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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

REVIEW

Role of three-dimensional printing and artificial intelligence in the management of hepatocellular carcinoma: Challenges and opportunities

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Abstract

Hepatocellular carcinoma (HCC) constitutes the fifth most frequent malignancy worldwide and the third most frequent cause of cancer-related deaths. Currently, treatment selection is based on the stage of the disease. Emerging fields such as three-dimensional (3D) printing, 3D bioprinting, artificial intelligence (AI), and machine learning (ML) could lead to evidence-based, individualized management of HCC. In this review, we comprehensively report the current applications of 3D printing, 3D bioprinting, and AI/ML-based models in HCC management; we outline the significant challenges to the broad use of these novel technologies in the clinical setting with the goal of identifying means to overcome them, and finally, we discuss the opportunities that arise from these applications. Notably, regarding 3D printing and bioprinting-related challenges, we elaborate on cost and cost-effectiveness, cell sourcing, cell viability, safety, accessibility, regulation, and legal and ethical concerns. Similarly, regarding AI/ML-related challenges, we elaborate on intellectual property, liability, intrinsic biases, data protection, cybersecurity, ethical challenges, and transparency. Our findings show that AI and 3D printing applications in HCC management and healthcare, in general, are steadily expanding; thus, these technologies will be integrated into the clinical setting sooner or later. Therefore, we believe that physicians need to become familiar with these technologies and prepare to engage with them constructively.

Key Words: Artificial intelligence; Machine learning; Three-dimensional printing; Bioprinting; Hepatocellular carcinoma; Liver cancer

Core Tip: The opportunities that arise from the application of three-dimensional (3D) printing and 3D bioprinting in the management of hepatocellular carcinoma (HCC) include resident education, patient education, preoperative planning, fabrication of custom-made medical tools, liver models for antitumor drug development, and patient-derived HCC models for targeted treatment selection. Similarly, the opportunities that arise from the application of artificial intelligence/machine learning in the management of HCC include targeted screening for patients with chronic hepatitis B and C infections, non-invasive early detection of HCC, increased diagnostic accuracy, frameworks for evidence-based, individualized treatment allocation, and prognostic models for the prediction of patient outcomes including overall survival, disease-free survival, and recurrence that could be used for patient and family counseling.

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes the fifth most frequent malignancy worldwide and the third most frequent cause of cancer-related deaths[1]. The factors that predispose to HCC development include chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol, metabolic liver disease, and exposure to different toxins[2]. Currently, the diagnosis of HCC is mainly based on multiphasic computed tomography (CT) and magnetic resonance imaging (MRI), whose findings are standardized based on the Liver Reporting and Data System (LI-RADS) developed by the American College of Radiology[3,4]. The cornerstone of treatment selection for HCC patients is the stage of the disease. The most prominent staging system acknowledged in United States and EU guidelines is the Barcelona Clinic Liver Cancer (BCLC) classification system[3,5]. Liver transplantation, hepatic resection, and ablative techniques are recommended for the very early and early stages of the disease, while transarterial chemoembolization (TACE) and oral sorafenib are recommended for the intermediate and advanced stages of the disease, respectively[5,6]. While the BCLC classification is generally accepted, teams report the need for an individualized approach in HCC management[7,8]. Emerging fields such as three-dimensional (3D) printing, artificial intelligence (AI), machine learning (ML), and novel biomarkers that allow the classification of HCC at a molecular level could facilitate our efforts to reach individualized treatment in HCC management.

3D printing is defined as the "translation" of a computer-generated image into a 3D solid object. It involves the use of materials, which are printed into consecutive thin layers[9]. Despite originally emerging from non-medical disciplines to serve the demand of rapid engineering of design prototypes, 3D printing has, since then, found extensive applications in medicine, including education and training, simulation, anatomical comprehension, surgical planning, surgical tools, and patient counseling[9,10]. From the combination of 3D printing and tissue engineering the field of bioprinting has emerged[11]. Bioprinting uses 3D printing-based methods to utilize biomaterials, growth factors, and cells for fabricating biomedical parts with a complex and precise internal and external structure that ultimately imitates natural tissue characteristics[12,13]. Notably, the concept of bioprinting functional organs and tissues could ameliorate the consequences of the current imbalance between the supply and demand of organs for transplantation.

AI is an umbrella term that describes any application where tasks typically associated with human intelligence are conducted by computer systems instead[14,15]. AI is a cluster of interrelated fields with a core aspect in common; they are all driven by computing power and Big Data advancements. In healthcare, the field of AI and ML, has profound applications. ML models could be described as models educated from past data to predict future data[16]. In the past decade, the healthcare industry has been established as a data-rich science, with a profound increase in the amount of generated data each year, with data becoming an omnipresent concept[17]. These extensive repositories of data could not be managed by traditional software. AI promises to analyze them and turn them into meaningful insights. The management of HCC is a fruitful field for AI application since it generates enormous amounts of data, including clinical data, histopathologic images, gene sequencing, long-non coding RNA and microRNA expression profiling, ultrasound (US) imaging, CT imaging, and MRI.

In this study, we aim to comprehensively review the applications of 3D printing and AI in HCC management, present the opportunities that arise from these applications, and finally identify the current challenges of integrating these technologies into the healthcare system to identify means to overcome them.

SEARCH STRATEGY

We conducted a literature review of the Scopus, Cochrane, and Medline databases using the following algorithms or queries: (1) [(3D printing OR 3D printing OR three-dimensional printing OR rapid prototyping OR additive manufacturing) AND (hepatocellular carcinoma OR liver cancer OR hepatic cancer OR HCC)]; and (2) [(machine learning OR artificial intelligence OR support vector machine OR neural networks OR deep learning OR computer-aided OR computer-assisted) AND (hepatocellular carcinoma OR liver cancer OR hepatic cancer OR HCC)]. The two authors (Christou CD, Tsoulfas G) reviewed the articles for eligibility independently, and any disagreements were resolved through discussion between them. Finally, the authors similarly reviewed the reference lists of eligible articles to identify further eligible articles, books, and other forms of publication. Publications written in any other language other than English were excluded. Publications of abstracts were also excluded. In addition, animal studies and studies conducted with animal cells were also excluded. The literature review was completed on March 30, 2021.

APPLICATIONS OF 3D PRINTING AND BIOPRINTING IN HCC MANAGEMENT

3D printing

In liver surgery, 3D printing could be used for educational purposes and preoperative planning. Regarding education, 3D printed models enhance physicians' knowledge base at all levels of expertise. New residents can become familiar with the complex liver anatomy, build confidence, and thus be more efficient surgical team members[18-20]. Specifically, in a study where forty-five residents were trained by: (1) Images from multi-detector CT; (2) A virtual 3D reconstruction model; and (3) A 3D printed model, residents in the latter group assessed and assigned tumor location faster and more precisely[21]. 3D printed models have been employed for educational purposes in choledochal and hepatobiliary laparoscopic operations[22,23]. Also, 3D printed models could be used in patient education to help the patients reach a higher understanding of their disease and the proposed procedure, thus enhancing communication and trust, increasing cooperation, and facilitating obtaining informed consent[20]. In liver transplantation, 3D printed models could be used from living donors to facilitate the donors' understanding of the procedure and its risks. Focusing on educational use for HCC, Streba *et al*[24] developed ten personalized 3D liver models of patients with HCC, which were given to a group of medical students and residents to interact with. The vast majority of the participants agreed that the models were easy to interact with and valuable in gaining further knowledge about specific aspects of tumor morphology[24]. However, a significant number of the participants did not find the models' weight as expected, and the majority agreed that the models' texture was different to their expectation [24].

Regarding preoperative planning, in 2013, Zein *et al*[25] in a study investigating the role of 3D printing in liver transplantation, produced six 3D printed liver models, three of living donors and three of their respective recipients. The study aimed to produce models of volumetric accuracy and anatomical precision that could unveil any unsuitable anatomy between the donors and the recipients, particularly regarding the vascular and biliary tract of the liver[25]. The authors reported a mean dimensional error for the entire model of less than 4 mm and less than 1.3 cm for the vascular diameters [25]. Similarly, other studies have used 3D printed liver models as part of the preoperative planning of major or complex hepatic resections[26-30].

Focusing on HCC preoperative planning, Xiang *et al*[31] reported the case of a patient with HCC and rare variations of the abdominal blood vessels, particularly the portal vein, for whom 3D printed models were constructed to aid the preoperative planning. Notably, the model helped the physicians decide between two different surgical plans, performing, consequently, a hepatectomy with the highest residual volume[31]. In a different study, Perica *et al*[32] developed a four-stage production process (CT data acquisition, image segmentation, image data editing, and 3D printing) to construct a scaled-down 3D printed liver model of a patient with HCC. In a questionnaire given to radiologists, the 3D models were perceived as having a minimal value in diagnostic radiology, while for surgeons, the 3D models were found to be valuable in preoperative surgical planning[32]. Kuroda *et al*[33] reported two patients with HCC for whom 3D printed models were used to delineate intrahepatic vessels to facilitate preoperative planning. In the first case, the 3D printed model was used to identify the regional Glissonian pedicle, while in the second, to reveal the diverging pattern of the dorsal and ventral branches of the intrahepatic vessels of the anterior section[33]. Regarding laparoscopic liver resections, Witowski *et al*[34] proposed in a recent study a 3D printing-based decision-making system for preoperative planning of laparoscopic hepatic resection performed with intraoperative US guidance. The protocol was implemented in nineteen patients, including four patients with HCC[34]. Information from the 3D printed models changed the initially planned surgical approach in 26% of cases[34].

Besides educational purposes and preoperative planning, 3D printed models have applications in the diagnosis and treatment of HCC. Regarding diagnosis, Damiati *et al*[35] developed a hybrid 3D printed electrochemical biosensor that could detect liver cancer using immunochemistry. 3D printed capillary

Table 1 Artificial intelligence applications in the prevention of hepatocellular carcinoma

	First author	Parameters employed	AI classifier	Sizes of the training/validation sets	Outcomes	Performance	Ref.
1	Wang J	Genetic and epigenetic biomarkers	Several	137 HCC and 431 non-HCC patients	HCC screening	0.910-0.950[1,2], 0.897-0.938[1,3], 75.0-91.5[2,4], 66.4-90.6[3,4], 1.0-88.8[2,5], 0.5-87.9[3,5]	[47]
2	Nam JY	Laboratory results, clinicopathological parameters	DNN	424/316[3] patients	HCC development in HBV cirrhosis	0.719[1,2], 0.782[1,3]	[48]
3	Xia Q	Long non-coding RNAs	Several	38 healthy samples, 45 chronic HBV patients, 46 liver cirrhosis, and 46 HCC patients	HCC development in HBV cirrhosis	71.1-89.5[3,6]	[49]
4	Chen S	HBV reverse transcriptase gene sequencing	RF, SVM, KNN	307 chronic HBV patients (202/105), 237 HCC patients (159/78)	HCC development in HBV cirrhosis	RF: 0.902-0.903[1,2], 0.903-0.943[1,3], SVM: 0.879-0.924[1,2], 0.727-0.858[1,3], KNN: 0.680-0.737[1,2], 0.734-0.747[1,3]	[50]
5	Hashem S	Laboratory results, clinicopathological parameters	Several	3099 chronic HCV patients1324 HCC patients	HCC development in HCV cirrhosis	93.2-95.6[3,6], 0.955-0.990[1,3], 86.3-91.8[3,4], 93.9-97.3[3,5]	[51]
6	Audureau E	Laboratory results, clinicopathological parameters	Several	836/668[7]	HCC development in HCV cirrhosis	0.633-0.807[1,2], 0.623-0.715[1,7]	[52]
7	Ioannou GN	Clinical/laboratory data extracted directly from electronic health records	DNN	48151 patients with HCV-related cirrhosis (training:test = 9:1)	HCC development in HCV cirrhosis	0.759-0.806[1,3]	[53]
8	Singal AG	Laboratory results, clinicopathological parameters	RF	442/1050[7]	HCC development in cirrhosis	0.71[1,2], 0.64[1,7]	[54]

[1]Area under the receiver operating curve or c-index.

