete or partial responses as well as stable or progressive disease following TACE, Peng *et al.* trained an algorithm using residual CNN on 562 patients and externally validated it on 89 and 138 patients with an AUC of at least 0.94^[81]. To create AI-based predictive risk factors for overall survival after TACE and to assist in predicting MVI, Liu *et al.* applied both ML and DL techniques to CT image radiomics features^[79]. Similar to this, Zhang *et al.* created a DL signature using CT scans of HCC cases receiving TACE and sorafenib^[80].

On the other hand, Abajian *et al.* combined pretherapeutic MR images from 36 patients with clinical parameters to develop prediction models^[78]. The accuracy of the derived models in estimating the response to TACE treatment was 78%^[78]. It is interesting to note that other researchers evaluated a deep NN approach based on auto-context to identify and distinguish between various types of liver tissue following TACE (viable, necrosis) on multi-parameter MR images, thereby avoiding the laborious manual creation of MRI-based features^[39]. Oezdemir *et al.* had a similar objective when they extracted handmade HCC microvascular characteristics from CEUS pictures^[82]. The last model was created and validated by Liu *et al.* utilizing CEUS cine data. The model's AUC for TACE response prediction was 0.93^[86].

Transarterial radioembolization

For patients with locally advanced HCC, one study assessed radiomics using MRI data to determine early response to 90yttrium transarterial radioembolization^[83]. They discovered four radiomics parameters that were highly sensitive early response predictors, surpassing other evaluation techniques (mRECIST, RECIST)^[83].

Thermal ablative therapies

Patients with early-stage (BCLC-0) cancer may benefit from percutaneous thermal ablation^[104,105]. Researchers evaluated the treatment response to microwave ablation by measuring the ablative margin using MR images^[105]. They created an unsupervised landmark-constrained CNN-based deformable image registration technique that effectively predicted local tumor growth over two years in order to reduce registration errors brought on by respiratory motion and thermal tissue deformation^[105]. According to a new study, a CT-based peritumoral radiomics signature is more accurate than a tumoral radiomics signature at predicting early recurrence in HCC following curative tumor excision or ablation^[87].

AI SYSTEMS FOR MONITORING TREATMENT RESPONSE FROM IMAGING AND BIOMARKERS

Following HCC therapy, decisions are guided by regular monitoring for recurrence and response to treatment; however, the sensitivity and specificity of indicators such as imaging, liver function tests, and proteins to detect progression are low^[106]. When AI is used with longitudinal patient data, the response can be evaluated sooner and with enhanced precision, as ML can integrate patterns from several laboratories, subsequent investigations, and biomarkers correlated with outcomes^[107]. A DL model predicted progression-free survival after HCC treatment with an accuracy of over 80% using time series imaging and lab data^[108]. AI can automatically classify follow-up scans as either progressive, stable, or responsive diseases, which could help guide therapy changes by identifying resistance or recurrence^[107-109].

CURRENT CHALLENGES FOR AI APPLICABILITY

Despite the fact that AI has a lot of potential for managing HCC and healthcare in general, its application in clinical settings is still relatively uncommon because of several obstacles^[110]. AI tools that aid in the diagnosis and treatment of diseases may be considered medical devices and should be subject to the applicable regulations, which makes regulating AI models challenging^[110]. Aside from the intellectual property

concerns that are brought up, the FDA and the European Commission have both published plans on AI in medical device law to address this issue, especially when changes are made after the device is placed on the market^[110,111]. Another problem with applicability is the inaccuracy of AI models; the available health datasets may be biased and have problems with data quality. These problems may result from incorrect labeling, a lack of standardization, or missing data^[110]. In AI-based models, overfitting and spectrum biases are common^[112]. CNN, which is widely utilized in models based on radiological imaging, is especially susceptible to overfitting^[112].

