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Original Research Article

Artificial Intelligence and Machine Learning in Hepatocellular Carcinoma Screening, Diagnosis and Treatment - A Comprehensive Systematic Review

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Abstract: ***Background***: Medical image analysis plays a crucial role in the screening, monitoring, diagnosis, and prognosis of diseases. Hepatocellular Carcinoma (HCC) often remain asymptomatic in their early stages. Timely identification and intervention are crucial to prevent the progression to decompensated liver diseases and advanced-stage HCC, minimizing morbidity and mortality. ***Methodology***: This study examined twenty relevant research articles that met the inclusion criteria. Utilizing the PRISMA criteria, a systematic search was conducted on PubMed/MEDLINE and Google Scholar for studies on HCC screening employing Artificial Intelligence (AI) and Machine Learning (ML). The search focused on the keywords "artificial intelligence" and "hepatocellular carcinoma," with inclusion criteria specifying studies in the English language published in and after 2020. Exclusions were made for histology, animal research, and investigations conducted before 2020. Titles and abstracts were thoroughly reviewed, and any discrepancies were discussed. ***Results***: The comprehensive review reveals the transformative impact of AI and ML on HCC screening, diagnosis, and therapy. ML models demonstrated effectiveness in early HCC diagnosis, distinguishing hepatic lesions, predicting treatment responses, and assessing recurrence risks across various techniques. Integration of mass spectrometry-based technologies, advanced imaging, and real-world data significantly improved diagnostic accuracy and clinical decision support. AI models exhibited diagnostic expertise with potential applications in therapy suggestions, personalized surveillance, and prognostic evaluations. However, further validation and seamless integration into clinical practice are essential for realizing their full potential. ***Conclusion***: This systematic study underscores the progress made in the application of AI and ML in HCC screening, diagnosis, and treatment. Numerous studies highlight the capability of AI and ML systems to enhance hepatocellular

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carcinoma diagnosis, predict outcomes, and optimize therapy. The enduring and versatile nature of these technologies points towards a revolutionary future in personalized and efficient HCC management.

Keywords: Liver Cancer, Hepatocellular carcinoma, Artificial Intelligence, Machine Learning, Screening, diagnosis, AI, ML.

INTRODUCTION

Liver cancer, with a global annual incidence exceeding 800,000 cases, ranks as the sixth most prevalent primary cancer and the fourth leading cause of cancer-related deaths globally [1, 2]. Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) constitute the two primary forms of liver malignancies, with HCC representing 80-90% and CCA accounting for 10-15% of primary liver cancers [2].

Current diagnostic and therapeutic approaches for HCC involve monitoring individuals with liver disease using abdominal ultrasonography to detect nodules larger than 1 cm and measuring elevated blood α-fetoprotein levels (>20 ng/mL), as outlined by Marrero *et al*., in 2019 [3]. Despite advancements in imaging tools such as multiphase computed tomography (CT) and magnetic resonance imaging (MRI), accurate diagnosis in non-cirrhotic patients often necessitates a liver biopsy [4]. Following diagnosis, the care of HCC requires an individualized strategy considering factors like tumor stage, patient performance level, and the percentage of functioning liver [5].

Liver metastases complicate the treatment of liver cancer, with colorectal cancer (CRC) being the predominant source of liver metastases [6]. These metastases significantly impact prognosis and quality of life, necessitating specific strategies such as liver resection, ablation, locoregional treatments, chemotherapy, and targeted therapies [7, 8].

In light of these challenges, the emergence of artificial intelligence (AI) provides a promising opportunity to revolutionize the detection and treatment of liver tumors. AI, including machine learning (ML) and deep learning (DL), holds significant potential in utilizing large multi-parametric data for more precise diagnosis and personalized treatment decisions [9]. This comprehensive systematic review aims to explore the application of ML and DL techniques in the screening, diagnosis, and treatment of hepatocellular cancer. Additionally, we will address the challenges encountered in applying AI in HCC, CCA, and CRC liver metastases, providing insights into future possibilities.

Artificial Intelligence (AI) is a concept involving the use of computer programs for complex tasks related to human learning behaviors, probabilistic reasoning, and knowledge representation [10]. AI has revolutionized healthcare, particularly in the realm of HCC screening, diagnosis, and therapy.

Machine Learning (ML), a branch of AI, uses datasets to develop algorithms capable of learning and performing specific tasks, such as categorizing or analyzing outcomes [11]. ML plays a crucial role in developing predictive models by fitting them to data and objectively recognizing patterns [12]. It has found applications in various medical sectors, including medical education [13].

Machine learning can be categorized into three main types: supervised learning, unsupervised learning, and reinforcement learning [15]. Supervised learning involves training algorithms using labeled data to anticipate outcomes accurately. Unsupervised learning identifies patterns within unlabeled data, while reinforcement learning allows models to make sequential decisions by learning from repeated attempts at different actions [16].

