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Artificial Intelligence in hepatology, liver surgery and transplantation: Emerging applications and frontiers of research

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Abstract

The integration of artificial intelligence (AI) and augmented realities into the medical field is being attempted by various researchers across the globe. As a matter of fact, most of the advanced technologies utilized by medical providers today have been borrowed and extrapolated from other industries. The introduction of AI into the field of hepatology and liver surgery is relatively a recent phenomenon. The purpose of this narrative review is to highlight the different AI concepts which are currently being tried to improve the care of patients with liver diseases. We end with summarizing emerging trends and major challenges in the future development of AI in hepatology and liver surgery.

Key Words: Liver disease; Machine learning; Deep learning; Artificial neural networks; Transplantation; Hepatectomy

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Core Tip: Much of the advanced technologies utilized by medical providers today have

quality classification

Grade A (Excellent): 0
 Grade B (Very good): B
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

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INTRODUCTION

Artificial intelligence (AI) is gradually changing the way that medicine is being practiced across the world, with technological advancements in the field of imaging, navigation and robotic intervention. It is increasingly being used for risk stratification, genomics, imaging and diagnosis, precision medicine, and drug discovery. The introduction of AI in hepatology and liver surgery is more recent and it has a strong root in machine learning (ML)-based algorithms, imaging and navigation, with early techniques focused on feature detection and computer-assisted intervention for both pre-operative planning and intra-operative guidance. AI-based solutions can assist in timely detection of liver tumors, more precise diagnosis and predicting disease course as well as outcomes. Diseases affecting the liver are heterogeneous and complex in nature, caused by various etiological factors, such as genetics, sex, ethnicity, body mass index (commonly known as BMI), environmental exposures to toxins, and comorbid conditions like diabetes mellitus. AI-based approaches could be highly useful in analyzing these various types of complex data in hepatology practice and research.

Components of AI systems can be broadly classified into expert system, search algorithm, ML, and deep learning (DL)[1]. Among them, ML is the most commonly used term, which can be considered as a branch of AI in which computers learn from data, with emphasis on computational algorithms, and analyze tons of data within no time[1]. ML can be of supervised or unsupervised learning. Supervised learning can be defined as a kind of ML which helps in predicting a known outcome, based on inputs, in the presence of an expert 'supervisor'[2]. While unsupervised learning is another type of ML, which can discover naturally occurring patterns without a pre-defined outcome, in the absence of an expert 'supervisor'[2]. The artificial neural network (ANN) is a type of statistical system used to derive outputs, based on interactions of weighted inputs and outputs and it mimics the intricate architecture of neuronal networks in the brain[3]. One other subset of ML is DL, which uses automatic discovery of representations from raw data (representation learning) for detection or classification[4]. Convolutional neural network (CNN) is a kind of DL ANN which utilizes multiple building blocks, such as pooling layers and convolution layers, and performs feature extraction to yield final output[5]. CNNs can be considered as one of the most successful DL models, due to their exceptional capability for processing spatial information[6]. Another type of neural network, known as recurrent neural network, utilizes feedback connections and displays great accuracy in labelling and forecasting sequential data[7]. Radiomics is another method in AI that extracts innumerable features from radiographic images by using data-characterization algorithms[8]. These radiomic features have the potential to unearth many characteristics of a disease that fail to be appreciated by the naked eye examination of a clinician. Radiomics can be coupled with AI, as it is capable of handling a massive amount of data in contrast to the traditional statistical methods[9]. Almost all AI techniques require a large dataset comprising laboratory and radiological findings, and outcome data. In the future, AI will definitely be useful in supporting clinical decisions, minimizing medical errors, and forecasting clinical outcomes. In this article, we will review the emerging role of AI in the management liver diseases, liver surgery

and liver transplantation.

AI IN LIVER DISEASES

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic globally, in part attributable to the increasing incidence of obesity and insulin resistance resulting in liver accumulation of free fatty acids and triglycerides. NAFLD patients are at higher risk of liver-related as well as cardiovascular-related mortality, and it is rapidly becoming the chief indication for liver transplantation[10,11]. Besides, NAFLD has been identified as a major risk factor for hepatocellular carcinoma (HCC)[12]. ML has been explored extensively for pattern recognition in NAFLD (Table 1). Timely identification of patients with NAFLD is paramount to arrest the disease progression to cirrhosis and related complications. Liver biopsy remains the gold standard for definitive diagnosis but it is invasive and inappropriate for screening. The development of non-invasive advanced imaging, biochemical and genetic tests as well as AI techniques will undoubtedly offer clinicians a great deal of information in the near future that can be utilized for early diagnosis and targeted treatment options.

