Review

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Artificial intelligence and its role in guiding liver-directed therapy for hepatocellular carcinoma: Is it ready for prime time?

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Abstract

Artificial intelligence (AI) is an innovative discipline in medicine, impacting both hepatology and hepato-pancreato-biliary surgery, ensuring reliable outcomes because of its repeatable and efficient algorithms. A considerable number of studies about the efficiency of AI in the management of hepatocellular carcinoma (HCC) have been published. While its diagnostic role is well recognized, providing large amounts of quantitative radiological HCC features, its use in HCC treatment is still debated. Innovative use of AI may help to select the best approach for each patient as it is able to predict the outcomes after resection and/or other treatments. In this review, we assess the role of AI in selecting the best therapeutic option and predicting long-term risks after surgical or interventional treatments for HCC patients. Further studies are needed to consolidate AI applications.

Keywords: Artificial intelligence, precision medicine, HCC, hepatocellular carcinoma

INTRODUCTION

The concept of artificial intelligence (AI) was developed as early as the 1950s[1], though it gained

prominence decades later. AI is defined as a branch of informatics engaged in the design of software capable of providing performance to solve real-world problems, whose results must be equal to or better than human ones. It applies to several fields, including medicine[2,3].

Machine learning (ML) is part of AI in which computer programs learn from data, improving with experience. It is already a validated medical technique based on handcrafted features, while deep learning (DL) is a more recent subfield of ML[4].

In ML, clinicians and researchers list quantitative visual features and put them in a classification algorithm that allows them to categorize data[5]. Random Forest (RF) and support vector machines (SVM) are among the most used ML models.

On the other hand, DL can be considered as a more complex branch of ML that requires specific hardware and usually analyzes more parameters than the basic ML. DL was designed with human neuroanatomy in mind, and it is organized in multiple layers (from input to output data, with more intermediate layers in between)[6]. Artificial neural networks (ANNs) are the principal branch of DL, with convolutional neural networks (CNNs) being a subset of ANNs algorithm [Figure 1][7,8]. A neural network is divided into three levels (layers): input layer, output layer, and hidden layer. The input layer comprises the data available for the analysis and the outcome layers comprise the outcome. The network learns how to associate an input with a specific output through the utilization of examples. Once the "network training" is completed, it can link new outputs to other inputs not used during the previous phase[9]. DL is not a handcrafted system. It automatically finds features associated with a particular outcome [Table 1].

The use of AI methodologies in healthcare research increased during the last decade as a result of the advantageous ability to receive, process and interpret the complex mathematical elaboration of a large amount of data using only computer algorithms[8].

Notably, AI has proven its efficacy in skin cancer management, diagnosis of diabetic retinopathy and eye disease, identification of prostate cancer and brain metastasis, polyp detection during colonoscopy, and fractures identification on X-Ray[10-15].

HCC represents the fifth most widespread primitive cancer and one of the principal causes of malignancy-related death in the world[16]. HCC diagnosis is based on its characteristic radiological features in association with an α-fetoprotein (AFP) increase, and does not generally require a liver biopsy[17]. The radiological criteria widely known as LI-RADS (Liver Imaging Reporting and Data System) achieved good reliability by reducing imaging interpretation, facilitating communication with referring physicians, and improving research quality[18,19].

The cornerstone of treatment selection for HCC patients is the stage of the disease. For instance, liver transplantation (LT), liver resection (LR), or radiofrequency ablation (RFA) are all recommended in very-early and early-stage HCC[20]. In this context, identifying novel approaches to predict outcomes for each specific treatment among HCC patients is of paramount importance[6].