Rational

Hepatocellular Carcinoma (HCC) poses a global health challenge, emphasizing the need for improved detection and treatment methods. This article provides a concise overview of recent breakthroughs in cancer research utilizing artificial intelligence (AI), particularly deep learning (DL). The discussion delves into the disruptive impact of AI on cancer care and research, acknowledging advancements and significant challenges. The synthesis of AI and cancer research holds immense potential but presents substantial hurdles. Focused on the recent publications, this systematic review ensures an up-to-date understanding of the evolving landscape in HCC research, incorporating the latest technological and research developments. This approach enhances the reliability and currency of our review in the rapidly advancing field of HCC management.

Objective

The objective of this systematic review is to conduct a comprehensive assessment and summary of the existing research in the field, focusing on the utilization of artificial intelligence (AI) and machine learning (ML) techniques in the detection, screening, diagnosis and management of Hepatocellular Carcinoma. Specifically, our aim is to explore the accuracy of AI methods in identifying Hepatocellular Carcinoma and assess the current state of knowledge in the field of AI for this purpose.

MATERIALS AND METHODS

Database Search:

To conduct this comprehensive systematic review, an extensive search of pertinent literature was executed on major databases, including Google Scholar and PubMed//MEDLINE. Employing a strategic approach, we utilized Boolean operators (AND, OR, NOT) in conjunction with key Medical Subject Headings (MeSH) phrases and keywords. The aim of the search was to identify studies investigating the application of Artificial Intelligence (AI) and Machine Learning (ML) in the screening, diagnosis, and treatment of Hepatocellular Carcinoma. The user's search queries encompassed a variety of topics, such as "Artificial Intelligence," "Machine Learning," "Hepatocellular Carcinoma," “classification,” “detection,” “segmentation,” “computer-aided diagnosis,” “non-alcoholic fatty acid liver disease,” “acute liver diseases,” "Screening," "Diagnosis," "Treatment," "Algorithm," "Deep Learning," "Image Analysis," "Predictive Modelling," and "Precision Medicine." The methodology was meticulously documented to ensure transparency and replicability.

Inclusion and Exclusion Criteria:

Pre-established inclusion and exclusion criteria were implemented to ensure consistency and comprehensiveness in the study selection process. The inclusion criteria involved publications published in peer-reviewed journals and written in English. To capture the most recent contributions, emphasis was placed on original quantitative research articles and conference abstracts published in and after 2020, considering the rapidly evolving landscape of both time and technology. The focus of the research was specifically on investigating the application of artificial intelligence (AI) and machine learning (ML) in the context of hepatocellular carcinoma, with a specific emphasis on human participants. This review exclusively concentrates on research addressing the diagnosis, screening, and therapy of AI in hepatocellular carcinoma, deliberately narrowing the focus to ensure a higher degree of accuracy and detail in the assessment. Conversely, the exclusion criteria encompassed studies unrelated to AI and ML applications in this specific context, histological studies, animal research, publications in languages other than English, conference abstracts, reviews, and articles lacking sufficient data or methodological details.

Study Selection:

The initial screening phase involved two independent reviewers assessing titles and abstracts based on predefined criteria to determine the inclusion and exclusion of studies. Subsequently, a thorough examination of complete articles was undertaken for those meeting the initial screening criteria. Discrepancies among reviewers were resolved through discussion and, when necessary, input from a third reviewer was sought. This entire process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, with the PRISMA flow diagram used to visually depict the research selection process.

RESULTS

Adhering to the rigorous PRISMA guidelines, our systematic literature search thoroughly examined an extensive database of 2,082 records, as illustrated in Figure 1, showcasing a comprehensive and methodical methodology. Initially, 370 duplicate records were successfully identified and removed, enhancing the efficiency of the dataset for thorough screening. Out of the remaining 1,712 entries, 985 articles were excluded as they were published before the 2020 timeframe specified for our analysis. Additionally, 46 records were eliminated for not meeting the criteria of primary research, and an additional 25 were discarded due to being written in languages other than English. The decision was made to exclude 28 publications with undefined outcomes, ensuring that the selected studies provided clear and relevant findings. Another 213 papers, which examined organs outside the specified area of interest, were deliberately excluded with attention to detail. Demonstrating our commitment to strict inclusion requirements, 28 entries were excluded due to difficulties in retrieving data. Four animal studies were intentionally omitted from the study. Following a systematic and methodical approach, we included 20 articles in our evaluation that aligned with our stringent criteria (Table). The systematic methodology, in line with the PRISMA criteria, underscores the thoroughness and comprehensiveness employed in identifying, evaluating, and including relevant studies, ensuring the credibility and reliability of the literature pool for our research.

