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Artificial intelligence in liver ultrasound

AI in liver ultrasound

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Abstract

Artificial intelligence (AI) is playing an increasingly important role in the medicine, especially in the field of medical imaging. It can be used to diagnose diseases and predict certain status and possible events that may happen. Recently, more and more studies have confirmed the value of AI based on ultrasound in the evaluation of diffuse liver diseases and focal liver lesions (FLLs). It can assess the severity of liver fibrosis and non-alcoholic fatty liver, differentially diagnose benign and malignant liver lesions, distinguish primary and secondary liver cancer, and predict the curative effect of liver cancer treatment and recurrence after treatment, and predict microvascular invasion (MVI) in hepatocellular carcinoma (HCC). These studies have great clinical application potential in the near future. The purpose of this review is to comprehensively introduce the current status and future perspectives of AI in liver ultrasound.

Key Words: Machine learning; Deep learning; Radiomics; Diffuse liver diseases; Focal liver diseases; Ultrasound

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Core Tip: Artificial intelligence (AI) is playing an increasingly important role in medicine, especially in the field of medical imaging. Currently, there is a need of a comprehensive review to introduce the application of AI based on ultrasound in diffuse and focal liver lesions. In this article, we introduce the application of AI in the assessment of liver fibrosis and non-alcoholic fatty liver and the differentiation of focal liver lesions. In addition, we discuss the performance of AI based on ultrasound in predicting curative effect, prognosis and microvascular invasion in hepatocarcinoma. Lastly, we illustrate the future prospect of AI in liver ultrasound.

INTRODUCTION

In the past several years, liver diseases have affected millions of lives and become ¹one of the main causes of illness and death in the world^[1]. It is reported that more than one-fifth of the Chinese are affected by liver diseases, such as liver fibrosis, liver cancer and non-alcoholic fatty liver disease (NAFLD), contributing to the health loss unambiguously. Therefore, paying more attention to liver diseases is of great significance.

Artificial intelligence (AI) was defined as the research of algorithms which enable machines have the ability of reasoning and performing functions such as solving problems, recognizing object and word, inferring world states, and making decisions^[2]. As far as I am concerned, AI is a precise prediction technique that automates learning and recognizes patterns in data. Apart from this, AI has been already extensively applied to medical diagnosis, especially in medical image analysis. This application mainly relies on deep learning, a subfield of machine learning. Deep learning is on the frontier of AI, which is based on deep neural networks (DNNs) with more than one hidden layer. ¹¹Convolutional neural networks (CNNs) are a branch of DNNs that are particularly useful for recognizing image and have stimulated a large amount of interest from industry, academia, and clinicians^[3].

Comparing with other medical imaging techniques, ultrasound is noninvasive and more portable, which can also provide real-time imaging. In recent years, AI-powered ultrasound has become more mature and come closer to regular clinical applications in order to reduce the subjective and improve the efficient of ultrasound diagnosis^[4]. Many studies have confirmed the value of AI in the evaluations of thyroid nodule, breast lesion and liver lesion classification by ultrasound. In addition to these applications, other AI applications in ultrasound have also been explored and achieved great progress.

In liver medical imaging, ¹²AI can make a quantitative assessment by recognizing imaging information automatically to provide physicians assistance to make more precise and comprehensive imaging diagnosis^[5]. This technique has been extensively applied to ¹⁰computed tomography (CT), positron emission tomography-computed

tomography (PET-CT), magnetic resonance image (MRI) and ultrasound to diagnose liver lesions. For instance, deep learning based on CT and PET-CT not only can be used to detect liver new tumors and metastatic liver malignancy, but also predict the primary origin of liver metastasis^[6-8].

There are also many studies have illustrated the application of AI in liver ultrasound, while a comprehensive review of AI in this field is lacking. In this review, we will introduce the application of AI based on ultrasound in both diffuse liver diseases, including liver fibrosis and steatosis, and focal liver lesions (FLLs), including their differential diagnosis and predicting curative effect, prognosis and microvascular invasion (MVI) of hepatocellular carcinoma (HCC). The main structure of this review was illustrated in figure 1.