ARTIFICIAL INTELLIGENCE, RADIOMICS AND HEPATOCELLULAR CARCINOMA

Radiomics has rapidly emerged as a personalized medicine technology due to its ability to extract quantitative data from radiological images that cannot be detected by the human eye. It provides crucial information that can be processed, reducing errors, and optimizing timing in a diagnostic-therapeutic

Table 1. A schematization of the difference between artificial intelligence, machine learning, and deep learning

	Artificial intelligence	**Machine learning**	**Deep learning**
Definition	Branch of informatics engaged in designing software capable of providing performance by imitating human thinking and action	Subset of AI that automates analytical model building	Subset of ML based on artificial neural networks
Application	Building programs that utilize software to solve problems	Providing systems with the ability to automatically learn and improve performance from experience and data utilization	Providing systems with the ability to automatically process data and create patterns, improving performance via neural networks

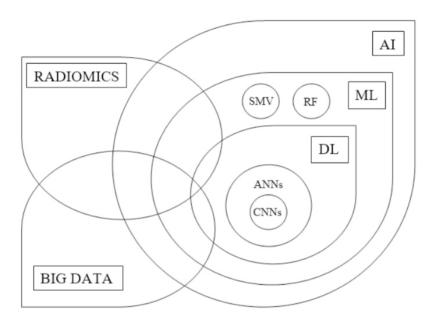AI: Artificial intelligence; ML: machine learning.

Figure 1. Relationship between artificial intelligence, machine learning, deep learning, and radiomics. AI: Artificial intelligence; ML: machine learning; RF: random forest; SMV: support vector machine; DL: deep learning; ANNs: artificial neural networks; CNNs: convolutional neural networks. This is an original image, created by the authors.

setting[21]. Its development is based on technological improvements and AI[8]. Radiomics generally includes several steps in its workflow:

- acquisition of images,

- selection of the region of interest (segmentation), which defines the volume for the features extraction phase,

- elaboration of features by software with pre- or post-processing tools (exploratory analysis),

- creation of a statistical model to select main data capable of predicting the objective of the analysis (model building)[22].

Each phase presents some criticalities and sources of variability that can affect the validity of the final model. Nevertheless, repeatable and efficient algorithms ensure reliable outcomes because of AI[23].

The refinement of prognostic models is fundamental to avoid unnecessary procedures and facilitate the individual management of HCC patients[24]. In the era of personalized medicine, the innovative use of AI might analyze certain tumor characteristics to predict the risk for recurrence or survival after resection, optimizing their effects with standardized risk stratification models[25].

LIVER TRANSPLANTATION

LT is the principal curative therapy for early-stage HCC[17]. Unfortunately, not all patients can benefit from it because the demand for LT exceeds the donor organ availability, and most of them undergo a subsidiary treatment, such as LR[26,27].

Linear regression and standard predictive modeling are fundamental for organ selection. Nowadays, donor risk index (DRI), model for end-stage liver disease (MELD), survival outcome following LT (SOFT), and the balance of risk score (BAR) are widely accepted models[28-31]. However, AI models are showing great potential in predicting LT short and long-term outcomes.

ML classifiers can be used to: list potential liver recipients and eventually remove them from the waiting list, and help to match and prognosticate candidates who may benefit from LT[32]. Moreover, they may identify factors that influence recurrence and survival and increase the use of marginal organs[32,33].

In terms of prediction, ANNs are the most popular classifiers due to their excellent capacity to analyze the numerous data involved in LT, including donor and recipient variables[34].

Most articles available focus on the risk of liver failure and overall survival at 3 months and/or at 1 year[34,35]. Briceño *et al.* explained that many of the current predictive models (i.e., MELD, DRI, SOFT, BAR) are too simplistic, because they assume a linearity among survival and LT variables, pointing out that LT follows a nonlinear pattern[35]. For this reason, ML scoring systems, using ANNs in conjunction with clinical judgment, represent the best way to predict the probability of graft survival and liver failure. ANNs allowed the authors to predict 3-month outcomes, achieving an area under the curve (AUC) of 0.82 and an accuracy of 0.91.

Some articles examined graft survival in the very short term, considering survival predictors at less than 30 days. Lau *et al.* elaborated an ANNs model to encourage clinical decisions, specifically for marginal organ allocation[36]. They identified the top 15 donor and recipient characteristics from a dataset of 276 variables, obtaining an AUC of 0.84, which is higher compared to traditional scoring systems.

Liu *et al.* focused on the prediction of patient survival after LT and created a ML model which includes patient's blood tests within 9 days before surgery[37]. Their experimental model outperformed the MELD score in predicting postoperative survival, achieving a specificity of 0.815 and an AUC of 0.771.

