Artificial Intelligence in

Gastroenterology

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Application of artificial intelligence in hepatology: Minireview

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Abstract

With the rapid advancements in computer science, artificial intelligence (AI) has become an intrinsic part of our daily life and clinical practices. The concepts of AI, such as machine learning, deep learning, and big data, are extensively used in clinical and basic research. In this review, we searched for the articles in PubMed and summarized recent developments of AI concerning hepatology while focusing on the diagnosis and risk assessment of liver diseases. Ultrasound is widely conducted for the routine surveillance of hepatocellular carcinoma along with tumor markers. Computer-aided diagnosis is useful in the detection of tumors and characterization of space-occupying lesions. The prognosis of hepatocellular carcinoma can be estimated *via* AI using large-scale and high-quality training datasets. The prevalence of nonalcoholic fatty liver disease is increasing worldwide and pivotal concern in the field is who will progress and develop hepatocellular carcinoma. Most AI studies require a large dataset, including laboratory or radiological findings and outcome data. AI will be useful in reducing medical errors, supporting clinical decisions, and predicting clinical outcomes. Thus, cooperation between AI and humans is expected to improve healthcare.

Key words: Artificial intelligence; Deep learning; Machine learning; Hepatocellular carcinoma; Prognosis; Computer-aided diagnosis

Core tip: Artificial intelligence (AI) plays a significant role in our daily life and the research field. In this review, we summarized the recent findings of AI concerning hepatology. AI will be useful in the detection and diagnosis of liver tumors and the discrimination of high-risk patients for hepatic decompensation and hepatocellular

carcinoma development. Furthermore, AI can be utilized in basic research, such as in the interpretation of genomics, transcriptomics, and proteomics. We hope that this review will help in future management.

INTRODUCTION

Recent developments in artificial intelligence (AI)-related techniques have shown a remarkable improvement in the field of healthcare[1]. Among others, AI comprises search algorithms, expert systems, machine learning, and deep learning[2]. Machine learning requires feature characteristics input by a human; however, technical advances achieved by innovation in computer science leads to a more sophisticated deep learning method[3]. Deep learning provides new insight into existing diseases but not into why the chosen parameters cannot be interpreted or understood. The issue of ensuring the balance between white box and black box AI is widely debated among the research community[4]. Nevertheless, exploration and translation of black box AI could lead to a better understanding of the disease mechanism. Moreover, it could pave the way for novel discoveries in their treatment.

Such advances in hepatology can be useful for detecting tumors and screening high-risk populations for hepatocellular carcinoma (HCC) development. A curable treatment for HCC can be adopted when the tumors are found in early stages[5]. Routine ultrasonography is widely accepted as a screening method for HCC[6]. However, an ultrasound (US) is highly dependent on the sonographer's skill. Thus, AI detection systems can be used for efficient detection.

Infections from the hepatitis B virus and hepatitis C virus are well-recognized risk factors for hepatic decompensation and HCC development[7-9]. In addition, nonalcoholic fatty liver disease (NAFLD) has been recently identified as a risk factor. The prevalence of NAFLD is increasing and has been estimated at 24% worldwide. Its incidence is observed to be highest in South America and the Middle East followed by Asia, United States, and Europe[10,11]. Chronic liver diseases cause liver fibrosis and progresses through mild fibrosis to cirrhosis. Liver fibrosis is also one of the well-known risk factors for hepatic decompensation and HCC development[12,13]. Any chronic liver disease could be worse without proper treatments. To determine who is at high-risk for HCC development and disease progression in such a population is a crucial clinical question. The deep learning methods are expected to be useful in identifying high-risk patients. In this review, we summarize the recent advances of AI in hepatology and discuss their clinical implications. In this review, we searched for the literature in PubMed and summarized recent developments of AI concerning hepatology.

CURRENT AI METHODOLOGY

AI systems can be roughly divided into four categories: search algorithm, expert system, machine learning, and deep learning. Machine learning generates a mathematical algorithm from the training dataset and utilizes it to predict outcomes or make decisions[14]. Moreover, machine learning is divided into supervised and unsupervised learning. In a supervised learning model, the algorithm learns from a labeled dataset (individual parameters and outcomes). Conversely, deep learning is based on the neural network structure inspired by the human brain. There are different types of neural networks in deep learning, and representative types are artificial neural network, convolutional neural network (CNN), and recurrent neural network.

Artificial neural network is a computational analysis tool inspired by the biological nervous system[15]. It consists of three layers: input, hidden, and output. Each layer comprises several "neurons," and the hidden layer processes the input and the output

layer produces the result. Through an appropriate training process, the weights among the neural connections are adjusted to optimize the result.

