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Contents

Quarterly Volume 5 Number 1 April 30, 2024

EDITORIAL

ORIGINAL ARTICLE

Observational Study

Artificial Intelligence in Gastroenterology

Quarterly Volume 5 Number 1 April 30, 2024

Contents

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

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EDITORIAL

Application of artificial intelligence in the prediction of immunotherapy efficacy in hepatocellular carcinoma: Current status and prospects

Wei Zhang, Li-Ning Song, Yun-Fei You, Feng-Nan Qi, Xiao-Hong Cui, Ming-Xun Yi, Guang Zhu, Ren-An Chang, Hai-Jian Zhang

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Abstract

Artificial Intelligence (AI) has increased as a potent tool in medicine, with promising oncology applications. The emergence of immunotherapy has transformed the treatment terrain for hepatocellular carcinoma (HCC), offering new hope to patients with this challenging malignancy. This article examines the role and future of AI in forecasting the effectiveness of immunotherapy in HCC. We highlight the potential of AI to revolutionize the prediction of therapy response, thus improving patient selection and clinical outcomes. The article further outlines the challenges and future research directions in this emerging field.

Key Words: Artificial intelligence; Hepatocellular carcinoma; Immunotherapy; Predictive modeling

Core Tip: Recently, there has been a lot of progress in predicting the effect of immunotherapy for hepatocellular carcinoma using artificial intelligence, but it also faces serious challenges. Therefore, in this article we summarize and discuss these issues.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most prevalent primary liver cancer and a top contributor to global cancer mortality, is frequently detected at an advanced stage, offering few treatment choices and a bleak prognosis[1,2]. Traditional treatment modalities, such as surgery, radiotherapy, and chemotherapy, have been the mainstay of HCC management, but their efficacy is frequently limited by tumor recurrence and adverse side effects[3-5]. With the advent of immunotherapy, the treatment landscape for HCC has been changed, offering new hope to patients with this aggressive form of liver cancer[6,7]. Immunotherapy has shown promising results in improving survival rates. It is being evaluated in various stages of HCC treatment, from its role in the adjuvant setting to its use in advanced stages of the disease[4,6,8].

Despite progress, the heterogeneity of HCC and the complexity of the tumor microenvironment (TME) hinder consistent, durable responses across all patient groups[9]. Predicting which patients will benefit from these treatments remains a significant challenge. Currently, ongoing clinical trials and research efforts are focused on understanding the mechanisms of resistance and identifying biomarkers to predict immunotherapy response[10,11]. This is where artificial intelligence (AI) comes into play, offering a new dimension to these efforts. AI has the potential to analyze complex biomedical data, identifying patterns that could predict treatment outcomes. Integrating AI into clinical practice may lead to more personalized, effective treatment strategies, optimizing patient care and resource use[12].

AI models have achieved remarkable success in various medical applications, such as diagnostic imaging, genomics, and drug discovery. In the context of HCC, AI applications extend to predicting patient prognosis, and treatment response, and even suggesting potential therapeutic targets[13,14]. However, the application of AI in predicting the efficacy of immunotherapy for HCC remains nascent, with numerous challenges yet to be overcome.

The evolution of immunotherapy for HCC

Historically, the initial attempts to harness the immune system to combat HCC centered around cytokine-based therapies, such as interferon-alpha and interleukin-2. Later, it was realized that immune checkpoints, such as CTLA-4 and PD-(L)1, could be manipulated to improve anti-tumor immunity[15].

The first breakthrough in the immunotherapy of HCC came with the approval of nivolumab, a PD-1 inhibitor, for use in patients with advanced HCC who had previously received sorafenib[7]. More recently, researchers have explored combination therapies, such as PD-L1 inhibitors with CTLA-4 inhibitors or with other therapeutic modalities like targeted therapies and locoregional treatments, which are predicated on the potential to synergize different mechanisms of action to enhance anti-tumor responses[16]. For example, the combination of atezolizumab and bevacizumab demonstrated improved survival outcomes relative to sorafenib in the IMbrave150 trial[5].

Despite these advances, the response to immunotherapy in HCC remains variable, with a significant proportion of patients not experiencing benefit. Consequently, this variability has spurred ongoing research into biomarkers that can predict response to immunotherapy.

The potential of AI in oncology

AI, encompassing a wide area of computer science, works toward building systems able to accomplish functions commonly needing human cognition. Among these subfields are machine learning (ML), deep learning (DL), natural language processing, and robotics[17,18]. In the field of oncology, the potential role of AI is to enhance diagnosis, and treatment, and predict treatment outcomes or disease progression.