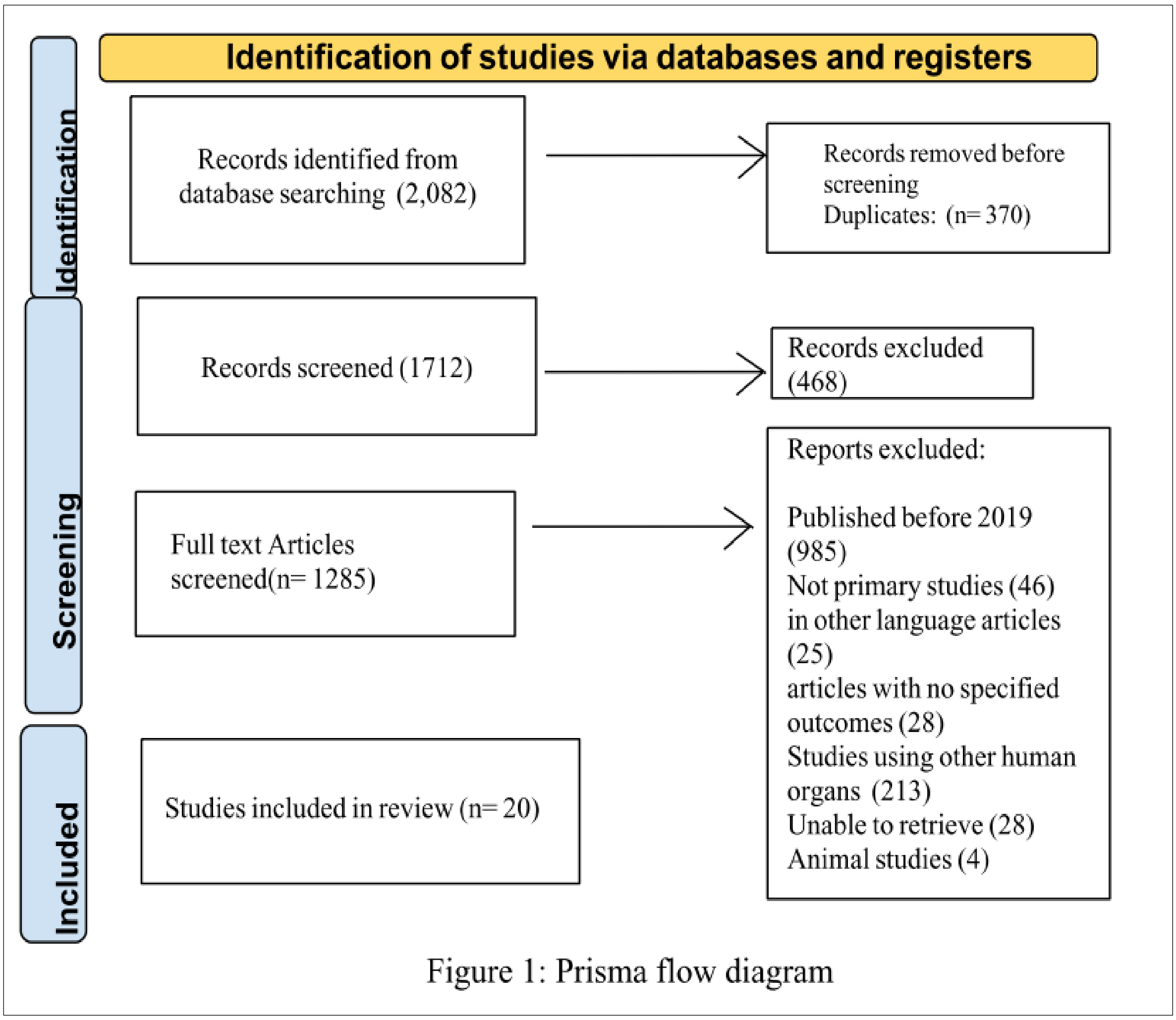

Figure 1: Prisma flow diagram

The application of artificial intelligence (AI) and machine learning (ML) in HCC research has led to significant advancements in screening, diagnosis, and therapy. In a recent study, machine learning-driven ultrasonics demonstrated the ability to accurately differentiate between focal nodular hyperplasia (FNH) and atypical hepatocellular cancer (aHCC). The integration of ultrasonics characteristics with radiologist scores resulted in a substantial improvement in diagnostic performance, highlighting its potential utility in clinical settings [17]. Additionally, researchers developed prognostic models for Hepatocellular Carcinoma (HCC) in patients with Chronic Hepatitis C (CHC). These models focused on crucial variables such as age, Alpha-fetoprotein (AFP), Alkaline Phosphatase (ALP), albumin, and total bilirubin. The straightforward and precise nature of these models, which are both basic and highly accurate, demonstrates practical applications in predicting the presence of HCC [18].

Researchers developed a machine-learning model for predicting the recurrence of hepatocellular carcinoma (HCC), with the Random Forest algorithm exhibiting superior performance compared to other tested models. The study found that important variables identified by the model could be leveraged to guide healthcare decisions, ultimately leading to improved patient outcomes [19]. In a separate study conducted by Giordano *et al.*, the integration of mass spectrometry-based methods with artificial intelligence proved successful in identifying and categorizing liver cancer. The diagnostic precision achieved was above 94%, highlighting the potential of AI to enhance patient outcomes through real-time decision-making [20].

