

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2022 October 28; 3(4): 96-116



MINIREVIEWS

- 96 Role of artificial intelligence in the diagnosis and treatment of hepatocellular carcinoma
Mokhria RK, Singh J

ORIGINAL ARTICLE**Prospective Study**

- 105 Dietary counseling based on artificial intelligence for patients with nonalcoholic fatty liver disease
Kusano Y, Funada K, Yamaguchi M, Sugawara M, Tamano M

ABOUT COVER

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The *AIG* is now abstracted and indexed in Reference Citation Analysis, China Science and Technology Journal Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

<p>NAME OF JOURNAL <i>Artificial Intelligence in Gastroenterology</i></p> <p>ISSN ISSN 2644-3236 (online)</p> <p>LAUNCH DATE July 28, 2020</p> <p>FREQUENCY Bimonthly</p> <p>EDITORS-IN-CHIEF Rajvinder Singh, Ferruccio Bonino</p> <p>EDITORIAL BOARD MEMBERS https://www.wjgnet.com/2644-3236/editorialboard.htm</p> <p>PUBLICATION DATE October 28, 2022</p> <p>COPYRIGHT © 2022 Baishideng Publishing Group Inc</p>	<p>INSTRUCTIONS TO AUTHORS https://www.wjgnet.com/bpg/gerinfo/204</p> <p>GUIDELINES FOR ETHICS DOCUMENTS https://www.wjgnet.com/bpg/GerInfo/287</p> <p>GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH https://www.wjgnet.com/bpg/gerinfo/240</p> <p>PUBLICATION ETHICS https://www.wjgnet.com/bpg/GerInfo/288</p> <p>PUBLICATION MISCONDUCT https://www.wjgnet.com/bpg/gerinfo/208</p> <p>ARTICLE PROCESSING CHARGE https://www.wjgnet.com/bpg/gerinfo/242</p> <p>STEPS FOR SUBMITTING MANUSCRIPTS https://www.wjgnet.com/bpg/GerInfo/239</p> <p>ONLINE SUBMISSION https://www.f6publishing.com</p>
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 E-mail: bpgoffice@wjgnet.com <https://www.wjgnet.com>



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

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Lu G, China; Wan Y, China

Received: June 7, 2022

Peer-review started: June 7, 2022

First decision: July 14, 2022

Revised: July 30, 2022

Accepted: September 13, 2022

Article in press: September 13, 2022

Published online: October 28, 2022



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Abstract

Artificial intelligence (AI) evolved many years ago, but it gained much advancement in recent years for its use in the medical domain. AI with its different subsidiaries, *i.e.* deep learning and machine learning, examine a large amount of data and performs an essential part in decision-making in addition to conquering the limitations related to human evaluation. Deep learning tries to imitate the functioning of the human brain. It utilizes much more data and intricate algorithms. Machine learning is AI based on automated learning. It utilizes earlier given data and uses algorithms to arrange and identify models. Globally, hepatocellular carcinoma is a major cause of illness and fatality. Although with substantial progress in the whole treatment strategy for hepatocellular carcinoma, managing it is still a major issue. AI in the area of gastroenterology, especially in hepatology, is particularly useful for various investigations of hepatocellular carcinoma because it is a commonly found tumor, and has specific radiological features that enable diagnostic procedures without the requirement of the histological study. However, interpreting and analyzing the resulting images is not always easy due to change of images throughout the disease process. Further, the prognostic process and response to the treatment process could be influenced by numerous components. Currently, AI is utilized in order to diagnose, curative and prediction goals. Future investigations are essential to prevent likely bias, which might subsequently influence the analysis of images and therefore restrict the consent and utilization of such models in medical practices. Moreover, experts are required to realize the real utility of such approaches, along with their associated potencies and constraints.

Key Words: Hepatocellular carcinoma; Artificial intelligence; Deep learning; Machine learning; Support vector machines; Artificial neural networks

Core Tip: Globally, hepatocellular carcinoma is a major cause of illness and fatality. Although substantial progress has been made in the treatment strategy for hepatocellular carcinoma, managing it is still a major issue. Artificial intelligence in the area of gastroenterology, especially in hepatology, is particularly useful for various investigations of hepatocellular carcinoma because it is a commonly found tumor and has specific radiological features that enable diagnostic procedures without the requirement of histological study. Artificial intelligence is utilized to diagnose, curative and prediction goals.

