**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 67146

**Manuscript Type:** REVIEW

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

Christou CD *et al*. 3D printing and AI in HCC management

Chrysanthos D Christou, Georgios Tsoulfas

**Chrysanthos D Christou, Georgios Tsoulfas,** Department of Transplantation Surgery, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54622, Greece

**Author contributions:** Christou CD performed the screening of articles for eligibility and drafted the manuscript; Tsoulfas G performed the screening of articles for eligibility and edited the manuscript.

**Corresponding author: Georgios Tsoulfas, MD, PhD, Associate Professor, Surgeon,** Department of Transplantation Surgery, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, 49 Konstantinoupoleos Street, Thessaloniki 54622, Greece. tsoulfasg@gmail.com

**Received:** April 15, 2021

**Revised:** August 24, 2021

**Accepted: March 25, 2022**

**Published online:**

**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

Christou CD, Tsoulfas G. Role of three-dimensional printing and artificial intelligence in the management of hepatocellular carcinoma: Challenges and opportunities. *World J Gastrointest Oncol* 2022; In press

**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 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] investigated the therapeutic value of 3D printing template-assisted radioactive 125I 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 distribution[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 studywhere 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 1-4summarize 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 (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 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 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-quantifiable 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.

**ACKNOWLEDGEMENTS**

The authors declare no conflict of interest for this article. The authors received no specific funding for this work.

**REFERENCES**

1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0186-y]

3 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]

4 **Mitchell DG**, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. *Hepatology* 2015; **61**: 1056-1065 [PMID: 25041904 DOI: 10.1002/hep.27304]

5 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu**; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

6 **Cillo U**, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A, D'Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol* 2006; **44**: 723-731 [PMID: 16488051 DOI: 10.1016/j.jhep.2005.12.015]

7 **Reig M**, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Systemic therapy for hepatocellular carcinoma: the issue of treatment stage migration and registration of progression using the BCLC-refined RECIST. *Semin Liver Dis* 2014; **34**: 444-455 [PMID: 25369306 DOI: 10.1055/s-0034-1394143]

8 **Roberts SK**, Gazzola A, Lubel J, Gow P, Bell S, Nicoll A, Dev A, Fink MA, Sood S, Knight V, Hong T, Paul E, Mishra G, Majeed A, Kemp W; Melbourne Liver Group. Treatment choice for early-stage hepatocellular carcinoma in real-world practice: impact of treatment stage migration to transarterial chemoembolization and treatment response on survival. *Scand J Gastroenterol* 2018; **53**: 1368-1375 [PMID: 30394145 DOI: 10.1080/00365521.2018.1517277]

9 **Mitsouras D**, Liacouras P, Imanzadeh A, Giannopoulos AA, Cai T, Kumamaru KK, George E, Wake N, Caterson EJ, Pomahac B, Ho VB, Grant GT, Rybicki FJ. Medical 3D Printing for the Radiologist. *Radiographics* 2015; **35**: 1965-1988 [PMID: 26562233 DOI: 10.1148/rg.2015140320]

10 **Pietrabissa A**, Marconi S, Negrello E, Mauri V, Peri A, Pugliese L, Marone EM, Auricchio F. An overview on 3D printing for abdominal surgery. *Surg Endosc* 2020; **34**: 1-13 [PMID: 31605218 DOI: 10.1007/s00464-019-07155-5]

11 **Mironov V**, Boland T, Trusk T, Forgacs G, Markwald RR. Organ printing: computer-aided jet-based 3D tissue engineering. *Trends Biotechnol* 2003; **21**: 157-161 [PMID: 12679063 DOI: 10.1016/S0167-7799(03)00033-7]

12 **Zadpoor AA**, Malda J. Additive Manufacturing of Biomaterials, Tissues, and Organs. *Ann Biomed Eng* 2017; **45**: 1-11 [PMID: 27632024 DOI: 10.1007/s10439-016-1719-y]

13 **Melchels FPW,** Domingos MAN, Klein TJ, Malda J, Bartolo PJ, Hutmacher DW. Additive manufacturing of tissues and organs. *Prog Polym Sci* 2012; **37**: 1079-1104 [DOI: 10.1016/j.progpolymsci.2011.11.007]

14 **Trends in China,** **Europe, and the United States**. ArtificiaI Intelligence: How knowledge is created, transferred, and used. In: Artificial Intelligence: a multifaceted field. Amsterdam: Elsevier. 2018: 24-27

15 **Russell SJ,** Norvig P. Artificial intelligence: a modern approach. 2021

16 **Cruz JA**, Wishart DS. Applications of machine learning in cancer prediction and prognosis. *Cancer Inform* 2007; **2**: 59-77 [PMID: 19458758]

17 **Statista.** Total amount of global healthcare data generated in 2013 and a projection for 2020. [cited 1 April 2021]. Available from: https://www.statista.com/statistics/1037970/global-healthcare-data-volume/

18 **Tsoulfas G,** Bangeas PI, Suri JS. 3D Printing: Applications in Medicine and Surgery. In: Ziogas IA, Zein NN, Quintini C, Miller CM, Tsoulfas G. Three-dimensional (3D) printing and liver transplantation. Amsterdam: Elsevier. 2020: 97-116 [DOI: 10.1016/B978-0-323-66164-5.00007-6]

19 **Watson RA**. A low-cost surgical application of additive fabrication. *J Surg Educ* 2014; **71**: 14-17 [PMID: 24411417 DOI: 10.1016/j.jsurg.2013.10.012]

20 **Yang T**, Tan T, Yang J, Pan J, Hu C, Li J, Zou Y. The impact of using three-dimensional printed liver models for patient education. *J Int Med Res* 2018; **46**: 1570-1578 [PMID: 29436243 DOI: 10.1177/0300060518755267]

21 **Yang T**, Lin S, Xie Q, Ouyang W, Tan T, Li J, Chen Z, Yang J, Wu H, Pan J, Hu C, Zou Y. Impact of 3D printing technology on the comprehension of surgical liver anatomy. *Surg Endosc* 2019; **33**: 411-417 [PMID: 29943060 DOI: 10.1007/s00464-018-6308-8]

22 **Tang R**, Ma L, Li A, Yu L, Rong Z, Zhang X, Xiang C, Liao H, Dong J. Choledochoscopic Examination of a 3-Dimensional Printing Model Using Augmented Reality Techniques: A Preliminary Proof of Concept Study. *Surg Innov* 2018; **25**: 492-498 [PMID: 29909727 DOI: 10.1177/1553350618781622]

23 **Burdall OC**, Makin E, Davenport M, Ade-Ajayi N. 3D printing to simulate laparoscopic choledochal surgery. *J Pediatr Surg* 2016; **51**: 828-831 [PMID: 27085850 DOI: 10.1016/j.jpedsurg.2016.02.093]

24 **Streba CT**, Popescu S, Pirici D, Gheonea IA, Vlădaia M, Ungureanu BS, Gheonea DI, Ţenea-Cojan TŞ. Three-dimensional printing of liver tumors using CT data: proof of concept morphological study. *Rom J Morphol Embryol* 2018; **59**: 885-893 [PMID: 30534830]

25 **Zein NN**, Hanouneh IA, Bishop PD, Samaan M, Eghtesad B, Quintini C, Miller C, Yerian L, Klatte R. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. *Liver Transpl* 2013; **19**: 1304-1310 [PMID: 23959637 DOI: 10.1002/lt.23729]

26 **Oshiro Y**, Mitani J, Okada T, Ohkohchi N. A novel three-dimensional print of liver vessels and tumors in hepatectomy. *Surg Today* 2017; **47**: 521-524 [PMID: 27456277 DOI: 10.1007/s00595-016-1383-8]

27 **Igami T**, Nakamura Y, Hirose T, Ebata T, Yokoyama Y, Sugawara G, Mizuno T, Mori K, Nagino M. Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: preliminary experience. *World J Surg* 2014; **38**:3163-3166 [PMID: 25145821 DOI: 10.1007/s00268-014-2740-7]

28 **Javan R**, Zeman MN. A Prototype Educational Model for Hepatobiliary Interventions: Unveiling the Role of Graphic Designers in Medical 3D Printing. *J Digit Imaging* 2018; **31**: 133-143 [PMID: 28808803 DOI: 10.1007/s10278-017-0012-4]

29 **Baimakhanov Z**, Soyama A, Takatsuki M, Hidaka M, Hirayama T, Kinoshita A, Natsuda K, Kuroki T, Eguchi S. Preoperative simulation with a 3-dimensional printed solid model for one-step reconstruction of multiple hepatic veins during living donor liver transplantation. *Liver Transpl* 2015; **21**: 266-268 [PMID: 25302632 DOI: 10.1002/lt.24019]

30 **Madurska MJ**, Poyade M, Eason D, Rea P, Watson AJ. Development of a Patient-Specific 3D-Printed Liver Model for Preoperative Planning. *Surg Innov* 2017; **24**: 145-150 [PMID: 28134003 DOI: 10.1177/1553350616689414]

31 **Xiang N**, Fang C, Fan Y, Yang J, Zeng N, Liu J, Zhu W. Application of liver three-dimensional printing in hepatectomy for complex massive hepatocarcinoma with rare variations of portal vein: preliminary experience. *Int J Clin Exp Med* 2015; **8**: 18873-18878 [PMID: 26770510]

32 **Perica E**, Sun Z. Patient-specific three-dimensional printing for pre-surgical planning in hepatocellular carcinoma treatment. *Quant Imaging Med Surg* 2017; **7**: 668-677 [PMID: 29312871 DOI: 10.21037/qims.2017.11.02]

33 **Kuroda S**, Kobayashi T, Ohdan H. 3D printing model of the intrahepatic vessels for navigation during anatomical resection of hepatocellular carcinoma. *Int J Surg Case Rep* 2017; **41**: 219-222 [PMID: 29096348 DOI: 10.1016/j.ijscr.2017.10.015]

34 **Witowski J**, Budzyński A, Grochowska A, Ballard DH, Major P, Rubinkiewicz M, Złahoda-Huzior A, Popiela TJ, Wierdak M, Pędziwiatr M. Decision-making based on 3D printed models in laparoscopic liver resections with intraoperative ultrasound: a prospective observational study. *Eur Radiol* 2020; **30**: 1306-1312 [PMID: 31773294 DOI: 10.1007/s00330-019-06511-2]

35 **Damiati S**, Küpcü S, Peacock M, Eilenberger C, Zamzami M, Qadri I, Choudhry H, Sleytr UB, Schuster B. Acoustic and hybrid 3D-printed electrochemical biosensors for the real-time immunodetection of liver cancer cells (HepG2). *Biosens Bioelectron* 2017; **94**: 500-506 [PMID: 28343102 DOI: 10.1016/j.bios.2017.03.045]

36 **Joo I**, Kim JH, Park SJ, Lee K, Yi NJ, Han JK. Personalized 3D-Printed Transparent Liver Model Using the Hepatobiliary Phase MRI: Usefulness in the Lesion-by-Lesion Imaging-Pathologic Matching of Focal Liver Lesions-Preliminary Results. *Invest Radiol* 2019; **54**: 138-145 [PMID: 30379728 DOI: 10.1097/RLI.0000000000000521]

37 **Trout AT**, Batie MR, Gupta A, Sheridan RM, Tiao GM, Towbin AJ. 3D printed pathological sectioning boxes to facilitate radiological-pathological correlation in hepatectomy cases. *J Clin Pathol* 2017; **70**: 984-987 [PMID: 28596154 DOI: 10.1136/jclinpath-2016-204293]

38 **Han T**, Yang X, Xu Y, Zheng Z, Yan Y, Wang N. Therapeutic value of 3-D printing template-assisted 125I-seed implantation in the treatment of malignant liver tumors. *Onco Targets Ther* 2017; **10**: 3277-3283 [PMID: 28740402 DOI: 10.2147/OTT.S134290]

