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A New Tool for the Diagnosis and Management of Viral Hepatitis: Artificial Intelligence

Viral Hepatitin Teşhisi ve Yönetiminde Yeni Bir Araç: Yapay Zeka

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ABSTRACT

Artificial intelligence (AI) is rapidly transforming the field of hepatology, offering promising solutions for the diagnosis and treatment management of viral hepatitis. This review examines the various applications of AI in hepatology, including detection of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) using radiological (ultrasound, computed tomography, and magnetic resonance imaging) and pathological images, identification of individuals at high risk for viral hepatitis and its complications early identification of liver diseases through analysis of electronic health record data prediction of prognosis in HCC. Despite the remarkable potential of AI in hepatology, several challenges remain. Ethical concerns regarding data privacy, algorithmic biases, and regulatory compliance must be addressed. Collaborative efforts between healthcare professionals and data scientists are essential to navigate these challenges and unlock the full potential of AI in transforming hepatology.

Keywords: Artificial intelligence, cirrhosis, deep learning, HCC, chronic viral hepatitis, machine learning

ÖZ

Yapay zeka (AI), viral hepatitin tanısı, prognozun tahmini ve tedavi yönetimi için umut verici çözümler sunarak hepatoloji alanını hızla dönüştürmektedir. Bu derleme, radyolojik (ultrason, bilgisayarlı tomografi ve manyetik rezonans görüntüleme) ve patolojik görüntüleri kullanarak karaciğer fibrozu, siroz ve hepatoselüler karsinomun (HCC) saptanması, viral hepatit ve komplikasyonları için yüksek risk altındaki bireylerin belirlenmesi elektronik sağlık kaydı verilerinin analizi yoluyla karaciğer hastalıklarının erken teşhisi HCC'de prognozun tahmin edilmesi dahil olmak üzere hepatolojide yapay zekanın çeşitli uygulamalarını incelemektedir. AI'nın hepatolojideki dikkate değer potansiyeline rağmen, bazı zorluklar devam etmektedir. Veri gizliliği, algoritmik önyargılar ve mevzuat uyumluluğuna ilişkin etik kaygıların ele alınması gerekmektedir. Sağlık uzmanları ve veri bilimcileri arasındaki işbirlikçi çabalar, zorlukların üstesinden gelmek ve hepatolojiyi dönüştürmede yapay zekanın tüm potansiyelini ortaya çıkarmak için çok önemlidir.

Anahtar Kelimeler: Yapay zeka, siroz, derin öğrenme, HCC, kronik viral hepatit, makine öğrenmesi

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Introduction

Liver diseases cover a broad spectrum of illnesses, from common conditions such as viral hepatitis to more severe ones like cirrhosis and hepatocellular carcinoma (HCC) (1). Despite their clinical importance, the diagnosis and treatment of liver diseases have often been challenging because of the complex nature of liver functions and the complexity of diseases that can develop (2).

Artificial intelligence (AI), including machine learning (ML) and deep learning (DL) techniques, has emerged as a transformative force in different fields of healthcare, including hepatology (3,4). Recent advancements in AI have revealed novel perspectives in understanding, diagnosing, and managing liver diseases (4). This comprehensive review aims to provide an in-depth exploration of the various applications of AI in hepatology, elucidating its pivotal role in disease diagnosis, tailoring individualized treatments, optimizing decision-making, predicting patient outcomes, and facilitating continuous monitoring.

Let us start by delving into the foundational principles of AI, data sourcing, and preprocessing. By delving into these principles, we can gain a deeper insight into how these technologies can

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effectively tackle the complexities encountered in various aspects of hepatology. Subsequently, we will investigate the application of AI in addressing hepatology's challenges, delving into the specific AI technologies and data that can be harnessed for this purpose. In addition, we will explore the practical implementations of AI in hepatology and the potential outcomes that may arise. Finally, we will engage in a discussion concerning the ethical and regulatory dimensions, along with the challenges and future directions of this dynamic field.

With this review, I hope to make AI more understandable and to enable you to see the great opportunities it offers today in overcoming the difficulties in the diagnosis and management of viral hepatitis.