APPLICATION OF AI IN DIFFUSE LIVER DISEASE

There are a variety of diffuse liver diseases which can be asymptomatic or cause severe liver dysfunction, and many of them may lead to cirrhosis, hepatic carcinoma and death. We will introduce the applications of AI based on ultrasound in two common diffuse liver diseases, i.e., liver fibrosis and steatosis.

1. Liver fibrosis

Liver fibrosis is the early step of cirrhosis and an important pathological basis of HCC^[9], therefore, the early detection and prevention of liver fibrosis is essential in clinical setting. However, although liver biopsy is the golden criterion for classifying liver fibrosis using the Metavir score^[10] or New Inuyama classification^[11] to distribute the score ranging from F0 (no fibrosis) to F4 (cirrhosis), there still remains controversial regarding the use of tissue examination for assessment of liver fibrosis in clinical practice. On account of liver biopsy is invasive and the liver fibrosis is not equably distributed in liver, there are an increasing number of credible, noninvasive and available approaches being widely applied in clinical practice. Recently, a large number of noninvasive techniques have been used to prevent adverse outcomes through the application of AI based on ultrasound.

1.1 AI based on B-mode ultrasound

As early as twenty years ago, AI was used to assist the diagnosis of liver fibrosis. Ahmed *et al* creatively proposed an approach which employed fuzzy reasoning techniques to identify diffuse liver diseases automatically by using digital quantitative features measured from the ultrasound images^[12]. They extracted parameters only from B-mode images, and the results revealed that this approach had higher specificity and sensitivity for the diagnosis of liver fibrosis than the statistical classification techniques, which had a certain effect but could not help much.

Apart from this, a novel deep multi-scale texture network based entirely on B-mode ultrasound images proposed recently seems to be more convenient^[13]. The area-under-the receiver operating characteristics curve (AUROC) of this approach were 0.92 for significant fibrosis (\geq F2) and 0.89 for cirrhosis (F4) on validation group, which outperformed than ultrasonographers and three serum biomarkers in some ways during diagnosis. Although it cannot be used to realize liver fibrosis staging now, it has an excellent potential in the future workflow.

1.2 AI based on doppler ultrasound

On the basis of grey-scale parameters from B-mode images, doppler parameters of intrahepatic blood vascular were added as essential parameters. Eventually, five ultrasonographic variables, including the liver parenchymal, thickness of the spleen, the hepatic vein waveform, hepatic artery pulsatile index and damping index, were selected as the input neurons. A data optimization procedure was used in artificial neural networks (ANNs) for the diagnosis of liver fibrosis, which achieved an AUC of 0.92^[14]. Although this model proved to predict liver cirrhosis accurately, it still could not provide a specific grading.

1.3 AI based on elastography

In recent years, with the development of ultrasound, studies proposed computer-aided techniques based on elastography that is of great importance in ultrasound images to identify and stage liver fibrosis. Real-time tissue elastography (RTE) is one of the recently developed elastography techniques. In a study, 11 images features were

extracted directly from the RTE software which was installed in the ultrasound system to quantify the patterns of the RTE images^[15]. Then the data was processed and input into four classical classifiers. The results showed that the performance of the adopted classifiers was much better than the previous liver fibrosis index method, which predicted the stage of fibrosis using RTE images and multiple regression analysis. The good performance in this study demonstrated the machine learning had the potential to be powerful tools for staging liver fibrosis.

Nowadays, most applications of AI in evaluating the stage of liver fibrosis were based on shear wave elastography (SWE). An automated approach including the image quality check, region of interest (ROI) selection, and CNN classification based on SWE showed a more accurate detection of \geq F2 fibrosis levels than a previously published baseline approach, with an AUC of 0.89 vs. 0.74^[16]. The deep learning radiomics also presented the potential diagnostic performance in chronic hepatitis B patients compared with two-dimensional SWE^[17]. AI could help stage liver fibrosis more accurate with the assistance of elastography.

2 Liver steatosis

Hepatic steatosis, characterized by the accumulation of fat droplets in hepatocytes, can develop to nonalcoholic fibrosis, steatohepatitis, cirrhosis, and even HCC^[18-19]. Early detection and treatment may halt or reverse NAFLD progression^[19]. As a consequence, there is a critical need to develop noninvasive imaging methods to assess hepatic steatosis. Noninvasive liver imaging methods including CT, MRI and ultrasound have been intensively investigated^[20].