AI does not yet have a widely recognized role in LT. However, because of the lack of deceased donor organs, it is crucial to acquire and standardize a method to help clinicians to maximize LT. In this context, a recent multicenter Korean study[38] developed and validated a novel AI model, MoRAL-AI, to predict cancer recurrence after LT. The study involved 563 HCC patients from three principal LT centers in Korea who underwent LT. Some of the most influencing factors in MoRAL-AI were tumor diameter and number, AFP, age, and portal invasion. The MoRAL-AI demonstrated a C-index of 0.75, showing a significantly better capacity for predicting cancer recurrence after LT compared to standard predictive models.

Similarly, Ivanics *et al.* gathered data from 739 transplanted patients, including preoperative imaging, locoregional therapy and response, and post-transplantation outcomes, to elaborate an AI model with the purpose of predicting HCC recurrence with excellent results[39].

According to ClinicalTrials.gov (https://clinicaltrials.gov/), we are waiting for the final results of a study (NCT05200195) by Lai *et al.*, which includes more than 4000 transplanted HCC patients during the period 2000-2018 (international cohort, 3670 patients across 17 centers in Europe and Asia; external validation cohort, 356 patients transplanted at the Columbia University, New York). This large international study would prove that AI might be widely used in clinical settings in the near future.

The review of the literature is summarized in Table 2.

LIVER RESECTION

The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines[40] recommends LR for patients with very-early/early-stage HCC (stage 0-A) and well-preserved liver function.

Although the increasing evolution of surgery and the accuracy of perioperative clinical monitoring, post-hepatectomy liver failure (PHLF) is one of the most alarming complications after LR, particularly in cirrhotic patients, and is associated with a high risk of postoperative mortality[41]. The accurate assessment of the volume of the future liver remnant (FRL) is pivotal to reducing PHLF. Despite the globally accepted role of contrast-enhanced tomography scan (CT) for FLR assessment, recent fully automated liver volume assessments are showing good speed and accuracy compared to manual segmentation[42,43].

Accurate knowledge of liver anatomy is critical for any successful LR to reduce the risk of PHLF. In several cases, liver anatomy is so complex that it is difficult to reconstruct it mentally during LR, and preoperative imaging might be insufficient. Nowadays, FLR may be estimated with better accuracy, and HCC resectability may be carefully assessed thanks to innovative 3D visualization techniques[44]. However, 3D simulation techniques are costly and time-consuming. ML could be exploited to accelerate the 3D modelling process through quicker image acquisition and segmentation[45].

Several scoring systems are employed in clinical practice to determine the quality of the liver and predict PHLF, including Child-Pugh grade, MELD, albumin-bilirubin (ALBI), platelet-albumin-bilirubin (PALBI), the aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis index (FIB-4)[29,46-50]. However, most of these scoring systems are not always reliable for PHLF prediction. In this context, Mai *et al.* developed and validated an ANNs model in which they included blood tests (platelet count, total bilirubin, prothrombin time, and aspartate aminotransferase) and expected FLR[50]. This study showed a significantly more accurate prediction of severe PHLF (AUC value of 0.880) compared to the predictive systems.

Despite significant progress in the management of HCC, the recurrence rate after LR is still high (70%-80%) and is associated with a poor prognosis[51,52]. At the moment, there are no reliable risk stratification models for HCC recurrence after LR.

Several clinical features including number of nodules, maximum nodule diameter, cytological differentiation, and microvascular invasion (MVI) have been used to predict HCC recurrence, using a conventional Cox proportional hazards regression model[53-56], without satisfactory results.