What is AI and How Does It Work?

AI Fundamentals

AI is a branch of computer science concerned with building machines that can perform intelligent tasks such as learning, recognizing patterns, problem solving, and decision making (5,6,7). Expert systems, also known as "hard-coded" AI systems, were dominant in AI in the pre-ML era. They relied on manually encoded rules and knowledge bases to solve problems, essentially replicating the expertise of human experts in a specific domain (8,9).

ML is a subfield of AI that focuses on developing algorithms that can learn from data without being explicitly programed. Instead of manually coding each step, ML algorithms can analyze large datasets and identify patterns, enabling them to make predictions and decisions on their own (9,10).

DL is a subfield of ML that uses artificial neural networks to learn from data. Neural networks are inspired by the structure and function of the human brain, and they can learn complex patterns and relationships that would be difficult or impossible to learn with traditional ML algorithms (10,11). ML requires human engineering and domain expertise to design feature extractors and structure data, whereas DL does not require structured data. DL has been highly successful in various applications, including image recognition, natural language processing, speech recognition, machine translation, and medical diagnosis (11,12,13,14).

AI is not magic. You may think of ML as a model that learns from historical data to forecast future data. Furthermore, AI is not a new technology. Its roots can be traced back to the 1950s (14,15).

Role of Data in Training AI Models for Healthcare

Data play a crucial role in training AI models for healthcare. It serves as the fuel that powers these models, enabling them to learn and improve over time. AI models learn by analyzing vast amounts of data. This includes medical records, imaging scans, lab results, genetic information, and patient surveys. These data points serve as examples for the model, allowing it to identify patterns and relationships between different variables. As the model analyzes more data, it refines its understanding and adjusts its internal parameters. This process of continuous learning ensures that the model becomes increasingly accurate and reliable. The type and quality of data used for training significantly impact the model's performance (16).

Data Sources and Data Pre-processing

AI algorithms rely on various data sources, including medical records, imaging data [e.g., computed tomography (CT) scans, magnetic resonance imagings (MRI)], genomic data, histopathological data, and clinical notes. Data preprocessing, which involves cleaning, normalization, and feature extraction, is a critical step to ensure the data's suitability for AI model training (3,9).

Types of Data

Structured data include medical records, laboratory results, and insurance claims, which are typically stored in databases and are easily accessible for training algorithms. Unstructured data include medical images, pathology reports, and clinical notes, which require additional processing and extraction techniques to be used by AI models. Real-time data includes data generated by wearable devices, sensors, and medical monitoring systems, which can be used to provide continuous feedback and improve the performance of AI models in real-time settings (9).

Data Quality

The quality of training data significantly affects an AI model's accuracy. Ensuring data accuracy, completeness, and absence of errors or biases is critical (16).

AI Applications Using Radiological Images for Viral Hepatitis

AI is rapidly transforming the field of radiology, and AI applications for radiological analysis in patients with viral hepatitis are no exception (17,18,19). AI algorithms can be trained on large datasets of medical images to identify patterns and features that may be indicative of viral hepatitis or its complications. This can help radiologists to detect and diagnose viral hepatitis and its complications more accurately and efficiently, even in cases where the findings are subtle or equivocal (19,20,21). Here are some specific examples of AI applications using radiological images in patients with viral hepatitis.

Identifying the Features of Liver Fibrosis and Cirrhosis on Ultrasound (US), CT, and MRI

Hepatic fibrosis is a crucial milestone in chronic liver disease, significantly impacting disease prognosis. However, the conventional method of detecting hepatic fibrosis involves a rather invasive procedure known as liver biopsy, which necessitates the removal of a small liver tissue sample for microscopic examination. Fortunately, AI algorithms present a promising avenue for identifying subtle indicators of liver fibrosis and cirrhosis through US, CT, and MRI images (22,23,24,25).