For diagnosis, DL algorithms that analyze low-dose computed tomography (CT) scans can detect early-stage lung cancer with precision comparable to expert radiologists, potentially leading to earlier and more effective interventions [19]. Similarly, applying DL algorithms to whole-slide pathology images can aid pathologists in identifying cancerous tissues, thus significantly expediting the diagnostic process and enhancing diagnostic accuracy and efficiency[20]. Using AI integrated with machines and DL in radiomics can help to more accurately define tissue characteristics[21].

Regarding treatment, AI's integration and analysis of genomic data alongside clinical histories enable the creation of personalized treatment plans that predict patient benefits from specific therapies. Zhang *et al*[22] utilized Garson's algorithm, Lek's profile, local interpretable model-agnostic explanations, and partial dependence plots to aid clinicians and medical policymakers in understanding artificial neural networks, powerful tools for effectively predicting outcome variable relationships.

Additionally, AI also aids in anticipating treatment outcomes, helping to optimize treatment regimens by forecasting patient responses and potential side effects based on historical data. For instance, DL algorithms, in particular convolutional networks, utilize imaging data to track tumor advancement or decline, offering impartial markers for modifying the treatment process[23]. AI models integrate various patient data, such as genetic information, clinical histories, and imaging findings, to predict disease progression. This comprehensive approach leads to more accurate prognostic assessments than traditional methods, which often consider fewer data points[24]. Survival convolutional neural networks integrate histology images and genomic biomarkers using DL to predict patient outcomes, surpassing current clinical methods for predicting overall survival (OS) in glioma patients[25]. Huang *et al*[26] identified 10 signature genes from a pool of 166 stem cell-related genes using the least absolute shrinkage operator (LASSO) and multivariate Cox regression analysis. They found that this signature effectively predicted the response to chemotherapy in lung adenocarcinoma patients. Furthermore, in Ding *et al*'s experiment, the mirlncRNA signature, comprising five notable lncRNAs, not only differentiates molecular typing and identifies the related tumor immune subtypes and their chromatin accessibility, but also underscores the immune efficacy and drug sensitivity of tumor immune subtypes[27].

The role of AI in predicting immunotherapy efficacy in HCC

ML, a subset of AI, may become a powerful tool for predicting the response of HCC patients to immunotherapy. ML models, like support vector machines (SVMs), have been utilized for predicting HCC recurrence, screening drugs, identifying potential targets, and determining which patients are more likely to experience recurrence with specific treatments[24,28-30]. Shi *et al*[31] examined peripheral blood mononuclear cells from various cohorts, creating an AdaBoost-SVM logistic model that can identify early-stage HCC *via* immune markers, surpassing alpha-fetoprotein in accuracy.

DL, another subset of AI, uses algorithms to model and understand complex patterns in data. Zeng *et al*[32] explored three DL approaches (patch-based, classic MIL, and CLAM) to create and verify AI-based pathology models for predicting immune and inflammatory gene signatures. Their findings suggest that these signatures could be associated with heightened sensitivity to immunotherapy in patients with advanced HCC.

Additionally, genomic data also play a crucial role in predicting treatment responses. AI models have been trained to identify genetic mutations and expression profiles that correlate with better immunotherapy outcomes. Gong *et al*[33] utilized ML to develop a risk scoring system known as 'neutrophil-derived signature' (NDS), comprising 10 crucial genes. The RiskScore of NDS showed higher accuracy compared to clinical variables and was associated with increased malignancy levels. Consequently, the predictive prowess of DL models can guide clinicians in identifying patients who stand to gain the most from immunotherapy, fostering personalized and efficacious treatment approaches. Xie *et al*[34] found that the m6A- and ferroptosis-lncRNA signature, which has significant prognostic value, provides new perspectives in distinguishing 'cold' and 'hot' tumors and could have important implications for personalized therapy to improve the survival rate of HCC patients. Feng *et al*[35] utilized the LASSO and CoxBoost algorithms to combine and create a signature from 11 natural killer cell-related genes. This provided a new method for evaluating the prognosis and immunotherapeutic response of HCC patients. Dai *et al*[36] employed the LASSO regression model to create an immune-related gene-based prognostic index. This index can predict immune cell infiltration in the HCC TME, as well as the response to immunotherapy. Shen *et al*[37] used genes related to aging to create a predictive model. Through Spearman correlation analysis, they found that the model's risk score was closely related to Mismatch Repair and expression of immune checkpoints.