CNN is an image-based machine learning method that is directly inspired by the visual cortex of the brain[16]. A basic CNN consists of convolution layers, nonlinear layers, and pooling layers. CNNs are currently one of the most successful deep learning models because of their unique ability to process spatial information[17].

Recurrent neural network is a type of neural network with feedback connections[18,19]. It exhibits great performance in labeling and predicting sequential data. A prominent example of sequential data is natural language. Recurrent neural network maintains the history of input data within the network, and the output is produced from the past input. In the following sections, we discuss related studies from the literature. The content is summarized in Table 1.

DIAGNOSIS OF LIVER DISEASES AND TUMOR DETECTION

Currently, imaging examinations are displayed and stored as digital images. Furthermore, computer-aided diagnosis/detection (CAD) has already been applied for chest nodule detection[20] and cerebral aneurysm detection[21]. Recently, Mei *et al*[22] reported an AI system that used chest computed tomography along with clinical symptoms, exposure history, and laboratory testing to enable rapid diagnosis of coronavirus disease 19. The results of this AI system depicted an area under the receiver operating characteristics (AUROC) of 0.92[22].

However, the CAD system is costly, and regular maintenance is required for its use. Nevertheless, it can help healthcare workers in diagnosing and detecting tumors. The first CAD system was approved by the Food and Drug Administration for mammography in 1998[23]. Nowadays, the CAD system uses deep learning for the analysis and classification of medical images[16]. Big data availability and increased chip processing capability enable foreseeable advances in deep learning-based systems. The following section summarizes the recent AI research on focal and diffuse liver diseases.

Detection of focal liver diseases

Hassan *et al*[24] used the stacked sparse auto-encoder system to detect HCC, hemangioma, and liver cysts from US images. They used a four-step framework as follows. First, the processing images were enhanced while the background noises were reduced. Subsequently, liver segmentation was conducted using the level set method and fuzzy c-means clustering algorithm. Next, stacked sparse auto-encoder was employed to identify latent features from unlabeled input data in an unsupervised manner. Finally, a softmax layer was used to diagnose different focal liver diseases. The sensitivity and specificity of the proposed deep learning system were 98.0% and 95.7%, respectively[24]. Sato *et al*[25] developed a machine-learning model for predicting HCC in 539 HCC-positive and 1043 non-HCC patients at a tertiary referral center, and the AUROC of the model for HCC was 0.940 compared to 0.766, 0.644, and 0.683 for alpha-fetoprotein, des-gamma-carboxyprothrombin, and Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein, respectively.

Staging of diffuse liver diseases

Biswas *et al*[26] reported that deep learning techniques were superior to conventional machine learning techniques for detecting fatty liver disease through US examinations. The study was based on 63 patients (27 healthy and 36 abnormal), and the AUROCs of the support vector machine, extreme learning machine, and deep learning were 0.79, 0.92, and 1.0, respectively. Byra *et al*[27] employed an Inception-ResNet-v2 CNN pre-trained on ImageNet for NAFLD diagnoses using US examinations in 55 obese patients admitted for bariatric surgery. They used a wedge biopsy liver sample as the reference standard. The AUROC of the approach was 0.9777, compared to 0.9590 for the conventional hepatorenal index. The detection of steatosis is beneficial in the field of hepatology. However, more data are needed for better AI applications, and resources, such as liver biopsy samples, are limited because of their invasiveness.

Recently, US elastography has been widely used in clinical practice for noninvasive diagnosis of liver fibrosis stages and as a surrogate marker for clinical outcomes such as HCC development, liver failure, and rupture of esophageal varices[28-31]. Wang *et al*[32] reported deep learning radiomics for shear wave elastography, and the AUROC of the model for diagnosis of cirrhosis was 0.97 (95% confidence interval: 0.94-0.99), which outperformed the biomarkers. Generally, the stiffness value of US elastography is

Table 1 Clinical applications of artificial intelligence

	Samples	Diagnosis	AI technique	Accuracy, %	AUROC	Ref.
Focal liver disease detection	US	Benign tumors	DL	97.2	NA	[23]
	Serum tests, clinical data	HCC	ML (gradient boosting)/DL	87.34/83.54	0.940/0.884	[25]
Diffuse liver disease staging	US	FLD	DL/SVM/ELM	100/82/92	1.0/0.79/0.92	[26]
	US	NAFLD	DL	NA	0.9777	[27]
	Elastography	Cirrhosis	DL	NA	0.97	[32]
Risk assessment	Clinical, pathohistological data	Poorer survival after HCC resection	2 DL models	NA	0.78, 0.75 (c-index)	[35]
	Sequence data	Poorer survival after HCC resection	DL	NA	0.68 (c-index)	[36]
	Clinical data	HCC development	ML	NA	0.64 (c-index)	[37]
	Clinical, histological data	1-yr and 3-yr clinical outcomes	ML	NA	0.78, 0.76	[38]