39 **Wang Z**, Chapiro J, Schernthaner R, Duran R, Chen R, Geschwind JF, Lin M. Multimodality 3D Tumor Segmentation in HCC Patients Treated with TACE. *Acad Radiol* 2015; **22**: 840-845 [PMID: 25863795 DOI: 10.1016/j.acra.2015.03.001]

40 **Liapi E**, Hong K, Georgiades CS, Geschwind JF. Three-dimensional rotational angiography: introduction of an adjunctive tool for successful transarterial chemoembolization. *J Vasc Interv Radiol* 2005; **16**: 1241-1245 [PMID: 16151066 DOI: 10.1097/01.RVI.0000174283.03032.8E]

41 **Yao R**, Xu G, Mao SS, Yang HY, Sang XT, Sun W, Mao YL. Three-dimensional printing: review of application in medicine and hepatic surgery. *Cancer Biol Med* 2016; **13**: 443-451 [PMID: 28154775 DOI: 10.20892/j.issn.2095-3941.2016.0075]

42 **Datta P**, Barui A, Wu Y, Ozbolat V, Moncal KK, Ozbolat IT. Essential steps in bioprinting: From pre- to post-bioprinting. *Biotechnol Adv* 2018; **36**: 1481-1504 [PMID: 29909085 DOI: 10.1016/j.biotechadv.2018.06.003]

43 **Xie F**, Sun L, Pang Y, Xu G, Jin B, Xu H, Lu X, Xu Y, Du S, Wang Y, Feng S, Sang X, Zhong S, Wang X, Sun W, Zhao H, Zhang H, Yang H, Huang P, Mao Y. Three-dimensional bio-printing of primary human hepatocellular carcinoma for personalized medicine. *Biomaterials* 2021; **265**: 120416 [PMID: 33007612 DOI: 10.1016/j.biomaterials.2020.120416]

44 **Zhang X**, Morits M, Jonkergouw C, Ora A, Valle-Delgado JJ, Farooq M, Ajdary R, Huan S, Linder M, Rojas O, Sipponen MH, Österberg M. Three-Dimensional Printed Cell Culture Model Based on Spherical Colloidal Lignin Particles and Cellulose Nanofibril-Alginate Hydrogel. *Biomacromolecules* 2020; **21**: 1875-1885 [PMID: 31992046 DOI: 10.1021/acs.biomac.9b01745]

45 **Sun L**, Yang H, Wang Y, Zhang X, Jin B, Xie F, Jin Y, Pang Y, Zhao H, Lu X, Sang X, Zhang H, Lin F, Sun W, Huang P, Mao Y. Application of a 3D Bioprinted Hepatocellular Carcinoma Cell Model in Antitumor Drug Research. *Front Oncol* 2020; **10**: 878 [PMID: 32582546 DOI: 10.3389/fonc.2020.00878]

46 **Ma X**, Yu C, Wang P, Xu W, Wan X, Lai CSE, Liu J, Koroleva-Maharajh A, Chen S. Rapid 3D bioprinting of decellularized extracellular matrix with regionally varied mechanical properties and biomimetic microarchitecture. *Biomaterials* 2018; **185**: 310-321 [PMID: 30265900 DOI: 10.1016/j.biomaterials.2018.09.026]

47 **Wang J**, Jain S, Chen D, Song W, Hu CT, Su YH. Development and Evaluation of Novel Statistical Methods in Urine Biomarker-Based Hepatocellular Carcinoma Screening. *Sci Rep* 2018; **8**: 3799 [PMID: 29491388 DOI: 10.1038/s41598-018-21922-9]

48 **Nam JY**, Sinn DH, Bae J, Jang ES, Kim JW, Jeong SH. Deep learning model for prediction of hepatocellular carcinoma in patients with HBV-related cirrhosis on antiviral therapy. *JHEP Rep* 2020; **2**: 100175 [PMID: 33117971 DOI: 10.1016/j.jhepr.2020.100175]

49 **Xia Q**, Shu Z, Ye T, Zhang M. Identification and Analysis of the Blood lncRNA Signature for Liver Cirrhosis and Hepatocellular Carcinoma. *Front Genet* 2020; **11**: 595699 [PMID: 33365048 DOI: 10.3389/fgene.2020.595699]

50 **Chen S**, Zhang Z, Wang Y, Fang M, Zhou J, Li Y, Dai E, Feng Z, Wang H, Yang Z, Li Y, Huang X, Jia J, Li S, Huang C, Tong L, Xiao X, He Y, Duan Y, Zhu S, Gao C. Using Quasispecies Patterns of Hepatitis B Virus to Predict Hepatocellular Carcinoma With Deep Sequencing and Machine Learning. *J Infect Dis* 2021; **223**: 1887-1896 [PMID: 33049037 DOI: 10.1093/infdis/jiaa647]

51 **Hashem S**, ElHefnawi M, Habashy S, El-Adawy M, Esmat G, Elakel W, Abdelazziz AO, Nabeel MM, Abdelmaksoud AH, Elbaz TM, Shousha HI. Machine Learning Prediction Models for Diagnosing Hepatocellular Carcinoma with HCV-related Chronic Liver Disease. *Comput Methods Programs Biomed* 2020; **196**: 105551 [PMID: 32580053 DOI: 10.1016/j.cmpb.2020.105551]

52 **Audureau E**, Carrat F, Layese R, Cagnot C, Asselah T, Guyader D, Larrey D, De Lédinghen V, Ouzan D, Zoulim F, Roulot D, Tran A, Bronowicki JP, Zarski JP, Riachi G, Calès P, Péron JM, Alric L, Bourlière M, Mathurin P, Blanc JF, Abergel A, Chazouillères O, Mallat A, Grangé JD, Attali P, d'Alteroche L, Wartelle C, Dao T, Thabut D, Pilette C, Silvain C, Christidis C, Nguyen-Khac E, Bernard-Chabert B, Zucman D, Di Martino V, Sutton A, Pol S, Nahon P; ANRS CO12 CirVir group. Personalized surveillance for hepatocellular carcinoma in cirrhosis - using machine learning adapted to HCV status. *J Hepatol* 2020; **73**: 1434-1445 [PMID: 32615276 DOI: 10.1016/j.jhep.2020.05.052]

53 **Ioannou GN**, Tang W, Beste LA, Tincopa MA, Su GL, Van T, Tapper EB, Singal AG, Zhu J, Waljee AK. Assessment of a Deep Learning Model to Predict Hepatocellular Carcinoma in Patients With Hepatitis C Cirrhosis. *JAMA Netw Open* 2020; **3**: e2015626 [PMID: 32870314 DOI: 10.1001/jamanetworkopen.2020.15626]

54 **Singal AG**, Mukherjee A, Elmunzer BJ, Higgins PD, Lok AS, Zhu J, Marrero JA, Waljee AK. Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. *Am J Gastroenterol* 2013; **108**: 1723-1730 [PMID: 24169273 DOI: 10.1038/ajg.2013.332]

55 **Sato M**, Morimoto K, Kajihara S, Tateishi R, Shiina S, Koike K, Yatomi Y. Machine-learning Approach for the Development of a Novel Predictive Model for the Diagnosis of Hepatocellular Carcinoma. *Sci Rep* 2019; **9**: 7704 [PMID: 31147560 DOI: 10.1038/s41598-019-44022-8]

56 **Zhao X**, Dou J, Cao J, Wang Y, Gao Q, Zeng Q, Liu W, Liu B, Cui Z, Teng L, Zhang J, Zhao C. Uncovering the potential differentially expressed miRNAs as diagnostic biomarkers for hepatocellular carcinoma based on machine learning in The Cancer Genome Atlas database. *Oncol Rep* 2020; **43**: 1771-1784 [PMID: 32236623 DOI: 10.3892/or.2020.7551]

57 **Zhang ZM**, Tan JX, Wang F, Dao FY, Zhang ZY, Lin H. Early Diagnosis of Hepatocellular Carcinoma Using Machine Learning Method. *Front Bioeng Biotechnol* 2020; **8**: 254 [PMID: 32292778 DOI: 10.3389/fbioe.2020.00254]

58 **Tao K**, Bian Z, Zhang Q, Guo X, Yin C, Wang Y, Zhou K, Wan S, Shi M, Bao D, Yang C, Xing J. Machine learning-based genome-wide interrogation of somatic copy number aberrations in circulating tumor DNA for early detection of hepatocellular carcinoma. *EBioMedicine* 2020; **56**: 102811 [PMID: 32512514 DOI: 10.1016/j.ebiom.2020.102811]

59 **Li G**, Shi H, Wang X, Wang B, Qu Q, Geng H, Sun H. Identification of diagnostic long non‑coding RNA biomarkers in patients with hepatocellular carcinoma. *Mol Med Rep* 2019; **20**: 1121-1130 [PMID: 31173205 DOI: 10.3892/mmr.2019.10307]

60 **Schmauch B**, Herent P, Jehanno P, Dehaene O, Saillard C, Aubé C, Luciani A, Lassau N, Jégou S. Diagnosis of focal liver lesions from ultrasound using deep learning. *Diagn Interv Imaging* 2019; **100**: 227-233 [PMID: 30926443 DOI: 10.1016/j.diii.2019.02.009]

61 **Yang Q**, Wei J, Hao X, Kong D, Yu X, Jiang T, Xi J, Cai W, Luo Y, Jing X, Yang Y, Cheng Z, Wu J, Zhang H, Liao J, Zhou P, Song Y, Zhang Y, Han Z, Cheng W, Tang L, Liu F, Dou J, Zheng R, Yu J, Tian J, Liang P. Improving B-mode ultrasound diagnostic performance for focal liver lesions using deep learning: A multicentre study. *EBioMedicine* 2020; **56**: 102777 [PMID: 32485640 DOI: 10.1016/j.ebiom.2020.102777]

62 **Virmani J**, Kumar V, Kalra N, Khandelwal N. Neural network ensemble based CAD system for focal liver lesions from B-mode ultrasound. *J Digit Imaging* 2014; **27**: 520-537 [PMID: 24687642 DOI: 10.1007/s10278-014-9685-0]

63 **Shiraishi J**, Sugimoto K, Moriyasu F, Kamiyama N, Doi K. Computer-aided diagnosis for the classification of focal liver lesions by use of contrast-enhanced ultrasonography. *Med Phys* 2008; **35**: 1734-1746 [PMID: 18561648 DOI: 10.1118/1.2900109]

64 **Zhou J**, Wang W, Lei B, Ge W, Huang Y, Zhang L, Yan Y, Zhou D, Ding Y, Wu J, Wang W. Automatic Detection and Classification of Focal Liver Lesions Based on Deep Convolutional Neural Networks: A Preliminary Study. *Front Oncol* 2020; **10**: 581210 [PMID: 33585197 DOI: 10.3389/fonc.2020.581210]

65 **Yasaka K**, Akai H, Abe O, Kiryu S. Deep Learning with Convolutional Neural Network for Differentiation of Liver Masses at Dynamic Contrast-enhanced CT: A Preliminary Study. *Radiology* 2018; **286**: 887-896 [PMID: 29059036 DOI: 10.1148/radiol.2017170706]

66 **Shi W**, Kuang S, Cao S, Hu B, Xie S, Chen S, Chen Y, Gao D, Chen Y, Zhu Y, Zhang H, Liu H, Ye M, Sirlin CB, Wang J. Deep learning assisted differentiation of hepatocellular carcinoma from focal liver lesions: choice of four-phase and three-phase CT imaging protocol. *Abdom Radiol (NY)* 2020; **45**: 2688-2697 [PMID: 32232524 DOI: 10.1007/s00261-020-02485-8]

67 **Todoroki Y**, Iwamoto Y, Lin L, Hu H, Chen YW. Automatic Detection of Focal Liver Lesions in Multi-phase CT Images Using A Multi-channel &amp; Multi-scale CNN. *Annu Int Conf IEEE Eng Med Biol Soc* 2019; **2019**: 872-875 [PMID: 31946033 DOI: 10.1109/EMBC.2019.8857292]