Imaging of liver with ultrasound (US) is considered as a keystone for the initial diagnosis of NAFLD as it is widely available and image acquisition is easy. Magnetic resonance imaging (MRI) with proton density fat fraction (PDFF) has been considered as the reference standard in the quantification of hepatic steatosis; however, this technique has its own limitations, like cost and limited availability[13]. Methods exist for sonographic diagnosis of NAFLD, but these are often qualitative. Han *et al*[14] attempted to develop and evaluate DL algorithms that use radiofrequency data for NAFLD assessment, with MRI-derived PDFF as the reference. The investigators analyzed data of 204 prospectively enrolled adult research participants. The image acquisition was conducted *via* a typical right intercostal approach, with a 1–4 MHz curved probe and time-gain compensation, with the addition of 10 radiofrequency frames acquired during a breath-hold in shallow expiration. They found that DL algorithms with radiofrequency US data are very precise for diagnosis of NAFLD and hepatic fat fraction quantification with fairly good correlation (Pearson $r = 0.85$) with MRI PDFF when other causes of steatosis are excluded[14]. In another study, Byra *et al* [15] used CNN to automatically detect the amount of fat in liver from US images and showed high accuracy [area under the curve (AUC) of 0.98] compared to gold-standard liver biopsy, thus showing that ML can help in overcoming the issue of inter-operator variability as well.

ML-based algorithms were also used for early identification of patients with high risk for development of hepatic steatosis. Perveen *et al*[16] used a systematic ML-based decision-tree method to analyze data from electronic medical records in four Canadian populations and accurately predicted risk of development and progression of NAFLD. A similar application of ML to predict and screen for NAFLD in a Chinese population was carried out by Ma *et al*[17] and showed high accuracy, sensitivity and specificity. In a comparison study of different ML-based algorithms, the investigators found that all ML-based algorithms were found to be more efficient than the hepatic steatosis index (commonly known as HSI; F-measure 0.524) and the Fatty Liver Index (commonly known as FLI; F-measure, 0.318) and the Bayesian network model performed the best of 11 ML-based algorithms in the classification of patients with NAFLD (F-measure, 0.655).

ML-based algorithms have been deployed to analyze images from liver biopsy by using 47 unique liver biopsy images with manual annotations, performed by two pathologists. Vanderbeck *et al*[18] devised a classification algorithm. By utilizing a color analysis protocol, the algorithm was able to find out key features in biopsy specimens (macrosteatosis, portal veins, sinusoids and bile ducts) with good precision and high recall (> 82%)[18]. Similarly, Gawrieh *et al*[19] developed an AI-based tool to accurately quantify hepatic fibrosis and architectural pattern in liver biopsy specimens. These examples show that various ML tools may be chosen for application in appropriate situations for a specific problem.

Viral hepatitis

Progression to cirrhosis is an important event to be monitored in patients with hepatitis B virus (HBV) as well as hepatitis C virus (HCV) infections. Rates of progression to cirrhosis vary dramatically across individuals and not all patients progress to cirrhosis. Accurate risk stratification is essential to avoid excess monitoring

Table 1 Review of articles where artificial intelligence has been studied in the context of non-alcoholic liver disease