Several online systems have been developed to aid in staging hepatic fibrosis, offering accessible and efficient tools for clinicians. These computer-aided diagnosis systems generally work by incorporating specific patient data or test results into algorithms or scoring systems such as METAVIR and FIB-4 scores. The input parameters include laboratory values, patient demographics, and imaging findings. Algorithms then compute a score or index that correlates with the degree of fibrosis, aiding clinicians in staging liver fibrosis and guiding further diagnostic or treatment decisions (6,26).

These algorithms can discern nuanced changes in liver texture, volume, echogenicity, elasticity analysis, and vascularity. Popa et al. (27), in their systematic review encompassing 24 articles analyzing AI-assisted imaging techniques, concluded that these non-invasive AI-driven methods perform on par with human experts in accurately detecting and staging liver fibrosis.

In a prospective study conducted by Wang et al. (28), 1990 two-dimensional shear wave elastography (2D-SWE) images of 398 chronic hepatitis B patients who underwent liver biopsy from 12 hospitals were included. This study evaluated the performance of a developed DL Radiomics of elastography (DLRE) model using 2D-SWE images and a convolutional neural network (CNN) algorithm. Results indicated that the DLRE model outperformed other methods, including 2D-SWE and/or biochemical markers (APRI, FIB-4), in predicting liver fibrosis stages. Specifically, it exhibited significantly higher diagnostic accuracy than other techniques. It accurately predicted cirrhosis (F4) with 97% accuracy and advanced fibrosis (≥F3) with 98% accuracy. Moreover, unlike the varying cut-off values proposed when determining the degree of fibrosis using 2D-SWE, the DLRE model's performance remained consistent even when applied to different training cohorts (28).

This breakthrough offers a substantial advantage to clinicians, enabling them to diagnose and monitor the progression of liver disease in patients with viral hepatitis without resorting to invasive procedures.

Detection of HCC on US, CT, and MRI Images

Detecting HCC using imaging techniques like US, CT scans, and MRI presents several challenges. First, HCC lesions can vary in size and appearance, making it challenging to distinguish small tumors from surrounding healthy tissue or benign nodules. This difficulty increases when differentiating early-stage HCC from dysplastic or cirrhotic nodules (29,30). Second, especially when these liver lesions occur together with cirrhosis or steatosis, it becomes difficult for radiologists to distinguish malignant features among complex lesion types (31,32). Finally, the accuracy of HCC detection can be influenced by the skill and experience of the radiologist interpreting the images. Variability in interpretation can affect diagnostic reliability (33). AI algorithms can be used to detect HCC on CT and MRI images with high accuracy, even in the early stages. This is important because HCC is a major complication of chronic viral hepatitis, and early detection is essential for improving patient outcomes (34). AI models excel in identifying and characterizing liver lesions, including HCC, cysts, and metastatic tumors. They can accurately distinguish between benign and malignant lesions, thereby aiding in early cancer diagnosis (35).

B-mode US is the first recommended imaging test for focal liver lesions because of its cost-effectiveness and real-time diagnostic capability. However, it has limitations compared with other tomographic imaging modalities, such as equipment quality, physician expertise, and lack of perfusion information (36,37). In a multicenter study with external validation, a DCNN-US model developed using CNN achieved 92% accuracy in distinguishing malignant liver masses from benign ones. The diagnostic performance of this model was compared with that of 236 radiologists, demonstrating significantly higher accuracy than even experienced radiologists with 15 years of expertise (92% vs. 76.1%) (36).

In another study comparing the performance of different human experts with varying levels of experience in classifying four focal lesions (HCC, metastatic tumor, hemangioma, cyst), the AI system, developed using B-mode US and a CNN algorithm, outperformed human experts with an accuracy rate of 89.1%. In contrast, the median number of human experts stood at 67.3%. Furthermore, the likelihood of accurate diagnosis by the AI system increases with more training data, whereas in human experts, as the experience level decreases, the accuracy rate could be as low as 40% (35). Consequently, DL models can serve as a rapid and reliable "second opinion" tool for radiologists, particularly in cases where imaging features are ambiguous (35,36,38). In the future, AI's aid promises biopsy-equivalent data from radiological images, even through cost-effective, noninvasive US scans, revolutionizing diagnostic capabilities.