68 **Matake K**, Yoshimitsu K, Kumazawa S, Higashida Y, Irie H, Asayama Y, Nakayama T, Kakihara D, Katsuragawa S, Doi K, Honda H. Usefulness of artificial neural network for differential diagnosis of hepatic masses on CT images. *Acad Radiol* 2006; **13**: 951-962 [PMID: 16843847 DOI: 10.1016/j.acra.2006.04.009]

69 **Liang W**, Shao J, Liu W, Ruan S, Tian W, Zhang X, Wan D, Huang Q, Ding Y, Xiao W. Differentiating Hepatic Epithelioid Angiomyolipoma From Hepatocellular Carcinoma and Focal Nodular Hyperplasia via Radiomics Models. *Front Oncol* 2020; **10**: 564307 [PMID: 33123475 DOI: 10.3389/fonc.2020.564307]

70 **Hamm CA**, Wang CJ, Savic LJ, Ferrante M, Schobert I, Schlachter T, Lin M, Duncan JS, Weinreb JC, Chapiro J, Letzen B. Deep learning for liver tumor diagnosis part I: development of a convolutional neural network classifier for multi-phasic MRI. *Eur Radiol* 2019; **29**: 3338-3347 [PMID: 31016442 DOI: 10.1007/s00330-019-06205-9]

71 **Wang CJ**, Hamm CA, Savic LJ, Ferrante M, Schobert I, Schlachter T, Lin M, Weinreb JC, Duncan JS, Chapiro J, Letzen B. Deep learning for liver tumor diagnosis part II: convolutional neural network interpretation using radiologic imaging features. *Eur Radiol* 2019; **29**: 3348-3357 [PMID: 31093705 DOI: 10.1007/s00330-019-06214-8]

72 **Jansen MJA**, Kuijf HJ, Veldhuis WB, Wessels FJ, Viergever MA, Pluim JPW. Automatic classification of focal liver lesions based on MRI and risk factors. *PLoS One* 2019; **14**: e0217053 [PMID: 31095624 DOI: 10.1371/journal.pone.0217053]

73 **Zhen SH**, Cheng M, Tao YB, Wang YF, Juengpanich S, Jiang ZY, Jiang YK, Yan YY, Lu W, Lue JM, Qian JH, Wu ZY, Sun JH, Lin H, Cai XJ. Deep Learning for Accurate Diagnosis of Liver Tumor Based on Magnetic Resonance Imaging and Clinical Data. *Front Oncol* 2020; **10**: 680 [PMID: 32547939 DOI: 10.3389/fonc.2020.00680]

74 **Kiani A**, Uyumazturk B, Rajpurkar P, Wang A, Gao R, Jones E, Yu Y, Langlotz CP, Ball RL, Montine TJ, Martin BA, Berry GJ, Ozawa MG, Hazard FK, Brown RA, Chen SB, Wood M, Allard LS, Ylagan L, Ng AY, Shen J. Impact of a deep learning assistant on the histopathologic classification of liver cancer. *NPJ Digit Med* 2020; **3**: 23 [PMID: 32140566 DOI: 10.1038/s41746-020-0232-8]

75 **Chen M**, Zhang B, Topatana W, Cao J, Zhu H, Juengpanich S, Mao Q, Yu H, Cai X. Classification and mutation prediction based on histopathology H&amp;E images in liver cancer using deep learning. *NPJ Precis Oncol* 2020; **4**: 14 [PMID: 32550270 DOI: 10.1038/s41698-020-0120-3]

76 **Lin H**, Wei C, Wang G, Chen H, Lin L, Ni M, Chen J, Zhuo S. Automated classification of hepatocellular carcinoma differentiation using multiphoton microscopy and deep learning. *J Biophotonics* 2019; **12**: e201800435 [PMID: 30868728 DOI: 10.1002/jbio.201800435]

77 **Yamashita R**, Long J, Saleem A, Rubin DL, Shen J. Deep learning predicts postsurgical recurrence of hepatocellular carcinoma from digital histopathologic images. *Sci Rep* 2021; **11**: 2047 [PMID: 33479370 DOI: 10.1038/s41598-021-81506-y]

78 **Roy M**, Kong J, Kashyap S, Pastore VP, Wang F, Wong KCL, Mukherjee V. Convolutional autoencoder based model HistoCAE for segmentation of viable tumor regions in liver whole-slide images. *Sci Rep* 2021; **11**: 139 [PMID: 33420322 DOI: 10.1038/s41598-020-80610-9]

79 **Giordano S**, Takeda S, Donadon M, Saiki H, Brunelli L, Pastorelli R, Cimino M, Soldani C, Franceschini B, Di Tommaso L, Lleo A, Yoshimura K, Nakajima H, Torzilli G, Davoli E. Rapid automated diagnosis of primary hepatic tumour by mass spectrometry and artificial intelligence. *Liver Int* 2020; **40**: 3117-3124 [PMID: 32662575 DOI: 10.1111/liv.14604]

80 **Guo LH**, Wang D, Qian YY, Zheng X, Zhao CK, Li XL, Bo XW, Yue WW, Zhang Q, Shi J, Xu HX. A two-stage multi-view learning framework based computer-aided diagnosis of liver tumors with contrast enhanced ultrasound images. *Clin Hemorheol Microcirc* 2018; **69**: 343-354 [PMID: 29630528 DOI: 10.3233/CH-170275]

81 **Bharti P**, Mittal D, Ananthasivan R. Preliminary Study of Chronic Liver Classification on Ultrasound Images Using an Ensemble Model. *Ultrason Imaging* 2018; **40**: 357-379 [PMID: 30015593 DOI: 10.1177/0161734618787447]

82 **Brehar R**, Mitrea DA, Vancea F, Marita T, Nedevschi S, Lupsor-Platon M, Rotaru M, Badea RI. Comparison of Deep-Learning and Conventional Machine-Learning Methods for the Automatic Recognition of the Hepatocellular Carcinoma Areas from Ultrasound Images. *Sensors (Basel)* 2020; **20** [PMID: 32485986 DOI: 10.3390/s20113085]

83 **Mao B**, Ma J, Duan S, Xia Y, Tao Y, Zhang L. Preoperative classification of primary and metastatic liver cancer via machine learning-based ultrasound radiomics. *Eur Radiol* 2021; **31**: 4576-4586 [PMID: 33447862 DOI: 10.1007/s00330-020-07562-6]

84 **Almotairi S**, Kareem G, Aouf M, Almutairi B, Salem MA. Liver Tumor Segmentation in CT Scans Using Modified SegNet. *Sensors (Basel)* 2020; **20** [PMID: 32164153 DOI: 10.3390/s20051516]

85 **Budak Ü**, Guo Y, Tanyildizi E, Şengür A. Cascaded deep convolutional encoder-decoder neural networks for efficient liver tumor segmentation. *Med Hypotheses* 2020; **134**: 109431 [PMID: 31669758 DOI: 10.1016/j.mehy.2019.109431]

86 **Nayak A**, Baidya Kayal E, Arya M, Culli J, Krishan S, Agarwal S, Mehndiratta A. Computer-aided diagnosis of cirrhosis and hepatocellular carcinoma using multi-phase abdomen CT. *Int J Comput Assist Radiol Surg* 2019; **14**: 1341-1352 [PMID: 31062266 DOI: 10.1007/s11548-019-01991-5]

87 **Krishan A**, Mittal D. Ensembled liver cancer detection and classification using CT images. *Proc Inst Mech Eng H* 2021; **235**: 232-244 [PMID: 33183141 DOI: 10.1177/0954411920971888]

88 **Chen WF**, Ou HY, Liu KH, Li ZY, Liao CC, Wang SY, Huang W, Cheng YF, Pan CT. In-Series U-Net Network to 3D Tumor Image Reconstruction for Liver Hepatocellular Carcinoma Recognition. *Diagnostics (Basel)* 2020; **11** [PMID: 33374672 DOI: 10.3390/diagnostics11010011]

89 **Khan AA**, Narejo GB. Analysis of Abdominal Computed Tomography Images for Automatic Liver Cancer Diagnosis Using Image Processing Algorithm. *Curr Med Imaging Rev* 2019; **15**: 972-982 [PMID: 32008524 DOI: 10.2174/1573405615666190716122040]

90 **Mokrane FZ**, Lu L, Vavasseur A, Otal P, Peron JM, Luk L, Yang H, Ammari S, Saenger Y, Rousseau H, Zhao B, Schwartz LH, Dercle L. Radiomics machine-learning signature for diagnosis of hepatocellular carcinoma in cirrhotic patients with indeterminate liver nodules. *Eur Radiol* 2020; **30**: 558-570 [PMID: 31444598 DOI: 10.1007/s00330-019-06347-w]

91 **Mao B**, Zhang L, Ning P, Ding F, Wu F, Lu G, Geng Y, Ma J. Preoperative prediction for pathological grade of hepatocellular carcinoma via machine learning-based radiomics. *Eur Radiol* 2020; **30**: 6924-6932 [PMID: 32696256 DOI: 10.1007/s00330-020-07056-5]

92 **Preis O**, Blake MA, Scott JA. Neural network evaluation of PET scans of the liver: a potentially useful adjunct in clinical interpretation. *Radiology* 2011; **258**: 714-721 [PMID: 21339347 DOI: 10.1148/radiol.10100547]

93 **Trivizakis E**, Manikis GC, Nikiforaki K, Drevelegas K, Constantinides M, Drevelegas A, Marias K. Extending 2-D Convolutional Neural Networks to 3-D for Advancing Deep Learning Cancer Classification With Application to MRI Liver Tumor Differentiation. *IEEE J Biomed Health Inform* 2019; **23**: 923-930 [PMID: 30561355 DOI: 10.1109/JBHI.2018.2886276]

94 **Oestmann PM**, Wang CJ, Savic LJ, Hamm CA, Stark S, Schobert I, Gebauer B, Schlachter T, Lin M, Weinreb JC, Batra R, Mulligan D, Zhang X, Duncan JS, Chapiro J. Deep learning-assisted differentiation of pathologically proven atypical and typical hepatocellular carcinoma (HCC) versus non-HCC on contrast-enhanced MRI of the liver. *Eur Radiol* 2021; **31**: 4981-4990 [PMID: 33409782 DOI: 10.1007/s00330-020-07559-1]

95 **Bousabarah K**, Letzen B, Tefera J, Savic L, Schobert I, Schlachter T, Staib LH, Kocher M, Chapiro J, Lin M. Automated detection and delineation of hepatocellular carcinoma on multiphasic contrast-enhanced MRI using deep learning. *Abdom Radiol (NY)* 2021; **46**: 216-225 [PMID: 32500237 DOI: 10.1007/s00261-020-02604-5]

96 **Kim J**, Min JH, Kim SK, Shin SY, Lee MW. Detection of Hepatocellular Carcinoma in Contrast-Enhanced Magnetic Resonance Imaging Using Deep Learning Classifier: A Multi-Center Retrospective Study. *Sci Rep* 2020; **10**: 9458 [PMID: 32527998 DOI: 10.1038/s41598-020-65875-4]

97 **Jian W**, Ju H, Cen X, Cui M, Zhang H, Zhang L, Wang G, Gu L, Zhou W. Improving the malignancy characterization of hepatocellular carcinoma using deeply supervised cross modal transfer learning for non-enhanced MR. *Annu Int Conf IEEE Eng Med Biol Soc* 2019; **2019**: 853-856 [PMID: 31946029 DOI: 10.1109/EMBC.2019.8857467]

98 **Wu Y**, White GM, Cornelius T, Gowdar I, Ansari MH, Supanich MP, Deng J. Deep learning LI-RADS grading system based on contrast enhanced multiphase MRI for differentiation between LR-3 and LR-4/LR-5 liver tumors. *Ann Transl Med* 2020; **8**: 701 [PMID: 32617321 DOI: 10.21037/atm.2019.12.151]