Ref.	Dataset	Number	ML algorithms	Problem	Performance measures
Byra <i>et al</i> [15], 2018	Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Poland	55	Deep CNN	Automatically diagnose the amount of fat in the liver from US images	AUROC, Delong statistical test, lasso regression method, Spearman correlation coefficient, Meng test
Perveen <i>et al</i> [16], 2018	CPCSSN	667907	Decision tree	Classification, NAFLD progression risk	Micro- and Macro-average of Precision, Recall and F-measure, MCC, AUROC
Ma <i>et al</i> [17], 2018	First Affiliated Hospital, College of Medicine, Zhejiang University, China	10508	Several, Weka open source software	Classification, feature selection	Accuracy, specificity, precision, recall (<i>i.e.</i> sensitivity), and the F-measure
Vanderbeck <i>et al</i> [18], 2014	Medical College of Wisconsin, Milwaukee, United States	59	SVM	Automated assessment of histological features of NAFLD	Precision rate, recall rate, and AUROC
Meffert <i>et al</i> [68], 2014	SHIP	4222	Boosting algorithm, discrimination and calibration plots	Scoring system for hepatic steatosis risk	Discrimination (AUROC) and calibration
Sowa <i>et al</i> [69], 2014	University Hospital Essen	82	Logistic regression, decision trees, SVM, RF	Distinguish NAFLD from ALD	Sensitivity, specificity, and accuracy
Kuppili <i>et al</i> [70], 2017	Instituto Superior Tecnico, University of Lisbon, Portugal	63	Extreme Learning Machine-SLFFNN	Stratification of FLD disease in US liver images	AUROC, reliability and stability analysis
Sorino <i>et al</i> [71], 2020	MICOL cohort	2970	SVM	Stratify NAFLD risk to reduce need for imaging	Accuracy, variance, calculated confidence limits (95%), the weight of each model (as a %) and the number of ultrasound examinations it could avoid
Wu <i>et al</i> [72], 2019	New Taipei City Municipal Hospital Banqiao Branch	577	ANN, NB, RF, LR	Diagnosis and risk stratification in NAFLD	Accuracy, sensitivity, specificity

ALD: Alcoholic liver disease; ANN: Artificial neural network; AUROC: Area under the receiver operating characteristic; CNN: Convolutional neural network; CPCSSN: Canadian Primary Care Sentinel Surveillance Network; FLD: Fatty liver disease; LR: Logistic regression; MCC: Matthews correlation coefficient; MICOL: Multi-centre Italian study on cholelithiasis; ML: Machine learning; NAFLD: Non-alcoholic fatty liver disease; NB: Naïve Bayes; RF: Random forest; SHIP: Study of Health in Pomerania; SLFFNN: Single-layer feed-forward neural network; SVM: Support vector machine; US: Ultrasound.

of slow progressors as well as for appropriate monitoring of rapid progressors, for timely treatment. Availability of highly accurate risk prediction models would facilitate proactive identification of patients in need of more intensive monitoring and management. ML methods were used for genetic analyses of various HCV strains and was then applied to recognize relevant genetic markers related to fibrosis progression in HCV[20]. Shousha *et al*[21] combined data-mining strategies and ML algorithms (NN algorithms) using IL28B genotype and biochemical markers to predict advanced fibrosis in HCV patients, yielding a higher performance than both aspartate aminotransferase-to-platelet ratio index (commonly known as APRI) and fibrosis-4 (commonly known as FIB-4).

Primary sclerosing cholangitis

ML has been useful in patients with primary sclerosing cholangitis (PSC) throughout the disease course, from diagnosis to prediction of liver decompensation risk and post-transplant survival. Ringe *et al*[22] showed that PSC-compatible cholangiographic changes on 3D-magnetic resonance cholangiopancreatography (commonly known as MRCP) can be detected by DL algorithms with high sensitivity (95%) and low mean absolute error (7%). The PSC Risk Estimation Tool (referred to as PREsTo), which was developed by Eaton *et al*[23] using a gradient boosting machine (commonly known as GBM) algorithm, has been validated in an international multicenter cohort to accurately predict risk of liver decompensation in these patients and has also been shown to be far more accurate than existing prediction systems. LT in PSC patients is a contentious issue in view of the association with inflammatory bowel disease and risk of colorectal neoplasia and cholangiocarcinoma. Due to limited organ availability, identifying individuals who are most likely to benefit from the procedure is of paramount importance in patient selection. Andres *et al*[24] analyzed data of 2769 PSC patients from the Scientific Registry of Transplant Recipients (referred to as SRTR) database using a novel multitime-point calibrated model for the prediction of individual survival after LT. The accuracy of the model in predicting long-term survival was shown to surpass the traditional Cox regression analysis, which completely fails at 10 years.