Mo *et al.*, devised a machine-learning algorithm aimed at recommending treatments post-Transarterial Chemoembolization (TACE), leading to improved progression-free survival. The incorporation of significant factors into the model suggests potential advantages for machine learning-assisted medical decision-making [21]. In another study, Ren *et al*., utilized ultrasonic signals derived from ultrasound images to predict the pathological grading of hepatocellular carcinoma (HCC). Their integrated model demonstrated exceptional efficacy, offering a noninvasive and preoperative method for accurately forecasting HCC grade [22]. A separate investigation developed a Random Survival Forest (RSF) model to predict the risk of HCC following sustained virological response (SVR) in patients with chronic hepatitis C. The study highlighted the RSF model's high capacity to distinguish between individuals, suggesting its utility for personalized monitoring of HCC risk [23]. Additionally, researchers employed Convolutional Neural Networks (CNN) to identify and diagnose localized liver lesions from static ultrasound images. The findings suggest that CNNs have the potential for real-time detection in clinical environments [24].

A Clinical Decision Support System (CDSS) was developed to offer treatment recommendations and predict overall survival for hepatocellular carcinoma (HCC). The system exhibited outstanding performance in guiding initial treatment choices [25]. In a separate study, researchers introduced a deep-learning artificial intelligence (AI) system specifically crafted for the identification of HCC using CT imaging [26]. This AI system displayed superior accuracy in comparison to radiologists. The remarkable precision and accuracy of this tool underscore its potential as a valuable asset in clinical practice, calling for further validation through prospective clinical studies.

A study devised three artificial intelligence (AI) models dedicated to diagnosing liver tumors through ultrasonography (US) images, surpassing the capabilities of human specialists in distinguishing between various cases. The AI models showcase the ability to reduce human errors in ultrasound diagnosis, highlighting the significance of AI in enhancing diagnostic precision [27]. In a different study, a supervised learning framework was developed to classify hepatocellular carcinoma (HCC) using microarray data [28]. This approach yielded valuable insights into gene communities associated with HCC. The framework proves to be a highly efficient method for detecting gene communities, with the potential to unveil essential processes and biomarkers.

He *et al*., demonstrated a notable improvement in the accuracy of diagnosing primary hepatic cancer (PHC) in patients by employing a bias field correction algorithm in MRI images. This underscores the promising capability of AI algorithms in enhancing the diagnosis and prognostic evaluation of MRI scans [29]. In another study, Zeng *et al*., illustrated that the AI model accurately estimated the expression of ABRS from histological slides, and this estimation correlated with increased progression-free survival in patients treated with atezolizumab–bevacizumab [30]. This statement emphasizes the capacity of AI to serve as a biomarker, providing significant insights into the outcomes of patients with hepatocellular carcinoma (HCC) and potentially assisting in the development of tailored medicines. Furthermore, researchers investigated the efficacy of Recurrent Neural Network (RNN) models in predicting HCC risk using unprocessed longitudinal data. Their findings revealed that RNN models outperformed traditional Logistic Regression (LR) models in terms of performance [31].

Tang *et al*., identified alterations in the glycopattern of saliva and employed a machine learning Random Forest (RF) method to develop accurate diagnostic models for hepatocellular carcinoma (HCC). This novel approach offers a hopeful path for diagnosing HCC, emphasizing the capacity of non-invasive biomarkers to enhance diagnostic precision [32]. Another study explored the correlation between elevated T cell and CD8 T cell levels and improved long-term survival in patients with HCC. Results, validated by an Artificial Neural Network (ANN) model surpassing conventional prognostic models, underscore the significance of circulating T cells and CD8 T cells in evaluating and forecasting long-term survival in HCC patients [33].

Zhang *et al*., developed an artificial intelligence (AI) deep learning model for detecting cases of Hepatitis B Virus (HBV)-infected patients with Alpha-Fetoprotein (AFP)-negative Hepatocellular Carcinoma (HCC) using B-mode ultrasonography. The strong diagnostic capability of the Xception model indicates its potential as a helpful aid for patients afflicted with HBV [34]. In a separate study, XGBoost and 3D-Convolutional Neural Network (3D-CNN) models were employed, utilizing CT data to provide preoperative predictions of microvascular invasion (MVI). The consistent performance of both models in the training and validation sets suggests their efficacy in predicting MVI, potentially assisting in decision-making support for HCC therapy [35].

Hence, the integration of artificial intelligence (AI) and machine learning (ML) technologies into hepatocellular carcinoma (HCC) research exhibits potential for improving diagnostic accuracy, aiding in treatment decision-making, and evaluating prognosis. These findings underscore the potential of cutting-edge technologies to completely transform the management of HCC. However, it is crucial to continue researching, validating, and integrating these technologies into clinical practice to properly understand and harness their influence.