[2]Training.

[3]Internal validation.

[4]Sensitivity (%).

[5]Specificity (%).

[6]Accuracy (%).

[7]External validation/testing.

CCA: Cholangiocarcinoma; CNN: Convolutional neural network; CT: Computed tomography; DNN: Deep neural network; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; KNN: K-nearest neighbor; RF: Random forest; SVM: Support vector machine; WSI: Whole-slide image.

channels were used to efficiently guide and constrain the sample containing cells of a human HCC cell line (HepG2)[35]. This study demonstrates how the combination of traditionally fabricated parts and 3D printed parts could enable the use of optimal materials for the model's various components. In a different study, Joo *et al*[36] used enhanced MRI scans of twenty patients with multiple focal liver lesions, including patients with HCC. Twenty transparent 3D printed liver models were constructed with color-coded anatomical structures that included 98 focal liver lesions[36]. The authors evaluated these models' role in increasing the detection rate of focal liver lesions by pathologists and radiologists [36]. Notably, during the gross pathologic examination, the per focal lesion detection rate significantly improved when utilizing the 3D model[36]. A sub-analysis revealed that these models' positive impact was more remarkable for smaller focal liver lesions[36]. Following hepatic resection, Trout *et al*[37] have proposed a 3D printing-based protocol for anatomically oriented, uniform sectioning of resected hepatic specimens to facilitate accurate tumor mapping and a precise radiological-pathological correlation. The protocol was applied in thirteen patients (including HCC patients), achieving a close correlation between imaging and gross pathology[37]. Regarding non-operative treatment, Han *et al*[38] invest-igated the therapeutic value of 3D printing template-assisted radioactive ^{125}I seed implantation for the treatment of malignant liver tumors. In their study, fifteen patients (six with HCC) received the 3D-assisted treatment, and twenty-five (ten with HCC) did not[38]. Notably, the 3D printed template-assisted treatment significantly shortened the operation time and optimized the radiation-dose distri-bution[38]. TACE is the prominent treatment choice for intermediate HCC. 3D visualization and 3D printed models could be used to clearly display the tumor's blood supply and facilitate the super-selective embolization of all the feeding arteries[39,40].

Bioprinting
3D bioprinted scaffolds have several advantages compared with other tissue engineering methods, such

as greater accuracy, fast reconstruction, and good integration[41]. Unlike traditional scaffold fabrication methods, 3D bioprinting skips the cell-seeding process since, during the fabrication process, the cells are dispersed at the desired locations[42]. Xie *et al*[43] expanding their department's work on mice, recently published a study where they constructed patient-specific 3D bioprinted HCC models. Primary HCC cells were isolated from six operated patients' liver specimens and were mixed with gelatin and sodium alginate to form the bio-ink[43]. The models were printed in a layer-by-layer manner and demonstrated cell viability at days 7 and 28 after the printing of 95% and 80%, respectively[43]. In addition, the resulting models retained compared to their patient-derived HCC: (1) The expression pattern of the biomarker a-fetoprotein; (2) A high level of concordance of the single nucleotide variants; and (3) The mutational pattern of key HCC gene mutations[43]. Finally, the models were used to assess the efficacy of four commonly used targeted drugs for HCC to reveal correlations between drug sensitivity and key HCC mutations[43]. Therefore, 3D bioprinted liver models could be used to develop patient-specific drugs for HCC patients. 3D bioprinted organoids could revolutionize the current drug development process by substituting early phases of clinical trials.

Other studies have used human HCC cell lines to construct 3D bioprinted liver models. Zhang *et al* [44] combined alginate with cellulose nanofibril hydrogels and colloidal lignin particles to fabricate precise nano-composite scaffolds. Consequently, HepG2 cells were used to conduct cell viability tests that demonstrated the proliferation of the cells at the scaffold's surface and within the scaffolding structure and a steady increase in density of HepG2 cells from day one up to day five in all the scaffolds. In a recent study, Sun *et al*[45] using HepG2 cells, formed a bio-ink to develop 3D bioprinted models to evaluate the effect of antitumor drugs. During the *in vitro* culture, the models preserved cell viability above 90%[45]. Compared to 2D-HepG2 cultures, the 3D bioprinted models retained higher expression levels of HCC-related biomarkers and mRNAs over the culture time[45]. Finally, the 2D and 3D models were compared based on their response to antitumor drugs[45]. The 3D models demonstrated higher drug resistance due to their higher expression of drug-resistance-related genes[45]. In another study, Ma *et al*[46] constructed a 3D bioprinted liver decellularized extracellular matrix model that was consequently used to compare the *in vitro* cultures of the HepG2 cell line in 3D-based scaffolds with conventional tissue-engineered liver constructs. The 3D bioprinted model demonstrated improved cell viability and gene expression. In addition, the authors investigated how the stiffness of the scaffolds impacted the growth of the cultures[46]. Their results support that stiff scaffolds, which better represent a cirrhotic liver, demonstrate a slower growth rate of HepG2 cells and lower cell viability[46]. In a different study, a different human HCC cell line (SMMC-7721) was used to develop 3D bioprinted models with and without microfluidic chips to pharmacodynamically test the effect of a chimeric IgG1 anti-CD147 monoclonal antibody[44]. During cell culture, the models maintained a cell survival rate of 96.21%[44]. The 3D models with microfluidic chips were found to be less vulnerable to the increase in drug dosage[44]. The authors concluded that these results are more consistent with animal studies due to the model's microenvironment and biomimetic drug transport efficiency[44].

APPLICATIONS OF AI IN HCC MANAGEMENT

AI/ML-based tools have been developed to prevent, diagnose, and treat HCC and for HCC prognosis. Tables 1-4 summarize the studies we identified that developed AI/ML-based models for the management of HCC.

Prevention

Regarding HCC screening, genetic and epigenetic biomarkers have been utilized to develop several AI/ML-based models aiming for a urine test to screen for HCC[47]. AI/ML tools based on data automatically mined from patients' hospital records could be used to stratify the risk of HCC development and for HCC early detection in patients with chronic HBV and HCV infection. These models could be used to reliably identify patients who are more susceptible to developing HCC and who would greatly benefit from a sustained virological response (SVR). Specifically for HBV cirrhosis, a recent study developed a deep neural network (DNN) employing only non-invasive parameters to predict the development of HCC[48]. Other studies have employed data from gene sequencing and expression patterns. Specifically, in a study, data from circulating long non-coding RNAs were employed to develop an AI/ML model that isolated distinctive signatures of expression of 171 different long non-coding RNAs that distinguish the healthy control group from patients with chronic HBV, liver cirrhosis, and HCC[49]. Another study developed four different models that used data from reverse transcriptase gene sequencing to predict the patients with HBV who would develop HCC[50]. A random forest (RF)-based model outperformed the rest with an area under the receiver operating curve (AUROC) in the independent validation of 0.96[50].

Regarding the development of HCC in HCV cirrhosis, several AI/ML-based tools were developed in a new study using routinely collected data to predict HCC development in patients with HCV infection [51]. In the same spirit, in a recent study, several AI/ML-based models were developed that employ laboratory results and clinicopathological parameters that predict HCC development in patients with

HCV before and after achieving SVR[52]. A recent study investigated whether a DNN could surpass the performance of conventional logistic regression (LR) models in predicting HCC development in patients with chronic HCV infection[53]. Notably, the DNN had outperformed the LR model with longitudinal inputs[53]. Finally, a study utilizing laboratory results and clinicopathological parameters developed a RF model to predict HCC development in a cohort of patients with Child-Pugh A and B cirrhosis, which was externally validated in a cohort of patients with HCV cirrhosis[54].

Diagnostics

Following prevention, several studies have focused on developing AI/ML-based models for the early detection of HCC. In a study, clinicopathological and laboratory data were employed to develop several AI/ML-based models for the early detection of HCC[55]. Notably, a gradient boosting-based model achieved the highest predictive value[55]. In another study, data from the expression profiles of microRNAs of patients with HCC were analyzed, and the five microRNAs with the optimal predictive value were used to develop several AI/ML models for the non-invasive, early diagnosis of HCC[56]. In a different study focusing on early detection, data from gene expression profiles were used to develop a support vector machine (SVM) model that outstandingly identifies patients with HCC[57]. In a recent study, data from somatic copy number abbreviations acquired from circulating tumor DNA was employed to develop an RF-based model for the early detection of HCC in a cohort of patients with chronic HBV infection[58]. Finally, several AI/ML-based models were developed in a different study using data from biomarkers (long non-coding RNA and microRNA expression) to identify patients with HCC[59].

Several studies have developed AI/ML-based models to distinguish between the various focal liver lesions (having a non-binary output). US imaging has been used to develop a convolutional neural network (CNN) that initially distinguishes focal lesions between benign and malignant and then classifies them into five different types of focal liver lesions (angioma, HCC, metastasis, cyst, focal nodular hyperplasia)[60]. In a recent, multi-center study, US imaging along with clinical parameters were used to develop a CNN model that classifies 16 different focal liver lesions[61]. Interestingly, the model's accuracy was comparable with that of contrast-enhanced CT but inferior to MRI[61]. B-mode has been used in a study to develop a neural network ensemble-based computer-aided diagnosis (CAD) model that classifies normal liver and four different focal liver lesions, including HCC[62]. Similarly, a different artificial neural network (ANN)-based CAD model was developed using contrast-enhanced US microflow imaging that differentiates HCC from metastasis and hemangioma, and classifies the HCC lesions into well, moderately, and poorly differentiated[63].