Liver space occupying lesions and underlying liver disease

The application of ML toward image recognition has evolved into facial recognition software programs which are commonly used in smartphones. Employing this feature in healthcare, Park *et al*[7] were able to create an algorithm based on recurrent neural network to accurately predict visual field examination, thereby aiding in the diagnosis of optic neuropathies. Others have utilized similar ML tools in detection of lung nodules and cerebral aneurysms[25]. Recently, such computer-aided diagnosis/detection has been used in hepatology as well. Hassan *et al*[26] used a stacked sparse auto encode system based on support vector machines to differentiate HCC, hemangioma and liver cysts from US images. This method was shown to have 97.2% accuracy, outperforming software based on other DL algorithms. A DL system was developed by Schmauch *et al*[27] to diagnose and categorize space occupying lesions in the liver into malignant or benign tumors. By means of a supervised training using a database of 367 US images together with the radiological reports, the resulting algorithm could detect and characterize the lesions with a mean receiver operating characteristic of 0.93 and 0.916, respectively[27]. Although this model needs validation, it could warn of possible malignant lesions and boost the diagnostic yield of US for liver lesions. Another study used the patient's clinical data along with MRI sequences to devise an automated classification system cataloguing such hepatic lesions as cyst, adenoma, hemangioma, HCC and metastasis, with acceptable sensitivity and specificity rates[28]. A retrospective study analyzed the yield of an ANN, composed of three layers, for classifications of liver lesions by means of contrast-enhanced CT into five groups (A, classic HCC; B, malignant tumors apart from HCC; C, indeterminate masses, dysplastic nodules or early HCC and benign masses other than cysts or hemangiomas; D, hemangiomas; E, cysts)[29]. They obtained a high accuracy for the classification of hepatic lesions after supervised training using data from more than 55000 images, particularly for the distinction between groups A-B and C-D[30].

Diagnosis of HCC is currently based on imaging, tumor markers and sometimes biopsy. However, several other routine tests, such as biomarkers of liver inflammation, liver function test and viral markers, can help in prediction of HCC risk. The contribution of each variable toward accurate HCC prediction could be identified by data mining analysis of large volumes of data of patients with HCC and this in turn could help in the formation of a prediction model. This was attempted by Sato *et al*[31] when they analyzed data from 4242 patients at the University of Tokyo's hospital liver clinic. The patients were divided into those who had HCC diagnosed at first presentation (who formed the HCC-positive group of 539 patients) and others who developed HCC in follow-up (who formed the HCC-negative group of 1043 patients) after eliminating those with insufficient data. The available data was analyzed, and the gradient boosting provided the highest predictive accuracy for the presence of HCC (87.34%) and produced an AUC of 0.940. By using a cut-off of 200 ng/mL for alpha-fetoprotein (AFP), 40 mAu/mL for Des-gamma carboxyprothrombin (DCP), and 15% for AFP-L3, the accuracies of AFP, DCP, and AFP-L3 for predicting HCC were 70.67% (AUC: 0.766), 74.91% (AUC: 0.644), and 71.05% (AUC: 0.683), respectively[31]. Furthermore, an innovative model devised by Książek *et al*[31], used patient information, such as

viral status, occurrence of comorbidities and laboratory results to forecast the development of HCC. This is based on 23 quantitative and 26 qualitative features and has attained an 88.5% accuracy for this prediction model. When analyzing large data sets, ML models have proven superior over the classical statistical regression models. This framework of identifying optimal classifiers is the path towards fine-tuning personalized medicine.

Another important arena in the management of HCC is risk stratification for recurrence, which has been facilitated by the ability to digitize pathology slides. Saillard *et al*[32] showed that DL algorithms based on digitized slides were more accurate in predicting survival of HCC patients after liver resection compared to scores formed using various clinical, biological and pathological factors. Another DL model by Chaudhary *et al*[33] used data from The Cancer Genome Atlas to identify a subgroup of HCC patients with inactivation mutations in *TP53* genes, frequent *BIRC5* expressions and stemness markers (*KRT19* and *EPCAM*), and a high proportion of activated Akt and Wnt signaling pathways associated with aggressive tumors[33].