Ultrasound is the first-line examination of identifying liver steatosis results compared with other approaches. It is shown that enlarged liver with a greater number of echoes caused by fat droplets interacting with the ultrasound, and the liver is brighter and more hyperechoic compared with the right kidney on ultrasound. The image is qualitative and relies on the subjective judgement of the operator, which will definitely lead to variable results and low reproducibility^[21]. To overcome the observer bias, a series of quantitative and semi-quantitative parameters including attenuation and

backscatter coefficients, the hepato-renal index (HRI) and ultrasound envelope statistic parametric imaging (known as speckle statistics) have been implemented on ultrasound, some of which represent excellent reproducibility and reliability^[21-24]. At present, almost all the studies published mainly concentrated on NAFLD.

It is reported that the detection of moderate and severe steatosis based on ultrasound had an 84.8% sensitivity and a 93.6% specificity, while mild steatosis had an even lower sensitivity^[25]. Recently, some researchers have applied AI to improve the ultrasound detection rate of NAFLD, and the results were promising. Table 1 shows the studies using AI based on ultrasound to access steatosis. All these studies showed that AI had the tremendous potential in helping diagnose liver steatosis and some studies attempted to optimize CNN models. In the future, classifying the degree of liver steatosis with the assist of the AI could be a trend.

2.1 Qualitative evaluation

Deep learning has been applied to qualitatively evaluate NAFLD. An approach of assessing fatty liver disease by utilizing deep learning based on CNNs with B-mode images was proposed^[26]. Later, they incorporated 135 participants with known or suspected NAFLD to investigate the function of four liver views (three views in transverse plane, including hepatic veins at the confluence with the inferior vena cava, right portal vein and right posterior portal vein, and one view in sagittal plane that is liver and kidney view) in the assessment^[27]. The study assessed attention maps for liver assessment based on CNNs, which illustrated that the available image features provided by each view could offer help in assessing liver fat. Unlike the study developed previously, although the latter had a bigger sample, MRI proton density fat fraction (PDFF) was used as reference standard which was not precise enough compared with liver biopsy.

On the basis of deep learning, a novel framework combining transfer learning with fine-tuning was proposed^[28]. Although this study revealed the new framework outperformed than CNN, this conclusion was not convinced cause the radiologists'

qualitative score was the reference standard. This framework was also utilized in other studies and achieved a good performance.

With the development of deep learning, Chou *et al* established two-class, three-class, and four-class prediction models to classify different severity steatosis by making the use of B-mode ultrasound images from 2070 patients^[29]. Although liver biopsy is the gold criteria, the deep learning model could select eligible patients for a liver biopsy by evaluating the severity of fatty liver preliminarily, which would reduce unnecessary test.

Different deep learning algorithms tend to have different performances. The combined deep learning algorithms based on B-mode images were performed a highest AUROC of 0.9999 and a best accuracy of 0.9864 compared with every single one of the algorithms^[30]. Therefore, in the future studies, selecting an optimal algorithm is important.

2.2 Quantitative evaluation

AI has also been applied to quantitatively evaluate NAFLD.

2.2.1 Radiofrequency signal

Using radiofrequency signals could get rid of the lost or change of data during original data translating to B-mode ultrasound images. A study acquired the diagnosis and the fat fraction of NAFLD by inputting the original data based on one-dimensional algorithms^[31]. They obtained a 97% sensitivity, 94% specificity and the positive predictive value is up to 97%, which proved utilizing original ultrasound radiofrequency was not only able to be applied in diagnosing NAFLD, but also be applied to quantify liver fat fraction in clinic. Similarly, in an animal experiment, a CNN model based on radiofrequency signals was proved to have a better performance than the traditional quantitative ultrasound when classifying steatosis^[32].