Table 1: Articles included in the systematic review

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
1	Li *et al*., 2020, Machine learning-based ultrasonics improves the diagnostic performance in differentiating focal nodular hyperplasia and atypical hepatocellular carcinoma (17)	Retrospective	226	Support Vector Machine (SVM) along with ultrasonics	The distinction between atypical hepatocellular carcinoma (aHCC) and focal nodular hyperplasia (FNH) may be made with precision using machine learning-based ultrasonics. Diagnostic performance is much enhanced when ultrasonics characteristics and the radiologist's score are combined. When it comes to differential diagnostic prediction, ultrasonics outperforms radiologists, and accuracy is increased when combined with the radiologist's score.
2	Hashem *et al*., 2020, Machine learning prediction models for diagnosing hepatocellular carcinoma with HCV-related chronic liver disease (18)	Retrospective observational study	4423	Alternating Decision Tree, Classification and Regression Tree, Linear Regression, Reduce Pruning Error Tree	Created machine learning-based CHC-related HCC prediction models. - HCC is predicted by age, AFP, ALP, albumin, and total bilirubin. - AUROC (95.5%-99%) and accuracy (93.2%-95.6%) were high for HCC classification models. Excellent HCC prediction is possible using simple age and chemistry models.
3	Liu *et al*., 2020, Accurate prediction of responses to transarterial chemoembolization for patients with hepatocellular carcinoma by using artificial intelligence in contrast-enhanced ultrasound (19)	Retrospective	130	DL Radiomics, ML L Radiomics	Built and validated AI-based radiomics models to predict personalized HCC responses to the first TACE session using CEUS cines. DLS-based radiomics outperforms traditional machine learning models in accuracy. For accurate and personalized HCC TACE response prediction, DL-based radiomics uses CEUS cines.

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
4	Mega *et al*., 2020, Supervised machine learning techniques for the prediction of hepatocellular carcinoma recurrence (20)	Retrospective	166	Random Forest, (SVM), (KNN), Logistic Regression with Elastic Net Algorithm (ENET)	Used several non-parametric models to create a machine-learning HCC recurrence model. Random Forest performed best (AUC 0.712). Age, MELD, no obesity, diagnostic type, BMI, and BCLC predicted. ML, particularly Random Forest, predicted HCC recurrence, suggesting it might be a useful clinical tool with bigger sample sizes.
5	Giordano *et al*., 2020, Rapid automated diagnosis of primary hepatic tumor by mass spectrometry and artificial intelligence (21)	Cross-sectional	222	Random Forest (RF) and Support Vector Machine (SVM)	Created a mass spectrometry-AI system for quick and objective liver cancer diagnosis and categorization. Diagnostic accuracy approached 94% for HCC and MFCCC. MS and AI offer accurate and fast liver cancer detection, which may enhance patient outcomes through real-time decision-making.
6	Mo *et al*., 2022, Improving Adjuvant Liver-Directed Treatment Recommendations for Unresectable Hepatocellular Carcinoma: An Artificial Intelligence-–Based Decision-Making Tool (22)	Retrospective	237	Feedforward ML model	Created a machine-learning algorithm to propose HCC therapy post-TACE. SBRT and RFA enhanced progression-free survival. Cause, stage, and albumin-bilirubin grade predicted cirrhosis. ML model treatment recommendations enhanced progression-free survival for post-TACE HCC patients, showing ML-guided medical decision-making may be beneficial.
7	Ren *et al*., 2021, Preoperative prediction of pathological grading of hepatocellular carcinoma using machine learning-	Cross-sectional study	193	Support Vector Machine	Ultrasonic signals from ultrasound pictures predicted HCC pathology. The combined model performed best with AUCs of 0.874, 0.849, and 0.770 on various datasets.

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
	based ultrasonics: A multicenter study (23)				Machine learning-based ultrasonic signals predict HCC grade preoperatively and noninvasively, with higher performance and generalization.
8	Minami *et al*., 2023, Machine learning for individualized prediction of hepatocellular carcinoma development after the eradication of hepatitis C virus with antivirals (24)	Multicentre cohort study	1742	DeepSurv, Gradient Boosting, RSF, Cox proportional hazard model	Created and validated an RSF model to predict chronic hepatitis C HCC risk post-SVR. The RSF model allowed personalized prediction curves and provided the best discrimination (c-index: 0.839). Validation and cost-effectiveness analysis might enable personalized surveillance. RSF models with high predictive ability can stratify HCC risk post-SVR for personalized monitoring.
9	Tiyarattanachai *et al*., 2021, Development and validation of artificial intelligence to detect and diagnose liver lesions from ultrasound images (25)	Retrospective cohort study	3487	Convolutional Neural Network	Created and tested a CNN to identify and diagnose FLLs in ultrasonography still pictures. CNN detected HCC with good specificity and negative predictive value. Internal and external validation cohorts perform similarly. CNN successfully detected and characterized frequent FLLs in USG pictures, indicating the necessity for real-time clinical detection.
10	Choi *et al*., 2020, Development of a machine learning-based clinical decision support system for hepatocellular carcinoma (26)	Retrospective cohort	1021	Random Forest (RF)	Created CDSS for HCC therapy and survival prediction. For treatment decisions, the multi-step classifier model performed well (81.0%-88.4% accuracy). CDSS guided the first HCC therapy efficiently. The new HCC-CDSS model supports initial HCC treatment decisions with excellent treatment