After HCC resection, vascular microinvasion (VMI) is considered as one of the major predictive factors of recurrence. In a recent publication by Dong *et al*[34], radiomic algorithms based on US images were used to elaborate radiomic signatures with the potential to aid in the preoperative prediction of VMI and to classify patients with VMI into low risk (≤ 5 MVI in adjacent liver tissue and ≤ 1 cm from the tumor) and high-risk groups (> 5 MVI or MVI in liver tissue and > 1 cm from the tumor) with promising results. Moreover, researchers have validated CT-based ANN and deep CNN to predict survival of HCC patients[35,36]. Ji *et al*[35] designed a novel three-feature radiomic signature of the contrast-enhanced CT image, where performance was enhanced by combining it with clinical features [concordance-index (c-index): 0.63–0.69 vs 0.73–0.801]. Wang and colleagues[36] employed multiphase CT radiomics features along with clinical models to yield a combined model (AUC: 0.82).

Tsilimigras *et al*[37] attempted to identify the most important prognostic factors in the pre- and postoperative setting for each Barcelona Clinic Liver Cancer (BCLC) stage by using a ML method. The investigators used a Classification and Regression Tree (CART) model to analyze data drawn from an international multi-institutional database. The preoperative CART model selected AFP and Charlson comorbidity score as the first and second most important preoperative factors of overall survival among BCLC-0/A patients, whereas radiologic tumor burden score was the best predictor of overall survival among BCLC-B patients. The postoperative CART model showed the lymphovascular invasion as the best postoperative predictor of long-term survival among BCLC-0/A patients, whereas tumor burden score remained the best predictor of long-term outcomes among BCLC-B patients in the postoperative setting[37].

AI algorithms were also successfully employed to predict response to transarterial chemoembolization (commonly known as TACE) and radiofrequency ablation (commonly known as RFA)[38–42]. A fully automated ML algorithm was proposed by Morshid *et al*[38] using the clinical information and features of CT images and to forecast the response to the treatment by TACE. Using the combination of BCLC stage and quantitative imaging features, the investigators attained a prediction accuracy of 74.2% against using just the BCLC stage alone. Liu *et al*[41] validated three AI-based predictive models (one deep and two ML), using radiomic features of contrast-enhance US scans. In that study, the DL model was found to be superior to the two other methods in assigning patients in the validation cohort to either objective-response to TACE or non-response, with a decent accuracy (AUC: 0.93)[41]. Wu *et al*[42] developed an ANN-based on 15 clinical features to predict 1-year and 2-year disease-free survival of patients who underwent CT-guided percutaneous RFA in early stages of HCC. The accuracy of the model was better when predicting 1-year disease-free survival than 2-year disease-free survival, with an accuracy of 85.0% and 67.9%, respectively[42].

AI IN LIVER SURGERY

Surgery offers the best chance of cure for patients with liver tumors. However, surgical removal of liver tumors is challenging because of its complex anatomy and concerns about functional liver remnant. Accurate knowledge of liver anatomy is thus a key point for any successful hepatic resection or living donor LT (LDLT). Even a minor change in the surgical plan can have a dramatic impact on the surgical outcome. The anatomy is so complex that it is often difficult to reconstruct it mentally based on CT or MRI images alone. Over decades, intraoperative visualization of preoperative image data in hepatic surgery has been a hot research topic for computer scientists and

clinicians. The introduction of AI in liver surgery is more recent and it mainly focuses on imaging and navigation that make pre-operative planning and intra-operative guidance easier. 3D visualization techniques and 3D printing technology can significantly benefit the understanding and display of surgical anatomy. ML has been applied in various aspects of the 3D printing technique to improve the whole design and manufacturing workflow[43]. Virtual liver resection can be performed before actual surgery using 3D visualization techniques to assess the resectability of the lesion and calculate future liver remnant (FLR)[44]. In LDLT, 3D imaging can predict the requirement for vascular reconstruction based on the vascular anatomy of the donor liver, resulting in improved safety and outcome of LDLT[44]. The application of 3D printing technology in liver surgery has been evaluated in a few studies. In pediatric LDLT, 3D-printed liver models have been found useful in evaluating discrepancies in size between small pediatric recipients and adult liver grafts[45]. Nevertheless, there are still many issues (like cost and time of manufacturing) that must be addressed before 3D printing can become more accepted and widespread. ML could be exploited to solve these problems by streamlining the 3D modelling process through rapid medical image segmentation and improved patient selection and image acquisition [46].