In a recent study, a CNN was developed, employing images from multi-phasing CT scans, to classify focal liver lesions as benign or malignant automatically and then distinguish between HCC, intrahepatic cholangiocarcinoma (CCA), metastasis, cyst, hemangioma, and focal nodular hyperplasia[64]. A different CNN was developed using dynamic contrast-enhanced CT scans to classify focal liver lesions into five different lesion types[65]. In another study, different multiphasic CT scan models (four-phase, three-phase without portal-venous phase, and three-phase without pre-contrast phase) were used to develop multiphase convolutional dense networks to distinguish between HCCs and other focal liver lesions[66]. Similarly, multiphasic CT imaging was used to develop a CNN to classify five different focal liver lesions[67]. An ANN was developed in a different study employing 33 features (24 radiological and nine clinical) to differentiate among several lesions (hemangioma, metastasis, intrahepatic peripheral CCA, and HCC)[68]. Regarding the radiologists' performance, when the ANN's output was taken into account, their performance improved significantly (AUROC = 0.888-0.934)[68]. In a different study, data from CT and MRI radiomics were used to develop an RF model to differentiate between HCC, hepatic epithelioid angiomyolipoma, and focal nodular hyperplasia[69]. Multi-phasic MRI imaging was used in another study to develop a CNN that classifies six different focal liver lesions and distinguishes between the LI-RADS classes 1 and 5[70,71]. MRI was employed in a different study to develop an extremely randomized trees classifier-based model that differentiates five different focal liver lesion types[72]. Finally, in a recent study, MRI images were employed to develop a CNN that could distinguish seven different focal liver lesions (cyst, hemangioma, focal nodular hyperplasia, benign nodules, HCC, metastasis, and other than HCC primary malignancy)[73].

Histopathologic data could also be employed to develop AI/ML models for HCC diagnosis. A recent study developed a CNN employing hematoxylin and eosin-stained whole slide imaging (WSI) to distinguish patients with HCC and CCA[74]. The model was used prospectively to evaluate the impact of AI-assisted diagnosis on diagnostic accuracy[74]. Interestingly, the model did not benefit the mean diagnostic accuracy of all 11 pathologists in a statistically significant manner[74]. However, it managed to significantly increase diagnostic accuracy in a sub-cohort of 9 pathologists with well-defined expertise [74]. In a similar study, the CNN employing hematoxylin and eosin-stained WSI was used to distinguish between healthy liver from HCC, classify HCC based on the grade of differentiation, and predict the presence of HCC-related gene mutations[75]. Another study used multiphoton microscopy images to develop a CNN that classifies images as well, moderately and poorly differentiated HCC[76]. A different study developed two CNNs, a model to detect HCC lesions in hematoxylin and eosin-stained WSI, and another model to predict recurrence following surgical resection[77]. In a different study, supervised and unsupervised ML methods were combined to develop a convolutional autoencoder

Table 2 Artificial intelligence application in hepatocellular carcinoma diagnosis

	First author	Diagnostic modality	AI classifier	Sizes of the training/validation sets	Outcomes	Performance	Ref.
1	Sato M	Laboratory results, clinicopathological parameters	Several	1582 patients	HCC early detection	81.65-87.36[1,2], 0.870-0.940[3,2]	[55]
2	Zhao X	MicroRNA expression profiles	Several	392 patients	HCC early detection	RF: 0.982[3], SVM: 0.970[3], DT: 0.831[3]	[56]
3	Zhang ZM	Gene expression profiles	SVM	1333/336 HCC samples	HCC early detection	100[1,2], 100[2,4], 100[2,5], 0.9597[3,6], 91.93[4,6], 100[5,6]	[57]
4	Tao K	Circulating tumor DNA	RF-based	209/76[6]/99[6]	HCC early detection	0.874-0.933[1,2], 0.812-0.920[3,6]	[58]
5	Li G	MicroRNA and long non-coding RNA expression profiles	SVM, RF, DT	361 patients	HCC early detection	RF: 0.992[1,2], 95.6[2,4], 100[2,5]; SVM: 0.992[2,3], 97.2[2,4], 98.0[2,5]; DT: 0.927[2,3], 98.3[2,4], 92.0[2,5]	[59]
6	Schmauch B	US imaging	CNN	109 images with focal liver lesions	Classification of benign from malignant focal liver lesions; classification among five focal liver lesions	0.916-0.942[2,3]; 0.886-0.954[2,3]	[60]
7	Yang Q	US imaging, clinical parameters	CNN	16500/4125[2]/3718[6] US images	Classification among 16 different focal liver lesions	0.859-0.966[3,7], 0.765-0.925[2,3], 0.750-0.924[3,6]	[61]
8	Virmani J	B-mode US imaging	NNE	108 images	Classification among normal liver and four focal liver lesions	95.0[1,2]	[62]
9	Shiraishi J	Microflow imaging of contrast-enhanced US	ANN	103 focal liver lesions	Classification among HCC, metastasis, and hemangioma; histopathological grade	86.9-93.8[1,2]; 50.0-79.2[1,2]	[63]
10	Zhou J	Multiphasic CT scans	CNN	616 liver lesions	Classification of benign and malignant lesions. Classification of 6 types of focal liver lesions	76.6-88.4[2,4,5], 82.5[1,2], 0.921[2,3], 46.4-93.1[2,4], 91.9-98.6[2,5], 73.4[1,2], 0.766-0.983[2,3]	[64]
11	Yasaka K	Contrast-enhancedCT imaging	CNN	460/100[6] patients	Classification among five types of focal liver lesions	95[1,7], 84[1,6], 33-100[4,6]	[65]
12	Shi W	Multiphasic CT scans	MP-CDN	449 focal lesions. Training:validation ratio = 8:2	Classification between HCC and non-HCC focal lesions	0.811-0.856[1,2], 0.862-0.925[2,3], 0.744-0.923[2,4], 0.725-0.941[2,5]	[66]
13	Todoroki Y	Multiphasic CT imaging	CNN	89 patients	Classification among five focal liver lesions	79-100[2,4]	[67]
14	Matake K	Clinicopathological parameters, CT imaging	ANN	120 patients	Classification among four types of focal liver lesions	0.961[2,3]	[68]
15	Liang W	CT and MRI radiomics	RF	170 CT scans; 137 MRI scans	Classification of three types of focal liver lesions	CT model: 0.996[3,7], 0.879[2,3]. MRI model: 0.999[3,7], 0.925[2,3]	[69]
16	Hamm CA	Multiphasic MRI imaging	CNN	434/60 lesions	Classification among six types of focal liver lesions; identify HCC; classification of LI-RADS	92[2,4], 98[2,5]; 0.992[2,3]; 94[4,6], 97[2,5]	[70,71]
17	Jansen MJA	MRI imaging	Extremely randomized trees classifier	95 patients	Classification among five different focal liver lesions	85-92[1,2], 62-93[2,4], 56-93[2,5]	[72]
18	Zhen SH	MRI scans	CNN	1210/201[6]	Classification among seven different focal liver lesions	0.841-0.987[3,6], 40.5-100[4,6], 86.4-99.5[5,6]	[73]
19	Kiani A	Hematoxylin and eosin-stained WSI	CNN	20[7]/26[2]/80[6] WSIs	Classification of HCC and CCA	88.5[1,2], 84.2[1,6]	[74]

20	Chen M	Hematoxylin and eosin-stained WSI	CNN	491 WSIs (402 HCC, 89 normal liver tissue)	Classification of HCC and normal liver tissue; histopathological grade	0.960[1,2], 0.961[2,3]; 89.6[1,2]	[75]
21	Lin H	Multiphoton microscopy	CNN	217 images	Histopathological grade	0.812-0.941[1,2], 0.891-0.917[2,3]	[76]
22	Yamashita R	Hematoxylin and eosin-stained WSI	CNN	28/4[2]/30[6] WSIs	HCC lesion detection	0.952[2,3], 0.956[3,6]	[77]
23	Roy M	Hematoxylin and eosin-stained WSI	CAE	50 WSIs	Segmentation of viable tumors	91-95[1,2]	[78]
24	Giordano S	PESI-MS	SVM, RF	117 HCCs, 50 CCA, 151 non-tumor group	Classification of HCC, CCA, and non-tumor groups	SVM: 95.1-98.5[1,6]; RF: 94-94.9[1,6]	[79]
25	Guo LH	Contrast-enhanced ultrasound imaging	MKL	93 lesions	Classification of benign from malignant focal liver lesions	90.41[1,2], 93.56[2,4], 86.89[2,5]	[80]
26	Bharti P	US imaging	Several	189 images	Classify among normal liver, chronic liver disease, cirrhosis, and HCC	96.6[1,2], 95.5-96.9[2,4], 98.0-99.8[2,5]	[81]
27	Brehar R	US imaging	CNN	268 patients	Classification between HCC and cirrhotic parenchyma	84.84-91[1,2], 0.91-0.95[2,3], 86.79-94.37[2,4], 82.95%-88.38%[2,5]	[82]
28	Mao B	Ultrasound radiomics	Several	114 patients	Classify primary from metastatic liver cancer	0.729-0.808[1,2], 0.737-0.793[2,3], 0.775-0.868[2,4], 0.667-0.880[2,5]	[83]
29	Almotairi S	CT imaging	CNN	20 CT scans	Tumor segmentation	98.8[1,7]	[84]
30	Budak Ü	CT imaging	CNN	20 CT scans	Tumor segmentation	Volumetric overlap error: 9.05%[2]	[85]
31	Nayak A	Multiphasic CT imaging	SVM	40 patients	Classification between HCC and cirrhotic parenchyma	80-86.9[1,2], 0.93[2,3]	[86]
32	Krishan A	CT scans	Several	1638 CT scans	Identification of liver lesions; classification between HCC and metastasis	98.39-100[1,2], 0.99-1.00[2,3]; 76.38-87.01[1,2], 0.77-0.99[2,3]	[87]
33	Chen WF	CT scans	SED	300 CT scans	Tumor segmentation	0.992[1], 0.95[2,3]	[88]
34	Khan AA	CT scans	Several	179 patients	Classification between HCC and hemangioma	96.6-98.3[1,6], 0.94-0.97[3,6], 94.23-97.03[5,6]	[88]
35	Mokrane FZ	Multiphasic CT radiomics	Several	106/36[2]/36[6]	Classification between HCC and non-HCC lesions	0.81[3,7], 0.81[4,7], 0.72[5,7], 0.72[2,3], 0.66[3,6]	[90]
36	Mao B	CT radiomics, clinical parameters	Gradient boosting	237/60[6] patients	Histopathological grade	61.18-97.05[1,6], 0.7071-0.9964[3,7], 60.67-95.51[4,7], 51.35-80.41[5,7], 48.33-70.00[1,6], 0.6128-0.8014[3,6], 43.48-65.22[4,6], 37.84-81.08[5,6]	[91]
37	Preis O	PET/CT imaging	ANN	98 patients	Classification between benign and malignant liver lesions	0.896-0.905[2,3]	[92]
38	Trivizakis E	Diffusion-weighted MRI	CNN, SVM	134 patients	Classification between primary liver cancer and metastasis	85.5[1,7], 83[1,2], 0.80[2,3], 93[2,4], 67[2,5]	[93]
39	Oestmann PM	Multiphasic MRI scans	CNN	150/10[2]	Classification of HCC and non-HCC lesions	94.1[1,7], 87.3[1,2], 0.912[2,3]. For HCC: 92.7[2,4], 82.0[2,5]. For non-HCC: 82.0[2,4], 92.7[2,5]	[94]
40	Bousabarah K	MRI scans	CNN, RF	174 patients/ 231 lesions	HCC detection	0.66-0.75[2,4], 0.55-0.73[4,6]	[95]
41	Kim J	MRI scans	CNN	455[2,7]/54[6]	HCC detection	0.97[2,3], 94[2,4], 99[2,5], 0.90[3,6], 87[4,6], 93[5,6]	[96]
42	Jian W	Non-enhanced MRI	CNN	75/40[6] HCCs	HCC detection	65.00-77.00[1,6], 0.70-0.82[3]	[97]

		scans				[,6], 64.55-78.18[4,6], 65.56-75.56[5,6]	
43	Wu Y	Multiphasic MRI imaging	CNN	89 HCCs	Classification between LI-RADS 3 and LI-RADS 4/5	0.767-0.900[1,6], 0.90-0.95[3], [,6], 0.76-1.00[4,6], 0.633-0.807[5,6]	[98]

[1]Accuracy (%).