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
					recommendations and survival prediction.
11	Wang *et al*., 2021, Development of an AI system for accurately diagnosing hepatocellular carcinoma from computed tomography imaging data (27)	Prospective diagnostic study	7512	Deep Learning (DL)	Developed CT-based deep-learning AI HCC detection method. The AI system performed well (AUROC 0.887 internal, 0.883 external). Radiologists-like accuracy and F1 metric. Patients with many tumors and severe fibrosis stages have higher HCC risk. HCC detection by AI systems is more accurate and precise than radiologists. Further validation requires prospective clinical studies.
12	Nishida *et al*., 2022, Artificial intelligence (AI) models for the ultrasonographic diagnosis of liver tumors and comparison of diagnostic accuracies between AI and human experts (28)	Prospective observational	Not provided	Convolutional Neural Network	Built three ultrasonography (US)-based AI liver tumor diagnostic models. Diagnostic accuracy was 86.8%, 91.0%, and 91.1% for four tumor types. Outperformed human specialists in benign/malignant and four-class discrimination. AI models outperformed liver tumor specialists, suggesting ultrasound diagnosis mistakes might be reduced.
13	Lacalamita *et al*., 2023, Artificial intelligence and complex network approaches reveal potential gene biomarkers for hepatocellular carcinoma. (29)	Supervised learning framework	Patients and controls using microarray data	Hierarchical Community Detection	Created a microarray-based supervised learning system for HCC classification. Over 90% accurate identification of 20 gene communities separating healthy and malignant samples. Two communities with significant biological functions were above 80% accurate. Explainable artificial intelligence (XAI) revealed gene contributions. The methodology effectively identifies HCC gene communities, possibly

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
					exposing key processes and indicators.
14	He *et al*., 2022, Artificial Intelligence Algorithm in Classification and Recognition of Primary Hepatic Carcinoma Images under Magnetic Resonance Imaging (30)	Clinical study	Experimental group 52, Primary Hepatic Carcinoma control group: 52	Bias field correction algorithm	In PHC MRI images, the bias field correction technique improves diagnostic accuracy. Pathological grade associated with perfusion measures. In PHC patients, the bias field correction technique improves MRI diagnosis, and perfusion parameters help prognosis.
15	Zeng *et al*., 2023, Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab–bevacizumab in patients with hepatocellular carcinoma: a multicenter retrospective study (31)	Retrospective multicenter study	Development 336 patients, validation; 225 patients	(ABRS-P) model derived from clustering-constrained attention multiple instance learning (CLAM) pipeline	The AI model correctly assesses ABRS expression from histological slides, improving progression-free survival in atezolizumab–bevacizumab patients. AI on digital slides may improve targeted therapy by predicting HCC patient outcomes.
16	Loannou *et al*., 2020, Assessment of a deep learning model to predict hepatocellular carcinoma in patients with hepatitis C cirrhosis (32)	Prognostic study	48151 patients	Deep learning recurrent neural network models	RNN models using raw longitudinal data predict HCC risk better than LR models. Strategic outreach and surveillance are possible using deep learning RNN models that identify high-risk HCV-related cirrhosis patients.
17	Tang *et al*., 2022, Diagnosis of hepatocellular carcinoma based on salivary protein glycopatterns and machine learning algorithms (33)	Diagnostic study	118 samples	Least Absolute Shrinkage and Selector Operation, Random Forest	Machine learning (RF algorithm) and salivary glycopattern alterations are efficient HCC diagnostic models. Detecting saliva glycol pattern changes using machine learning may help diagnose HCC.
18	Liu *et al*., 2022, A novel prognostic score based on artificial intelligence in hepatocellular carcinoma: A long-	Prognostic study	3427	Artificial Neural Network	Long-term HCC survival improves with higher T and CD8 T cell numbers. ANNs outperform conventional prognostics. HCC patients' long-term survival may be assessed

S. NO	Authors, Year, Title	Study Design	Participants	Machine Learning Techniques	Key Findings and Conclusion
	term follow-up analysis (34)				and predicted using circulating T cells, CD8 T cells, and ANNs.
19	Zhang *et al*., 2022, Deep Learning for Approaching Hepatocellular Carcinoma Ultrasound Screening Dilemma: Identification of α-Fetoprotein-Negative Hepatocellular Carcinoma From Focal Liver Lesion Found in High-Risk Patients (35)	Retrospective cohort	HBV patients infected with FLL	Deep Learning (Xception, DenseNet121, InceptionV3)	AFP-negative HCC detection from B-mode ultrasonography in HBV-infected patients using AI-based deep learning. Xception model has 93.68% AUC. 96.08, 76.92, 86.41, and 87.50% sensitivity, specificity, accuracy, and F1-score.
20	Jiang *et al*., 2021, Preoperative identification of microvascular invasion in hepatocellular carcinoma by XGBoost and deep (36)	Observational study	405	XGBoost, 3D-CNN	Preoperative MVI prediction utilizing CT images using XGBoost and 3D-CNN models. Both models have comparable training and validation AUROCs. The Predicted MVI-negative group had considerably superior mean recurrence-free survival. XGBoost and 3D-CNN models accurately forecast MVI before surgery. Potential for HCC treatment decision-making help.