Table 2. A summary of the articles describing the role of artificial intelligence in the prediction of hepatocellular carcinoma recurrence and/or survival after liver transplantation

Author	Year	Country	Method	Aim	Findings
Kazemi *et al.*[33]	2019	Iran	ML	To identify effective factors for patient survival after LT	The model predicted survival based on 26 identified effective factors. The AUC and model sensitivity were 0.90 and 0.81
Briceño *et al.*[35]	2014	Spain	ANNs	To use ANNs for D-R matching in LT and to compare its accuracy with validated scores	The models showed their best performance in predicting the probability of graft-survival (90.79%) and -loss (71.42%) for each D-R pair
Lau *et al.*[36]	2017	Australia	ML	To predict graft failure using donor and recipient factors, based on local data sets	The combination of factors used in DRI with the MELD score obtains an AUC of 0.764, whereas survival outcomes after LT score obtain an AUC of 0.638
Liu *et al.*[37]	2020	Taiwan	ML	To predict 30-day postoperative survival based on patient's preoperative physiological measurement values	The model achieves an AUC of 0.771 and a specificity of 0.815, showing superior discrimination power in predicting postoperative survival
Nam *et al.*[38]	2020	Korea	AI	To develop a novel model to predict tumor recurrence after LT by adopting AI (MoRAL-AI)	The largest weighted parameter in the MoRAL-AI was tumor diameter, followed by AFP, age, and PIVKA-II. The MoRAL-AI had better predictability of tumor recurrence after LT than conventional models
Ivanics *et al.*[39]	2022	Canada	ML	To leverage ML to develop an accurate post-LT HCC recurrence prediction calculator, to optimize the utility of limited donor organs	The model performed well with a concordance of 0.72 (95%CI: 0.63-0.81) and was not significantly outperformed

ML: Machine learning; LR: liver resection; DFS: disease-free survival; LT: liver transplantation; AUC: area under the curve; ANNs: artificial neural networks; D-R: donor-recipient; DRI: donor risk index; MELD: model for end-stage liver disease; AI: artificial intelligence; AFP: α-fetoprotein; PIVKA-II: protein induced by vitamin K absence-II; HCC: hepatocellular carcinoma; CI: confidence interval.

Biomarkers, including gene mutational status, proteins, and micro-RNA (miRNA), have been shown to be better survival predictors than TNM staging[57,58].

MVI represents an independent predictive factor of recurrence after LR and is consequently associated with poor prognosis[59]. Radiomic signatures have been elaborated, focusing on preoperative MVI detected on CT or magnetic resonance imaging (MRI), to enable HCC recurrence prediction[60-62]. Moreover, Dong *et al.* used radiomic algorithms based on grayscale ultrasound images to predict MVI in patients affected by HCC and scheduled for surgery[63].

Ho *et al.* explored the 1-, 3- and 5-year disease-free survival (DFS) prediction in HCC patients undergoing LR using ANNs[64]. The ANNs model collected demographic data, clinical features, surgical details, and outcomes, outperforming the conventional logistic regression models for prediction accuracy.

Saillard *et al.* elaborated a survival prediction model for HCC patients who underwent LR[65]. They processed all the HCC digital slides to create a DL model, achieving higher accuracy compared to main scores that include clinical, biological, and pathological features.

Schoenberg *et al.* recruited 181 patients who underwent partial LR and used their data to develop a ML algorithm to predict DFS after LR[26]. This model was built on 26 preoperatively laboratory variables and standard clinical-pathological parameters. A RF-based workflow was employed to process data, reporting 6 relevant DFS predictors: modified Glasgow Prognostic Score (mGPS), partial thromboplastin time (aPTT), C-reactive protein (CRP), age at surgery, largest tumor size and number of lesions.

Ji *et al.* acquired data from 470 patients to elaborate preoperative and postoperative ML-based radiomics models to predict HCC recurrence after LR[66]. The available preoperative CT imaging, AFP value, ALBI

grade and liver cirrhosis were used to create the preoperative model. The postoperative model was created by adding the presence of satellite nodules to the other predictors. The two models presented a C-index of 0.733 and 0.801, respectively, showing a superior accuracy after comparison with other non-radiomic models.

Zheng *et al.* tried to predict both HCC recurrence and postoperative survival in patients with solitary HCC, who were selected for LR using a ML-based radiomics model[67]. This model reached a good predictive survival accuracy with a C-index of 0.71. Moreover, adding TNM and Barcelona Clinic Liver Cancer (BCLC) stage to this model, they demonstrated a further increase of C-index.

Similarly, Zhang *et al.* used a radiomics model based on dynamic contrast-enhanced MRI to predict the survival of patients who underwent LR for HCC[62]. The tumor, perilesional, and non-tumoral parenchyma imaging was used to obtain three radiomics scores. The non-tumoral parenchyma score had the highest prognostic role showing a C-index of 0.72.