99 **Tsilimigras DI**, Mehta R, Moris D, Sahara K, Bagante F, Paredes AZ, Farooq A, Ratti F, Marques HP, Silva S, Soubrane O, Lam V, Poultsides GA, Popescu I, Grigorie R, Alexandrescu S, Martel G, Workneh A, Guglielmi A, Hugh T, Aldrighetti L, Endo I, Pawlik TM. Utilizing Machine Learning for Pre- and Postoperative Assessment of Patients Undergoing Resection for BCLC-0, A and B Hepatocellular Carcinoma: Implications for Resection Beyond the BCLC Guidelines. *Ann Surg Oncol* 2020; **27**: 866-874 [PMID: 31696396 DOI: 10.1245/s10434-019-08025-z]

100 **Liu F**, Liu D, Wang K, Xie X, Su L, Kuang M, Huang G, Peng B, Wang Y, Lin M, Tian J, Xie X. Deep Learning Radiomics Based on Contrast-Enhanced Ultrasound Might Optimize Curative Treatments for Very-Early or Early-Stage Hepatocellular Carcinoma Patients. *Liver Cancer* 2020; **9**: 397-413 [PMID: 32999867 DOI: 10.1159/000505694]

101 **Choi GH**, Yun J, Choi J, Lee D, Shim JH, Lee HC, Chung YH, Lee YS, Park B, Kim N, Kim KM. Development of machine learning-based clinical decision support system for hepatocellular carcinoma. *Sci Rep* 2020; **10**: 14855 [PMID: 32908183 DOI: 10.1038/s41598-020-71796-z]

102 **Christou CD**, Tooulias A, Tsolakidis A, Papayiannis V, Pianetcki-Tsiantzi B, Tsoulfas G, Papadopoulos VN. Management of Hepatocellular Carcinoma in the Era of Individualized Therapy: The Experience of a Greek Tertiary Center. *Ochsner J* 2020; **20**: 272-278 [PMID: 33071659 DOI: 10.31486/toj.19.0092]

103 **Liao H**, Long Y, Han R, Wang W, Xu L, Liao M, Zhang Z, Wu Z, Shang X, Li X, Peng J, Yuan K, Zeng Y. Deep learning-based classification and mutation prediction from histopathological images of hepatocellular carcinoma. *Clin Transl Med* 2020; **10**: e102 [PMID: 32536036 DOI: 10.1002/ctm2.102]

104 **Gu J**, Zhao Z, Zeng Z, Wang Y, Qiu Z, Veeravalli B, Poh Goh BK, Kunnath Bonney G, Madhavan K, Ying CW, Kheng Choon L, Hua TC, Chow PKH. Multi-Phase Cross-modal Learning for Noninvasive Gene Mutation Prediction in Hepatocellular Carcinoma. *Annu Int Conf IEEE Eng Med Biol Soc* 2020; **2020**: 5814-5817 [PMID: 33019296 DOI: 10.1109/EMBC44109.2020.9176677]

105 **Chen G**, Wang R, Zhang C, Gui L, Xue Y, Ren X, Li Z, Wang S, Zhang Z, Zhao J, Zhang H, Yao C, Wang J, Liu J. Integration of pre-surgical blood test results predict microvascular invasion risk in hepatocellular carcinoma. *Comput Struct Biotechnol J* 2021; **19**: 826-834 [PMID: 33598098 DOI: 10.1016/j.csbj.2021.01.014]

106 **Zhang Y**, Lv X, Qiu J, Zhang B, Zhang L, Fang J, Li M, Chen L, Wang F, Liu S, Zhang S. Deep Learning With 3D Convolutional Neural Network for Noninvasive Prediction of Microvascular Invasion in Hepatocellular Carcinoma. *J Magn Reson Imaging* 2021; **54**: 134-143 [PMID: 33559293 DOI: 10.1002/jmri.27538]

107 **Wang G**, Jian W, Cen X, Zhang L, Guo H, Liu Z, Liang C, Zhou W. Prediction of Microvascular Invasion of Hepatocellular Carcinoma Based on Preoperative Diffusion-Weighted MR Using Deep Learning. *Acad Radiol* 2021; **28** Suppl 1: S118-S127 [PMID: 33303346 DOI: 10.1016/j.acra.2020.11.014]

108 **Liu QP**, Xu X, Zhu FP, Zhang YD, Liu XS. Prediction of prognostic risk factors in hepatocellular carcinoma with transarterial chemoembolization using multi-modal multi-task deep learning. *EClinicalMedicine* 2020; **23**: 100379 [PMID: 32548574 DOI: 10.1016/j.eclinm.2020.100379]

109 **Jiang YQ**, Cao SE, Cao S, Chen JN, Wang GY, Shi WQ, Deng YN, Cheng N, Ma K, Zeng KN, Yan XJ, Yang HZ, Huan WJ, Tang WM, Zheng Y, Shao CK, Wang J, Yang Y, Chen GH. Preoperative identification of microvascular invasion in hepatocellular carcinoma by XGBoost and deep learning. *J Cancer Res Clin Oncol* 2021; **147**: 821-833 [PMID: 32852634 DOI: 10.1007/s00432-020-03366-9]

110 **Cucchetti A**, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanello M, Grazi GL, Golfieri R, Grigioni WF, Pinna AD. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study. *J Hepatol* 2010; **52**: 880-888 [PMID: 20409605 DOI: 10.1016/j.jhep.2009.12.037]

111 **Mai RY**, Lu HZ, Bai T, Liang R, Lin Y, Ma L, Xiang BD, Wu GB, Li LQ, Ye JZ. Artificial neural network model for preoperative prediction of severe liver failure after hemihepatectomy in patients with hepatocellular carcinoma. *Surgery* 2020; **168**: 643-652 [PMID: 32792098 DOI: 10.1016/j.surg.2020.06.031]

112 **Shi HY**, Lee KT, Lee HH, Ho WH, Sun DP, Wang JJ, Chiu CC. Comparison of artificial neural network and logistic regression models for predicting in-hospital mortality after primary liver cancer surgery. *PLoS One* 2012; **7**: e35781 [PMID: 22563399 DOI: 10.1371/journal.pone.0035781]

113 **Liu D**, Liu F, Xie X, Su L, Liu M, Xie X, Kuang M, Huang G, Wang Y, Zhou H, Wang K, Lin M, Tian J. Accurate prediction of responses to transarterial chemoembolization for patients with hepatocellular carcinoma by using artificial intelligence in contrast-enhanced ultrasound. *Eur Radiol* 2020; **30**: 2365-2376 [PMID: 31900703 DOI: 10.1007/s00330-019-06553-6]

114 **Morshid A**, Elsayes KM, Khalaf AM, Elmohr MM, Yu J, Kaseb AO, Hassan M, Mahvash A, Wang Z, Hazle JD, Fuentes D. A machine learning model to predict hepatocellular carcinoma response to transcatheter arterial chemoembolization. *Radiol Artif Intell* 2019; **1** [PMID: 31858078 DOI: 10.1148/ryai.2019180021]

115 **Peng J**, Kang S, Ning Z, Deng H, Shen J, Xu Y, Zhang J, Zhao W, Li X, Gong W, Huang J, Liu L. Residual convolutional neural network for predicting response of transarterial chemoembolization in hepatocellular carcinoma from CT imaging. *Eur Radiol* 2020; **30**: 413-424 [PMID: 31332558 DOI: 10.1007/s00330-019-06318-1]

116 **Abajian A**, Murali N, Savic LJ, Laage-Gaupp FM, Nezami N, Duncan JS, Schlachter T, Lin M, Geschwind JF, Chapiro J. Predicting Treatment Response to Intra-arterial Therapies for Hepatocellular Carcinoma with the Use of Supervised Machine Learning-An Artificial Intelligence Concept. *J Vasc Interv Radiol* 2018; **29**: 850-857.e1 [PMID: 29548875 DOI: 10.1016/j.jvir.2018.01.769]

117 **Zhu Y**, Gao W, Guo Z, Zhou Y, Zhou Y. Liver tissue classification of en face images by fractal dimension-based support vector machine. *J Biophotonics* 2020; **13**: e201960154 [PMID: 31909553 DOI: 10.1002/jbio.201960154]

118 **Liang Z**, Zhou Q, Yang J, Zhang L, Liu D, Tu B, Zhang S. Artificial intelligence-based framework in evaluating intrafraction motion for liver cancer robotic stereotactic body radiation therapy with fiducial tracking. *Med Phys* 2020; **47**: 5482-5489 [PMID: 32996131 DOI: 10.1002/mp.14501]

119 **Liu Y**, Lei Y, Wang T, Kayode O, Tian S, Liu T, Patel P, Curran WJ, Ren L, Yang X. MRI-based treatment planning for liver stereotactic body radiotherapy: validation of a deep learning-based synthetic CT generation method. *Br J Radiol* 2019; **92**: 20190067 [PMID: 31192695 DOI: 10.1259/bjr.20190067]

120 **Taebi A**, Vu CT, Roncali E. Estimation of Yttrium-90 Distribution in Liver Radioembolization using Computational Fluid Dynamics and Deep Neural Networks. *Annu Int Conf IEEE Eng Med Biol Soc* 2020; **2020**: 4974-4977 [PMID: 33019103 DOI: 10.1109/EMBC44109.2020.9176328]

121 **Tong Z**, Zhou Y, Wang J. Identifying potential drug targets in hepatocellular carcinoma based on network analysis and one-class support vector machine. *Sci Rep* 2019; **9**: 10442 [PMID: 31320657 DOI: 10.1038/s41598-019-46540-x]

122 **Chaudhary K**, Poirion OB, Lu L, Garmire LX. Deep Learning-Based Multi-Omics Integration Robustly Predicts Survival in Liver Cancer. *Clin Cancer Res* 2018; **24**: 1248-1259 [PMID: 28982688 DOI: 10.1158/1078-0432.CCR-17-0853]

123 **Chicco D**, Oneto L. Computational intelligence identifies alkaline phosphatase (ALP), alpha-fetoprotein (AFP), and hemoglobin levels as most predictive survival factors for hepatocellular carcinoma. *Health Informatics J* 2021; **27**: 1460458220984205 [PMID: 33504243 DOI: 10.1177/1460458220984205]

124 **Liu X**, Lu J, Zhang G, Han J, Zhou W, Chen H, Zhang H, Yang Z. A Machine Learning Approach Yields a Multiparameter Prognostic Marker in Liver Cancer. *Cancer Immunol Res* 2021; **9**: 337-347 [PMID: 33431375 DOI: 10.1158/2326-6066.CIR-20-0616]

125 **Shi HY**, Lee KT, Wang JJ, Sun DP, Lee HH, Chiu CC. Artificial neural network model for predicting 5-year mortality after surgery for hepatocellular carcinoma: a nationwide study. *J Gastrointest Surg* 2012; **16**: 2126-2131 [PMID: 22878787 DOI: 10.1007/s11605-012-1986-3]

126 **Chiu HC**, Ho TW, Lee KT, Chen HY, Ho WH. Mortality predicted accuracy for hepatocellular carcinoma patients with hepatic resection using artificial neural network. *ScientificWorldJournal* 2013; **2013**: 201976 [PMID: 23737707 DOI: 10.1155/2013/201976]

127 **Qiao G**, Li J, Huang A, Yan Z, Lau WY, Shen F. Artificial neural networking model for the prediction of post-hepatectomy survival of patients with early hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; **29**: 2014-2020 [PMID: 24989634 DOI: 10.1111/jgh.12672]

128 **Guo L**, Wang Z, Du Y, Mao J, Zhang J, Yu Z, Guo J, Zhao J, Zhou H, Wang H, Gu Y, Li Y. Random-forest algorithm based biomarkers in predicting prognosis in the patients with hepatocellular carcinoma. *Cancer Cell Int* 2020; **20**: 251 [PMID: 32565735 DOI: 10.1186/s12935-020-01274-z]

129 **Saillard C**, Schmauch B, Laifa O, Moarii M, Toldo S, Zaslavskiy M, Pronier E, Laurent A, Amaddeo G, Regnault H, Sommacale D, Ziol M, Pawlotsky JM, Mulé S, Luciani A, Wainrib G, Clozel T, Courtiol P, Calderaro J. Predicting Survival After Hepatocellular Carcinoma Resection Using Deep Learning on Histological Slides. *Hepatology* 2020; **72**: 2000-2013 [PMID: 32108950 DOI: 10.1002/hep.31207]