DISCUSSION

The integration of machine learning and artificial intelligence has significantly improved the early detection and personalized management of hepatocellular carcinoma (HCC). A research study demonstrated the heightened precision in diagnostic accuracy through the application of Support Vector Machine (SVM)-based ultrasonics. The combination of ultrasonic features and radiologist assessments further enhances accuracy, establishing it as a valuable tool for distinguishing between different conditions [17]. In the study conducted by Hashem *et al*., clinical factors and machine learning algorithms were employed to predict the occurrence of hepatocellular carcinoma (HCC) in individuals with chronic liver disease resulting from hepatitis C virus (HCV). Accurate prediction of HCC can be achieved using age and chemistry models, presenting a practical option for diagnosis [18].

Liu *et al*., employed artificial intelligence in contrast-enhanced ultrasound (CEUS) to predict the outcomes of transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). The utilization of radiomics based on deep learning exhibited superior predictive capabilities for TACE response and personalized treatment in comparison to conventional machine learning models [36]. Researchers applied supervised machine learning to predict the recurrence of hepatocellular carcinoma (HCC). The Random Forest algorithm demonstrated robust performance, indicating that machine learning, particularly the Random Forest method, has the potential to accurately forecast HCC recurrence and serve as a valuable tool in therapy [19]. Giordano *et al*., devised a rapid approach for diagnosing primary hepatic cancer using mass spectrometry and artificial intelligence (AI). The high diagnostic accuracy implies the ability to swiftly and objectively identify liver cancer, enabling prompt decision-making that could potentially enhance patient outcomes [20].

Another study enhanced the efficacy of subsequent liver-directed therapy for inoperable hepatocellular carcinoma (HCC) post transarterial chemoembolization (TACE) using a feedforward machine learning model. The algorithm's improvement of progression-free survival suggests that integrating machine learning into decision-making leads to improved patient outcomes [21]. In a multicenter study, authors employed machine learning-based ultrasonics to preoperatively predict the pathophysiology of hepatocellular carcinoma (HCC). The non-invasive and accurate HCC grade prediction system enhances preoperative evaluations [22]. In 2023, Minami *et al.*, utilized machine learning to predict hepatocellular carcinoma (HCC) occurrence post the elimination of the hepatitis C virus. They proposed Discriminative Random Survival Forest models for personalized monitoring and surveillance [23]. A study developed and evaluated a Convolutional Neural Network (CNN) to identify liver irregularities in ultrasound pictures. The high specificity and negative predictive value of CNN make it a promising technique for real-time clinical identification of frequent localized hepatic lesions [24].

A Clinical Decision Support System (CDSS) for Hepatocellular Carcinoma (HCC) survival and therapy using a Random Forest algorithm was developed. The accuracy of treatment choice for initial hepatocellular carcinoma (HCC) therapy can be significantly improved by employing machine learning, as demonstrated by the impressive performance of the CDSS model developed by Choi *et al.*, [25]. In their study, Wang *et al.*, created an artificial intelligence system based on deep learning techniques to accurately detect hepatocellular carcinoma (HCC) by analyzing CT scans. The AI system outperformed radiologists, indicating the potential for more precise diagnostic tools and the need for future clinical studies [26]. Artificial intelligence (AI) models for diagnosing liver tumors using ultrasonography demonstrated superior performance compared to human counterparts. AI has the potential to reduce mistakes in the identification of liver tumors using ultrasound imaging, as shown by [27]. In their study, Lacalamita *et al.*, identified hepatocellular carcinoma (HCC) gene biomarkers by employing sophisticated network analysis and AI techniques. Their approach unveiled gene clusters, hepatocellular carcinoma (HCC) mechanisms and markers, and a novel avenue for investigating the molecular basis of HCC [28].

In a study, researchers refined the diagnosis of primary hepatic cancer (PHC) by applying bias field modification to magnetic resonance imaging. The study revealed that artificial intelligence enhances the accuracy of imaging diagnosis [29]. Another study assessed the responsiveness of hepatocellular carcinoma (HCC) patients to atezolizumab-bevacizumab treatment, employing an artificial intelligence (AI) pathology model. The predictive capabilities of AI were demonstrated by its ability to forecast treatment outcomes, evidenced by the enhanced progression-free survival of patients undergoing targeted therapy [30]. A study examined the use of deep learning recurrent neural network (RNN) models to predict hepatocellular carcinoma (HCC) in patients with cirrhosis. The RNN models, utilizing raw longitudinal data, suggested that strategic outreach and monitoring in high-risk groups would be more effective in predicting HCC risk compared to logistic regression models [31]. Tang *et al.*, utilized salivary protein glycopatterns and machine learning techniques to detect hepatocellular carcinoma (HCC). The study demonstrated that Random Forest machine learning algorithms effectively detected Hepatocellular Carcinoma (HCC) by analyzing variations in salivary glycopatterns [32].