AUROC: Area under the receiver operating characteristics; c-index: Confidence interval; DL: Deep learning; ELM: Extreme learning machine; FLD: Fatty liver disease; HCC: Hepatocellular carcinoma; ML: Machine learning; NAFLD: Nonalcoholic fatty liver disease; SVM: Support vector machine; US: Ultrasonography; NA: Not available.

considered to be affected by inflammation, obstructive jaundice, liver congestion, fasting, and steatosis[33,34]. Deep learning methods integrating stiffness values and elastograms with other clinicopathological factors will be powerful tools for the diagnosis of liver fibrosis.

RISK ASSESSMENT OF LIVER DISEASE

The risk assessment of HCC is crucial for the apt management of patients with chronic liver diseases. Saillard *et al*[35] implemented two deep learning algorithms based on whole digitized slides for predicting the survival of HCC patients after hepatic resection. They first created a composite score using clinical, biological, and pathological factors for survival prediction. However, both deep learning models reported higher performance than the composite score. An expert pathologist examined the high-risk and low-risk slides obtained from the models. Subsequently, the pathologist observed that the high-risk group had cellular atypia, vascular spaces, and macrotrabecular architectural pattern. In contrast, the low-risk group had tumoral fibrotic stroma, immune cells, and fibrosis in both tumor and nontumor areas[35]. These findings will lead to further research focusing on the inflammatory reaction against HCC.

The deep learning model proposed by Chaudhary *et al*[36] integrated RNA sequencing (15629 genes), miRNA sequencing (365 miRNA), and methylation data (19883 genes) from The Cancer Genome Atlas. The model detected a critical subgroup that was associated with frequent *TP53* inactivation mutations, higher levels of stemness markers (*KRT19* and *EPCAM*), tumor marker (*BIRC5*) expression, and activated Wnt and Akt signaling pathways[36]. Deep learning models regarding the prognosis of chronic liver disease patients have not yet been fully evaluated. Thus, machine models have been used to determine the prognostic model in several studies[37,38]. A deep learning model requires a considerable amount of data than a traditional machine learning algorithm. Therefore, machine learning sometimes fits in clinical settings with limited datasets. Singal *et al*[37] used a random forest model to predict HCC development in Child A or B cirrhotic patients. The model was validated through the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis cohort and depicted better performance than the traditional regression analysis. Konerman *et al*[38] used the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial cohort to construct a random forest model to predict outcomes of patients with chronic hepatitis C and validated it with 1007 patients during a median of 4.9 years of the observation period. The AUROC for 1 year and 3 years risk of clinical outcomes was 0.78 (95% confidence interval: 0.73-0.83) and 0.76 (95% confidence interval: 0.69-0.81).

LIMITATIONS OF AI TECHNOLOGY

Although the algorithms mentioned above are promising, AI has several limitations[39]. First, it may not be possible to understand how and why the model is created. Second, AI does not conform to personal preferences and legal responsibility. If the AI makes a wrong decision, who will be held accountable for this result? Moreover, a biased AI could affect the outcome of several patients. Therefore, careful attention should be paid to the interpretation of AI's decision. Third, to avoid the overfitting problem, multicenter studies with high-quality datasets to validate the models are required. Fourth, the protection of privacy and security of data is crucial. The personal medical history should be protected and hacking or manipulating the model should be strictly avoided.

CONCLUSION

Digitalization of image examinations and big data availability has resulted in advancements to the AI system represented by deep learning research, especially in the detection of liver diseases. There exists a robust gold standard, *i.e.* histological diagnosis obtained by either biopsy or resection for the detection of liver tumors. However, for the surveillance of NAFLD patients, the gold standard is not just the degree of fat accumulation but also the clinical outcomes of who will develop HCC and who will progress to liver failure. The quality of deep learning models highly depends on the training dataset. A large volume of high-quality data is required to build an accurate and useful AI system for identifying liver diseases.

The application of AI in medical imaging has a good prospect and value. It has been reported that successful applications of AI technologies in endoscopic images for esophageal cancer[40], gastric cancer[41-43], small intestinal cancer[40], colorectal cancer[44,45], analysis of computed tomography for pancreatic cancer[46,47], and others[48-50]. Hepatologists should learn from these other areas.

AI will also be an essential element in the management of liver diseases to reduce medical errors, select the best treatment, and predict outcomes. Nevertheless, even with further advances in computer science, decisions on real clinical practices are affected by the patient's will, treatment availability, and financial issues. Moreover, social rapport plays a vital role in building a patient's trust and satisfaction[51]. Thus, cooperation between humans and AI is expected to improve healthcare in the future.

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