2.2.2 HRI model based on CNNs

HRI model based on CNNs can also be studied for NAFLD evaluation^[33]. Cha *et al* reported the automated approach had no significant difference in hepatic measurements and HRI calculations compared with experienced radiologists, which

indicated that the aid of deep learning could reduce the radiologists' workload and improve the residents' diagnostic accuracy. In this study, an automated HRI calculation algorithm was used, including ¹liver and kidney segmentation, kidney ROI extraction, liver ROI extraction, and calculation of the HRI.

APPLICATION OF AI IN FOCAL LIVER LESIONS (FLLS)

HCC is the most conventional original malignant FLL, which is the sixth most common cancer in human beings, as well as the fourth primary reason of death related with cancer in the world^[1]. Hence, early accurate differential diagnosis of malignant and benign FLL is important for the management, and prognosis of patients^[34].

Ultrasound is the first-line imaging modality to identify FLLs in clinical workflow. The development of AI provides a new method to improve the accuracy of ultrasound in diagnosing FLLs. Compared with radiologists viewing anatomical images, AI can better reflect monolithic tumors morphology, as well as capture both granular and radiological patterns in specific task, which are tough by normal human vision^[35]. Figure 2 illustrated the flowchart of the application of deep learning and radiomics in FLLs. Studies have confirmed the application of AI can improve the diagnostic performance of ultrasound for FLLs (Table 2).

1 Differential diagnosis of FLLs

1.1 AI based on B-mode Ultrasound

1.1.1 Differentiate malignant and benign lesions

AI has been widely used in differentiating malignant and benign FLLs based on B-mode ultrasound. Gray level co-occurrence matrix could be used in extracting features from B-mode images, which was used in differentiating malignant and benign FLLs combined with fuzzy support vector machine^[36]. This study achieved the AUC of 0.984 and 0.971 in database 1 and database 2 respectively, which confirmed the feasibility of AI in this field.

With the development of AI, deep learning plays a more vital role in the differential diagnosis of FLLs. A CNN with ResNet50 was utilized to recognize benign from

malignant through ultrasonography of solid liver lesions, which performance was comparable to expert radiologists^[37]. But this study did not evolve other information except ultrasound images such as clinical factors. In another study, after adding seven clinical factors, a multi-center study obtained a higher accuracy, sensitivity and specificity compared with radiologists with 15-year experience, and the AUC for recognizing malignant from benign lesions reached up to 0.924 in external validation cohort^[38].

However, these studies above just involved several common FLLs in clinic, more kinds of FLLs may confuse the diagnosis and reduce the accuracy. Similar to the previous study, there was also a multi-center study estimating internal validation and external validation cohorts, which had a larger volume of training data and involved more varieties of FLLs, including cysts, HCCs, hemangiomas, focal fatty infiltration, and focal fatty sparing^[39]. Although they obtained a lower sensitivity because more kinds of diseases were included, the performance in external validation cohorts was still satisfactory. Besides, they are trying to utilize videos as training materials to realized real-time analysis in future workflow. This novel approach would offer great convenience to radiologists in helping differentiate FLLs.

1.1.2 Differentiate different FLLs

AI could also be used in the classification of FLLs. In order to optimize feature sets, a hybrid textural feature extraction system was proposed^[40] by Hwang *et al*. In their preliminary study, a high accuracy was observed in classifying cysts vs. hemangiomas and cysts vs. malignant lesions, but when classifying hemangiomas vs. malignant lesions by extracting multiple ROI, the accuracy was only 80%. However, the proposed approach exhibited a better accuracy in all classification groups by quantifying the key features in ultrasound images, especially in classifying hemangioma vs. malignant, with an accuracy of 96.13%.

Later, a sparse autoencoder system based on deep learning was proposed in diagnosing cysts, hemangiomas, and malignant lesions, which outperformed the three progressive

techniques including K-Nearest Neighbor, multi-support vector machine and Naive Bayes with an overall accuracy of 97.2%^[41].

These two studies^[40-41] just focused on three kinds of FLLs. An algorithm that could simultaneously detect and characterize FLLs based on deep learning was proposed in diagnosing HCC, focal nodular hyperplasia, cysts, hemangiomas and metastasis, which achieved an average AUC of 0.916^[42]. This study yielded promising results by using a small amount of data, using larger databases would increase the accuracy of this model.