Automated hepatic volumetry

It is widely accepted that accurate assessment of volume of FLR can reduce post-hepatectomy liver failure. Hepatocytes in the remnant liver after resection must overcome necrosis and regenerate sufficiently to preserve synthetic function which requires an adequate volume of functional FLR. Widely followed limits of FLR for safe resection range between 20% and 30% for normal liver and 30% and 40% in those with underlying liver disease. Several imaging modalities have been experimented in liver volume assessment, including even conventional US and 3D US[47,48]. However, contrast-enhanced CT scan is globally accepted for FLR assessment, pre-transplant LD evaluation and for assessment of response to FLR volume induction. The first described method of liver volume assessment based on manually tracing the entire liver was time-consuming but precise. Recently, semi-automatic and automatic segmentation techniques using mathematical models, such as the ones reported by Suzuki *et al*[49] and Nakayama *et al*[50], have shown good accuracy. A CNN-based algorithm has been developed by Wang *et al*[51] to fully automate liver volume assessment from CT as well as MRI. A similar algorithm developed by Winkel *et al*[52] has shown good accuracy, speed and good agreement with manual segmentation. The criticism of fully automatic segmentation is that it often can be unsuccessful for some CT images that are low in contrast or have missing edges due to similar intensity of adjacent organs or machine artifact.

Surgical navigation systems

Surgical navigation systems have been playing a crucial role in neurosurgery and spinal surgery for many years; yet, they have not become established as standard in liver surgery. This is largely due to the technical challenge of navigating a moving organ. The surgical navigation system must be able to measure the intraoperative alterations in position and shape of the liver due to respiration and surgical manipulation, in order to adapt the preoperative navigation data to the current situation. Techniques like augmented virtuality (referred to as AV), augmented reality (referred to as AR) and mixed reality can be used to synchronize 3D reconstructed images with real-time surgery and can offer a safe and reliable surgical navigation method. Accurate surgical navigation can better guide laparoscopic surgeons to perform hepatectomy and improve the safety of surgery. In a preliminary trial, Phutane *et al* [53] demonstrated that AR-based hepatectomy for HCC could help detect intrahepatic tumors, decide the transection plane, and locate the hepatic veins, which can result in improved safety of operation by reducing bleeding and duration of surgery. The laparoscopic hepatectomy navigation system (LHNS) is a multimodal assistant system presented by Zhang *et al*[54] which consists of a fusion model of CT-based 3D models with indocyanine green (commonly known as ICG) fluorescence images. LHNS was used for real-time visualization of the relationship between liver lesions and intrahepatic anatomical structures. Using LHNS, the optimal cutting plane for the liver resection can be planned preoperatively. The system consisted of preoperative model segmentation, intraoperative laparoscopic stereo surface reconstruction, intraoperative laparoscopic posture tracking modules and intraoperative registration. Authors retrospectively compared the clinical outcomes of patients who underwent the laparoscopic hepatectomy using the LHNS (LHNS group) with patients who underwent the procedure without LHNS guidance (non-LHNS group). They found that the LHNS

group had significantly less blood loss, less intraoperative blood transfusion rate and a shorter postoperative hospital stay than the non-LHNS group. There was no significant difference in operative time and the overall complication rate between the two groups. The LHNS system was also helpful to clearly delineate the liver transection line in most cases[54]. Ntourakis *et al*[55] reported in a pilot study that AR helped in detecting missing lesions after chemotherapy for CRLM and obtaining a margin negative resection status without any local recurrence at a median follow-up of 22 mo. Application of AR in robotic hepatectomy can enhance the ability of the surgeon to achieve a safe tumor resection with adequate peritumoral margin[56,57].

AI to predict postoperative morbidity

AI algorithms are also being used to predict postoperative morbidity and recurrence of tumor after surgery. Post-hepatectomy liver failure is a worrisome complication after major liver resection for HCC and is the chief cause of postoperative mortality. Early identification and timely intervention are vital to avoid the mortality associated with it. Mai *et al*[58] attempted to validate an ANN model to forecast severe post-hepatectomy liver failure in patients with HCC who underwent partial hepatectomy (353 patients). They found that the predictive performance of the ANN model for severe post-hepatectomy liver failure surpassed the traditional logistic regression model and normally used scoring systems[58].

AI IN LIVER TRANSPLANTATION

Liver transplantation is a complex process that involves analysis of numerous variables related to both donor and recipient and expert decisions that are essential for long-term graft and patient survival. The high number of variables involved often makes the decision-making process difficult. In such a circumstance, ML techniques play an important role, with the ability to build accurate models for liver graft survival.