130 **Zhong BY**, Ni CF, Ji JS, Yin GW, Chen L, Zhu HD, Guo JH, He SC, Deng G, Zhang Q, Li PC, Yu H, Song JJ, Teng GJ. Nomogram and Artificial Neural Network for Prognostic Performance on the Albumin-Bilirubin Grade for Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization. *J Vasc Interv Radiol* 2019; **30**: 330-338 [PMID: 30819473 DOI: 10.1016/j.jvir.2018.08.026]

131 **Zhong BY**, Yan ZP, Sun JH, Zhang L, Hou ZH, Yang MJ, Zhou GH, Wang WS, Li Z, Huang P, Zhang S, Zhu XL, Ni CF. Prognostic Performance of Albumin-Bilirubin Grade With Artificial Intelligence for Hepatocellular Carcinoma Treated With Transarterial Chemoembolization Combined With Sorafenib. *Front Oncol* 2020; **10**: 525461 [PMID: 33392064 DOI: 10.3389/fonc.2020.525461]

132 **Zhang L**, Xia W, Yan ZP, Sun JH, Zhong BY, Hou ZH, Yang MJ, Zhou GH, Wang WS, Zhao XY, Jian JM, Huang P, Zhang R, Zhang S, Zhang JY, Li Z, Zhu XL, Gao X, Ni CF. Deep Learning Predicts Overall Survival of Patients With Unresectable Hepatocellular Carcinoma Treated by Transarterial Chemoembolization Plus Sorafenib. *Front Oncol* 2020; **10**: 593292 [PMID: 33102242 DOI: 10.3389/fonc.2020.593292]

133 **Mähringer-Kunz A**, Wagner F, Hahn F, Weinmann A, Brodehl S, Schotten S, Hinrichs JB, Düber C, Galle PR, Pinto Dos Santos D, Kloeckner R. Predicting survival after transarterial chemoembolization for hepatocellular carcinoma using a neural network: A Pilot Study. *Liver Int* 2020; **40**: 694-703 [PMID: 31943703 DOI: 10.1111/liv.14380]

134 **Liu X**, Hou Y, Wang X, Yu L, Wang X, Jiang L, Yang Z. Machine learning-based development and validation of a scoring system for progression-free survival in liver cancer. *Hepatol Int* 2020; **14**: 567-576 [PMID: 32556865 DOI: 10.1007/s12072-020-10046-w]

135 **Ho WH**, Lee KT, Chen HY, Ho TW, Chiu HC. Disease-free survival after hepatic resection in hepatocellular carcinoma patients: a prediction approach using artificial neural network. *PLoS One* 2012; **7**: e29179 [PMID: 22235270 DOI: 10.1371/journal.pone.0029179]

136 **Bedon L**, Dal Bo M, Mossenta M, Busato D, Toffoli G, Polano M. A Novel Epigenetic Machine Learning Model to Define Risk of Progression for Hepatocellular Carcinoma Patients. *Int J Mol Sci* 2021; **22** [PMID: 33499054 DOI: 10.3390/ijms22031075]

137 **Schoenberg MB**, Bucher JN, Koch D, Börner N, Hesse S, De Toni EN, Seidensticker M, Angele MK, Klein C, Bazhin AV, Werner J, Guba MO. A novel machine learning algorithm to predict disease free survival after resection of hepatocellular carcinoma. *Ann Transl Med* 2020; **8**: 434 [PMID: 32395478 DOI: 10.21037/atm.2020.04.16]

138 **Wu CF**, Wu YJ, Liang PC, Wu CH, Peng SF, Chiu HW. Disease-free survival assessment by artificial neural networks for hepatocellular carcinoma patients after radiofrequency ablation. *J Formos Med Assoc* 2017; **116**: 765-773 [PMID: 28117199 DOI: 10.1016/j.jfma.2016.12.006]

139 **Divya R**, Radha P. An Optimized HCC Recurrence Prediction Using APO Algorithm Multiple Time Series Clinical Liver Cancer Dataset. *J Med Syst* 2019; **43**: 193 [PMID: 31115780 DOI: 10.1007/s10916-019-1265-x]

140 **Huang Y**, Chen H, Zeng Y, Liu Z, Ma H, Liu J. Development and Validation of a Machine Learning Prognostic Model for Hepatocellular Carcinoma Recurrence After Surgical Resection. *Front Oncol* 2020; **10**: 593741 [PMID: 33598425 DOI: 10.3389/fonc.2020.593741]

141 **Shen J**, Qi L, Zou Z, Du J, Kong W, Zhao L, Wei J, Lin L, Ren M, Liu B. Identification of a novel gene signature for the prediction of recurrence in HCC patients by machine learning of genome-wide databases. *Sci Rep* 2020; **10**: 4435 [PMID: 32157118 DOI: 10.1038/s41598-020-61298-3]

142 **Wang W**, Chen Q, Iwamoto Y, Han X, Zhang Q, Hu H, Lin L, Chen YW. Deep Learning-Based Radiomics Models for Early Recurrence Prediction of Hepatocellular Carcinoma with Multi-phase CT Images and Clinical Data. *Annu Int Conf IEEE Eng Med Biol Soc* 2019; **2019**: 4881-4884 [PMID: 31946954 DOI: 10.1109/EMBC.2019.8856356]

143 **Ji GW**, Zhu FP, Xu Q, Wang K, Wu MY, Tang WW, Li XC, Wang XH. Machine-learning analysis of contrast-enhanced CT radiomics predicts recurrence of hepatocellular carcinoma after resection: A multi-institutional study. *EBioMedicine* 2019; **50**: 156-165 [PMID: 31735556 DOI: 10.1016/j.ebiom.2019.10.057]

144 **Xu D**, Sheng JQ, Hu PJ, Huang TS, Lee WC. Predicting hepatocellular carcinoma recurrences: A data-driven multiclass classification method incorporating latent variables. *J Biomed Inform* 2019; **96**: 103237 [PMID: 31238108 DOI: 10.1016/j.jbi.2019.103237]

145 **Jianzhu B**, Shuang L, Pengfei M, Yi Z, Yanshu Z. Research on Early Warning Mechanism and Model of Liver Cancer Rehabilitation Based on CS-SVM. *J Healthc Eng* 2021; **2021**: 6658776 [PMID: 33520150 DOI: 10.1155/2021/6658776]

146 **Liao H**, Xiong T, Peng J, Xu L, Liao M, Zhang Z, Wu Z, Yuan K, Zeng Y. Classification and Prognosis Prediction from Histopathological Images of Hepatocellular Carcinoma by a Fully Automated Pipeline Based on Machine Learning. *Ann Surg Oncol* 2020; **27**: 2359-2369 [PMID: 31916093 DOI: 10.1245/s10434-019-08190-1]

147 **Saito A**, Toyoda H, Kobayashi M, Koiwa Y, Fujii H, Fujita K, Maeda A, Kaneoka Y, Hazama S, Nagano H, Mirza AH, Graf HP, Cosatto E, Murakami Y, Kuroda M. Prediction of early recurrence of hepatocellular carcinoma after resection using digital pathology images assessed by machine learning. *Mod Pathol* 2021; **34**: 417-425 [PMID: 32948835 DOI: 10.1038/s41379-020-00671-z]

148 **Liang JD**, Ping XO, Tseng YJ, Huang GT, Lai F, Yang PM. Recurrence predictive models for patients with hepatocellular carcinoma after radiofrequency ablation using support vector machines with feature selection methods. *Comput Methods Programs Biomed* 2014; **117**: 425-434 [PMID: 25278224 DOI: 10.1016/j.cmpb.2014.09.001]

149 **An C**, Jiang Y, Huang Z, Gu Y, Zhang T, Ma L, Huang J. Assessment of Ablative Margin After Microwave Ablation for Hepatocellular Carcinoma Using Deep Learning-Based Deformable Image Registration. *Front Oncol* 2020; **10**: 573316 [PMID: 33102233 DOI: 10.3389/fonc.2020.573316]

150 **Nam JY**, Lee JH, Bae J, Chang Y, Cho Y, Sinn DH, Kim BH, Kim SH, Yi NJ, Lee KW, Kim JM, Park JW, Kim YJ, Yoon JH, Joh JW, Suh KS. Novel Model to Predict HCC Recurrence after Liver Transplantation Obtained Using Deep Learning: A Multicenter Study. *Cancers (Basel)* 2020; **12** [PMID: 33003306 DOI: 10.3390/cancers12102791]

151 **Rodriguez-Luna H**, Vargas HE, Byrne T, Rakela J. Artificial neural network and tissue genotyping of hepatocellular carcinoma in liver-transplant recipients: prediction of recurrence. *Transplantation* 2005; **79**: 1737-1740 [PMID: 15973178 DOI: 10.1097/01.tp.0000161794.32007.d1]

152 **Guo D**, Gu D, Wang H, Wei J, Wang Z, Hao X, Ji Q, Cao S, Song Z, Jiang J, Shen Z, Tian J, Zheng H. Radiomics analysis enables recurrence prediction for hepatocellular carcinoma after liver transplantation. *Eur J Radiol* 2019; **117**: 33-40 [PMID: 31307650 DOI: 10.1016/j.ejrad.2019.05.010]

153 **Lau L**, Kankanige Y, Rubinstein B, Jones R, Christophi C, Muralidharan V, Bailey J. Machine-Learning Algorithms Predict Graft Failure After Liver Transplantation. *Transplantation* 2017; **101**: e125-e132 [PMID: 27941428 DOI: 10.1097/TP.0000000000001600]

154 **Briceño J**, Cruz-Ramírez M, Prieto M, Navasa M, Ortiz de Urbina J, Orti R, Gómez-Bravo MÁ, Otero A, Varo E, Tomé S, Clemente G, Bañares R, Bárcena R, Cuervas-Mons V, Solórzano G, Vinaixa C, Rubín A, Colmenero J, Valdivieso A, Ciria R, Hervás-Martínez C, de la Mata M. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol* 2014; **61**: 1020-1028 [PMID: 24905493 DOI: 10.1016/j.jhep.2014.05.039]

155 **Ershoff BD**, Lee CK, Wray CL, Agopian VG, Urban G, Baldi P, Cannesson M. Training and Validation of Deep Neural Networks for the Prediction of 90-Day Post-Liver Transplant Mortality Using UNOS Registry Data. *Transplant Proc* 2020; **52**: 246-258 [PMID: 31926745 DOI: 10.1016/j.transproceed.2019.10.019]

156 **AlAli AB**, Griffin MF, Butler PE. Three-Dimensional Printing Surgical Applications. *Eplasty* 2015; **15**: e37 [PMID: 26301002]

157 **Witowski JS**, Coles-Black J, Zuzak TZ, Pędziwiatr M, Chuen J, Major P, Budzyński A. 3D Printing in Liver Surgery: A Systematic Review. *Telemed J E Health* 2017; **23**: 943-947 [PMID: 28530492 DOI: 10.1089/tmj.2017.0049]

158 **Tack P**, Victor J, Gemmel P, Annemans L. 3D-printing techniques in a medical setting: a systematic literature review. *Biomed Eng Online* 2016; **15**: 115 [PMID: 27769304 DOI: 10.1186/s12938-016-0236-4]

159 **Murphy SV**, De Coppi P, Atala A. Opportunities and challenges of translational 3D bioprinting. *Nat Biomed Eng* 2020; **4**: 370-380 [PMID: 31695178 DOI: 10.1038/s41551-019-0471-7]

160 **Lee W**, Debasitis JC, Lee VK, Lee JH, Fischer K, Edminster K, Park JK, Yoo SS. Multi-layered culture of human skin fibroblasts and keratinocytes through three-dimensional freeform fabrication. *Biomaterials* 2009; **30**: 1587-1595 [PMID: 19108884 DOI: 10.1016/j.biomaterials.2008.12.009]