In 2022, Liu and colleagues introduced a prognostic score for hepatocellular carcinoma (HCC) that incorporates circulating T cells, specifically CD8 T cells, and Artificial Neural Networks (ANNs) based on artificial intelligence (AI). The study showed that AI can forecast the long-term survival of patients with hepatocellular carcinoma (HCC) [33]. Zhang *et al.*, identified hepatocellular carcinoma (HCC) cases testing negative for alpha-fetoprotein (AFP) using deep learning techniques in ultrasonic screening. Xception, an AI-based deep learning algorithm, demonstrated great sensitivity and specificity in identifying AFP-negative HCC in patients at high risk [34]. Researchers employed XGBoost and 3D-CNN models to accurately detect hepatocellular carcinoma (HCC) microvascular invasion (MVI) before surgery. Both models accurately anticipated MVI, enhancing the process of determining treatment options and ultimately benefiting the patients [35]. The study indicates that AI and ML have a transformative impact on the diagnosis, treatment, and prognosis of HCC. These advancements have the potential to enhance patient outcomes and facilitate preparation for clinical trials.

The integration of artificial intelligence (AI) and machine learning (ML) into the realm of hepatocellular carcinoma (HCC) is advancing rapidly, as evident from valuable insights gleaned through various systematic reviews. Singh *et al.*, underscore the escalating incidence of morbidity and mortality linked to HCC, attributing it to delayed diagnosis and treatment, especially in cases of asymptomatic early-stage disease. They advocate for the incorporation of AI technology in medical radiology, proposing that diagnostic imaging techniques could serve as primary treatment modalities for chronic liver disease and HCC. Our research aligns with this premise, demonstrating that AI significantly enhances the accuracy and efficiency of diagnoses in clinical processes [36].

Another systematic review acknowledges substantial progress in the use of AI for detecting biomarkers in liver cancer diagnosis and treatment. Emphasizing the need for further research and validation to ensure the reliability and applicability of AI-based models, their findings align with our research, showcasing AI's potential in accurately predicting the risk, stage, prognosis, treatment response, and recurrence of liver malignancies. The call for additional investigation and collaboration resonates with our commitment to advancing AI technologies continually within the HCC framework [37]. Kutaiba *et al*., present the application of deep learning algorithms employing CT scans to categorize fibrosis phases. They acknowledge constraints such as significant variability, retrospective study designs, and the lack of external confirmation, mirroring our view that, while deep learning experiments exhibit potential, their broader applicability is constrained by similar challenges. The plea to share datasets and enhance study representativeness underscores widespread agreement on the importance of thorough validation and collaborative efforts in the AI and HCC domain [38].

Qiu *et al*., and Yin *et al*., offer valuable insights into the field of colorectal cancer (CRC), emphasizing the substantial impact of AI on various clinical aspects such as detection, diagnosis, therapy evaluation, and prognosis prediction. While focusing on CRC, their discussions parallel the potential trajectory of AI applications in HCC [39, 40]. The challenges mentioned, including validation, interpretability, and secure data management, align with the overarching considerations stated in our systematic review of HCC. The anticipated contribution of AI in enhancing screening, diagnosis, and therapy assessment aligns with the potential revolutionary impact we envision in the context of HCC [39, 40]. The application of artificial intelligence and machine learning in cancer diagnosis and treatment has been extensively researched in various studies [41, 42]. Consequently, the amalgamation of these various systematic studies provides a comprehensive overview of the rapid evolution of AI and ML applications in cancer detection and treatment. The shared emphasis on the need for ongoing research, validation, and collaboration underscores the collective understanding that, while AI holds significant promise, its integration into clinical practice must be approached cautiously and evidence-based to fully leverage its capabilities across various cancer types, including Hepatocellular Carcinoma.

Limitations

While the potential is evident, the systematic review acknowledges various inherent limitations within the existing literature. The existence of heterogeneity in research, encompassing differences in methodology and patient populations, poses challenges in generalizing findings to broader clinical contexts. Additionally, the retrospective nature of numerous studies and the limited external validations underscore the need for further prospective research to validate the practicality and reliability of AI and ML models in HCC settings.

Clinical Implications

Incorporating AI and ML into the clinical practice of HCC holds profound implications. The use of contemporary imaging tools to enhance early detection, predict treatment responses, and offer personalized therapeutic recommendations signifies the onset of a new era in HCC care. The findings suggest that these technologies have the potential to become integral components of decision-making processes, leading to enhanced and tailored treatments for HCC patients. However, to realize these implications in a clinical context, it is essential to embark on collaborative efforts, conduct additional validation studies, and carefully consider ethical and interpretability considerations.

CONCLUSION

Our systematic review demonstrates the encouraging progress of Artificial Intelligence (AI) and Machine Learning (ML) applications in the field of Hepatocellular Carcinoma (HCC) screening, diagnosis, and management. Many research articles emphasize the capability of artificial intelligence (AI) and machine learning (ML) algorithms to improve the accuracy of diagnosis, prediction of outcomes, and optimization of treatment for patients with hepatocellular carcinoma (HCC). The durability and numerous applications of these technologies provide insight into the revolutionary future of personalized and effective HCC management.

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