AI models, particularly those based on ML and DL, have several advantages over traditional statistical methods in predicting outcomes and treatment responses in HCC. Traditional methods often rely on predefined clinical and pathological criteria, which may not capture the complex biological interactions underlying HCC progression and response to treatment. In contrast, AI models can integrate a wide range of data types and identify non-linear relationships within the data[30,38]. Comparative studies have shown that AI models can outperform traditional scoring systems and clinical judgment in prognostication and treatment prediction. For instance, the random survival forests model showed greater accuracy in predicting early recurrence of HCC after surgery compared to COX proportional hazard models[39]. Moreover, AI-driven tools can continuously learn and improve as they are exposed to new data, a feature that static traditional models lack.

Moreover, AI has been instrumental in discovering novel biomarkers for HCC. Through the analysis of large datasets, DL can uncover subtle correlations between biomarkers and treatment responses that may not be apparent to human investigators. Liang *et al*[40] introduced an interpretable human-centric DL-guided framework, Pathological-biomarker-finder, to aid pathologists in identifying new tissue biomarkers using effective DL models.

Given the promising prospects of AI in predicting the immunotherapy efficacy of HCC, an increasing array of predictive variables is being incorporated into clinical practice. These variables include risk-scoring systems, gene phenotypes, and other types of biomarkers. For instance, Hatanaka *et al*[41] conducted a multicenter retrospective analysis that employed the modified Gustave Roussy Immune (GRIm) score as a new prognostic tool for HCC patients treated with atezolizumab and bevacizumab. Their findings indicated that a high GRIm score is a significant adverse factor for both progression-free survival (PFS) and OS. The retrospective analysis by Sangro *et al*[42] revealed an inflammatory gene signature consisting of four genes: CD274, CD8A, LAG3, and STAT1, which correlated with improved response rates and OS in advanced HCC patients treated with nivolumab. Similarly, the atezolizumab-bevacizumab response signature (ABRS), associated with PFS after starting treatment with atezolizumab-bevacizumab, includes genes like CXCR2P1, ICOS, and TIMD4[43]. Building on this, Zeng *et al*[44] developed a prediction model (ABRS-P) and found that patients with ABRS-P-high tumors had a significantly longer median PFS than those with ABRS-P-low tumors. In addition, Sun *et al*[45] used specific patient cohorts with advanced solid tumors to develop and validate a radiomic signature capable of predicting immunotherapy responses by assessing CD8 T cell infiltration in tumors. In another

clinical trial, researchers identified pre-existing CD8 T cells as a promising biomarker for forecasting responses to combined lenvatinib and PD-1 inhibitors in unresectable HCC[46].

Challenges in AI application to HCC immunotherapy

Despite these advancements, several challenges still impede the broader application of AI in predicting HCC immunotherapy efficacy. A significant challenge is the availability of high-quality, annotated datasets. AI models require large amounts of data to learn effectively; however, the scarcity of such datasets can limit the performance of these models[47]. Furthermore, AI models predicting immunotherapy outcomes need to be updated regularly to incorporate the latest clinical knowledge and patient data. Additionally, the heterogeneity of HCC presents another challenge, as it can vary greatly in its genetic makeup and clinical presentation. This variability can hinder AI models from generalizing their predictions effectively across different patient populations[11]. Furthermore, the interpretability of AI models, particularly DL models, remains a significant concern. The unclear and puzzling nature of these models can make it tough for healthcare professionals to comprehend the logic behind the predictions, which is essential for making well-informed clinical decisions[48].

The use of AI in healthcare also raises important ethical and regulatory considerations. Issues including patient privacy, data security, and informed consent must be addressed to ensure the ethical application of AI in predicting immunotherapy response[49].

Prospects and future directions

The integration of AI into clinical practice for predicting HCC immunotherapy response is an ongoing endeavor. A crucial part of this integration process is the thorough validation of AI models across various patient groups to ensure that the predictions are strong and dependable[50]. Additionally, the development of user-friendly AI platforms that healthcare professionals can easily access and utilize is another important aspect. To facilitate their adoption in routine practice, these platforms must be explicitly designed with a focus on clinical workflow integration[51].