161 **Poldervaart MT**, Gremmels H, van Deventer K, Fledderus JO, Oner FC, Verhaar MC, Dhert WJ, Alblas J. Prolonged presence of VEGF promotes vascularization in 3D bioprinted scaffolds with defined architecture. *J Control Release* 2014; **184**: 58-66 [PMID: 24727077 DOI: 10.1016/j.jconrel.2014.04.007]

162 **Norotte C**, Marga FS, Niklason LE, Forgacs G. Scaffold-free vascular tissue engineering using bioprinting. *Biomaterials* 2009; **30**: 5910-5917 [PMID: 19664819 DOI: 10.1016/j.biomaterials.2009.06.034]

163 **Pattanaik S**, Arbra C, Bainbridge H, Dennis SG, Fann SA, Yost MJ. Vascular Tissue Engineering Using Scaffold-Free Prevascular Endothelial-Fibroblast Constructs. *Biores Open Access* 2019; **8**: 1-15 [PMID: 30637179 DOI: 10.1089/biores.2018.0039]

164 **Yoon No D**, Lee KH, Lee J, Lee SH. 3D liver models on a microplatform: well-defined culture, engineering of liver tissue and liver-on-a-chip. *Lab Chip* 2015; **15**: 3822-3837 [PMID: 26279012 DOI: 10.1039/c5lc00611b]

165 **Chang R**, Emami K, Wu H, Sun W. Biofabrication of a three-dimensional liver micro-organ as an in vitro drug metabolism model. *Biofabrication* 2010; **2**: 045004 [PMID: 21079286 DOI: 10.1088/1758-5082/2/4/045004]

166 **Faulkner-Jones A**, Fyfe C, Cornelissen DJ, Gardner J, King J, Courtney A, Shu W. Bioprinting of human pluripotent stem cells and their directed differentiation into hepatocyte-like cells for the generation of mini-livers in 3D. *Biofabrication* 2015; **7**: 044102 [PMID: 26486521 DOI: 10.1088/1758-5090/7/4/044102]

167 **Lee SY**, Kim HJ, Choi D. Cell sources, liver support systems and liver tissue engineering: alternatives to liver transplantation. *Int J Stem Cells* 2015; **8**: 36-47 [PMID: 26019753 DOI: 10.15283/ijsc.2015.8.1.36]

168 **US Department of Health and Human Services Food and Drug Administration**. Technical Considerations for Additive Manufactured Medical Devices: Guidance for Industry and Food and Drug Administration Staff Document. [cited 1 April 2021]. Available from: https://www.fda.gov/files/medical%20devices/published/Technical-Considerations-for-Additive-Manufactured-Medical-Devices---Guidance-for-Industry-and-Food-and-Drug-Administration-Staff.pdf

169 **Tsoulfas G,** Bangeas PI, Suri JS. 3D Printing: Applications in Medicine and Surgery. In: Vidalis T. 3D printing and bioprinting: ethical and legal issues. Amsterdam: Elsevier. 2020: 51-68[DOI: 10.1016/B978-0-323-66164-5.00004-0]

170 **Andorno R**. The Precautionary Principle: A New Legal Standard for a Technological Age. *J Int Biotechnol Law* 2004; **1**: 11 [DOI: 10.1515/jibl.2004.1.1.11]

171 **Rinaldi T**, Colotti G. Use of organoids in medicinal chemistry: challenges on ethics and biosecurity. *Future Med Chem* 2019; **11**: 1087-1090 [PMID: 31280671 DOI: 10.4155/fmc-2018-0341]

172 **Pashkov V**, Harkusha A. 3-D bioprinting law regulation perspectives. *Wiad Lek* 2017; **70**: 480-482 [PMID: 28711892]

173 **Gilbert F**, O'Connell CD, Mladenovska T, Dodds S. Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine. *Sci Eng Ethics* 2018; **24**: 73-91 [PMID: 28185142 DOI: 10.1007/s11948-017-9874-6]

174 **Sugawara E**, Nikaido H. Properties of AdeABC and AdeIJK efflux systems of Acinetobacter baumannii compared with those of the AcrAB-TolC system of Escherichia coli. *Antimicrob Agents Chemother* 2014; **58**: 7250-7257 [PMID: 25246403 DOI: 10.1128/AAC.03728-14]

175 **FDA**. Artificial Intelligence and Machine Learning in Software as a Medical Device. [cited 1 April 2021]. Available from: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

176 **FDA**. Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device ( SaMD ) - Discussion Paper and Request for Feedback. [cited 1 April 2021]. Available from: https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-andMachine-Learning-Discussion-Paper.pdf

177 **Topol EJ**. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; **25**: 44-56 [PMID: 30617339 DOI: 10.1038/s41591-018-0300-7]

178 **Institute of Medicine**. Medical devices and the public’s health: The FDA 510(k) clearance process at 35 years. *The National Academies Press* 2011 [DOI: 10.17226/13150]

179 Artificial Intelligence and Machine Learning to Accelerate Translational Research: Proceedings of a Workshop-in Brief. Washington (DC): National Academies Press (US); 2018-Jul-24 [PMID: 30048078]

180 **Hwang TJ**, Kesselheim AS, Vokinger KN. Lifecycle Regulation of Artificial Intelligence- and Machine Learning-Based Software Devices in Medicine. *JAMA* 2019; **322**: 2285-2286 [PMID: 31755907 DOI: 10.1001/jama.2019.16842]

181 **Price WN 2nd**, Gerke S, Cohen IG. Potential Liability for Physicians Using Artificial Intelligence. *JAMA* 2019; **322**: 1765-1766 [PMID: 31584609 DOI: 10.1001/jama.2019.15064]

182 **Crawford K**, Calo R. There is a blind spot in AI research. *Nature* 2016; **538**: 311-313 [PMID: 27762391 DOI: 10.1038/538311a]

183 **Park SH**, Han K. Methodologic Guide for Evaluating Clinical Performance and Effect of Artificial Intelligence Technology for Medical Diagnosis and Prediction. *Radiology* 2018; **286**: 800-809 [PMID: 29309734 DOI: 10.1148/radiol.2017171920]

184 **Anwar SM**, Majid M, Qayyum A, Awais M, Alnowami M, Khan MK. Medical Image Analysis using Convolutional Neural Networks: A Review. *J Med Syst* 2018; **42**: 226 [PMID: 30298337 DOI: 10.1007/s10916-018-1088-1]

185 **Le Berre C**, Sandborn WJ, Aridhi S, Devignes MD, Fournier L, Smaïl-Tabbone M, Danese S, Peyrin-Biroulet L. Application of Artificial Intelligence to Gastroenterology and Hepatology. *Gastroenterology* 2020; **158**: 76-94.e2 [PMID: 31593701 DOI: 10.1053/j.gastro.2019.08.058]

186 **Parikh RB**, Teeple S, Navathe AS. Addressing Bias in Artificial Intelligence in Health Care. *JAMA* 2019; **322**: 2377-2378 [PMID: 31755905 DOI: 10.1001/jama.2019.18058]

187 **Loftus TJ**, Tighe PJ, Filiberto AC, Efron PA, Brakenridge SC, Mohr AM, Rashidi P, Upchurch GR Jr, Bihorac A. Artificial Intelligence and Surgical Decision-making. *JAMA Surg* 2020; **155**: 148-158 [PMID: 31825465 DOI: 10.1001/jamasurg.2019.4917]

188 **Shortliffe EH**, Sepúlveda MJ. Clinical Decision Support in the Era of Artificial Intelligence. *JAMA* 2018; **320**: 2199-2200 [PMID: 30398550 DOI: 10.1001/jama.2018.17163]

189 **National Research Council**. For the Record: Protecting Electronic Health Information. *The National Academies Press* 1997 [DOI: 10.17226/5595]

190 **Hern A**. Royal Free breached UK data law in 1.6 m patient deal with Google's DeepMind. The Guardian. [cited 1 April 2021]. Available from: https://scholar.google.com/scholar?hl=en&as\_sdt=0%2C5&q=Royal+Free+breached+UK+data+law+in+1.6m+patient+deal+with+Google%27s+DeepMind&btnG=

191 **U.S. Department OF Labor**. Employee Benefits Security Administration. [cited 1 April 2021]. Available from: https://www.dol.gov/agencies/ebsa

192 **Nundy S**, Montgomery T, Wachter RM. Promoting Trust Between Patients and Physicians in the Era of Artificial Intelligence. *JAMA* 2019; **322**: 497-498 [PMID: 31305873 DOI: 10.1001/jama.2018.20563]

193 Machine Bias-ProPublica. [cited 1 April 2021]. Available from: https://www.propublica.org/article/machine-bias-risk-assessments-in-criminal-sentencing

194 Ethical, social, and political challenges of artificial intelligence in health. [cited 1 April 2021]. Available from: https://ge2p2-center.net/2018/05/06/ethical-social-and-political-challenges-of-artificial-intelligence-in-health/

195 **Yang YJ**, Bang CS. Application of artificial intelligence in gastroenterology. *World J Gastroenterol* 2019; **25**: 1666-1683 [PMID: 31011253 DOI: 10.3748/wjg.v25.i14.1666]

196 **Vayena E**, Blasimme A, Cohen IG. Machine learning in medicine: Addressing ethical challenges. *PLoS Med* 2018; **15**: e1002689 [PMID: 30399149 DOI: 10.1371/journal.pmed.1002689]

197 **Al’Aref SJ,** Singh G, Baskaran L, Metaxas D. Machine Learning in Cardiovascular Medicine. [cited 1 April 2021]. Available from: http://public.eblib.com/choice/PublicFullRecord.aspx?p=6404325

198 **Fang C**, An J, Bruno A, Cai X, Fan J, Fujimoto J, Golfieri R, Hao X, Jiang H, Jiao LR, Kulkarni AV, Lang H, Lesmana CRA, Li Q, Liu L, Liu Y, Lau W, Lu Q, Man K, Maruyama H, Mosconi C, Örmeci N, Pavlides M, Rezende G, Sohn JH, Treeprasertsuk S, Vilgrain V, Wen H, Wen S, Quan X, Ximenes R, Yang Y, Zhang B, Zhang W, Zhang P, Zhang S, Qi X. Consensus recommendations of three-dimensional visualization for diagnosis and management of liver diseases. *Hepatol Int* 2020; **14**: 437-453 [PMID: 32638296 DOI: 10.1007/s12072-020-10052-y]

199 **Witowski JS**, Pędziwiatr M, Major P, Budzyński A. Cost-effective, personalized, 3D-printed liver model for preoperative planning before laparoscopic liver hemihepatectomy for colorectal cancer metastases. *Int J Comput Assist Radiol Surg* 2017; **12**: 2047-2054 [PMID: 28144830 DOI: 10.1007/s11548-017-1527-3]

200 **Yang H**, Sun L, Pang Y, Hu D, Xu H, Mao S, Peng W, Wang Y, Xu Y, Zheng YC, Du S, Zhao H, Chi T, Lu X, Sang X, Zhong S, Wang X, Zhang H, Huang P, Sun W, Mao Y. Three-dimensional bioprinted hepatorganoids prolong survival of mice with liver failure. *Gut* 2021; **70**: 567-574 [PMID: 32434830 DOI: 10.1136/gutjnl-2019-319960]

201 **Ruffle JK**, Farmer AD, Aziz Q. Artificial Intelligence-Assisted Gastroenterology- Promises and Pitfalls. *Am J Gastroenterol* 2019; **114**: 422-428 [PMID: 30315284 DOI: 10.1038/s41395-018-0268-4]

202 **Patel VL**, Shortliffe EH, Stefanelli M, Szolovits P, Berthold MR, Bellazzi R, Abu-Hanna A. The coming of age of artificial intelligence in medicine. *Artif Intell Med* 2009; **46**: 5-17 [PMID: 18790621 DOI: 10.1016/j.artmed.2008.07.017]

203 **US Food and Drug Administration**. Developing a Software Precertification Program: A Working Model. [cited 1 April 2021]. Available from: https://www.fda.gov/media/113802/download

