Artificial intelligence in liver diseases: improving diagnostics, prognostics and response prediction

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Table of contents

Supplementary materials and methods

Literature search

On 8th September 2021 we performed a systematic literature search on the PubMed Database (https://pubmed.ncbi.nlm.nih.gov/) using the following search terms: "(("Artificial Intelligence") OR ("AI") OR ("Machine learning") OR ("Deep Learning")) AND (("Liver disease") OR ("NASH") OR ("NAFLD") OR ("HCC") OR ("Liver cancer")) AND ((Radiology) OR (Pathology)) AND ((diagnostics) OR (prognostics) OR (treatment))". We excluded studies published before 1st January 2010. The search resulted in 686 articles which have been subsequently screened by abstract and title, using the systematic review tool Rayyan (https://www.rayyan.ai/) [112]. Our inclusion criteria were the following: 1. Human study, 2. Artificial intelligence/Deep Learning/Machine Learning methods used, 3. Related to pathology or radiology as clinical fields, 4. Method used for diagnostics, pronostics or treatment responses, 5. Dealing with liver diseases. The remaining 112 publications were then analyzed. No time restriction was applied. All search results were studies published between 7th January 2012 and 9th January 2021.

Data analysis for Figure 1

Figure 1A: "Others" includes countries with a maximum of two counts: Canada, Egypt, Hong Kong, Switzerland, Taiwan, Thailand, UK. Figure 1B: "Others" includes two technical papers and two studies combining diagnosis and prognosis. Figure 1C: "Other CLDs" includes diseases with a maximum of three counts. Figure 1D: "Others" includes input data with a maximum of one count.

Supplementary tables

Study	Year	Modality	HC/DL	Disease	Algorithm	Prediction	Highlight
Vanderbeck S et al. [23]	2014	H&E	HC	NAFLD	SVM	Diagnosis	Identify morphological tissue features
Vanderbeck S et al. [113]	2015	H&E	HC	NAFLD	SVM	Diagnosis	Detect lobular inflammation and hepatocellular ballooning
Li S et al.[32]	2017	N/A	DL	HCC	CNN	Diagnosis	HCC nuclei grading
Forlano R et al.[24]	2020	H&E, Sirius Red	HC	NAFLD	K-means	Diagnosis	Quantification of Steatosis, Inflammation, Ballooning and Fibrosis, diagnosing NASH
Gawrieh S et al. [28]	2020	Trichrome stain	HC	NAFLD	SVM	Diagnosis	Quantification and classification of hepatic fibrosis
Kiani A et al.[37]	2020	H&E	DL	HCC, CCC	CNN	Diagnosis	Classifying HCC vs. CCC and exploring the influence of the model on pathologists decisions
Leow WQ et al.[25]	2020	Unstained	HC	NASH	Linear regression, sequential feature selection	Diagnosis	Stratifying stage 1 and 2 NASH fibrosis
Liao H et al.[38]	2020	H&E	HC	HCC	RF, PCA	Diagnosis/Prognosis	Distinguish HCC from healthy liver and develop a risk score associated with overall survival
Roy M et al.[26]	2020	H&E	DL	Steatosis	CNN	Segmentation	Quantification of Steatosis
Saillard C et al.[40]	2020	H&E	DL	HCC	CNN	Prognosis	Survival after resection of HCC
Sun C et al.[35]	2020	H&E	DL	HCC	CNN	Diagnosis	Multiple instance learning model to diagnose HCC
Teramoto T et al.[20]	2020	H&E	HC	NAFLD	SVM	Diagnosis	Quantifying hepatocellular ballooning and classifying NASH and non-NASH NAFLD

Wang R et al.[34]	2020	Hyperspectral images	DL	HCC	CNN	Diagnosis	Diagnosing HCC from hyperspectral data of liver biopsies
Aatresh AA et al. [29]	2021	H&E	DL	HCC	CNN	Diagnosis	Classification of HCC in 4 histopathology classes
Khened M et al. [30]	2021	H&E	DL	HCC	CNN	Technical paper	End-to-end pipeline for Liver tissue segmentation and diagnosis of HCC
Lal S et al. [33]	2021	H&E	DL	Cancer	CNN	Segmentation	Segmentation of nuclei from liver cancer tissue
Pérez-Sanz F et al. [21]	2021	Sudan	HC	Steatosis	SVM, KNN, NN, Naive-Bayes	Diagnosis	Quantification of macrovesicular steatosis in donor livers
Qu H et al.[22]	2021	H&E, trichrome	DL	NAFLD	CNN	Diagnosis	Prediction of NAFLD Activity score and fibrosis stage
Roy M et al. [36]	2021	H&E	DL	HCC	CNN	Segmentation	HCC segmentation and classification of tumorous liver tissue
Saito A et al. [39]	2021	H&E	HC	HCC	SVM	Prognosis	Nuclei features for the prediction of recurrence after HCC resection
Shi JY et al.[41]	2021	H&E	DL	HCC	CNN	Prognosis	Development of a tumor risk score evaluating patients' outcomes
Taylor-Weiner A et al. [27]	2021	H&E	DL	NASH	CNN	Prognosis	Quantification of morphological features of NASH, fibrosis staging and prediction of disease progression
Wang X et al. [31]	2021	H&E	DL	HCC	CNN	Segmentation	Segmentation of HCC in liver tissue
Yamashita R et al. [42]	2021	H&E	DL	HCC	CNN	Prognosis	Prediction of postsurgical recurrence in HCC