AI Applications Using Histopathological Images for Viral Hepatitis

Histopathological examination of liver biopsies remains the gold standard for the diagnosis and staging of liver fibrosis, inflammation, and other pathological changes associated with viral hepatitis. However, analyzing these images manually is time-consuming and subjective, leading to potential variability in interpretation and diagnosis (39).

The advancement of AI and whole-slide imaging scanners has made it possible to combine the two technologies to reduce medical burden, increase diagnosis accuracy, and even forecast prognosis and gene mutations (25).

AI-powered algorithms can analyze histopathological images with remarkable accuracy and efficiency, offering several advantages.

Early Detection of Pre-Cancerous Lesions

AI can be trained to identify subtle changes in hepatocytes and other liver cells that may indicate the presence of pre-cancerous lesions, such as dysplastic nodules, even before they are visible to the naked eye (40). This can enable early intervention and potentially prevent the development of HCC.

In a study comparing the performance of pathologists (having different levels of experience) with a DL model (trained using histopathological H&E images and CNN algorithm) in the prediction of malignant-benign differentiation and gene mutations affecting prognosis in focal liver lesions, the performance of the model was found to be equivalent to that of a 5-year pathologist. The model achieved 96% accuracy in distinguishing between malignant and benign lesions and 86.9% accuracy in classifying HCC into good, moderate, and poor prognosis categories (41). These findings highlight the potential of CNN in helping pathologists detect gene mutations in HCC. This can enhance diagnostic accuracy and contribute to precision medicine.

HCC-SurvNet, an AI-assisted pathology tool, uses digital histopathological images to predict disease recurrence risk after primary surgical resection for HCC. Risk scoring categorizes patients into low-and high-risk subgroups, showing substantial variations in survival outcomes. This position HCC-SurvNet as a promising instrument to advance the clinical management of HCC patients, outperforming the standard Tumor-Node-Metastasis classification system in predictive accuracy (42).

Streamlining Workflow and Reducing Pathologist Workload

AI can automate many repetitive tasks involved in the analysis of histopathological images, such as image pre-processing, feature extraction, and quantitative analysis. This can free up pathologists' time to focus on complex cases and decision-making, thus improving overall workflow efficiency (43).

AI Applications Using Electronic Health Record (EHR) Data in Viral Hepatitis

Identifying High-Risk Individuals

AI algorithms can be used to analyze EHR data to identify individuals at high risk of developing viral hepatitis, such as those with a history of intravenous drug use, blood transfusions, or sexual contact with people with viral hepatitis. This information can guide targeted screening and prevention efforts (44).

Because a significant portion of the population goes undiagnosed, HCV remains a major infectious disease-related public health issue, even with the availability of very effective therapies (19,45). AI models can be trained to identify individuals with risk factors like past blood transfusions, intravenous drug use, or unsafe sexual practices, highlighting those who should be prioritized for testing. For instance, an easy-to-implement risk score for targeted HCV testing developed by Martínez-Sanz et al. (46), consists of five items (gender, place of origin, use of intravenous drugs, self-perceived risk of acquired HCV infection, and past hepatitis or unexplained liver disease) that achieved high diagnostic accuracy, with a sensitivity of 98% and a negative likelihood ratio of 0.05 for participants with low scores, ruling out HCV infection with high probability. Scores like this can provide a cost-effective alternative to universal screening (46).

Early Identification of Treatable Liver Diseases

AI algorithms can analyze EHR data to identify subtle changes in laboratory tests, vital signs, and other clinical data that may indicate viral hepatitis infection, even before symptoms appear. This can help clinicians diagnose the disease earlier and initiate treatment promptly. By analyzing historical trends and comparing them with established diagnostic criteria, AI models can aid in early detection and diagnosis, leading to better patient outcomes (44,47).

For instance, the intelligent liver function test system is an experimental approach developed for automatically diagnosing and staging liver disease in primary care based on abnormal liver function test results from routine laboratory samples. This system has been demonstrated to be more successful than the standard of care in diagnosing liver disease, which has increased the accuracy of diagnosis to over 90% and enhanced detection rates by 43% (48). This system can facilitate the early identification of treatable liver diseases, creating an opportunity for early intervention and improving patient outcomes at a low cost.