Citation: Mokhria RK, Singh J. Role of artificial intelligence in the diagnosis and treatment of hepatocellular carcinoma. *Artif Intell Gastroenterol* 2022; 3(4): 96-104

URL: <https://www.wjgnet.com/2644-3236/full/v3/i4/96.htm>

DOI: <https://dx.doi.org/10.35712/aig.v3.i4.96>

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignancy of the liver that 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 emerged in the 1950s[3], but only a few years ago it made real progress. It has been used in a variety of industries, *i.e.* image and natural language processing. In the field of medicine, AI is becoming increasingly significant. The utilization of AI is rapidly expanding and is increasingly useful in understanding gastrointestinal 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 examines 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, seem to be employed in various investigations in the medical discipline[7]. Deep learning (DL) has emerged as an emerging paradigm of ML 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, ML is a core branch of AI, and DL is used to implement it. The use of ML and DL to forecast the risk of gastric cancer has been successful[10]. **Figure 1** shows the correlation between AI, ML, and DL.

There are limitations in using AI in various areas of medicine. Looking back on many studies and applications of irrelevant databases having biases can influence the truthfulness of AI. Therefore, it is essential to design a bias-free, proposed, well-designed multicenter collaborative study, and various important aspects, such as economics, medical professional regulation, and ethical reviews, should not be ignored. Various terms associated with AI in this minireview are given in **Table 1**.

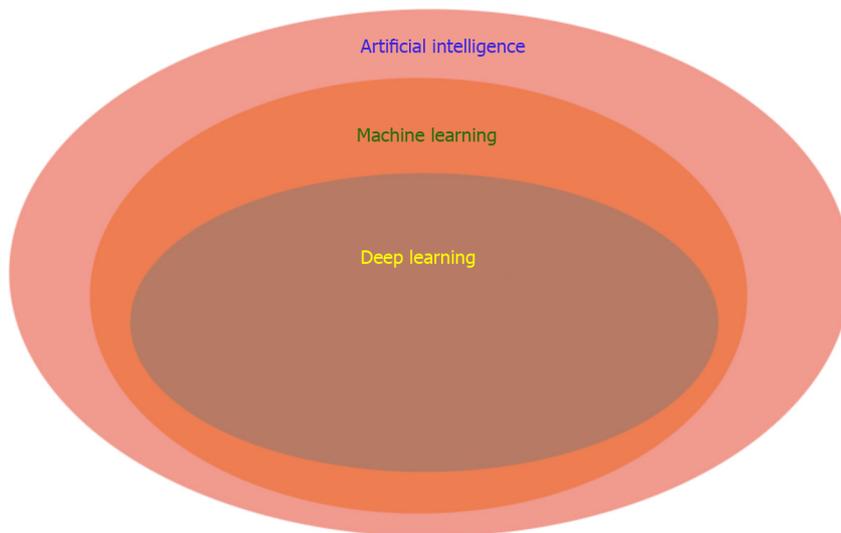
USE OF AI IN HCC DIAGNOSIS

The utility of AI can enhance diagnostic procedures in the area of liver cancer. CNN in the form of multilayered 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 (US) tests, abdominal computed tomography (CT), magnetic resonance imaging (MRI) of the abdomen, positron emission tomography (PET), and histology can benefit from CNN.

Table 1 Various terminology associated with artificial intelligence

Term	Definition
AI	The utilization of computers and associated techniques to mimic the sharp attitude and critical approach of humans
ML	It is a branch of AI and computer science that concerns the usage of data and algorithms to mimic the means that human beings ascertain and step by step upgrading its precision
ANN	It is a computational model in accordance with the structure and functions of biological neural networks. ANNs employ a nonlinear function to a loaded sum of inputs and model relations among them
CNN	It is a deep learning neural network intended to process structured arrays of data, <i>i.e.</i> radiological images
Deep learning	A branch of ML that tries to mimic the human brain and has the ability to gather data and do predictions with remarkable precision
AUC	AUC is an approach applied in ML to assess many used models to find out which have the higher performance
Accuracy	AI and ML technology employ algorithms to analyze data and perform predictions on the basis of such data. Although studies report that AI programs may regularly achieve accuracy levels of at least 95% and AI programs cannot verify the veracity of the data being examined, the overall accuracy is typically lower yet still higher than 80%
C-index (c-statistic)	It is an algorithm performance metric that takes values between 0 and 1 and explains how well the model fits the data

AI: Artificial intelligence; ANN: Artificial neural networks; AUC: Area under the curve; CNN: Convolutional neural network; ML: Machine learning.