1.2 AI based on Contrast-enhanced Ultrasound (CEUS)

It is reported that CEUS images had better sensitivity and specificity for differentiating between malignant and benign tumors compared with B-mode images, which indicated CEUS had a superior diagnostic performance. Combining AI with CEUS could not only differentiate benign and malignant FLLs, but also classify different kinds of malignant lesions.

AI could be used to differentiate malignant and benign FLLs based on three-phase CEUS images. A two-stage multiple-view learning that was the integration of deep canonical correlation analysis (DCCA) and multiple kernel learning (MKL) was used to fuse the characteristic of three-phase patterns in CEUS, presenting an accuracy of 90.41%^[43]. The proposed algorithm had both a low computational complex and a high predictive accuracy. But for multi-view CEUS images, utilizing a multi-modal feature fusion algorithm is necessary.

Compared with DCCA-MKL, the use of a three-dimensioned CNN (3D-CNN), which integrated the relationship between two temporally adjacent frames to extract features spatially and temporally, achieved a higher accuracy of 93.1%, sensitivity of 94.5% and specificity of 93.6%^[44]. But this algorithm still needs to be validated in the future work.

These two studies above^[43-44] exploited heterogeneous visual morphology to describe the difference between different liver masses. Apart from this method, time-intensity curve (TIC), which represents the contrast intensity constantly and generates the fitted curve of enhanced intensity during the process, was used in many studies.

SVM^[45-46] and deep learning^[47-48] based on TICs presented good performances in differentiate FLLs. A SVM-based image analysis system was used for FLLs classification and presented an AUC of 0.89^[45]. An ANN diagnostic system based on TICs was proved to have a similar accuracy and specificity with human in classifying five different liver tumors ten years ago^[47]. Later, deep learning became more mature, TICs of the arterial and the portal vein phases of CEUS videos were extracted on the basis of the deep belief networks, a kind of neural network that was composed of layers of Boltzmann machines, to analyze the extracted TICs^[48]. The accuracy of classifying benign from malignant lesions was 83.36% by means of this deep learning method. Exactly in this study, a novel evaluation procedure named leave-one-patient-out and custom DNNs were creatively presented. This study involved various types of liver lesions and compared the custom DNN designs with the state-of-the-art architectures and obtained a maximal accuracy of 88% by utilizing the proposed evaluation procedure in both pre-trained and trained from scratch models. This novel approach has a magnificent prospect for development, and it is worth investigating in the future work.

AI based on CEUS was proved to provide assistance in clinical settings as the reference and improve the performance of residents in the differentiation of benign and malignant FLLs^[49]. In the future, it probably plays a supporting role in clinic work. However, AI based on TICs tends to complicate the calculation because generating TICs is a time-consuming process. Therefore, developing new approaches to extract features from CEUS images is important.

2 The application of AI in predicting curative effect and prognosis of HCC

It was reported that the Edmondson-Steiner grade was a vital pre-operation predictor of tumor survival and recurrence after undergoing surgical resection^[50-51]. Owing to preoperative pathological differentiation grade can only be obtained by invasive biopsy^[52], it is necessary to explore a noninvasive method to predict therapeutic effect, recurrence, and metastasis to realize personalized treatment.

Some studies^[53-55] demonstrated the superiority of AI based on CEUS in predicting curative effect and prognosis in HCC. Although the results revealed a better performance of AI models compared with single clinical or ultrasound model, a better performance may be obtained by adding clinical factors in the future studies.

2.1 Predicting curative effect of HCC

Transarterial chemoembolization (TACE) is the first-line therapy in patients who are diagnosed as mid-stage HCC, and the response to the first TACE treatment is related to the subsequent curative effect and survival. Therefore, it is necessary to predict the personalized responses to first TACE of HCC patients. Deep learning radiomics-based CEUS model, machine learning radiomics-based B-Mode images model and machine learning radiomics-based TIC curve of CEUS model were established to realize this function^[53]. These models presented a better performance compared with HAP-score based on three indexes concerning liver function and tumor load, which will be of great benefit in selecting both first treatment and subsequent therapies after first TACE personally.