[2]Internal validation.

[3]Area under the receiver operating curve or c-index.

[4]Sensitivity (%).

[5]Specificity (%).

[6]External validation/testing.

[7]Training.

ANN: Artificial neural network; CAE: Convolutional autoencoder; CCA: Cholangiocarcinoma; CNN: Convolutional neural network; CT: Computed tomography; DNN: Deep neural network; DT: Decision tree; HCC: Hepatocellular carcinoma; LI-RADS: Liver imaging reporting and data system; MKL: Multiple kernel learning; MP-CDN: Multiphase convolutional dense networks; MRI: Magnetic resonance imaging; NGS: Next-generation sequencing; NNE: Neural network ensemble; PESI-MS: Probe electrospray ionization mass spectrometry; PET: Positron emission tomography; RF: Random forest; SED: Successive Encoder-Decoder; SVM: Support vector machine; US: Ultrasound; WSI: Whole-slide image.

(CAE) that employs WSI images for the automated segmentation of viable tumors[78]. Finally, in a recent study, probe electrospray ionization mass spectrometry was used on specimens from patients with HCC and mass-forming CCA to develop two AI/ML-based models to distinguish these primary liver malignancies[79].

US imaging has also been used to develop models that aid in HCC diagnosis. A multiple-kernel learning-based model was developed using contrast-enhanced US imaging to distinguish between benign and malignant liver tumors[80]. Several AI/ML-based models were developed using US images to classify normal liver, chronic liver disease, cirrhosis, and HCC[81]. A recently developed CNN model managed to outperform other conventional ML methods in distinguishing between HCC and surrounding cirrhotic parenchyma in US images[82]. Data from US radiomics were employed in a recent study to develop multiple AI/ML-based models to distinguish between primary liver cancer and metastasis[83]. Interestingly a conventional LR model outperformed all the AI models[83].

CT imaging could be used to develop AI/ML-based models that aid HCC diagnosis. In a study, segmentation of the liver tumors was achieved using a CNN developed using CT scans[84]. Similarly, two encoder-decoder CNNs were developed in another study to cascade segments of both the liver and lesions in CT images[85]. An SVM-based CAD model was developed in another study from multiphasic CT scans to distinguish between cirrhosis and HCC[86]. CT scans were employed in a different study to develop several AI/ML-based models to distinguish between HCC and secondary liver lesions[87]. In a different study, a Successive Encoder-Decoder model was developed to automatically interpret liver tumor segmentation through CT images for patients with HCC[88]. Another study developed several AI/ML-based models employing CT images to distinguish between HCC and hemangioma[89]. Multiphasic CT radiomics were used in a different study to develop several AI/ML-based models to distinguish between HCC and non-HCC liver lesions[90]. CT radiomics and clinical data were combined in another study to develop gradient boosting-based models to classify the histopathological grade of HCC[91]. Finally, positron emission tomographic (PET)/CT imaging was employed in a different study to distinguish between benign and malignant liver lesions[92].

Regarding MRI imaging, diffusion-weighted MRI was used to develop a CNN-based model to distinguish between primary liver cancer and metastasis[93]. A recent retrospective study developed a CNN that employed multiphasic MRI scans of patients with HCC. The model was trained with a combination of images that met the LI-RADS criteria (typical) and with images that did not (atypical) and aimed to distinguish between HCC and non-HCC lesions[94]. In a recent study, MRI scans were employed to develop a CNN-based model for the automatic detection and delineation of HCC[95]. In a multicenter, retrospective study, a CNN was developed that employed MRI scans to identify HCC lesions[96]. Notably, the model surpassed less experienced radiologists' performance in the diagnosis of small HCC lesions[96]. In just 3.4 s, the model was able to assess 100 photos[96]. Non-enhanced MRI scans have been used to develop a CNN that identifies HCC lesions[97]. Finally, in a recent study, multiphasic MRI scans were used to develop a CNN that distinguishes between LI-RADS 3 and LI-RADS 4/5 HCC[98].

Treatment

Data generated from clinicopathological parameters, serum biomarkers, gene and RNA profiles, and imaging could be combined to train AI/ML-based models to develop frameworks for the evidence-based, individualized treatment of patients with HCC, including targeted radiotherapy, chemotherapy, and immunotherapy. In an international, multi-institutional study, a CART model was developed that aimed to create a framework for treatment allocation beyond the BCLC staging system[99]. Based on predicting parameters of overall survival, the model generated six distinct prognostic groups of patients

Table 3 Artificial intelligence application in hepatocellular carcinoma treatment

	First author	Parameters employed	AI classifier	Sizes of the training/validation sets	Outcomes	Performance	Ref.
1	Tsilimigras DI	Laboratory results, clinicopathological parameters, tumor characteristics	CART	976	Determining factors of prognostic weight preoperatively within the BCLC staging system	-	[99]
2	Liu F	Contrast-enhanced US radiomics, laboratory tests, and clinicopathological parameters	CNN	293/126 patients	2-yr progression-free survival of patients following RFA or surgical resection	$0.754\text{-}0.784^{1,2}$, $0.726\text{-}0.741^{1,3}$	[100]
3	Choi GH	Demographics, laboratory results, tumor characteristics, clinicopathological parameters	RF	813/208 patients	Treatment recommendation. Survival prediction	$76.6\text{-}88.4^{3,4}$, $53.0\text{-}82.3^{3,5}$, $69.3\text{-}95.8^{3,6}$. $0.676\text{-}0.959^{1,3}$	[101]
4	Chen M	Hematoxylin and eosin-stained WSI	CNN	377 (training:validation = 3:1)/ 67^{7} patients	Mutation prediction	$89.6\text{-}94.0^{3,4}$, $0.720\text{-}0.805^{1,7}$	[75]
5	Liao H	Hematoxylin and eosin-stained WSI	CNN	$309/65^{3}/78^{7}$	Mutation prediction	$0.519\text{-}0.903^{1,3}$, $0.605\text{-}0.797^{1,7}$	[103]
6	Gu J	Multiphasic CT scans	CNN	14 patients	Mutation prediction	$67.7\text{-}77.3^{3,4}$	[104]
7	Chen G	Laboratory results	LIME	$1007/1085^{7}$ patients	MVI	$0.918^{1,2}$, $0.832^{1,3}$, $0.905^{1,7}$	[105]
8	Zhang Y	MRI scans	CNN	158/79 patients	MVI	$0.81^{1,2}$, $69^{2,5}$, $79^{2,6}$, $0.72^{1,3}$, $55^{3,5}$, $81^{3,6}$	[106]
9	Wang G	DWI	CNN	$60/40^{2}$ HCCs	MVI	$66.81\text{-}77.50^{2,3,4}$, $68.65\text{-}79.69^{1,2,3}$, $56.56\text{-}76.47^{2,3,5}$, $64.35\text{-}79.13^{2,3,6}$	[107]
10	Liu QP	CT radiomics	RF, SVM	494 patients	MVI	$0.84^{1,2}$, $0.79^{1,3}$	[108]
11	Jiang YQ	CT radiomics, clinical/laboratory parameters	Gradient boosting, CNN	405 patients [220 MVI (+)/185 MVI (-)]	MVI	Gradient boosting: $0.900\text{-}0.952^{1,2}$, $0.873\text{-}0.887^{1,3}$. CNN: $80.2\text{-}85.2^{3,4}$, $0.900\text{-}0.980^{1,2}$, $0.875\text{-}0.906^{1,3}$, $0.659\text{-}0.932^{3,5}$, $0.757\text{-}0.973^{3,6}$	[109]
12	Cucchetti A	Laboratory results, clinicopathological parameters, radiological data, histological data	ANN	$175/75^{3}$	MVI. Histopathological grade	$0.92^{1,2}$, $91.0^{3,4}$. $0.94^{1,2}$, $93.3^{3,4}$	[110]
13	Mai RY	Laboratory results, clinicopathological parameters, liver volumetry	ANN	265/88 patients	Posthemihepatectomy liver failure	$0.880^{1,2}$, $0.876^{1,3}$	[111]
14	Shi HY	Laboratory results, clinicopathological parameters, surgery parameters	ANN	22926 hepatectomies	In-hospital mortality following surgical resection	$97.28^{3,4}$, $0.84^{1,3}$, $95.93^{4,7}$, $0.82^{1,7}$, $78.40^{5,7}$, $94.57^{6,7}$	[112]
15	Liu D	US radiomics	CNN	89/41 patients	Classify full/partial response from stable disease/ progression in patients treated with TACE	$78\text{-}98^{2,4}$, $0.82\text{-}0.98^{1,2}$, $78.6\text{-}98.2^{2,5}$, $74.2\text{-}96.7^{2,6}$, $0.80\text{-}0.90^{3,4}$, $0.80\text{-}0.93^{1,3}$, $82.1\text{-}89.3^{3,5}$, $73.3\text{-}92.3^{3,6}$	[113]
16	Morshid A	Multiphasic CT scans, BCLC stage	CNN, RF	105 patients	Classify TACE-susceptible from TACE-refractory HCC	$62.9\text{-}74.2^{3,4}$, $0.733^{1,3}$	[114]
17	Peng J	CT imaging	CNN	$562/89^{7}/138^{7}$	Classification of complete response, partial response, stable disease, and progressive disease following TACE	$84.0^{2,4}$, $0.95\text{-}0.97^{1,2}$, $82.8\text{-}85.1^{4,7}$, $0.94\text{-}0.98^{1,7}$	[115]
18	Abajian A	MRI imaging, clinical data	RF	36 patients	Classification of responders and non-responders following TACE	$66^{3,4}$, $62.5^{3,5}$, $67.9^{3,6}$	[116]

19	Zhu Y	FF-OCT	SVM	285 en face images	Cancerous hepatic cell identification	0.9378[1,7]	[117]
20	Liang Z	X-ray imaging	CNN	2943/1542[3]/1442[7] images	Localization of fiducial markers	98.6[4,7]	[118]
21	Liu Y	CT/MRI imaging	Dense-cycle GAN	21 patients	Identify differences between synthetic CT and CT, and compare their dose distribution	-	[119]
22	Taebi A	Computational fluid dynamics	CNN	3804 samples	Yttrium-90 distribution in radioembolization	Mean square error: 0.54 ± 0.14	[120]
23	Tong Z	DNA profiling	SVM	43 patients	Drug target prediction	0.8827-0.8849[1,3], 53-65.44[3,5], 88.76-93.63[3,6]	[121]

[1]Area under the receiver operating curve or c-index.