204 **Christou CD**, Tsoulfas G. The Role of microRNA in Hepatic Ischemia/Reperfusion Injury. *Microrna* 2020; **9**: 248-254 [PMID: 31995027 DOI: 10.2174/2211536609666200129162531]

205 **Panesar S**, Cagle Y, Chander D, Morey J, Fernandez-Miranda J, Kliot M. Artificial Intelligence and the Future of Surgical Robotics. *Ann Surg* 2019; **270**: 223-226 [PMID: 30907754 DOI: 10.1097/SLA.0000000000003262]

206 **Kassahun Y**, Yu B, Tibebu AT, Stoyanov D, Giannarou S, Metzen JH, Vander Poorten E. Surgical robotics beyond enhanced dexterity instrumentation: a survey of machine learning techniques and their role in intelligent and autonomous surgical actions. *Int J Comput Assist Radiol Surg* 2016; **11**: 553-568 [PMID: 26450107 DOI: 10.1007/s11548-015-1305-z]

207 **Wang DD**, Qian Z, Vukicevic M, Engelhardt S, Kheradvar A, Zhang C, Little SH, Verjans J, Comaniciu D, O'Neill WW, Vannan MA. 3D Printing, Computational Modeling, and Artificial Intelligence for Structural Heart Disease. *JACC Cardiovasc Imaging* 2021; **14**: 41-60 [PMID: 32861647 DOI: 10.1016/j.jcmg.2019.12.022]

208 **Volonté F**, Pugin F, Bucher P, Sugimoto M, Ratib O, Morel P. Augmented reality and image overlay navigation with OsiriX in laparoscopic and robotic surgery: not only a matter of fashion. *J Hepatobiliary Pancreat Sci* 2011; **18**: 506-509 [PMID: 21487758 DOI: 10.1007/s00534-011-0385-6]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interest for this article. The authors received no specific funding for this work.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** American Association of Transplant Surgeons; American Gastroenterological Association; American Society of Transplantation; American Hepatico Pancreatico Biliary Association (AHPBA); International Liver Transplantation Society; American College of Surgeons.

**Peer-review started:** April 15, 2021

**First decision:** June 4, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Casaca W, Brazil **S-Editor:** Wang JJ **L-Editor:** Webster JR **P-Editor:**

**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 | 0.910-0.9501,2, 0.897-0.9381,3, 75.0-91.52,4, 66.4-90.63,4, 1.0-88.82,5, 0.5-87.93,5 | [47] |
| 2 | Nam JY | Laboratory results, clinicopathological parameters | DNN | 424/3163 patients | HCC development in HBV cirrhosis | 0.7191,2, 0.7821,3 | [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 | 71.1-89.53,6 | [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: 0.902-0.9031,2, 0.903-0.9431,3, SVM: 0.879-0.9241,2, 0.727-0.8581,3, KNN: 0.680-0.7371,2, 0.734-0.7471,3 | [50] |
| 5 | Hashem S | Laboratory results, clinicopathological parameters | Several | 3099 chronic HCV patients1324 HCC patients | HCC development in HCV cirrhosis | 93.2-95.63,6, 0.955-0.9901,3, 86.3-91.83,4, 93.9-97.33,5 | [51] |
| 6 | Audureau E | Laboratory results, clinicopathological parameters | Several | 836/6687 | HCC development in HCV cirrhosis | 0.633-0.8071,2, 0.623-0.7151,7 | [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 | 0.759-0.8061,3 | [53] |
| 8 | Singal AG | Laboratory results, clinicopathological parameters | RF | 442/10507 | HCC development in cirrhosis | 0.711,2, 0.641,7 | [54] |

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

2Training.

3Internal validation.

4Sensitivity (%).

5Specificity (%).

6Accuracy (%).

7External 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.

**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 | 81.65-87.361,2,0.870-0.9403,2 | [55] |
| 2 | Zhao X | MicroRNA expression profiles | Several | 392 patients | HCC early detection | RF: 0.9823, SVM: 0.9703, DT: 0.8313 | [56] |
| 3 | Zhang ZM | Gene expression profiles | SVM | 1333/336 HCC samples | HCC early detection | 1001,2, 1002,4, 1002,5, 0.95973,6, 91.934,6, 1005,6,  | [57] |
| 4 | Tao K | Circulating tumor DNA | RF-based | 209/766/996 | HCC early detection | 0.874-0.9331,2, 0.812-0.9203,6 | [58] |
| 5 | Li G | MicroRNA and long non-coding RNA expression profiles | SVM, RF, DT | 361 patients | HCC early detection | RF: 0.9921,2, 95.62,4, 1002,5; SVM: 0.9922,3, 97.22,4, 98.02,5; DT: 0.9272,3, 98.32,4, 92.02,5 | [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 | 0.916-0.9422,3; 0.886-0.9542,3 | [60] |
| 7 | Yang Q | US imaging, clinical parameters | CNN | 16500/41252/37186 US images | Classification among 16 different focal liver lesions | 0.859-0.9663,7, 0.765-0.9252,3, 0.750-0.9243,6 | [61] |
| 8 | Virmani J | B-mode US imaging | NNE | 108 images | Classification among normal liver and four focal liver lesions | 95.01,2 | [62] |
| 9 | Shiraishi J | Microflow imaging of contrast-enhanced US | ANN | 103 focal liver lesions | Classification among HCC, metastasis, and hemangioma; histopathological grade | 86.9-93.81,2; 50.0-79.21,2 | [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 | 76.6-88.42,4,5, 82.51,2, 0.9212,3, 46.4-93.12,4, 91.9-98.62,5, 73.41,2, 0.766-0.9832,3 | [64] |
| 11 | Yasaka K | Contrast-enhancedCT imaging | CNN | 460/1006 patients | Classification among five types of focal liver lesions | 951,7, 841,6, 33-1004,6 | [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 | 0.811-0.8561,2, 0.862-0.9252,3, 0.744-0.9232,4, 0.725-0.9412,5 | [66] |
| 13 | Todoroki Y | Multiphasic CT imaging | CNN | 89 patients | Classification among five focal liver lesions | 79-1002,4 | [67] |
| 14 | Matake K | Clinicopathological parameters, CT imaging | ANN | 120 patients | Classification among four types of focal liver lesions | 0.9612,3 | [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: 0.9963,7, 0.8792,3. MRI model: 0.9993,7, 0.9252,3 | [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  | 922,4, 982,5; 0.9922,3; 944,6, 972,5 | [70,71] |
| 17 | Jansen MJA | MRI imaging | Extremely randomized trees classifier | 95 patients | Classification among five different focal liver lesions | 85-921,2, 62-932,4, 56-932,5 | [72] |
| 18 | Zhen SH | MRI scans | CNN | 1210/2016 | Classification among seven different focal liver lesions | 0.841-0.9873,6, 40.5-1004,6, 86.4-99.55,6 | [73] |
| 19 | Kiani A | Hematoxylin and eosin-stained WSI | CNN | 207/262/806 WSIs | Classification of HCC and CCA | 88.51,2, 84.21,6 | [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 | 0.9601,2, 0.9612,3; 89.61,2 | [75] |
| 21 | Lin H | Multiphoton microscopy | CNN | 217 images | Histopathological grade | 0.812-0.9411,2, 0.891-0.9172,3 | [76] |
| 22 | Yamashita R | Hematoxylin and eosin-stained WSI | CNN | 28/42/306 WSIs | HCC lesion detection | 0.9522,3, 0.9563,6 | [77] |
| 23 | Roy M | Hematoxylin and eosin-stained WSI | CAE | 50 WSIs | Segmentation of viable tumors | 91-951,2 | [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: 95.1-98.51,6; RF: 94-94.91,6 | [79] |
| 25 | Guo LH | Contrast-enhanced ultrasound imaging | MKL | 93 lesions | Classification of benign from malignant focal liver lesions | 90.411,2, 93.562,4, 86.892,5 | [80] |
| 26 | Bharti P | US imaging | Several | 189 images | Classify among normal liver, chronic liver disease, cirrhosis, and HCC | 96.61,2, 95.5-96.92,4, 98.0-99.82,5 | [81] |
| 27 | Brehar R | US imaging | CNN | 268 patients | Classification between HCC and cirrhotic parenchyma | 84.84-911,2, 0.91-0.952,3, 86.79-94.372,4, 82.95%-88.38%2,5 | [82] |
| 28 | Mao B | Ultrasound radiomics | Several | 114 patients | Classify primary from metastatic liver cancer | 0.729-0.8081,2, 0.737-0.7932,3, 0.775-0.8682,4, 0.667-0.8802,5 | [83] |
| 29 | Almotairi S | CT imaging | CNN | 20 CT scans | Tumor segmentation | 98.81,7 | [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 | 80-86.91,2, 0.932,3 | [86] |
| 32 | Krishan A | CT scans | Several | 1638 CT scans | Identification of liver lesions; classification between HCC and metastasis | 98.39-1001,2, 0.99-1.002,3; 76.38-87.011,2, 0.77-0.992,3 | [87] |
| 33 | Chen WF | CT scans | SED | 300 CT scans | Tumor segmentation | 0.9921, 0.952,3 | [88] |
| 34 | Khan AA | CT scans | Several | 179 patients | Classification between HCC and hemangioma | 96.6-98.31,6, 0.94-0.973,6, 94.23-97.035,6 | [88] |
| 35 | Mokrane FZ | Multiphasic CT radiomics | Several | 106/362/366 | Classification between HCC and non-HCC lesions | 0.813,7, 0.814,7, 0.725,7, 0.722,3, 0.663,6 | [90] |
| 36 | Mao B | CT radiomics, clinical parameters | Gradient boosting | 237/606 patients | Histopathological grade | 61.18-97.051,6, 0.7071-0.99643,7, 60.67-95.514,7, 51.35-80.415,7, 48.33-70.001,6, 0.6128-0.80143,6, 43.48-65.224,6, 37.84-81.085,6 | [91] |
| 37 | Preis O | PET/CT imaging | ANN | 98 patients | Classification between benign and malignant liver lesions | 0.896-0.9052,3 | [92] |
| 38 | Trivizakis E | Diffusion-weighted MRI | CNN, SVM | 134 patients | Classification between primary liver cancer and metastasis | 85.51,7, 831,2, 0.802,3, 932,4, 672,5 | [93] |
| 39 | Oestmann PM | Multiphasic MRI scans | CNN | 150/102 | Classification of HCC and non-HCC lesions | 94.11,7, 87.31,2, 0.9122,3. For HCC: 92.72,4, 82.02,5. For non-HCC: 82.02,4, 92.72,5 | [94] |
| 40 | Bousabarah K | MRI scans | CNN, RF | 174 patients/ 231 lesions | HCC detection | 0.66-0.752,4, 0.55-0.734,6 | [95] |
| 41 | Kim J | MRI scans | CNN | 4552,7/546 | HCC detection | 0.972,3, 942,4, 992,5, 0.903,6, 874,6, 935,6 | [96] |
| 42 | Jian W | Non-enhanced MRI scans | CNN | 75/406 HCCs | HCC detection | 65.00-77.001,6, 0.70-0.823,6, 64.55-78.184,6, 65.56-75.565,6 | [97] |
| 43 | Wu Y | Multiphasic MRI imaging | CNN | 89 HCCs | Classification between LI-RADS 3 and LI-RADS 4/5 | 0.767-0.9001,6, 0.90-0.953,6, 0.76-1.004,6, 0.633-0.8075,6 | [98] |

1Accuracy (%).

2Internal validation.

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

4Sensitivity (%).

5Specificity (%).

6External validation/testing.

7Training.

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.

