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Role of artificial intelligence in the diagnosis and treatment of hepatocellular carcinoma

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Abstract

Artificial intelligence (AI) evolved many years before, but it gained much advancement in recent years for its use in the medical domain. AI with its different subsidiaries, i.e. deep learning (DL) and machine learning (ML), examine a large number of data and also performed an essential part in decision-making in addition to conquering the limitations related to human evaluation. DL tries to imitate the functioning of the human brain. It utilizes much more data and intricate algorithms. ML is AI-based on automated learning. It utilizes earlier given data and uses algorithms to arrange and identify models. Globally, hepatocellular carcinoma (HCC) is a major cause of illness and fatality. Although with substantial progress in the whole treatment strategy for HCC, managing it is still a major issue. AI in the area of gastroenterology especially in hepatology is particularly used for various investigations of HCC, because it is a commonly found tumour, and has specific radiological features which enable diagnostic procedures without the requirement of the histological study. Though interpreting and analyzing the resultant photographs is not always easy along with photographs change through the disease process. Further, the prognostic process and response to the treatment process could be influenced by numerous components. So, nowadays AI is utilized in order to diagnose, curative and prediction goals. That review defines the kind of AI utilized by several authors. Future investigations are essential to prevent likely biasness which might subsequently influence the analysis of

images/photographs and therefore restrict the consent and utilization of such models in medical practices. Moreover, experts require to realize the real utility of such approaches, along with their associated potencies and constraints.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignancy of the liver which is very lethal. It is the most commonly found primary adult liver malignancy. Worldwide, it is the third most common cause of cancer-related death[1]. According to the American Cancer Society, 42810 new liver and intrahepatic cholangiocarcinoma cases were detected in 2020, of which 30160 died[2]. Surgery (liver transplantation and resection) is the backbone of HCC treatment and is the only possible treatment option. Delamination or removal is an alternative treatment for small tumors. In addition, intra-arterial treatment and chemotherapy can control the disease to some extent[1]. In addition, HCC has certain radiological features that do not require histological examination for diagnosis. Therefore, the analysis and interpretation of diagnostic imaging procedures are not always easy as it changes during the disease course. The same applies to diagnosis/prognosis and treatment response, as they are influenced by numerous factors.

Artificial intelligence (AI) is the computer simulation of the human intelligence process. The concept of AI (artificial intelligence) emerged in the 1950s[3], but only a few years ago it makes real progress. It has been used in a variety of industries, i.e. image and natural language processing. In the field of medicine, artificial intelligence is becoming increasingly significant. The utilization of artificial intelligence (AI) is rapidly expanding and is increasingly useful in understanding gastrointestinal (GI) diseases[4-6]. The phrase "artificial intelligence" refers to a group of computer programs that attempt to mimic human brain capabilities i.e. learning and problem-solving. AI has evolved into a separate discipline called Machine learning (ML). ML examined data to develop algorithms that can recognize distinct behavior forms and confirm predictive models. ML focuses on developing mathematical models that assist machines in making predictions or judgments without being explicitly programmed. Various ML techniques, for instance, support vector machines (SVM), artificial neural networks (ANNs), classification, and regression trees seemed to be employed in various investigations in the medical discipline[7]. Deep learning (DL) has emerged as an emerging paradigm of machine learning for developing multilayered neural network algorithms, and approaches like convolutional neural network

(CNN), an ANN multilayer, have been widely accepted and used in radiological image analysis[8, 9].

In a nutshell, machine learning is a core branch of AI, and deep learning is used to implement it. The use of machine learning and deep learning to forecast the risk of gastric cancer (GC) has proved successful[10]. Figure 1 shows the correlation between artificial intelligence, machine learning, and deep learning.

USE OF AI IN HCC DIAGNOSIS

The utility of AI approaches to enhance diagnostic procedures in the area of liver cancer appears appropriate. CNN in the form of multi-layered ANN is interlinked and whole input data passes through every layer before being transformed to give output data. It is a more advanced version of DL that has its own learning capacity. Ultrasound tests, abdominal computed tomography, magnetic resonance imaging of the abdomen, positron emission tomography, and histology can benefit from CNN.

1. *Ultrasound of the abdomen*

HCC develops in cirrhotic livers most of the time, but not always. Clinical practice recommendations advocate routine abdominal ultrasonography in hepatic cirrhosis patients. This approach is used for detecting lesions that occupy space. Ultrasound is the primary machine for detecting hepatic disease and fresh lesions. Though, analysis of images is not straightforward and can be subject to interobserver variations.

To review the fundamental disorder, Bharti *et al*[11] established an ANN model that discriminates various phases of hepatic infection by analyzing ultrasound photos: normal liver, chronic liver disease, cirrhosis, and HCC. Further, this model's accurateness was found to be 96.6 percent[11]. An algorithm to analyze ultrasonic images was developed by Liu *et al*[12]. Liu *et al*[12] preferred the liver capsule to detect the existence of cirrhosis, even at an early stage when findings of a radiologist aren't clearly visible. By investigating the morphology of the liver capsule, Liu *et al*[12] predicted the presence or absence of cirrhosis with an area under the curve of 0.968.