As already discussed, most of the models are based on preoperative imaging. Otherwise, Shen *et al.* proposed a ML-radiomics model trained on CT imaging within one month after treatment (surgery or ablation)[68]. They analyzed lesions suspicious for HCC recurrence. The AUC, accuracy, specificity, and sensitivity of this model for detecting recurrence were 0.89, 0.86, 0.75 and 0.91, respectively.

According to ClinicalTrials.gov (https://clinicaltrials.gov/), Zhujiang *et al.* are employing the innovative Watson computer system (an AI platform developed by IBM®) to select the best treatment options for each patient affected by HCC. This innovative ML-based system acquires a large amount of structured and unstructured data and selects the main clinical features to guide surgical decisions. A more comprehensive and reliable ML-based decision model available in daily clinical practice should be created. In this context, Zhejiang *et al.*'s study might be crucial.

The review of the literature is summarized in Table 3.

RADIOFREQUENCY ABLATION

According to EASL[40], RFA is suggested for patients affected by HCC at very-early stage and early stage (BCLC stage 0 and A) with sufficient functional liver reserve[20]. RFA can also be considered as an effective bridging therapy to LT for cirrhotic patients with small HCCs, and a valuable treatment option for patients with unresectable HCfC[22,69].

HCC recurrence after RFA is currently still frequent. DFS at 5 years is more than 70% and this is due to concomitant risk factors, including underlying viral hepatitis and cirrhosis[70-72]. Therefore, a ML-based predictive model for HCC recurrence is needed for HCC patients who undergo RFA to support clinical decision-making. In this context, patients who are identified as high-risk subjects could be selected for a tight follow-up.

Wu *et al.* developed an ANNs model to predict 1- and 2-year DFS in HCC patients scheduled for RFA[73]. They found that this model, which includes 15 clinical variables, had a better prediction power than scores with limited inputs, reaching an AUC of 0.77 and 0.72 for 1-year and 2-year DFS, respectively.

Table 3. A summary of the articles describing the role of artificial intelligence in the prediction of hepatocellular carcinoma recurrence and/or survival after liver resection

Author	Year	Country	Method	Aim	Findings
Schoenberg et al.[26]	2020	Germany	ML	To develop a ML algorithm to predict which patients are sufficiently treated with LR	Six predictors identified: mGPS, aPTT, CRP, largest tumor size, number of lesions and age at the time of LR. Predictive value of the model 0.78
Mai et al.[50]	2020	China	ANNs	To establish and validate an ANNs model to predict severe PHLF	ANNs accurately predicted the risk of severe PHLF after hemihepatectomy
Ma et al.[60]	2019	China	Radiomics	To develop and validate a radiomics nomogram for preoperative prediction of MVI	The proposed radiomics nomogram can preoperatively predict MVI
Xu et al.[61]	2019	China	Radiomics	To develop radiomic features from CT to predict MVI and clinical outcomes	Good performance for predicting MVI and clinical outcomes, without providing statistically significant added value to radiographic scores
Zhang et al.[62]	2020	China	Radiomics	To evaluate the efficiency of gadoxetic acid-enhanced MRI-based radiomics features for prediction of OS after LR	The combined model incorporating clinic-radiological and radiomics features showed an improved predictive performance with C-index of 0.92
Dong et al.[63]	2020	China	Radiomics	To establish a radiomic algorithm based on grayscale US images for preoperative predictions of MVI	Potential value to facilitate preoperative prediction of MVI
Ho et al.[64]	2012	Taiwan	ANNs	To develop prediction models for 1-, 3- and 5-year DFS after LR	The ANNs model outperformed the LR and DT models for predicting disease-free survival
Saillard et al.[65]	2020	France	DL	To build models for predicting survival after LR	Models had a higher discriminatory power than a score combining all baseline variables and helped predict prognosis
Ji et al.[66]	2019	China	ML; radiomics	To explore the potential of radiomics coupled with ML algorithms to improve the predictive accuracy for HCC recurrence	The two models showed superior prognostic performance, with C-index of 0.733-0.801 compared with models without radiomics
Zheng et al.[67]	2018	China	Radiomics	To estimate postoperative recurrence and survival in patients with solitary HCC	The model had a better prognostic performance as compared with traditional staging systems
Shen et al.[68]	2021	China	Radiomics	To develop a radiomics algorithm, improving the performance of detecting recurrence, based on post-treatment CT images within one month	The algorithm integrated radiomic features of post-treatment CT and showed superior performance compared with the conventional AFP