DOI: 10.35712/aig.v3.i4.96 Copyright ©The Author(s) 2022.

Figure 1 Relationship between artificial intelligence, machine learning, and deep learning.

Ultrasound of the abdomen

HCC develops in cirrhotic livers most of the time but not always. Clinical practice recommendations advocate routine abdominal US in hepatic cirrhosis patients. This approach is used for detecting lesions that occupy space. US 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 discriminated various phases of hepatic infection by analyzing US images: normal liver, chronic liver disease, cirrhosis, and HCC. Further, this model's accuracy was found to be 96.6% [11]. An algorithm to analyze US 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 radiological findings are not 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 (AUC) of 0.968.

The human output is defined when it comes to identifying liver lesions from US images. Schmauch *et al*[13] developed a DL approach that could reveal and label benign and malignant space-occupying liver lesions. This system requires acceptance. It has the potential to improve the diagnostic yield of US and inform clinicians about potentially malignant lesions[13].

To improve the ability of contrast-enhanced US (C-US) for the detection of cancer-related characteristics, the use of AI has been utilized. Guo *et al*[14] confirmed how applying DL to the behavior of liver lesions observed on C-US in three phases (arterial, portal, and late) improved the accuracy, sensitivity, and specificity of the investigation undertaken.

Abdominal CT scan with intravenous contrast

When an US reveals a fresh liver lesion, further imaging procedures, primarily dynamic contrast-enhanced CT or MRI, are used to get an accurate diagnosis. In dynamic CT or MRI scans, the radiological behavior of liver lesions can be used to characterize the lesion. If CT scans of liver nodules reveal unclear behavior, then lesion biopsy is prescribed as per the recommendation of the European Association for the Study of the Liver guidelines[15]. As suggested by the American Association for the Study of Liver Diseases guidelines[16], there is the possibility of non-detection of a malignant lesion involved during the procedure or during close follow-up. A study was performed on 178 patients with cirrhosis and liver nodules by Mokrane *et al*[17], and they were unable to differentiate between neoplastic and non-neoplastic lesions in these patients, hence requiring a biopsy. On doing a biopsy, 77% of the lesions were malignant. By applying DL techniques, the AUC for classifying nodules as HCC or non-HCC was 0.70. By analyzing the output of three-layered ANN, Yasaka *et al*[18] with the help of contrast-enhanced CT classified liver masses into five groups: A (cholangiocarcinoma, hepatocholangiocarcinoma, or metastasis); B (other malignant tumors, *i.e.* cholangiocarcinoma, hepatocholangiocarcinoma, or metastasis); C (ambiguous masses, dysplastic nodules, or early HCC, and benign masses other than cysts or haemangiomas); D (haemangiomas); and E (cysts).

Assessing tumor load could be beneficial for detecting tumor relapse in follow-up CT scans. Vivanti *et al*[19] proposed an automated detecting procedure for recurrence on the basis of early manifestation of the tumor, its CT behavior, baseline tumor load/mass quantification, and follow-up. With an accuracy of 86%, this approach demonstrated a higher proportion of true positives in detecting tumor relapse.

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

Abdominal MRI

The use of CNN in MRI has also been investigated. Hamm *et al*[21] prepared and verified a CNN-based DL approach that identified 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/specificity of 0.80/0.78, 0.93/0.93, 0.84/0.82, 0.73/0.56, and 0.62/0.77 respectively[22].

PET

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

Histology

Even for experienced 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 images 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 HCC treatment are focused on analyzing specific tumor 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.