**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 | 0.754-0.7841,2, 0.726-0.7411,3 | [100] |
| 3 | Choi GH | Demographics, laboratory results, tumor characteristics, clinicopathological parameters | RF | 813/208 patients | Treatment recommendation. Survival prediction | 76.6-88.43,4, 53.0-82.33,5, 69.3-95.83,6. 0.676-0.9591,3 | [101] |
| 4 | Chen M | Hematoxylin and eosin-stained WSI | CNN | 377 (training:validation = 3:1)/ 677 patients | Mutation prediction | 89.6-94.03,4, 0.720-0.8051,7 | [75] |
| 5 | Liao H | Hematoxylin and eosin-stained WSI | CNN | 309/653/787 | Mutation prediction | 0.519-0.9031,3, 0.605-0.7971,7 | [103] |
| 6 | Gu J | Multiphasic CT scans | CNN | 14 patients | Mutation prediction | 67.7-77.33,4 | [104] |
| 7 | Chen G | Laboratory results | LIME | 1007/10857 patients | MVI | 0.9181,2,0.8321,3, 0.9051,7 | [105] |
| 8 | Zhang Y | MRI scans | CNN | 158/79 patients | MVI | 0.811,2, 692,5, 792,6, 0.721,3, 553,5, 813,6 | [106] |
| 9 | Wang G | DWI | CNN | 60/402 HCCs | MVI | 66.81-77.502,3,4, 68.65-79.691,2,3, 56.56-76.472,3,5, 64.35-79.132,3,6 | [107] |
| 10 | Liu QP | CT radiomics | RF, SVM | 494 patients | MVI | 0.841,2, 0.791,3 | [108] |
| 11 | Jiang YQ | CT radiomics, clinical/laboratory parameters | Gradient boosting, CNN | 405 patients [220 MVI (+)/185 MVI (-)] | MVI | Gradient boosting: 0.900-0.9521,2, 0.873-0.8871,3. CNN:80.2-85.23,4, 0.900-0.9801,2, 0.875-0.9061,3, 0.659-0.9323,5, 0.757-0.9733,6 | [109] |
| 12 | Cucchetti A | Laboratory results, clinicopathological parameters, radiological data, histological data | ANN | 175/753 | MVI. Histopathological grade | 0.921,2, 91.03,4. 0.941,2, 93.33,4 | [110] |
| 13 | Mai RY | Laboratory results, clinicopathological parameters, liver volumetry | ANN | 265/88 patients | Posthemihepatectomy liver failure | 0.8801,2, 0.8761,3 | [111] |
| 14 | Shi HY | Laboratory results, clinicopathological parameters, surgery parameters | ANN | 22926 hepatectomies | In-hospital mortality following surgical resection | 97.283,4, 0.841,3, 95.934,7, 0.821,7, 78.405,7, 94.576,7 | [112] |
| 15 | Liu D | US radiomics | CNN | 89/41 patients | Classify full/partial response from stable disease/ progression in patients treated with TACE | 78-982,4, 0.82-0.981,2, 78.6-98.22,5, 74.2-96.72,6, 0.80-0.903,4, 0.80-0.931,3, 82.1-89.33,5, 73.3-92.33,6 | [113] |
| 16 | Morshid A | Multiphasic CT scans, BCLC stage | CNN, RF | 105 patients | Classify TACE-susceptible from TACE-refractory HCC | 62.9-74.23,4, 0.7331,3 | [114] |
| 17 | Peng J | CT imaging | CNN | 562/897/1387 | Classification of complete response, partial response, stable disease, and progressive disease following TACE | 84.02,4, 0.95-0.971,2, 82.8-85.14,7, 0.94-0.981,7 | [115] |
| 18 | Abajian A | MRI imaging, clinical data | RF | 36 patients | Classification of responders and non-responders following TACE | 663,4, 62.53,5, 67.93,6 | [116] |
| 19 | Zhu Y | FF-OCT | SVM | 285 en face images | Cancerous hepatic cell identification | 0.93781,7 | [117] |
| 20 | Liang Z | X-ray imaging | CNN | 2943/15423/14427 images | Localization of fiducial markers | 98.64,7 | [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 | 0.8827-0.88491,3, 53-65.443,5, 88.76-93.633,6 | [121] |

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

2Training.

3Internal validation.

4Accuracy (%).

5Sensitivity (%).

6Specificity (%).

7External 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.

**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 | 0.701,2, 0.66-0.701,3, 0.67-0.821,4 | [122] |
| 2 | Chicco D | 50 laboratory and clinical parameters | Several | 165 patients with HCC | Overall survival | RF: 77.21, 0.7665; Linear SVM: 77.15, 0.7631; MLP: 72.75, 0.6951; Radial SVM: 68.05, 0.6631; DT: 65.95, 0.6501 | [123] |
| 3 | Liu X | Laboratory results, data from immunochemistry of peripheral blood mononuclear cells, tumor characteristics | GBA classifier | 136/563/1054 | Risk of HCC-related death | 0.8441,2, 0.8271,3, 0.8061,4 | [124] |
| 4 | Shi HY | Laboratory results, clinicopathological parameters, tumor characteristics | ANN | 22926 patients | 5-yr survival following surgical resection | 96.573,5, 0.8851,3, 97.434,5, 0.8711,4, 74.234,6 | [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 | 98.5-99.52,5, 0.980-0.9931,2, 99.7-1002,6, 96.2-99.22,7, 72.1-85.13,5, 0.798-0.8751,3, 71.4-88.63,6, 50.0-82.13,7 | [126] |
| 6 | Qiao G | Laboratory results, clinicopathological parameters, tumor characteristics | ANN | 362/1813/1044 patients | Survival following surgical resection | 0.8551,2, 80.002,6, 73.402,7, 0.8321,3, 78.673,6, 75.703,7, 0.8291,4, 77.424,6, 78.084,7 | [127] |
| 7 | Guo L | RNA sequencing | RF | 239/130 patients | Overall survival | 893,5 | [128] |
| 8 | Saillard C | Hematoxylin and eosin-stained WSI | CNN | 309/3424 WSIs | Survival following surgical resection | 0.75-0.781,2, 0.68-0.701,4 | [129] |
| 9 | Zhong BY | ALBI/CTP stage | ANN | 548/1154/1754 | Survival of patients treated with chemoembolization as monotherapy | ALBI-based: 0.7991,4, 0.7001,4; CTP-based: 0.7291,4, 0.8021,4 | [130] |
| 10 | Zhong BY | ALBI/CTP stage | ANN | 319/614/1244 | Survival of patients treated with chemoembolization and sorafenib | ALBI-based: 0.7161,4, 0.8231,4; CTP-based: 0.7791,4, 0.6931,4 | [131] |
| 11 | Zhang L | CT scans, clinical features | CNN | 120/813 patients | Survival of patients treated with chemoembolization and sorafenib | 0.7171,2, 0.7141,3 | [132] |
| 12 | Liu QP | CT radiomics, clinical parameters | DNN-DAE | 243 patients | Overall survival following TACE | 0.87-0.931,3 | [108] |
| 13 | Mähringer-Kunz A | Routine laboratory tests and clinicopathological parameters | ANN | 125/57 patients | 1-yr overall survival following TACE | 0.771,2, 0.831,3, 77.83,6, 81.03,7 | [133] |
| 14 | Liu X | Routine laboratory tests and clinicopathological parameters | ANN | 1480/637 patients  | Progression-free survival. Overall survival | 0.8661,2, 0.7301,3. 0.8771,2, 0.8041,3 | [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: 0.963-0.9891,2, 93.5-96.32,6, 91.6-97.92,7, 0.774-0.8641,3, 70.0-78.73,6, 54.2-92.73,7. DT: 0.675-0.8251,2, 19.6-94.82,6, 45.8-97.92,7, 0.561-0.7181,3, 0-88.53,6, 37.5-96.43,7 | [135] |
| 16 | Bedon L | DNA methylation profiling | RF-based | 300/74 specimens | 6-mo progression-free survival | 67.1-80.62,5, 64.8-80.24,5 | [136] |
| 17 | Schoenberg MB | Routine laboratory tests and clinicopathological parameters | RFS | 127/53 patients | Disease-free survival following resection | 0.766-0.7881,3 | [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 | 0.72-0.771,3, 56.3-63.63,6, 70.0-71.83,7 | [138] |
| 19 | Divya R | Laboratory results, clinicopathological parameters, tumor characteristics | APO, SVM, RF | 152 patients | Recurrence following RFA | 95.53,5, 95.13,6, 95.83,7 | [139] |
| 20 | Huang Y | Demographics, laboratory tests, tumor characteristics | GBS classifier | 5928/1483 patients | Recurrence following surgical resection. Overall survival | 0.7041,2, 0.697-0.7131,3. 0.565-0.7361,2, 0.551-0.7511,3 | [140] |
| 21 | Shen J | Disease-free related genes sequencing | DT, SVM | 315 HCC patients | Recurrence following surgical resection | DT: 74.195, 0.751, 70.414,5. SVM:80.655, 0.5951 | [141] |
| 22 | Wang W | CT radiomics, clinical data | CNN, SVM, RF | 167 patients  | Early recurrence following surgical resection | 0.723-0.8251,3 | [142] |
| 23 | Ji GW | CT radiomics, laboratory results, clinicopathological parameters | Several | 210/1073/1534 patients | Recurrence time following surgical resection | Radiomics model: 0.748-0.7521,2, 0.781-0.8011,3, 0.733-0.7411,4. Clinical model: 0.716-0.7271,2, 0.707-0.7391,3, 0.696-0.7161,4 | [143] |
| 24 | Xu D | Routine laboratory tests and clinicopathological parameters, intra-operative parameters | BN-based | 995 patients | Recurrence time following surgical resection | 0.573,5, 0.573,6 | [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, 95.75, 0.951 | [145] |
| 26 | Yamashita R | Hematoxylin and eosin-stained WSI | CNN | 299/533/1984 WSIs | Recurrence following surgical resection | 0.7241,3, 0.6831,4 | [77] |
| 27 | Liao H | Hematoxylin and eosin-stained WSI | RF | 491 WSIs | Overall survival | 0.563-0.7061,3, 0.565-0.6211,4 | [146] |
| 28 | Saito A | Hematoxylin and eosin-stained WSI | SVM | 69/894 | Recurrence time following surgical resection | 99.82,5, 68.1-80.64,5 | [147] |
| 29 | Liang JD | Laboratory results, clinicopathological parameters | SVM | 83 patients | Recurrence following RFA | 73-823,5, 0.60-0.691,3, 77-863,6, 73-823,7 | [148] |
| 30 | An C | MRI scans | CNN | 141 HCC lesions | Local tumor progression following MWA | 0.7281 | [149] |
| 31 | Nam JY | Routine laboratory tests and clinicopathological parameters | DNN | 349/214 patients | Post-transplant HCC recurrence | 0.62-0.751,3, 0.63-0.763,6, 0.46-0.623,7 | [150] |
| 32 | Nam JY | Laboratory results, clinicopathological parameters, tumor characteristics | DNN | 349/214 transplanted patients | Post-transplant HCC recurrence | 0.751,3, 763,6, 463,7 | [150] |
| 33 | Rodriguez-Luna H | Genotyping data from microsatellite mutations/deletions | ANN | 19 transplanted patients | Post-transplant HCC recurrence | 89.53,5 | [151] |
| 34 | Guo D | Laboratory results, clinicopathological parameters CT radiomics | LASSO | 93/40 transplanted patients | Recurrence free-survival following liver transplantation  | 0.675-0.7851,2, 0.705-0.7891,3 | [152] |
| 35 | Lau L | Laboratory results, clinicopathological parameters, donor characteristics | ANN, RF | 90/90 transplants | Graft failure/primary nonfunction. 3-mo graft failure | ANN: 0.734-0.8351,3; RF: 0.787-0.8181,3. ANN: 0.5591,3, RF: 0.7151,3 | [153] |
| 36 | Briceño J | Laboratory results, clinicopathological parameters, surgical parameters, donor characteristics | ANN | 1003 liver transplants | 3-mo graft failure | 0.806-0.8211,3 | [154] |
| 37 | Ershoff BD | Laboratory results, clinicopathological parameters, donor characteristics | DNN | 46035/11509 | 90-d post-transplant survival | 0.695-0.7081,3, 30.9-35.83,6, 88.1-90.83,7 | [155] |

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

2Training.

3Internal validation.

4External validation/testing.

5Accuracy (%).

6Sensitivity (%).

7Specificity (%).

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.