ML: Machine learning; LR: liver resection; mGPS: modified Glasgow Prognostic Score; aPTT: partial thromboplastin time; CRP: C-reactive protein; ANNs: artificial neural networks; PHLF: post-hepatectomy liver failure; MVI: microvascular invasion; CT: computed tomography; MRI: magnetic resonance imaging; OS: overall survival; US: ultrasound; DFS: disease-free survival; DT: decision tree; AFP: α-fetoprotein.

Liang *et al.* elaborated a predictive model for HCC recurrence focusing on patients who underwent RFA as their first treatment[74]. In this study, they tried to select few significant clinical features from a total of 16. They employed 5 widely used selection methods and combined them with SVM to develop a predictive model with better sensitivity and specificity.

Currently, the research, development, and clinical application of innovative post-RFA predictive models remain inadequate.

The review of the literature is summarized in Table 4.

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

HCC receives its blood supply primarily from hepatic artery branches. Hence, transcatheter arterial chemoembolization (TACE) represents a highly selective therapeutic option that might deliver a high concentration of chemotherapeutics to target tumors, sparing the surrounding hepatic tissue[75].

Table 4. A summary of the articles describing the role of artificial intelligence in the prediction of hepatocellular carcinoma recurrence and/or survival after radiofrequency ablation and transcatheter arterial chemoembolization

Author	Year	Country	Method	Aim	Findings
Wu et al.[73]	2017	Taiwan	ANNs	To build ANNs models with HCC-related variables to predict the 1- and 2-year DFS after RFA	Parameters for performance assessment of 1-year DFS prediction were: accuracy 85.0%, sensitivity 75.0%, specificity 87.5%, and an AUC 0.84. For 2-year DFS prediction, the values of accuracy, sensitivity, specificity, and AUC were 67.9%, 50.0%, 85.7%, and 0.75, respectively
Liang et al.[74]	2014	Taiwan	ML	To develop recurrence predictive models after RFA	The developed model had a sensitivity, specificity, accuracy, PPV, NPV, and AUC of 67%, 86%, 82%, 69%, 90%, and 0.69, respectively
Mähringer-Kunz et al.[81]	2020	Germany	ANNs	To develop a survival prediction model for patients undergoing TACE using novel ML algorithms and to compare it to conventional prediction scores	The model had a promising performance for predicting 1-year survival, with an AUC of 0.77 ± 0.13, a PPV of 87.5%, and a NPV of 68.0%
Liu et al.[82]	2020	China	Radiomics	To validate an AI-based radiomics strategy for predicting responses to a first TACE treatment by quantitatively analyzing CEUS	The AUC for the model was 0.93. It can be used to achieve accurate and personalized prediction
Oezdemi et al.[83]	2020	USA	ML	To predict the response to TACE using CEUS-derived imaging features	The model may help to provide personalized therapy planning. Number of vessels, number of bifurcations and vessel-to-tissue ratio are the dominant features for the prediction of long-term TACE response
Morshid et al.[84]	2019	USA	ML	To evaluate a fully automated ML algorithm that uses pre-therapeutic quantitative CT imaging features and clinical factors to predict response to TACE	The model's response prediction accuracy rate was 74.2%, using a combination of the BCLC stage plus quantitative imaging features vs. 62.9% using the BCLC stage alone
Peng et al.[85]	2020	China	ANNs	To train and validate a model of DL for the prediction of the response of patients with intermediate-stage HCC undergoing TACE	The model had an accuracy of 84.3% and AUC of 0.97, 0.96, 0.95, and 0.96 for complete response, partial response, and stable disease, respectively
Abajian et al.[86]	2018	USA	ML	To develop a method to predict response to TACE treatment prior to LR	The model predicted TACE response with an overall accuracy of 78%

ANNs: Artificial neural networks; HCC: hepatocellular carcinoma; DFS: disease-free survival; RFA: radiofrequency ablation; AUC: area under the curve; ML: machine learning; PPV: positive predictive value; NPV: negative predictive value; TACE: transcatheter arterial chemoembolization; AI: artificial intelligence; CEUS: contrast-enhanced ultrasound; CT: computed tomography; BCLC: Barcelona Clinic Liver Cancer; DL: deep learning; LR: liver resection.