[2]Training.

[3]Internal validation.

[4]Accuracy (%).

[5]Sensitivity (%).

[6]Specificity (%).

[7]External validation/ testing.

ANN: Artificial neural network; BCLC: Barcelona clinic liver cancer; CART: Classification and regression tree; CNN: Convolutional neural network; CT: Computed tomography; DWI: Diffusion-weighted imaging; FF-OCT: Full-field optical coherence tomography; GAN: Generative adversarial network; HCC: Hepatocellular carcinoma; LIME: Local Interpretable Model-agnostic Explanations; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; RF: Random forest; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; US: Ultrasound; WSI: Whole-slide image.

that could be utilized as a framework for treatment allocation[99]. Interestingly, the radiologic tumor burden score that is not part of the BCLC staging system was identified as the optimal predictor of outcomes for staged B patients[99]. In a different study, data from contrast-enhanced US radiomics, laboratory tests, clinicopathological parameters, and course of treatment were employed to develop a CNN that could be used to select between radiofrequency ablation (RFA) and surgical resection[100]. Specifically, in their cohort of patients, the authors concluded that if 17.3% of the RFA group and 27.3% of the operated patients swapped treatment, they would benefit from a 12% and 15% increase in the probability of 2-year progression-free survival, respectively[100]. Finally, an AI/ML-based clinical decision support system for patients with HCC was developed using several RF-based classifiers in a large cohort of patients[101]. The model was designed to offer treatment recommendations and predict the overall survival of patients with HCC. The conclusions of these studies could aid the re-evaluation of our current HCC management practices to an individualized, multimodal strategy[102].

Models that reliably predict the presence of particular mutations in HCC patients could be used as a tool for the early administration of appropriate treatment such as immunotherapy or multi-targeted tyrosine kinase inhibitors. In a recent study, a CNN was developed that employs images from hematoxylin and eosin-stained WSIs to predict the presence of specific mutations in patients with HCC [75]. A similar study developed a CNN that classifies HCC and then predicts the presence of specific mutations[103]. Finally, a CNN model was developed in a recent study based on multiphasic CT scans as a non-invasive prediction tool of particular mutations[104].

Several studies designed AI/ML-based models that preoperatively predict microvascular invasion (MVI) as reliable treatment allocation tools. In a recent study, an AI/ML-based model was developed as a non-invasive tool, employing only presurgical blood parameters to predict MVI in patients with HCC [105]. In a different study, a CNN was developed employing presurgical MRI scans in an effort to predict MVI[106]. Finally, another study developed a CNN, employing diffusion-weighted imaging from patients with HCC to predict MVI preoperatively[107]. Another study used CT radiomics data to develop an RF/SVM-based model that predicts MVI in patients with HCC[108]. Similarly, in a recent study, CT radiomics were combined with laboratory and clinical data to develop two models, a gradient boosting-based and a CNN-based, to predict MVI preoperatively[109]. Finally, an ANN was developed in a different study to predict MVI that notably outperformed a conventional LR model[110].

Several studies have investigated how AI/ML-based models could determine the response to treatment in patients with HCC. Focusing on hepatic resection, an ANN model was developed that predicts liver failure following hemihepatectomy, which could be used as the basis of a triage tool for intensive care[111]. Similarly, in a different study, an ANN model was developed to predict in-hospital mortality risk following hepatic resection[112]. The model outperformed conventional LR models. Interestingly, the study reported that the best single predictor of in-hospital mortality was the surgeon volume[112].

Besides hepatic resection, several studies have developed models to predict the response to TACE treatment. Particularly for response prediction in patients treated with TACE, US radiomics were used in a study to develop a CNN to classify patients with HCC who fully/partially respond to TACE from

patients who either remain stable or progress[113]. In a different study, multiphasic CT scans and the BCLC staging system were used to develop an AI/ML-based model to classify TACE-susceptible from TACE-refractory HCC[114]. CT imaging was also used in a different study to develop a CNN as a multi-class tool for complete response, partial response, stable disease, and progressive disease following TACE[115]. Another study used MRI to classify patients with HCC as responders and non-responders to TACE treatment[116].

In a recent study, images from full-field optical coherence tomography were used to develop an SVM model that recognizes hepatic cancerous cells as a tool to detect tumor boundaries for resection intraoperatively[117]. A different study used X-ray imaging to develop a CNN model as the basis of a framework that automatically detects fiducial markers, performs 3D position reconstruction, and evaluates intrafraction motion during stereotactic body radiation therapy for liver malignancies[118]. In another study, MRI and CT imaging were employed to develop a novel dense-cycle-generative adversarial network for the generation of synthetic CT scans that could be used to optimize treatment planning for liver stereotactic body therapy[119]. Data from computational fluid dynamics were used in another study to develop a CNN to estimate Yttrium-90 distribution during radioembolization[120]. Finally, in a study conducted in silico, an SVM model was used to identify potential drug targets for HCC treatment[121].

Prognosis

Several studies have focused on constructing AI/ML-based tools able to consistently predict patient outcomes (progression and disease-free survival, overall survival, and recurrence) in the context of HCC prognosis. Several ML algorithms were combined in a study to develop an AI model that employs data from DNA methylation and RNA and microRNA profiling to predict overall survival for patients with HCC[122]. Several AI/ML-based models were developed in a recent study, employing non-invasive parameters to predict survival in operated patients with HCC[123]. Another study developed a 20-features gradient-boosting survival classifier to stratify an HCC-related death risk into three distinct categories[124]. In a different nationwide study, an ANN model was developed to predict the 5-year survival of patients with HCC following hepatic resection[125]. Interestingly, the independent predictor with the strongest correlation to survival was the surgical volume of the surgeon[125]. The performance of the ANN was found to be superior to the LR's performance[125]. Likewise, in another study, the ANN model surpassed the performance of the LR model in predicting overall survival following surgical resection[126]. The ANN model was also able to identify more independent predictors of survival than the LR model[126]. In a prospective study, the ANN model's ability to predict the survival of operated patients with early staged HCC was compared with the performance of traditionally used staging systems; the ANN model outperformed all staging systems in all training and validation cohorts [127]. Data from RNA sequencing were employed, in a recent study, to develop an RF-based model that uses five biomarkers to predict patients' overall survival[128]. Finally, hematoxylin and eosin-stained WSIs were used in a different study to develop a CNN that predicts survival following resection[129].

Focusing on the survival of non-operated patients, in a recent study, an ANN was developed that employed albumin/bilirubin grade and Child-Turcotte-Pugh (CTP) grade to predict survival in patients with HCC who received as initial treatment a monotherapy with TACE[130]. In a similar study, albumin/bilirubin grade and CTP grade were used to develop an ANN to predict survival in patients who received as initial treatment the combination of TACE and sorafenib[131]. A different study, also considering patients treated with TACE and sorafenib, used CT scans instead to develop a CNN to predict survival[132]. Another study focusing on patients treated with TACE developed a DNN model to predict overall survival in patients with HCC[108]. Finally, an ANN-based model was developed employing routinely collected data to predict 1-year survival in HCC patients treated with TACE[133].

Different models have focused on predicting progression-free or disease-free survival. Such models could be used to design personalized follow-up schedules. A recent study employed routine laboratory results and clinicopathological data to develop an ANN that predicts progression-free survival and overall survival[134]. Notably, the model outperformed traditionally used classification systems. Similarly, in a retrospective study, data from operated patients were employed to develop an ANN, a decision tree, and an LR model for predicting the 1-, 3-, and 5-year disease-free survival[135]. The ANN model managed to outperform the other two models[135]. A recent study developed an RF model based on 34 epigenetic features of DNA methylation profiles to predict the 6-mo progression-free survival [136]. In another recent study, an RF model was developed employing routinely collected data to predict the disease-free survival of patients with HCC following surgical resection[137]. Finally, an ANN was developed in a different study to predict disease-free survival for patients with HCC treated with CT-guided RFA[138].

Besides survival, AI/ML-based tools have been used for predicting HCC recurrence following curative treatment. Specifically, several AI/ML-based tools were developed in a study, including an RF model, an SVM model, and an Artificial Plant Optimization model for predicting HCC recurrence following RFA[139]. In a recent study, a gradient boosting algorithm-based model was developed employing clinical parameters to predict patients' recurrence following surgical resection, as well as survival[140]. In a different study, gene sequencing data were used to develop AI/ML models to predict recurrence in patients with HCC following surgery[141]. Early recurrence has been the focus of a study

that combined different AI/ML classifiers to develop a model that predicts recurrence in operated patients with HCC[142]. In a different, multi-center study, several ML algorithms were used to develop AI/ML-based models to predict HCC recurrence following hepatic resection[143]. Notably, the models that employed CT radiomics outperformed the models that used clinical data[143]. A Bayesian network-based model was developed in another study aiming to classify patients according to the recurrence time (early, late) following hepatic resection[144]. Finally, a study focusing on patients with cancer recurrence following surgical resection developed an SVM model employing several clinical indicators to predict the time and location of HCC recurrence[145].

Hematoxylin and eosin-stained WSIs have been used to develop AI/ML-based models to predict recurrence in operated patients with HCC. A CNN was constructed in a recent study utilizing histopathologic images for predicting recurrence in HCC operated patients[77]. The model outperformed the conventional TNM classification system[77]. A different study developed an RF-based model to predict overall survival that notably performed comparably with the TNM classification system[146]. Finally, a study focusing on recurrence timing used hematoxylin and eosin-stained WSIs to develop an SVM model that predicts the early recurrence of HCC patients following resection[147].

Other studies have focused on predicting the recurrence of patients treated with ablative techniques. An SVM model was developed in a study using clinical data to predict recurrence in a group of patients with HCC who were treated with RFA[148]. In another study, an unsupervised landmark-constrained CNN-based deformable image registration technique was used to predict local tumor progression in patients with HCC treated with microwave ablation based on the ablative margin[149].