As biomedical data continuously accumulates and AI technology advances, we can expect the predictive capabilities of AI models to improve correspondingly. One promising area of future development involves integrating AI with other emerging technologies, such as liquid biopsy and single-cell sequencing. Analyses of circulating nucleic acids, often called 'liquid biopsies', can monitor treatment response, evaluate drug resistance emergence, and measure minimal residual disease[52]. Compared to traditional bulk sequencing, single-cell sequencing can analyze HCC at single-cell resolution, accurately identify different cell types, and uncover the heterogeneity of HCC cells[53]. Lu *et al*[54] previously developed a new diagnostic model for HCC using single-cell RNA sequencing data and discovered that patients with high-risk scores were less likely to benefit from immunotherapy. Another area of exploration is AI's role in dynamic prediction models, which can monitor patient responses in real time and adjust predictions accordingly. This approach has the potential to result in more predictable outcomes and treatment strategies that are personalized and adaptable[55].

In the future, AI applications are expected to benefit from the development of more advanced algorithms capable of processing complex biological data, which includes genomics, proteomics, and metabolomics. The goal of these algorithms will be to identify novel biomarkers and molecular signatures that can predict immunotherapy response in HCC patients[56]. The effectiveness of immunotherapy often relies on the interaction of immunomodulation in the TME[57]. By integrating multi-omics data, we will gain a more comprehensive understanding of the TME and its interactions with the immune system[58,59]. In addition, AI is poised to play a critical role in the design and implementation of clinical trials for HCC immunotherapy by identifying patient subgroups that are more likely to benefit from specific treatments. This will help categorize participants and improve the results of trials (Figure 1).

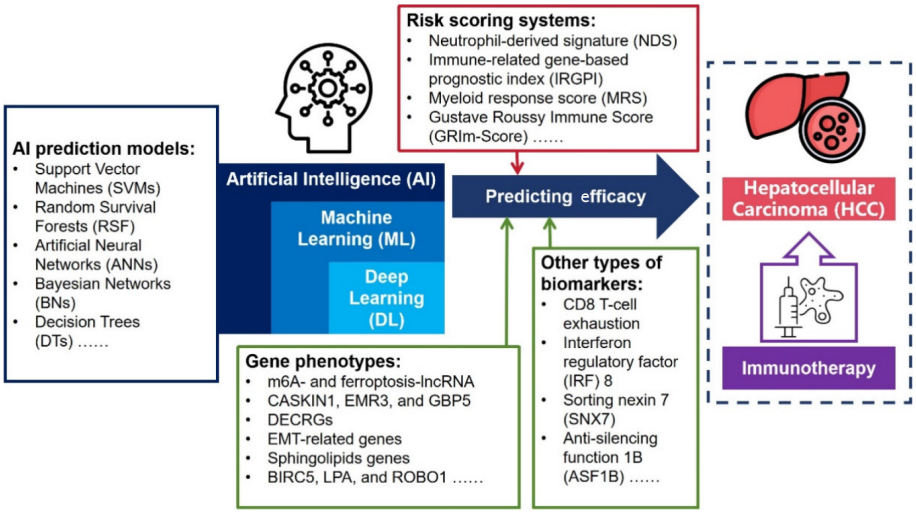

Figure 1 Schematic diagram of artificial intelligence in the prediction of immunotherapy efficacy in hepatocellular carcinoma. This

schematic diagram displays the application of artificial intelligence in the prediction of immunotherapy efficacy in hepatocellular carcinoma. It mentions several artificial intelligence prediction models closely connected to this article, along with risk scoring systems, gene phenotypes, and other types of biomarkers that have surfaced in recent research. AI: Artificial intelligence.

CONCLUSION

The current status of AI in predicting the efficacy of immunotherapy for HCC is marked by significant advancements and potential, tempered by challenges and considerations that must be addressed. The schematic diagram in Figure 1 displays the application of AI in predicting the effectiveness of immunotherapy for HCC. As AI technology evolves and becomes more integrated into healthcare, it possesses the potential to transform HCC prognosis and treatment through personalized and precise predictions for immunotherapy.

FOOTNOTES

Author contributions: Zhang W and Zhang HJ have access to all the data in this study and take responsibility for the integrity and accuracy of the data analyses. Zhang HJ, Zhu G, and Chang RA study concept and design; Zhang W drafted the manuscript; Song LN revised the manuscript; You YF, Qi FN, Cui XH, and Yi MX supervised the study and provided modification suggestions; All authors have read and approved the final manuscript; Zhang W and Song LN contributed equally to this work.

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