According to the BCLC classification, ACE is the gold standard for cirrhotic patients with multinodular, unresectable HCC (stage B) with preserved liver function[22,24].

One of the best outcome predictors for cirrhotic patients affected by stage B HCC is the response to the first TACE. Large tumors often respond unsatisfactorily to a single TACE session. Repeating sessions increase the risk of multiple adverse effects including liver and/or kidney failure, gastroduodenal ulceration, and death[76,77].

In this context, several conventional scoring systems have been created to support critical clinical decisions in case of uncertain retreatment with TACE, including Assessment for Retreatment with TACE (ART), Child-Pugh, Objective Radiological Response (SNACOR), and Child-Pugh and Response (ABCR)[78-80].

Mähringer-Kunz *et al.* developed an ANNs prediction model for survival after TACE combining all of the above-mentioned scores[81]. They elaborated a 1-year survival model obtaining better results compared to ART, SNACOR, and ABCR scores.

Liu *et al.* employed radiomics to predict personalized response to a first TACE session by quantitatively analyzing contrast-enhanced ultrasound (CEUS) cines[82]. This DL radiomics-based CEUS model established high reproducibility and presented an AUC of 0.93.

Oezdemir *et al.* used morphological and anatomical features detected by CEUS to create a ML-based predictive model for HCC patients treated with TACE[83]. Their study involved 36 HCC patients and revealed that number of vessels, number of bifurcations, and vessel-to-tissue ratio represented the principal features for the prediction of long-term TACE response, with an accuracy of 86%.

Morshid *et al.* managed to improve the accuracy of predicting HCC response to TACE thanks to a ML-based model, which combines BCLC stage and quantitative image features[84]. They achieved a prediction accuracy rate of 74.2%.

Peng *et al.* used preoperative CT images to elaborate a DL prediction model of response to TACE[85]. Notably, they focused on every possible occurrence after TACE: complete response, partial response, stable disease, and progressive disease. This DL model reached an accuracy of 84.3% and an AUC tending to 1 for each occurrence after TACE.

Abajian *et al.* used ML to combine MRI images with clinical data to predict response to TACE in a case series of 36 patients, reaching an overall accuracy of 78%[86].

Hypoxia is the main mechanism of cell death induction in embolization because it produces complex molecular changes, promoting cell death or cell survival depending on genetic features[87]. Recent studies used AI to focus on the efficacy of TACE by analyzing these genetic characteristics. For example, Ziv *et al.* developed the linear SVM (a ML supervised model) to study genetic mutations[88]. They managed to identify the upregulation of the WNT/β-catenin signaling pathway, which is highly sensitive to embolization.

The review of the literature is summarized in Table 4.

MEDICAL THERAPY

In the era of personalized medicine, the knowledge of HCC molecular features (i.e., genome, transcriptome, proteome, and metabolome) can help stratify tumor aggressiveness and choose the best therapy accordingly. Notably, the identification of commonly altered pathways has traditionally been more difficult in HCC than in other cancers. In this context, AI can be helpful in the fields of target-based therapeutic discovery, systems-based approaches, and immune HCC landscape definition[89].

The targeted therapy with Sorafenib is widely used as first-line therapy in advanced HCC patients, but it is associated with delicate dose-limiting toxicity and a high risk of drug resistance[90-92]. In this context, AI should emerge as a tool to individually predict the risk for adverse effects in this group of patients. Abuhelwa *et al.* developed a predictive model including bilirubin, hemoglobin, and sex to define subgroups at risk of developing severe hand-foot syndrome[93]. Their model was validated with ML.