More recently, a unique prediction CNN model was developed based on different abnormalities detected in ECG recordings of a total of 5212 patients who underwent liver transplantation at three Mayo Clinic transplant centers between 1988 and 2019. The DL-based model successfully differentiated patients with cirrhosis from control subjects with an accuracy of 90% (sensitivity: 84.9%; specificity: 83.2%) using only ECG images (49).

Predicting the Risk of Complications from Viral Hepatitis

AI algorithms can be used to analyze EHR data to predict the risk of developing complications from viral hepatitis, such as liver fibrosis, cirrhosis, and HCC (50). Recently, Wong et al. (51) developed a ML-based model tailored specifically to detect HCC in patients with chronic hepatitis infection. Known as the HCC ridge score (HCC-RS), this innovative model constructed using ML techniques demonstrates heightened accuracy compared with existing HCC risk assessment scores. Integrating HCC-RS into electronic health systems can enable real-time updates on HCC risk (51).

Despite the development of traditional regression models to predict HCC risk in the presence of cirrhosis (based on features like response to antiviral treatment, low platelet count, elevated aspartate aminotransferase: alanine aminotransferase ratio, male gender, advanced age, and core clinical findings), the fluctuation of HCC risk over time makes accurate prediction challenging for these models (52,53). Ioannou et al. (54) investigated this challenge by employing a DL approach. They analyzed data from 48,151 patients with HCV-related cirrhosis and tracked them for a minimum of 3 years post-cirrhosis diagnosis. They aimed to determine whether DL recurrent neural network (RNN) models, leveraging raw longitudinal EHRs, could offer enhanced performance in predicting HCC risk. The study found that RNN models exhibited notably better performance than traditional logistic regression models (ACC: 75% vs. 68%, $p<0.001$). This success suggests that DL models like RNNs hold significant potential in capturing temporal dynamics and long-term information, paving the way for improved predictions of HCC risk (54).

Challenges and Considerations

Ethical concerns constitute a primary area, especially regarding data privacy, confidentiality, and security. Ensuring that sensitive patient information remains protected and ethically used within AI frameworks is crucial. Additionally, addressing biases and disparities inherent in AI algorithms to prevent potential discriminatory outcomes is an ethical imperative (55,56).

Regulatory and legal aspects present another layer of complexity. Adhering to healthcare service regulations and obtaining necessary approvals, such as Food and Drug Administration clearance for medical devices integrated with AI, are essential. Ensuring compliance while advancing AI technologies is crucial for their ethical and lawful implementation (57).

The quality and integration of data are pivotal factors. Maintaining high standards of data quality, accuracy, and integrity is essential for the efficacy and reliability of AI-driven healthcare systems. Streamlining the integration of diverse datasets across healthcare platforms ensures comprehensive and cohesive AI-driven solutions (16).

Resistance to change within established healthcare systems poses a significant challenge. Implementing AI technologies often encounters reluctance due to shifts in traditional practices, necessitating thorough strategies for acceptance and adaptation within healthcare frameworks (58).

Addressing these multifaceted challenges is imperative to ensure the responsible and effective integration of AI into healthcare systems.

Conclusion

The advent of AI has ushered in a new era in hepatology, revolutionizing disease diagnosis, prognosis prediction, and management strategies. Despite the vast potential of AI in hepatology, significant challenges persist on ethical, regulatory, and technical fronts. Addressing concerns regarding data privacy, algorithmic biases, regulatory compliance, and inherent resistance to change is pivotal for the responsible and effective integration of AI into healthcare.

While AI integration holds promise for hepatology, it is crucial to highlight that these advancements are in ongoing development and require additional research and clinical trials for validation. Collaborative efforts between healthcare experts and data scientists, along with continuous innovation, are essential for realizing AI's full potential in enhancing patient outcomes and reshaping the field of hepatology.

Ethics

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