Focusing on liver transplantation, a team developed a DNN model that employs routinely collected data to predict HCC recurrence in patients receiving a living donor graft[150]. Notably, the model significantly outperformed all the conventionally used staging systems. An ANN model was developed employing data from genotyping for microsatellite mutations/deletion to predict post-transplant HCC recurrence[151]. Clinical data and CT radiomics were employed in a different study to develop a least absolute shrinkage and selection operator model to predict recurrence-free survival in transplanted HCC patients[152]. Several other studies have developed AI/ML-based tools for predicting liver graft survival following liver transplantation[153,154]. Specifically, in a multi-center study, an ANN model was developed for predicting the 3-mo graft loss and survival[154]. Notably, the model surpassed all the currently used scores, including the Donor Risk Index, the Model for End-stage Liver Disease, the Balance of Risk, and the Survival Outcome Following Liver Transplantation; their performance was found to be significantly lower with an AUROC range of 0.42-0.67[154]. An ANN and an RF model were developed in another study for predicting 30-d and 3-mo graft failure following transplantation[153]. Notably, these models outperformed the Model for End-stage Liver Disease and the Donor Risk Index [153]. Finally, in a study using data from the United Network for Organ Sharing, a DNN was developed to predict 90-d post-liver transplant survival[155]. Similarly, this model outperformed traditionally used classification systems[155].

CURRENT CHALLENGES

Challenges of 3D printing application in HCC management

Even though the cost related to 3D printing is steadily decreasing, it still remains the main challenge for the widespread application of 3D printing in healthcare facilities. The 3D printing-related cost consists of hardware, software, printing materials, and labor. Among the seven families of additive manufacturing as per the American Society for Testing And Materials International, those more frequently applied in the medical field are selective laser sintering, stereo lithography, laminated object manufacturing, fused deposition modeling, and inkjet printing[156]. Each of these 3D printing types has its characteristics regarding accuracy/precision, availability, printing speed, required materials, color capabilities, transparency, sterilization capability, biocompatibility, and cost[9]. The characteristics of each printing type define its cost. For example, while selective laser sintering printers are highly productive, with the ability to print complex structures with quick printing times, their cost is significantly higher, and their availability is limited compared with fused deposition modeling printers, which, although cheap, have low processing times and low accuracy[41,157].

The cost is also dependent on the size and complexity of the targeted structure. The liver is a large organ with complex anatomy; thus, the cost and time required to construct a 3D liver model are higher than other organs. A valid solution is scaling down the 3D models[26]. Studies usually overlook the costs associated with labor; however, they should be considered, particularly when evaluating cost-effectiveness ratios. Focusing on cost-effectiveness, it is essential to highlight that the additional cost/resources related to 3D printing should be evaluated in conjunction with the magnitude of the improvement in medical outcome. Unfortunately, based on a systematic review, only 7% of published studies related to 3D printing mention cost-effectiveness, and no study has evaluated cost-effectiveness in a quantitative manner[158].

In addition to cost, other challenges/limitations include the reliance of the 3D printed models' accuracy on the underlying 2D imaging data that makes them prone to imaging errors[41]. Therefore, high-accuracy imaging is a precondition of highly accurate 3D models. In addition, due to long printing times, 3D printing currently has no application in the emergency clinical setting, such as the rupture of an HCC tumor[18]. However, printing times are becoming shorter, with reports of 3D models printed within a single day. Another challenge is the limited availability of software for 3D printing in medicine and the absence of many visual aids and manipulation tools for postprocessing[9]. The shortcoming of limited software further deteriorates by the notable absence of specialists in 3D printing software and technologies in most healthcare facilities[34].

Bioprinting of 3D models faces its own challenges and limitations. High-resolution is particularly important in 3D bioprinting to facilitate proper interactions of the biomaterials, which are crucial for tissue development[42]. Particularly for the liver, a metabolically active tissue, the appropriate microenvironment should be created inside the 3D bioprinted model to retain its hepatocyte-like phenotype. The development of large-scale liver tissues with hepatocytes retaining viability and longer-term functionality following sequential differentiation is clearly a challenge[42]. Even though 3D bioprinted liver models are reported as superior to other tissue engineering methods in that regard, scaling up these models to a substantial volume to provide a significant *in vivo* liver function could prove to be a herculean task. The evolution and increased complexity of 3D bioprinting could reach a saturation point where the functional outcomes do not improve further[159]. Current 3D bioprinted tissues lack any vascular network and rely on diffusion for nutrient supply. The integration of a vascular network, particularly for the liver, which has a complex vascular network, could prove particularly challenging. Potential solutions include embedding angiogenic growth factors into the bio-ink, direct bioprinting of the vasculature, and sacrificial templates for fabricating perfusable microchannel networks[160-163]. Another challenge of 3D bioprinting is cell availability. Expanding the current applications of 3D bioprinted models would require reliable sources of human cell lines[164]. Current sources include specimens from hepatic resections and transplantations and fetal liver cells from abortion; these cell sources are all in limited supply, which could restrain research progress[164]. A potential solution could be the use of liver stem cells, immortalized hepatic cell lines, and minimally invasive cell harvesting[42, 165,166]. Compared to stem cells, adult hepatocytes propagate poorly and lose functionality more rapidly *in vitro*[167]. In summary, further research is required to investigate how these 3D bioprinted models behave *in vivo* in terms of viability, stability, retaining functionality, compatibility, and degradation rate of the polymer hydrogels before they could be implanted in a clinical setting. Finally, the logistics of healthcare facilities maintaining production chains for patient-specific tissues, given the biomaterials' environmental and time sensitivity, could prove impractical, creating the need for a centralized logistical model[159].

3D printing and mainly 3D bioprinting face regulatory, legal, and ethical challenges. 3D printable products should comply with existing control and manufacturing standards for medical devices and products. The Food and Drug Administration (FDA) published in 2017 the Technical Considerations for Additive Manufactured Medical Devices, which provides a framework for manufacturers and guidance regarding the main aspects of 3D printing, including hardware, software, validation procedures, and quality control[168]. As acknowledged by the guidelines, there is significant variability among the different types of additive manufacturing to the extent that each printing methodology requires different regulatory standards[168]. A genuine concern for 3D bioprintable organoids is safety. Even though "absolute" safety could not be guaranteed in any biomedical novelty, a comprehensive evaluation of benefits and risks is required to decide if it reaches a safety threshold[169]. However, bioprintable organoids significantly differ from novel drugs and could not be assessed by our current drug development evaluation processes. Due to the interindividual differences among patients, extrapolating on the safety of patient-tailored organoids is challenging. However, accumulated results and experience over a series of cases could serve as a basis to gain regulatory approval. The precautionary principle dictates that in applying novel technologies where our knowledge is limited and the uncertainty is high, a higher and stricter standard should be adopted compared with known biomedical products[170]. Another concern is obtaining genuine informed consent. For the patients donating, before consenting, the patients' autonomy and control over their biological condition should be established, and concerns regarding anonymity, data protection, future claims on their donated tissues, as well as these tissues intended short-term and long-term use should be addressed[169,171]. Similarly, before giving informed consent, transplanted patients' concerns regarding safety, short-term and long-term risks, the uncertainty involved, and potential unknown consequences should be addressed. Unlike with clinical trials where a drug is tested, the patient's withdrawal is impeded due to the irreversible nature of transplantation[172].

3D bioprinting faces several ethical challenges. An ethical advantage of 3D bioprinted organoids could be used in pre-clinical drug testing and significantly minimize the need for animals in the laboratory. An ethical concern is the potential use of donated biomaterials in the development of embryonic cell lines. Donors should be informed of this perspective before providing informed consent [169]. Generally, there are ethical concerns about whether all possible cell sources, including embryonic cell lines, pluripotent stem cells, or even animal cells, could be used for bioink fabrication[173]. Another ethically challenging point is the accessibility of 3D bioprinted materials. Since healthcare facilities may

be unable to be reimbursed for 3D bioprinted-related treatments, there is a justifiable concern that these treatments will be accessible only to those who can afford them[169]. To add to this concern, when 3D bioprinting is advanced enough to produce organs that are superior in certain aspects compared to human organs, 3D bioprinting technologies could be used for eugenic purposes[172]. With steadily decreasing prices and steadily increasing availability, there is an actual concern about unregulated 3D bioprinting research that could be used for malignant purposes, including bioterrorism[171]. Evidently, there is a need for a robust regulatory framework to address all these emerging concerns, which could be obtained by elaborating on our existing ethical and regulatory standards as encompassed in the Helsinki Declaration, the Oviedo Convention system, and UN's Declaration on Human Rights. However, the real challenge will not be to develop these regulatory frameworks but to ensure that they evolve in conjunction with the evolution of these technologies and are not outpaced by them.

Challenges of AI application in HCC management

The application of AI in HCC management, and healthcare in general, faces a plethora of challenges that include intellectual property concerns, liability, intrinsic bias, data protection and cybersecurity threats, ethical concerns, and lack of transparency. Regarding intellectual property, the first step for regulation is determining whether an AI/ML-based model should be classified as a medical device, a service, or a product. Assessing the intended usage of the developed model is critical. Tools designed to assist in diagnosing and treating diseases could be considered as medical devices and therefore should adhere to the respective regulations[174]. FDA receives an increasingly high number of submissions with regard to the marketing of AI/ML-based software and has recently published the Artificial Intelligence/ Machine Learning (AI/ML) – Based Software as a Medical Device (SaMD) Action Plan[175-177]. The action plan regards AI/ML-based software classified as medical devices and sets five pillars to facilitate the innovation and advancement of AI/ML-based software[175]. A different point of concern is the significant divergence of the original licensed product years after the approval[178]. These concerns regard both intellectual property and the safety of the tool. What are the rights of developers over their evolving products? Are the original product and the deviated model two entirely different products? While the original product is clearly protected under copyright law, it is unclear if the healthcare facility could have intellectual property demands over the final product that now encompasses data generated in the clinical setting[179]. In addition, there are concerns over the product's safety as it evolves and significantly deviates from its initial form. A regulatory framework should be established for AI/ML-based software that monitors these models throughout their lifecycle[180]. When it comes to regulation, rigid regulation suppresses and strangles innovation and creativity, while little regulation could have devastating and unintended ramifications. Therefore, the real challenge is finding the optimal balance between the two.

A different concern regarding AI/ML-based software applications relates to liability issues. As AI/ML-based models advance, they will eventually perform specific tasks better than physicians. How could physicians then legally justify their decision to ignore the recommendations presented by AI models? Could the AI models' recommendations become legally binding in the foreseeable future? And most importantly, who is liable, when during the AI-assisted management of a patient, an injury occurs? Currently, no legal precedent exists concerning the liability of AI-assisted case management, where a patient injury occurred[181]. In a recent legal analysis, the authors insightfully analyzed the various scenarios regarding liability when an AI model is involved in medical care. Based on the analysis, current law protects from liability when physicians follow the standard treatment care[181]. Unfortunately, that could lead to AI/ML-based tools having an affirmative role in patient management and not actually contributing to a higher level of care.