Use of radiomics

The examination and remedy measure of HCC is generally performed with imaging facilities i.e. C-US, CT, and MRI following investigation of assured tumor characteristics, *i.e.* vascularization or behavior after the addition of a contrasting substance[26]. These attributes are amenable to biases after analysis by radiologists, along with the absence of high-resolution dimensional images. Recently an advanced technology has emerged in the area of radiology and cancer which is known as radiomics[27]. This technology extracts a large amount of significant data from the radiological images and links this data with the related biological system. The study of 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 AI can play a role.

Assessment of surgical resection

The early reappearance of the tumor following operative removal is due to an 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 tumor 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 (VMI) is a self-sufficient prognostic component of relapse. VMI is linked with poor outcomes following tumor 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]. These techniques include exposure to radiation, are hard to execute, and are expensive. In a recent study, Dong *et al*[33] used grayscale US 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 images 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 helped in assessing survival after surgical resection on the basis of digitalized histological images of tumors.

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 unfavorable side effects and waste healthcare resources. 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 studies rely on image analysis, but some studies have also utilized genomic signatures. Morshid *et al*[39] developed an automatic ML algorithm that predicted TACE response using a mixture of quantitative CT image attributes and pretreatment patient clinical data. They obtained a prediction accuracy rate of 74.2% while working on combining the Barcelona Clinic Liver Cancer stage and quantitative image characteristics instead of applying the Barcelona Clinic Liver Cancer 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% 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% confidence interval: 0.80-0.98) for predicting TACE reaction.

Further research has combined MRI and clinical data with ML 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 78.0% accuracy, 62.5% sensitivity, and 82% specificity.

The efficacy of TACE 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]). With an AUC of 0.77, 78% sensitivity, and 81% specificity, they expected a 1-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 tumor responses following TACE. However, this study involved a small number of cases.

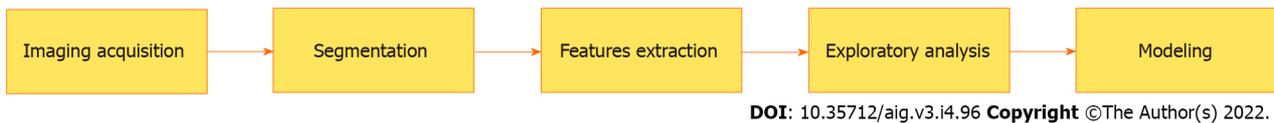


Figure 2 Stages of radiomics wherever artificial intelligence can play a role.

Radiofrequency ablation evaluation

Radiofrequency ablation has 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 that had undergone radiofrequency ablation and secured an AUC of 0.69, 67% sensitivity, and 86% 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]. They employed ML techniques (SVM) for the evaluation of DNA methylation data from 377 HCC samples and created three risk groups to expect complete survival and achieved a mean 10-fold cross-validation score of 0.95.

FUTURE PERSPECTIVES

To illustrate the effectiveness of AI for 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) to analyze liver masses and explore HCC. Additional significant points are the utilization of AI for interpretation of HCC behavior in cirrhotic and non-cirrhotic patients, in the differential diagnosis of primary and metastatic liver lesions[53], and particularly in the clinical detection of cholangiocarcinoma, which is difficult to differentiate from HCC with existing approaches and has distinct treatment methods 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 the detection of HCC (on the basis of premalignant variations, imaging, and biomarkers) as a result of its capability to examine huge datasets and combine data effectively. The perspective of AI techniques is immense in every stage in the handling of HCC, *e.g.*, 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 utilize healthcare resources. Numerous datasets (radiological images 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 tumor signature, which revolutionizes HCC detection in the 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

massive amounts of 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 the significant advancements, it is critical to ensure that medical protocols remain completely transparent.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Jitender Bhardwaj, Assistant Professor, Zoology Department, Kurukshetra University, Kurukshetra, Haryana, India, and Sh. Ram Narayan, Lecturer (English), Government High School, Karsa Dod, Karnal, Haryana, India for timely support.

FOOTNOTES

Author contributions: Mokhria RK designed the outline, performed data acquisition, contributed to the majority of the writing, and proofread the paper; Singh J coordinated the writing of the paper and proofread the paper.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior authors or other coauthors who contributed their efforts to this manuscript.

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S-Editor: Liu JH

L-Editor: Filipodia

P-Editor: Liu JH

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