Moreover, established methodologies for AI-driven data analysis and interpretation and uniform strategies for addressing missing data are still needed^[113]. Since the amount of data used for training AI models greatly influences their performance, it is crucial that large datasets become available and data sharing is promoted^[113]. Sharing trial and study data with individual participants could aid in the creation of datasets large enough and detailed enough to effectively train and evaluate AI models^[113]. However, patients have some ethical and privacy concerns about using residual current device (RCD) for AI model development and dataset sharing. Since little is known about how AI models make decisions based on their input, they are frequently referred to as “black boxes”^[113]. Accordingly, AI interventions have been incorporated into the commonly used SPIRIT and CONSORT guidelines^[114]. In that regard, the concept of AI-based treatment options has been included in the widely used SPIRIT and CONSORT guidelines^[114]. Figure 2 shows the main challenges in AI applications. The development of suitable evaluation frameworks in close coordination with regulatory organizations will facilitate the responsible application of AI technologies^[115]. Comparative effectiveness trials and cost-effectiveness studies will help define the proper clinical roles for validated AI tools^[115,116].

ACCEPTANCE OF AI AMONG HEALTHCARE PROFESSIONALS IN HOSPITALS

Healthcare experts have different perspectives about AI as a recently introduced change and its implementations^[117]. The process of accepting change is not easy. Although humans are known to oppose change in favor of the familiar status quo, acceptance is a crucial component in adopting and integrating recently introduced advancements, such as AI, into daily practice to improve workflow and efficiency^[118]. On the other hand, resistance rapidly increases due to the unpredictable handling of complicated situations and the required human-like performance^[118]. Conversely, acceptability is being investigated instead of acceptance. This is typically connected to concepts like transparency or comprehensibility, which are meant to immediately result in acceptance^[119]. When making deployment decisions, this process - which is utilized at the technical, legal, and managerial levels - is the only way to connect acceptance to acceptability^[119].

AI SYSTEMS' TRANSPARENCY AND INTERPRETABILITY

Model explanation techniques serve as a global explanation of the black box model by producing a more straightforward, globally interpretable approximation model. The actual factors utilized to make decisions are roughly represented by these simplified models. A target audience will be able to grasp good approximations that consistently “mimic the behavior of the black box”^[120]. A locally interpretable approximation model can also be used to “explain the prediction of the black box in understandable terms for humans for a specific instance or record”^[120]. These techniques just need to accurately explain the prediction on a particular input instance; they are not required to be universally interpretable^[12]. Model inspection techniques can also be used as a visual or written representation to help comprehend certain aspects of the black box model or its predictions, such as how sensitive the model is to changes in the value of specific features or which model components have the greatest influence on one or more particular decisions^[120].



Figure 2. Main challenges in AI application. AI: Artificial intelligence.

CONCLUSION

Numerous AI-based models have been created to alter and enhance how we treat HCC patients. AI's usefulness as a tool for image interpretation is still developing, particularly when it comes to diagnosis and treatment response. Despite significant advancements over the last decade, HCC management still needs to be improved. Current imaging research indicates that AI may play a part in HFL localization, characterization, and early HCC detection. AI can improve the efficacy of evaluating HCC post-treatment. It can also assist in treatment decision making by providing pre-therapeutic prognostication. In order to prove that these methods are effective in clinical settings, we must first compare the model's functioning to that of traditional staging systems and then conduct customized prospective studies of AI-based interventions. Standardizing and assessing AI algorithms on extensive datasets that mirror the heterogeneity of "real life" and enhance interpretability is essential. Although AI will undoubtedly be employed in patient care in the future, only doctors will be able to comprehend and consider each patient's needs, preferences, and beliefs to determine the optimal plan of action for each patient. Investigating the practical application of AI technologies in various clinical contexts and healthcare settings requires further research. Furthermore, it is thought to be crucial to develop and assess AI-driven clinical decision support systems designed especially for the management of HCC. A crucial first step in integrating these systems into standard care will be evaluating how well they improve patient outcomes, treatment planning, and diagnostic accuracy in actual clinical settings.

DECLARATIONS

Authors' contributions

Conceptualized the idea and planned the manuscript: El-Kassas M

Wrote the initial draft: Abdelhamed W

Revised, edited, and approved the final version: Abdelhamed W, El-Kassas M

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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