The human output is defined, when it comes to identifying liver lesions from ultrasound photos. Schmauch *et al*[13] developed a DL approach that can reveal and label benign and

The usefulness of liver segmentation in assessing lesions in the liver and managing good treatment is critical. Li *et al*[20] developed a CNN which could cause the segmentation of liver tumours on the basis of CT photographs having an accuracy of 82.67% ± 1.43%, which is better than existing approaches, allowing for more appropriate treatment planning.

3. *Abdomen's MRI*

The use of CNN in MRI has also been investigated. Hamm *et al*[21] prepared and verified a CNN-based DL approach that identifies MRI liver lesions with 92% accuracy, 92% sensitivity, and 98% specificity with a mean computation time of 5.6 milliseconds.

Further research has used more MRI sequences, risk components, and clinical information of the patient to create an automated classification method that classifies hepatic lesions as adenoma, cyst, haemangioma, HCC, and metastasis, having sensitivity and specificity of 0.8/0.78, 0.93/0.93, 0.84/0.82, 0.73/0.56, and 0.62/0.77, respectively[22].

4. *PET*

Preis *et al*[23] used a neural network to study hepatic intake of 18F along with data from the patient and clinical details to assess the results of 18F-FDG PET/CT (fluorine 18 fluorodeosyglucose positron emission tomography/computed tomography). Preis *et al*[23] obtained higher sensitivity and specificity to find malignancy of the liver which remains unrevealed visibly. So that method can help the radiologist in the analysis of PET.

5. *Histology*

Even for professional pathologists, determining the histopathological categorization of a liver lesion and distinction of tumor strain is critical to planning the treatment and prognosis assessment of the disease. Kiani *et al*[24] were concerned with the histopathological distinction between HCC and cholangiocarcinoma and employed AI to assist pathologists.

Others reported how a deep CNN can perform an automatic identification of HCC and discriminate normal tissue from malignant tissue, as well as identify key biological predictors, utilizing previous histopathological pictures of HCC[25].

USE OF AI FOR TREATING HCC

The specific biological variance among HCC patients hampers evidence-based clinical assessment among all patients. Hence, for optimizing treatment techniques and measuring the results, powerful standardized risk classification tools are required. AI has the potential to play a significant role in the treatment of HCC in this area. The majority of studies about the applicability of AI in the HCC treatment are focused on analyzing specific tumour attributes, i.e. radiological, histological, or genetic traits, or combining clinical data to estimate treatment response. Therefore, patients will be able to be better selected for certain treatment alternatives.

1. *Use of Radiomics*

The examination and remedy measure of HCC is generally performed with imaging facilities i.e. C-US, CT, and MRI, following investigating assured tumour characteristics i.e. vascularization or behaviour subsequently the addition of contrasting substance[26]. Above mentioned attributes are amenable to biases on analysis by radiologists, along with the absence of high-resolution dimensional photos. Recently an advanced technology has emerged in the area of radiology and cancer which is known as radiomics[27]. This technology helps in drawing a large amount of significant data from the radiological photographs and linking this data with the related biological system. The study of this complete data with AI software can give effective and accurate reports for proper diagnosis and prognosis[27, 28]. Figure 2 shows various stages of radiomics where artificial intelligence can play a role.

2. *In the assessment of surgical resection*

The early reappearance of the tumour following operative removal is due to unsatisfactory prognostic process. The recognition of clinical cases before surgical operation with more risk of relapse is essential to escape irrelevant treatment. Various computer models help to analyze specific tumour markers/features and assist in the prognosis of the risk of relapse before operative procedures. These models also help in the assessment of survival after surgical removal.

Vascular microinvasion has proved as a self-sufficient prognostic component of relapse. VMI is linked with feeble outcomes following tumour excision[29]. The accessibility of data regarding VMI preoperatively can be of high use. The radiological approach presently used in medical practice does not give a fair diagnosis.

Several studies explain radiomic signatures that presume the status of VMI preoperatively on the basis of contrast-enhanced CT[30, 31] or MRI[32]. Above mentioned techniques include exposure to radiation and are hard to execute and expensive. In a recent study, Dong *et al*[33], used grayscale ultrasound images based on radiomic algorithms to proceed with radiomic signatures in the prediction of VMI. By using radiomic techniques, Ji *et al*[34] developed prognostic models for relapse after excision surgery for assessing contrast-enhanced CT photographs and had a C-index value of 0.633-0.699. These models could be utilized for providing an individualized risk stratification for managing HCC individually.

ML techniques help in assessing survival after surgical resection as observed in many studies[35-37]. Recently, more advanced DL models help in assessing survival after surgical resection on the basis of digitalized histological photographs of tumours.