Lack of accuracy due to intrinsic biases is another primary concern when AI/ML-based models are applied. A primary reason for the lack of accuracy is the unavailability of volume, high-quality, high-variety, standardized datasets for the model's training. A secondary reason is that weaknesses in the datasets, such as incorrectly labeled cases and discrepancies in the data collection process, are inadvertently integrated into the model, limiting its accuracy[182]. Two significant types of bias encountered in AI/ML-based models are overfitting and spectrum bias. During the training of the models' algorithms, overfitting occurs when a model is customized for the training data (with outstanding evaluation metrics in the training data) but performs significantly poorer in the validation set[183]. CNNs, which, as demonstrated, are extensively used in the models for the management of HCC, are particularly vulnerable to overfitting[184]. On the other hand, spectrum bias occurs when the training dataset consists of samples not representative of the target population; thus, the model's performance is significantly reduced when applied in the intended clinical setting[183]. Another limitation of actual accuracy is the in silico nature of most studies, which should lower the expectations of similar performances when these models are applied in actual clinical settings.

Several measures could be taken to alleviate the impact of biases on AI/ML models' accuracy. First, a consistent way of reporting performance should be used to allow benchmarking and the drawing of meaningful comparisons among the plethora of studies[185]. Second, standardized data collection methods and evaluation systems for bias detection should be established to avoid the impact of low-quality data on the models' accuracy[186,187]. Finally, when these models are implemented in actual clinical settings, an approach similar to the clinical trial phases should be adopted[188].

Integrating AI into the clinical setting requires an entirely digital tracking of healthcare records. That could pose a significant concern and a justified reason to resist AI integration into healthcare since it will expand the amount of sensitive data to massive disclosures[189]. An example of such disclosure was the transfer of healthcare data from 1.6 million patients in the United Kingdom, which was ruled illegal [190]. Due to the nature of the data that it generates, the healthcare industry is particularly attractive as a potential target for cyberattacks. Steps have been taken under the Health Insurance Portability and Accountability Act to shield healthcare facilities from potential breaches of sensitive data[191]. However, AI introduces new dangers and vulnerabilities beyond traditional cybersecurity concerns. Cyberattacks could target AI models and introduce malignant data into the algorithms to manipulate the AI models' output. These vulnerabilities could significantly undermine the trust in AI software. Further steps are required to strengthen the information technology infrastructure in order to ensure the integrity of AI systems before they could be integrated into the healthcare system.

Several ethical challenges emerge from the inclusion of AI models into the patient's management. First, data sharing concerns could undermine the physician and the patient's trust and lead patients to conceal information[192]. Second, AI software is incapable of understanding non-quantifiable aspects of physicians' lives, such as understanding the patients' needs, sympathizing with their beliefs, and respecting their wishes. Finally, there are fears that prejudices relating to racism, sexism, and socioeconomic inequality included in the training datasets would be mistakenly included in the AI model. An infamous example is the COMPAS algorithm, which erroneously flagged black people as usual re-offenders[193]. To make things worse, the developers argued that their algorithm was not open to scrutiny since it was protected by intellectual property law[193]. It is, therefore, no surprise that around two-thirds of the population oppose AI/ML-based models to perform tasks, which physicians typically perform[194].

Finally, a last but also significant concern of integrating AI/ML-based software in the healthcare system is the lack of transparency. AI models are often described as black-boxes since there are non-interpretable, and their inner logic is hidden, which creates an intriguing ethical dilemma[195]. On the one hand, we could argue that applying technologies that we barely comprehend violates a fundamental tenet of medical ethics[196]. However, on the other hand, we could argue that withholding the application of AI models that could significantly benefit the patient's well-being is unethical[194]. To overcome this conundrum, regulators, developers, and physicians should cooperate to create a robust regulatory framework that increases transparency and addresses biases. A trustworthy AI/ML-based model should be built around the principles of credibility, transparency, reliability, auditability, and recoverability[197].

LIMITATIONS

This review has several limitations. First, despite our efforts to follow a tight search strategy, as a narrative review, this study is prone to selection bias. Second, we did not systematically evaluate each study's risk of bias using a risk assessment tool. Therefore, we advise the readers to keep in mind that each study has its own biases and limitations that are not elaborated in this review. Another point is that the majority of studies included were conducted in silico, and their models' reported performance could substantially deviate when applied in an actual clinical setting. Finally, our review is prone to publication bias, similar to every narrative review, since studies that developed AI models with poor performance are less likely to be published.

CONCLUSION

In this review, we have comprehensively presented the applications of 3D printing and AI in the management of HCC and summarized the current obstacles that hinder the general use of these technologies in the healthcare industry, and identified several means to overcome them. Several opportunities arise from the application of these technologies in the management of HCC. Particularly for 3D printing, these opportunities include educational purposes, both regarding the medical staff and the patients, preoperative planning, and the development of custom-made medical tools. Specifically, cheap patient-specific 3D printed hepatic models developed from radiology images could be used to aid surgical residents in becoming familiar with the complex liver anatomy[19]. In addition, 3D models have been developed to familiarize surgical residents with laparoscopic operations[22,23]. The work of Yang *et al* [20] demonstrated how 3D printed liver models could be used for patient education to reach a higher understanding of their disease, understand the potential risk of an operation, and facilitate obtaining informed consent.

3D printed models also facilitate the preoperative planning of patients operated for HCC. Several teams have demonstrated how 3D printed models could significantly improve the surgical outcome specifically for patients with rare variations of the abdominal blood vessels[31-33]. Optimizing preoperative planning could substantially reduce the operation time and improve surgical outcomes. In

Table 4 Artificial intelligence application in hepatocellular carcinoma prognosis

	First author	Parameters employed	AI classifier	Sizes of the training/validation sets	Outcomes	Performance	Ref.
1	Chaudhary K	DNA methylation, RNA, and microRNA profiling	Several	360 patients (training:validation = 6:4)	Overall survival	0.70[1,2], 0.66-0.70[1,3], 0.67-0.82[1,4]	[122]
2	Chicco D	50 laboratory and clinical parameters	Several	165 patients with HCC	Overall survival	RF: 77.2[1], 0.766[5]; Linear SVM: 77.1[5], 0.763[1]; MLP: 72.7[5], 0.695[1]; Radial SVM: 68.0[5], 0.663[1]; DT: 65.9[5], 0.650[1]	[123]
3	Liu X	Laboratory results, data from immunochemistry of peripheral blood mononuclear cells, tumor characteristics	GBA classifier	136/56[3]/105[4]	Risk of HCC-related death	0.844[1,2], 0.827[1,3], 0.806[1,4]	[124]
4	Shi HY	Laboratory results, clinicopathological parameters, tumor characteristics	ANN	22926 patients	5-yr survival following surgical resection	96.57[3,5], 0.885[1,3], 97.43[4,5], 0.871[1,4], 74.23[4,6]	[125]
5	Chiu HC	Laboratory results, clinicopathological parameters, tumor characteristics	ANN	434, 341, and 264 patients for 1-, 3-, and 5-year survival(training:validation = 8:2)	1-, 3-, and 5-yr overall survivalfollowing surgical resection	98.5-99.5[2,5], 0.980-0.993[1,2], 99.7-100[2,6], 96.2-99.2[2,7], 72.1-85.1[3,5], 0.798-0.875[1,3], 71.4-88.6[3,6], 50.0-82.1[3,7]	[126]
6	Qiao G	Laboratory results, clinicopathological parameters, tumor characteristics	ANN	362/181[3]/104[4] patients	Survival following surgical resection	0.855[1,2], 80.00[2,6], 73.40[2,7], 0.832[1,3], 78.67[3,6], 75.70[3,7], 0.829[1,4], 77.42[4,6], 78.08[4,7]	[127]
7	Guo L	RNA sequencing	RF	239/130 patients	Overall survival	89[3,5]	[128]
8	Saillard C	Hematoxylin and eosin-stained WSI	CNN	309/342[4] WSIs	Survival following surgical resection	0.75-0.78[1,2], 0.68-0.70[1,4]	[129]
9	Zhong BY	ALBI/CTP stage	ANN	548/115[4]/175[4]	Survival of patients treated with chemoembolization as monotherapy	ALBI-based: 0.799[1,4], 0.700[1,4]; CTP-based: 0.729[1,4], 0.802[1,4]	[130]
10	Zhong BY	ALBI/CTP stage	ANN	319/61[4]/124[4]	Survival of patients treated with chemoembolization and sorafenib	ALBI-based: 0.716[1,4], 0.823[1,4]; CTP-based: 0.779[1,4], 0.693[1,4]	[131]
11	Zhang L	CT scans, clinical features	CNN	120/81[3] patients	Survival of patients treated with chemoembolization and sorafenib	0.717[1,2], 0.714[1,3]	[132]
12	Liu QP	CT radiomics, clinical parameters	DNN-DAE	243 patients	Overall survival following TACE	0.87-0.93[1,3]	[108]
13	Mähringer-Kunz A	Routine laboratory tests and clinicopathological parameters	ANN	125/57 patients	1-yr overall survival following TACE	0.77[1,2], 0.83[1,3], 77.8[3,6], 81.0[3,7]	[133]
14	Liu X	Routine laboratory tests and clinicopathological parameters	ANN	1480/637 patients	Progression-free survival. Overall survival	0.866[1,2], 0.730[1,3]. 0.877[1,2], 0.804[1,3]	[134]
15	Ho WH	Laboratory results, clinicopathological parameters, surgery parameters	ANN, DT	427, 354, and 297 patients for 1-, 3-, and 5-yr survival (training:validation = 8:2)	1-, 3-, and 5-yr disease-free survival following surgical resection	ANN: 0.963-0.989[1,2], 93.5-96.3[2,6], 91.6-97.9[2,7], 0.774-0.864[1,3], 70.0-78.7[3,6], 54.2-92.7[3,7]. DT: 0.675-0.825[1,2], 19.6-94.8[2,6], 45.8-97.9[2,7], 0.561-0.718[1,3], 0-88.5[3,6], 37.5-96.4[3,7]	[135]
16	Bedon L	DNA methylation profiling	RF-based	300/74 specimens	6-mo progression-free survival	67.1-80.6[2,5], 64.8-80.2[4,5]	[136]
17	Schoenberg MB	Routine laboratory tests and clinicopathological parameters	RFS	127/53 patients	Disease-free survival following resection	0.766-0.788[1,3]	[137]