Organ allocation and donor-recipient matching

In a liver transplantation program, the major bottleneck in delivery of care now is organ availability. The United Network for Organ Sharing (commonly known as UNOS) survey has identified about a 20% drop-out of patients listed for liver transplantation[59]. Attempts to reduce this dropout rate by utilization of extended criteria donors (older donors, donors with fatty liver, donation after cardiac death donors) have resulted in inferior post-transplant outcomes and decreased utilization due to an increase in discarded grafts. This problem is expected to worsen in the coming years as growth in the general population is projected to overtake growth in the donor pool, thus potentially exacerbating the organ shortage and further increasing the waiting time for transplant. Such insights demonstrate the precious nature of each liver graft and the paramount importance of appropriate organ allocation to reduce waiting list mortality as well as to promote efficient utilization of available organs. A first attempt at guiding organ allocation using donor information was the quantitative donor risk index by Feng *et al*[60], which used a Cox regression model to predict graft failure using donor characteristics alone. The widely validated model for end-stage liver disease (MELD) score, which is the keystone of current allocation policy in the United States and worldwide, is based on the “sickest-first” principle, utilizing recipient information alone. Undoubtedly, a method which utilizes donor as well as recipient characteristics for appropriate pairing would ideally reduce waiting list mortality and organ wastage with good post-transplant survival. Many strategies, including ML, are being tried to reduce the discrepancy between the number of potential liver graft recipients and the number of organs available. This was attempted by Pérez-Ortiz *et al*[61] using ordinal regression and the support vector machine to arrive at a model that could be used in conjunction with the MELD score to allocate the organ to one of the first patients on the waiting list (according to MELD score) who would have a higher survival possibility. This can circumvent flaws in MELD score-based allocation and also eliminates futile transplants. The Optimized Prediction of Mortality (commonly known as OPOM) model developed by Bertsimas *et al*[62] employing ML optimal classification tree model in comparison with MELD-based allocation using Liver Simulated Allocation Model (commonly known as LSAM) has been shown to reduce waiting list mortality on average by 417.96 deaths every year. OPOM has been found to adhere more accurately to the “sickest-first” principle and utilizes more variables than the MELD and MELD-Na scores. Another neural

network-derived algorithm is the MPENSGA 2 developed by Cruz-Ramírez *et al*[63] which seeks to complement MELD-based allocation and improve its efficiency.

In 2014, a donor-recipient matching model was presented by Briceño *et al*[64] which can make the clinical decision-making easier in liver transplantation. The investigators used two ANN models: One was to enhance the probability of graft survival, and the other was to reduce the probability of graft loss. They analyzed variables of 64 donors and recipients from a set of 1003 LTs from a multicenter study. The chief aim was to devise an innovative decision-making system that can optimize the principles of fairness, efficiency and equity in allocating liver graft. They found that ANN models were significantly more accurate than already validated scores of graft survival [MELD, Delta MELD, donor-risk index (DRI), Survival Outcomes Following Liver Transplant (SOFT), the preallocation (P)-SOFT and balance-of-risk (BAR)][64]. Wingfield *et al*[65], from the United Kingdom, published the first ever systematic review of AI computing techniques being used in liver transplantation to predict individual patient graft survival. They concluded that AI techniques can provide high accuracy in predicting graft survival based on donors and recipient variables; additionally, compared with the standard techniques, AI methods had the benefits of being dynamic and able to be trained and validated within every population. Table 2 provides a concise review of recently published studies where AI-based algorithms have been applied to liver transplantation.

Challenges and prospects

It is evident from the above-mentioned studies that ML is going to be a powerful weapon in the armamentarium of the hepatologist and liver surgeon, with applications ranging from screening to postoperative follow-up. Given the recent advances in AI and the lack of any precedence, the Hippocratic philosophy of ‘do no harm’ should be at the forefront of any decision to integrate it into the clinical practice. There are some ethical and legal issues to be addressed before widespread adoption of AI into clinical practice. Data privacy and cyber security are the main ethical concerns. Next is the issue of accountability. For example, if a ML tool gives a wrong diagnosis or incorrectly assesses the hepatic volume, resulting in post-hepatectomy liver failure, whom should be held responsible?