3. *Assessment of transcatheter arterial chemoembolization*

According to Barcelona Clinical Liver Cancer (BCLC) classification, transcatheter arterial chemoembolization (TACE) exists as the preferred option for the treatment of intermediary B stage HCC[38]. The right choice of patients who can get benefit from this treatment is critical in order to minimize superfluous investigations that can lead to unfavourable side effects and waste healthcare costs. Studies based on AI approaches have been created as a trial to infer the feedback of TACE treatment and facilitate the proper selection of patients. The majority of the above-said studies rely on image analysis, but some studies have also utilized genomic signatures. Morshid *et al*[39] developed an automatic ML algorithm that predicts TACE response using a mixture of quantitative CT image attributes and pre-treatment patient clinical data. They got a prediction accuracy rate of 74.2% while working on combining the BCLC stage and quantitative image characteristics instead of applying the BCLC stage alone. Peng *et al*[40] used CT scans from 789 patients from three separate hospitals to verify a DL model for predicting TACE response. They were able to predict complete responses with an accuracy of 84 percent and an AUC of 0.97. Liu *et al*[41] developed and verified a DL radiomics-based C-US approach as a result of a quantitative assessment of C-US cine recordings. They demonstrated a high level of reproducibility and an AUC of 0.93 (95 percent CI: 0.80-0.98) for predicting TACE reaction.

Further research has combined MRI and clinical data with machine learning approaches to predict TACE response. Abajian *et al*[42] worked on 36 patients who had an MRI prior to TACE. They built a response prediction model with 78 percent accuracy, 62.5 percent sensitivity, and 82 percent specificity.

TACE's efficacy has also been tested by a post-treatment survival analysis of patients. Mähringer-Kunz *et al*[43] designed an ANN with every variable of main traditional prediction scores to produce a survival prediction model following TACE (ART[44], ABCR[45], and

SNACOR[46]). By an AUC of 0.77, 78 percent sensitivity, and 81 percent specificity, they expected a one-year survival rate that was better than the conventional scores.

Although radiomics have been used in the majority of investigations estimating the usage of AI to examine TACE. Some have also looked at genetic analysis to predict TACE response. Ziv *et al*[47] analyzed genetic mutations by applying SVM algorithms to look for tumour responses following TACE. However, this study involved a small number of cases.

4. *Radiofrequency ablation evaluation*

Radiofrequency ablation (RFA) had also been studied as a treatment for HCC in its early stages[38]. Liang *et al*[48] used SVM to create a prognostic model of HCC relapse. They investigated 83 HCC cases who had undergone RFA and secured an AUC of 0.69, 67 percent sensitivity, and 86 percent specificity. From this data, they could recognize patients with a greater chance of relapse.

HCC OVERALL SURVIVAL PREDICTION

Apart from the use of any therapy, AI approaches have been used to predict the overall survival of HCC patients. The observations by Dong *et al*[49] were based on current information on the relationship between anomalies in DNA methylation and HCC[50-52]. Above said researchers employed ML techniques (SVM) for the evaluation of DNA methylation data from 377 HCC samples and created 3 risk groups to expect complete survival and achieved a mean 10-fold cross-validation score of 0.95.

FUTURE PERSPECTIVES

To illustrate AI's effectiveness as medical assistance, further research is required that compares the output of medical staff with AI assistance vs experts lacking AI assistance. These studies should target elements linked to curing and prognosis, for instance, identifying ambiguous hepatic wounds, the existence of vascular invasion, and the reaction to percutaneous treatments, primarily, to analyze liver masses and to explore HCC. One more significant point is the utilization of AI for interpretation of HCC behaviour in cirrhotic and non-cirrhotic patients, in the differential diagnosis of primary and metastatic liver lesions[53], and particularly in clinical detection of cholangiocarcinoma, which could be difficult to differentiate with existing approaches and their handling and diagnosis are significantly distinct from HCC.

Simultaneously, healthcare providers must be trained for the integration of AI into everyday practice in the area of liver cancer.

SIGNIFICANCE OF THE STUDY

AI has guided in detecting HCC (on the basis of pre-malignant variations, imaging, and biomarkers) as a result of its capability to examine huge data and combine data effectively. The perspective of AI techniques is immense in every stage in the handling of HCC i.e. from early diagnosis to treatment options and prognostic and therapeutic response prognosis. These methods could promote accurate and personalized medicine to assist clinical practice and better expenses. Numerous datasets (Radiological pictures or pathologic data), could be utilized individually or in conjunction for accuracy better than that of conventional statistical means. Moreover, AI-based approaches can also assist in lowering interobserver variance while studying images, and leads to standardization.

INNOVATIVE CONTRIBUTIONS OF THE STUDY

The outcomes from many studies endorse the consolidation of the ML models with clinical/pathologic data and created clinical scores or biomarkers. Biomarkers detected by the incorporation of several '-omics' datasets lead to the recognition of a biochemical tumour signature, which revolutionizes HCC detection in near future.

CONCLUSION

One of the most significant advancements in recent years has been the utilization of AI technologies in medicine. It will almost certainly grow in popularity as a result of its utility in processing and analyzing the massive amounts of already available data. However, we should be attentive that there are some limitations that may reduce its acceptability and application in the medical field. Medical professionals need to understand the genuine value of AI and recognize the necessity for it to coexist with the essential requirement for human assessment. Regardless of AI's significant advancements, it is critical to ensure that medical protocols remain completely transparent.

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