2.2 Predicting prognosis of patients with HCC

Radiofrequency ablation and surgical resection are recommended for early-stage HCC. Deep learning could also be used to predict the progression-free survival (PFS) of these two therapies in HCC patients^[54]. Two models based on these two kinds of therapies provided a satisfactory prediction accuracy and calibrations of 2-year PFS. In another study^[55], a 3D-CNN model which would avoid missing information from CEUS images compared with extracting features from four-phase images was used, it was proved that predicting prognosis of different treatments in advance and swapping treatment timely would increase the 2-year PFS, which could contribute to a better prognosis.

3 The application of AI in predicting microvascular invasion (MVI) of HCC

MVI has proved to be the independent predictor of the recurrence and the poor outcomes of HCC. Therefore, making a ¹ non-invasive and accurate preoperative identification of MVI would be of great significance for HCC patients. The application

of AI in predicting MVI achieved good performance based on gray-scale ultrasound images and CEUS.

The radiomics score based on ultrasound of HCC was established and proved to be an independent predictor of MVI^[56]. The performance of clinical nomogram was improved significantly with the aid of radiomics score, which demonstrated the important role of this technique.

¹ Features of peri-tumoral area have been proved to be more accurate recently^[56]. The radiomic signatures on the basis of features of gross and peri-tumoral region (GPTR) showed the best performance compared with gross-tumoral region and peri-tumoral region^[57]. The AUC values of 0.726 based on features of GPTR and of 0.744 with the incorporation of essential clinical information were received eventually.

These studies^[56-57] mentioned above declared the application of AI based on gray-scale ultrasound, AI could be applied to CEUS in predicting MVI as well. Zhang *et al* extracted radiomics features ² from the B-mode, artery phase, portal venous phase, and delay phase images of preoperative CEUS to construct four radiomics scores based on the primary dataset^[58]. Then they used four radiomics scores and clinical factors for multivariate logistic regression analysis, which demonstrated that portal venous phase and delay phase radiomics ² score, tumor size, and alpha-fetoprotein (AFP) level were independent risk predictors in predicting MVI. The radiomics nomogram based on these four predictors indicated a better discrimination and a good calibration compared with ² clinical model (based on tumor size and AFP level) in both primary dataset (AUC: 0.849 vs. 0.690) and validation dataset (AUC: 0.788 vs. 0.661). This study developed a new non-invasive predictive nomogram based on CEUS, which could provide useful information in predicting MVI preoperatively and choosing a more appropriate surgical option.

CONCLUSION

In conclusion, AI can provide great assistance in the evaluation of diffuse liver diseases (including liver fibrosis and liver steatosis) and FLLs. Firstly, it could be applied to

identify and stage liver fibrosis on the basis of B-mode ultrasound, doppler ultrasound and elastography. Secondly, the application of deep learning could be used to make qualitative evaluation based entirely on B-mode images and quantitative evaluation based on radiofrequency signals and HRI, which would improve the ultrasound detection rate of NAFLD. Thirdly, AI not only had the ability to differentiate malignant FLLs from benign FLLs, but also could classify different kinds of FLLs and had a better performance compared with clinical indexes. Fourthly, we could predict the curative effect and prognosis of HCC treatment and choose an optimal personalized treatment previously. Lastly, AI based on B-mode ultrasound and CEUS could predict MVI of HCC preoperatively, which could be helpful for a more appropriate surgical planning. These applications had good specificity, accuracy and a comparable or even better performance compared with experts in the diagnosis and differentiation of liver diffuse and focal lesions.

There are also some limitations in the applications of AI in ultrasound. Firstly, it is difficult to prepare the large-scale dataset with ground truth, especially for medical images. Secondly, although deep learning is the widest used algorithm and has good performance in various studies, the interpretability and generalization of it is low. Thirdly, the input data may vary from different equipment and operators, which would influence the performance of AI. Lastly, because a large amount of data is needed to train and validate the established algorithms, the conclusions of many single-center studies were not convincing. Therefore, researchers are expected to conduct more multi-center studies and incorporate more samples as much as possible. At the same time, optimizing algorithms and creating standards for medical images are also necessary. In spite of medical images, researchers could also build the database containing important clinical factors to establish a more comprehensive AI model for future work.

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