18	Wu CF	Laboratory tests and clinicopathological parameters, treatment data	ANN	252 patients(training:validation = 8:2)	1-yr and 2-yr disease-free survival following RFA	0.72-0.77[1,3], 56.3-63.6[3,6], 70.0-71.8[3,7]	[138]
19	Divya R	Laboratory results, clinicopathological parameters, tumor characteristics	APO, SVM, RF	152 patients	Recurrence following RFA	95.5[3,5], 95.1[3,6], 95.8[3,7]	[139]
20	Huang Y	Demographics, laboratory tests, tumor characteristics	GBS classifier	5928/1483 patients	Recurrence following surgical resection. Overall survival	0.704[1,2], 0.697-0.713[1,3]. 0.565-0.736[1,2], 0.551-0.751[1,3]	[140]
21	Shen J	Disease-free related genes sequencing	DT, SVM	315 HCC patients	Recurrence following surgical resection	DT: 74.19[5], 0.75[1], 70.41[4],[5]. SVM: 80.65[5], 0.595[1]	[141]
22	Wang W	CT radiomics, clinical data	CNN, SVM, RF	167 patients	Early recurrence following surgical resection	0.723-0.825[1,3]	[142]
23	Ji GW	CT radiomics, laboratory results, clinicopathological parameters	Several	210/107[3]/153[4] patients	Recurrence time following surgical resection	Radiomics model: 0.748-0.752[1,2], 0.781-0.801[1,3], 0.733-0.741[1,4]. Clinical model: 0.716-0.727[1,2], 0.707-0.739[1,3], 0.696-0.716[1,4]	[143]
24	Xu D	Routine laboratory tests and clinicopathological parameters, intra-operative parameters	BN-based	995 patients	Recurrence time following surgical resection	0.57[3,5], 0.57[3,6]	[144]
25	Jianzhu B	Several including immune, tumor, nutrition, and indicators	CS-SVM	776 liver cancer recurrences	Recurrence time. Recurrence location	Mean square error = 9.2101, 95.7[5], 0.95[1]	[145]
26	Yamashita R	Hematoxylin and eosin-stained WSI	CNN	299/53[3]/198[4] WSIs	Recurrence following surgical resection	0.724[1,3], 0.683[1,4]	[77]
27	Liao H	Hematoxylin and eosin-stained WSI	RF	491 WSIs	Overall survival	0.563-0.706[1,3], 0.565-0.621[1,4]	[146]
28	Saito A	Hematoxylin and eosin-stained WSI	SVM	69/89[4]	Recurrence time following surgical resection	99.8[2,5], 68.1-80.6[4,5]	[147]
29	Liang JD	Laboratory results, clinicopathological parameters	SVM	83 patients	Recurrence following RFA	73-82[3,5], 0.60-0.69[1,3], 77-86[3,6], 73-82[3,7]	[148]
30	An C	MRI scans	CNN	141 HCC lesions	Local tumor progression following MWA	0.728[1]	[149]
31	Nam JY	Routine laboratory tests and clinicopathological parameters	DNN	349/214 patients	Post-transplant HCC recurrence	0.62-0.75[1,3], 0.63-0.76[3,6], 0.46-0.62[3,7]	[150]
32	Nam JY	Laboratory results, clinicopathological parameters, tumor characteristics	DNN	349/214 transplanted patients	Post-transplant HCC recurrence	0.75[1,3], 76[3,6], 46[3,7]	[150]
33	Rodriguez-Luna H	Genotyping data from microsatellite mutations/deletions	ANN	19 transplanted patients	Post-transplant HCC recurrence	89.5[3,5]	[151]
34	Guo D	Laboratory results, clinicopathological parameters CT radiomics	LASSO	93/40 transplanted patients	Recurrence free-survival following liver transplantation	0.675-0.785[1,2], 0.705-0.789[1,3]	[152]
35	Lau L	Laboratory results, clinicopathological parameters, donor characteristics	ANN, RF	90/90 transplants	Graft failure/primary nonfunction. 3-mo graft failure	ANN: 0.734-0.835[1,3]; RF: 0.787-0.818[1,3]. ANN: 0.559[1,3], RF: 0.715[1,3]	[153]
36	Briceño J	Laboratory results, clinicopathological parameters, surgical parameters, donor characteristics	ANN	1003 liver transplants	3-mo graft failure	0.806-0.821[1,3]	[154]

| 37 | Ershoff BD | Laboratory results, clinicopathological parameters, donor characteristics | DNN | 46035/11509 | 90-d post-transplant survival | 0.695-0.708[1,3], 30.9-35.8[3,6], 88.1-90.8[3,7] | [155] |

[1]Area under the receiver operating curve or c-index.

[2]Training.

[3]Internal validation.

[4]External validation/testing.

[5]Accuracy (%).

[6]Sensitivity (%).

[7]Specificity (%).

ALBI: Albumin-bilirubin; ANN: Artificial neural network; APO: Artificial plant optimization; BN: Bayesian network; CNN: Convolutional neural network; CS: Cuckoo-search; CT: Computed tomography; CTP: Child-Turcotte-Pugh; DNN: Deep neural network; DAE: Deep auto-encoder; DT: Decision tree; GBS: Gradient boosting survival; HCC: Hepatocellular carcinoma; LASSO: Least absolute shrinkage and selection operator; MLP: Multi-layer perceptron neural network; MRI: Magnetic resonance imaging; MWA: Microwave ablation; RF: Random forest; RFA: Radiofrequency ablation; SVM: Support vector machine; TACE: Transarterial chemoembolization; US: Ultrasound; WSI: Whole-slide image.

liver transplantation, the work of Zein *et al*[25] demonstrated how 3D printed models of high anatomical precision could be used to optimize the recipient-donor matching in graft allocation by unveiling any unsuitable anatomy between the donor and the recipient. In recently published consensus recommendations, it is strongly recommended that for complicated cases of HCC, 3D visualization is carried out to comprehend the course/variation of the portal vein and understand how it is related to the tumor[198]. In addition, 3D visualization is recommended as part of preoperative planning for centrally located HCC and/or complex vascular anatomy[198]. Finally, the works of Damiati *et al*[35] and Han *et al*[38] highlight the opportunity that arises from 3D printing in the fabrication of custom-made medical tools for the diagnosis and treatment of HCC.

3D printing is an evolving field in the medical disciplines, evident by the increasing number of publications each year[10]. It is pretty impressive that even though the majority of the studies regarding 3D printing report a significant improvement of the investigated medical outcome, only 14% of those studies support their findings in a quantitative manner, rendering their conclusions rather subjective [158]. This lack of consistency on how to report results precludes any meaningful comparison between studies. With the costs related to 3D printed models steadily decreasing, it is expected that 3D printing applications will significantly expand[199].

Bioprinting could potentially have a profound impact on liver surgery. Currently, the opportunities that arise from its application in HCC management include the development of 3D bioprinted hepatic scaffolds that could be used to develop antitumor drugs since 3D bioprinted models more precisely represent the microenvironment of HCC compared to other tissue engineering methods. Specifically, the work of Sun *et al*[45], who used HepG2, and the work of Xie *et al*[45], who used patient-derived HCC cells, demonstrate how 3D bioprinting could aid the individualized treatment of patients with HCC.

Liver transplantation is the only definitive treatment of liver failure. However, it is currently being restricted by the limited number of liver grafts. Promising results from animal studies demonstrate how 3D bioprinted liver organoids could be transplanted to prolong the survival of mice with liver failure [200]. These results raise the expectations that bioprintable liver grafts could be used in the future in regenerative medicine to ameliorate the burden of the liver graft shortage. However, despite a promising field, we should highlight that bioprinting is currently in its infancy.

The application of AI/ML-based models offers a plethora of opportunities in the management of HCC. First, in prevention, AI/ML models could be integrated into the healthcare system and analyze data directly from patients' healthcare records in real-time to flag patients at high risk of developing HCC. Current efforts include predicting HCC development in patients with chronic HBV infection[48] and chronic HCV infection[51-54]. Other studies focusing on prevention have developed AI/ML models employing genetic and epigenetic markers such as long-coding RNAs to screen for HCC[47,49,50]. These models demonstrate how AI could facilitate tailoring individualized follow-up schedules and identifying patients at a greater need to achieve a SVR. Following prevention, early detection is equivalently crucial in the management of HCC. Current efforts for early detection include studies that employ biomarkers to develop AI/ML models to detect HCC development[55-59].

In diagnostics, AI/ML models could enhance diagnostic accuracy in different diagnostic modalities. Specifically, current efforts include CAD models for detecting HCC either among a plethora of focal hepatic lesions or between HCC and non-HCC lesions. These models employ different diagnostic modalities, including US imaging[60-62,80,81], CT imaging[64-66,90,91], MRI[69-73], and PET/CT imaging[92]. Other studies employed hematoxylin and eosin-stained WSI to detect HCC lesions and classify the level of differentiation[74-79].

Regarding treatment, AI/ML models provide several opportunities to reduce the morbidity and mortality associated with HCC. These opportunities include the development of frameworks for

individualized, evidence-based treatment allocation[99,101], the prediction of the presence of certain mutations as a base for appropriate drug selection[75,103,104], the prediction of MVI presence to facilitate the appropriate treatment selection[105-110], and finally the prediction of the response to treatment, and particularly TACE, as a tool to identify patients who would benefit more from treatment [113-116].

Finally, regarding prognosis, AI/ML models could be used to predict patient outcomes. Such models could be used as the basis to counsel the patient and the patient's family. Recent initiatives include the prediction of overall survival[123-127], the prediction of progression-free survival[134-138], the prediction of survival of non-operated patients treated with TACE[130-133], and HCC recurrence following therapeutic treatment[77,139-142]. In liver transplantation, current efforts include models to predict post-transplant HCC recurrence and individual liver graft survival as tools to optimize the graft allocation procedure[150-155].

As demonstrated by our findings, there is a lack of consistency regarding the validation strategies employed by each study and the different metrics used to assess the models' performance. This lack of consistency significantly limits our ability to draw any meaningful comparisons among the models. A challenge for the future would be to develop a robust tool for presenting the performance of these models that would allow benchmarking.

Even though AI has been on the frontline for several decades, AI has not yet been integrated into the healthcare system. AI in medicine could be seen as a field that overpromises but invariably underdelivers. This is evident during AI winters, where the funding for AI research is halted due to the investors' dissatisfaction that AI does not progress at a rate at which they are comfortable investing[14]. Overcoming the current challenges of AI applications is a vital part of integrating AI in the healthcare industry.

Physicians should keep in mind that AI/ML-based models are simply medical tools that, similar to all medical tools, have weaknesses, biases, and limitations. Overelining on AI could exclude non-quanti-fiable information from decision-making, with unknown ramifications[194]. AI should not subsume out critical thinking and reasoning. The aim should therefore be an AI-assisted rather than an AI-driven clinical practice[201]. Furthermore, the integration of AI in healthcare must occur in conjunction with integrating sophisticated and robust evaluation tools that monitor the consequences of AI application in the clinical setting, and more importantly, the impact of these tools on patient outcomes[202]. A notable example is the Digital Health Innovation Action Plan supported by the FDA to facilitate the evaluation of developing medical software. It is based on the following five excellence criteria: Patient safety, product quality, proactive culture, cybersecurity responsibility, and clinical responsibility[203].

Finally, an intriguing challenge for the future is to combine emerging technologies, including 3D printing and 3D bioprinting, AI and ML, augmented reality, novel biomarkers, and robotics, into a unified, interrelated framework[204-208]. In this new, complex, and sophisticated clinical setting, physicians would reject oversimplifying an inherently complex field but rather embrace the complexity. Finally, are shown by our findings, AI and 3D printing applications in healthcare are steadily expanding; thus, these technologies will be integrated into the clinical setting sooner or later. Therefore, we believe that physicians need to become familiar with these technologies and prepare to engage with them constructively.

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FOOTNOTES

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