AI is going to be a major player in organ allocation, donor-recipient matching, and even in optimizing immunosuppressant doses[66,67]. AI can be employed *via* smartphones to remotely monitor patient health. However, like any other evolving technology, AI is not without shortcomings. The ability of ML to analyze large volumes of data is responsible for its most important handicap. Quality of the output is inexorably linked to the quality of input data. This is the case with conventional biostatistical methods as well. Hence, high-quality data collection is essential for the development of AI systems as data sets are the lifeblood of algorithms and statistical modelling on which AI systems are trained. So, it is the duty of all physicians to come forward to help drive these innovations rather than passively waiting for the technology to become useful in their practice. Hepatologists and liver surgeons should seek opportunities to partner with data scientists to capture novel forms of clinical data and help generate meaningful interpretations of that data. Moreover, the accuracy of any AI system can be affected by factors such as study design, data integration strategy, selection of ML model and the relevance of the selected ML model to the particular study setting. Hence, physicians must have clearly defined, clinically relevant questions that require AI technology as the analysis tool. Early work in ML has focused on individual areas, such as radiomics or genomics, but future work should be aimed more towards amalgamating these to form a comprehensive care plan of the patient.

CONCLUSION

To conclude, as the incorporation of AI into the management of liver diseases seems inevitable, training of clinicians in interpreting and applying it into the routine practice is of paramount importance. If appropriately designed and implemented, AI has the potential to revolutionize the way hepatology and liver surgery is taught and practiced, with the promise of a future optimized for high-quality patient care.

Table 2 Review of recently published studies where artificial intelligence-based algorithms have been applied to liver transplantation

Ref.	Dataset	Number	ML algorithms	Problem	Performance measures
Bertsimas <i>et al</i> [62], 2019	STAR dataset	-	OCT	Predict 3 mo waitlist mortality-OPOM	ROC curve
Cruz-Ramírez <i>et al</i> [63], 2013	Spanish multi-center study	-	Radial basis function NN	Improve donor-recipient matching using rule-based allocation – MPENSGA 2 algorithm	Accuracy, minimum sensitivity, ROC curve, RMSE, Cohen's kappa
Briceño <i>et al</i> [64], 2014	Spanish multi-center study	1003	Neural Net Evolutionary Programming	Improve equity in donor-recipient matching	Multiple regression analysis, simple logistic regression analysis, ROC curve
Ayllón <i>et al</i> [73], 2018	King's College Hospital, United Kingdom + MADR-E, Spain	1437	ANN	Classification, end-point (3 mo, 1 yr)	ROC curve
Wadhvani <i>et al</i> [74], 2019	UNOS	1482	RF	Classification, end-point (3 yr)	Chi-square test, <i>t</i> -test, Wilcoxon rank sum test
Dorado-Moreno <i>et al</i> [75], 2017	King's College Hospital, United Kingdom + MADR-E, Spain	1492	Ordinal ANN	Ordinal classification, four classes	MAE and the MZE, accuracy, GMS, AMAE
Guijo-Rubio <i>et al</i> [76], 2019	UNOS	39095	Cox, SVM, GB	Survival time	C-index, ROC curve, concordance index ipcw
Lee <i>et al</i> [77], 2018	Seoul National University Hospital	1211	Several ML methods compared, GBM found to be best	Prediction of AKI after liver transplant	ROC curve, accuracy
Lau <i>et al</i> [78], 2017	Austin Hospital, Melbourne, Australia	180	RF, ANN, logistic regression	Predict 30-d risk of graft failure	ROC curve

AKI: Acute kidney injury; AMAE: Average mean absolute error; ANN: Artificial neural network; c-index: Concordance index; GB: Gradient boosting; GBM: Gradient boosting machine; GMS: Geometric mean of the sensitivities; MADR-E: Model for Allocation of Donor and Recipient in España; MAE: Mean absolute error; MPENSGA: Memetic Pareto evolutionary non-dominated sorting genetic algorithm; ML: Machine learning; MZE: Mean zero-one error; NN: Neural network; OCT: Optimal classification tree; OPOM: Optimized prediction of mortality; RF: Random forest; RMSE: Root mean squared error; ROC: Receiver operating characteristic; STAR: Standard Transplant Analysis and Research; SVM: Support vector machine; UNOS: United Network for Organ Sharing.

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