The progress made in immunotherapy (IT) with checkpoint inhibitors plays an increasingly decisive role in controlling the progression of HCC[94]. AI represents an emerging tool to validate predictive markers and anticipate the effectiveness of this innovative medical therapy.

Table 5. Artificial intelligence applications in the therapy of hepatocellular carcinoma

Artificial intelligence and HCC treatment
Facilitates D-R matching for LT
Predicts short and long-term outcomes after LT
Predicts the risk of MVI after LR
Predicts PHLF after LR
Predicts RFS and OS after LR
Predicts RFS after RFA
Predicts response to TACE
Predicts medical therapy toxicity
Identifies markers associated with response to IT
Identifies new drug targets

HCC: Hepatocellular carcinoma; D-R: donor-recipient; LT: liver transplantation; MVI: microvascular invasion; LR: liver resection; PHLF: post-hepatectomy liver failure; RFS: recurrence-free survival; OS: overall survival; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; IT: immunotherapy.

Tumor immune microenvironment and cancer stem cells (CSCs) behavior are clearly related to HCC progression and drug resistance. ML has been recently applied to realize algorithms that highlight different stemness subtypes and predict response to IT according to the stemness index[95].

Sangro *et al.* reported how the expression of the inflammatory markers anti-programmed death 1 receptor (PD1) and PD-ligand 1 (PD-L1), and some particular immune gene signatures are associated with improved survival and response in patients treated with nivolumab, a PD1 inhibitor utilized in patients with advanced HCC[96]. In this setting, Zeng *et al.* trained CNNs using digital histological slides and gene signature status as labels and investigated three deep learning approaches to predict immune and inflammatory gene signatures directly from HCC histology[97]. The clustering-constrained attention multiple-instance learning (CLAM) model proved to be the best in predicting the upregulation of the immune gene signatures, with AUCs ranging from 0.78 to 0.91.

Lui *et al.* included 47 clinical variables in 6 different ML models to analyze the 1-year cancer-related mortality in advanced HCC patients treated with IT[98]. They demonstrated an optimal predictive capacity of ML compared to C-reactive protein and AFP in both the ImmunoTherapY score (CRAFITY) and ALBI score. In this study, it was also highlighted how baseline AFP, bilirubin, and alkaline phosphatase act as three common risk factors in all the models.

In the drug discovery setting, RF, SVM, neural networks, and the gradient boosting machine were compared by using nested cross-validation to evaluate the gene-disease association data from the Open Targets platform to predict therapeutic targets that are actively being pursued by pharmaceutical companies or are already on the market. On a test set, the neural network classifier achieved the best accuracy with an AUC of 0.76 in predicting novel targets[99].

Tong *et al.* employed the human protein-protein interaction (PPI) network to potentially map drug target genes working on a genetic dependency score[100]. They combined these manually collected drug target genes with gene expression profiles, and clinical data and they used SVM to build a drug target predictor. Similarly, Cetin-Atalay *et al.* used the CROssBAR innovative system to integrate a large number of biomedical data sources to define ligands of HCC-associated proteins as potential drug targets and repurpose known small molecule inhibitors as potential drug candidates[101]. They used ML as a virtual

screening in target identification and drug discovery, developing DL-based drug/compound-target protein interaction predictors.

Table 5 summarizes the applications of AI in the treatment of HCC.

CONCLUSION

AI has become an important tool in HCC diagnosis, revealing a large amount of quantitative radiological HCC features. It has also shown very promising results in the fields of segmentation, prediction of recurrence and survival after specific treatments, thanks to its ability to process large quantities of data. It might become crucial in defining a tailored approach for each patient and may be routinely used in clinical practice for HCC management. Nevertheless, based on its complexity and the need for further validation, additional studies are necessary to implement its acceptance and diffusion. The most skeptical opponents to AI should consider that it is a tool to support human intelligence, not replace it.

DECLARATIONS

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Authors' contributions
Made substantial contributions to conception and design of the study: Panettieri E, Campisi A
Made significant contributions to the writing of the manuscript: Campisi A, Bianchi V
Contributed to the production of the final draft and gave administrative, technical, and material support: Giuliante F, De Rose AM

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