Table S1. AI studies in liver histopathology.

Study	Year	Modality	HC/DL	Disease	Algorithm	Prediction	Application
Acharya UR et al. [114]	2012	Ultrasound	HC	FLD	Decision tree classifier	Diagnosis	Classification of normal vs. abnormal livers affected by fatty liver disease
Jiang H et al. [115]	2013	CT	HC	Cancer	SVM, particle swarm and local optimization	Diagnosis	Classification of normal liver, liver cancer, liver cirrhosis, and liver cyst
Kadoury S et al. [116]	2015	CT	HC	Cancer	Discriminant Grassmanian manifolds, conditional random fields	Segmentation	Metastatic liver tumor segmentation
Huang L et al. [117]	2016	CT	HC	Cancer, hemangioma	Single-block linear detection	Segmentation	Liver segmentation
Conze PH et al. [118]	2017	CT	HC	HCC	RF, hierarchical multi-scale tree	Segmentation	HCC tumor segmentation
Gatos I et al. [119]	2017	Ultrasound	HC	CLD	Stepwise regression analysis, SVM	Diagnosis	Classification of healthy vs. chronic liver disease-affected livers
Vorontsov E et al. [120]	2017	CT	DL	Tumor	Multilayer perceptron NN, deformable model	Segmentation	Metastatic liver tumor segmentation
Abajian A et al. [85]	2018	MRI + clinical data	HC	HCC	LR, RF	Prognosis	Prediction of response to TACE in HCC patients
Acharya UR et al. [121]	2018	Ultrasound	HC	Lesions	Bidirectional empirical mode decomposition, particle swarm optimization, PNN	Diagnosis	Classification of normal liver as well as benign and malignant focal liver lesions
Biswas M et al. [68]	2018	Ultrasound	DL	FLD	CNN	Diagnosis	Detection of and risk stratification for fatty liver disease
Byra M et al. [69]	2018	Ultrasound	DL	FLD	CNN, SVM, LASSO linear regression	Diagnosis	Detection of fatty liver disease and quantification of hepatic steatosis
Choi KJ et al. [73]	2018	CT	DL	Fibrosis	CNN	Segmentation/Diagnosis	Fibrosis stage classification
Li X et al. [64]	2018	CT	DL	Lesions	CNN	Segmentation	Liver and liver lesion segmentation

Ahn SH et al. [122]	2019	CT	DL	Organ segmentation	CNN	Segmentation	Segmentation of liver and organs at risk during radiation planning
Feng ST et al. [81]	2019	MRI	HC	HCC	LASSO LR, LR	Diagnosis	Preoperative MVI prediction in HCC patients who underwent curative hepatectomy
Gatos I et al. [123]	2019	Ultrasound	DL	Fibrosis	CNN	Diagnosis	Mask separating high and low temporal stability areas, classification of fibrosis in chronic liver disease
Graffy PM et al. [70]	2019	CT	DL	Steatosis	CNN	Segmentation	Quantification of liver steatosis
Guo D et al. [124]	2019	CT + clinical data	HC	HCC	LASSO, Cox	Prognosis	Prediction of HCC recurrence after liver transplantation
Hamm CA et al. [76]	2019	MRI	DL	Lesions	CNN	Diagnosis	Classification of hepatic lesions
He L et al. [125]	2019	MRI + clinical data	HC	Fibrosis	LASSO, SVM	Diagnosis	Classification of liver stiffness
Huo Y et al. [126]	2019	CT	DL	NAFLD	CNN	Segmentation/Diagnosis	Quantification of liver attenuation and detection of NAFLD
Jansen MJA et al. [127]	2019	MRI + clinical data	HC	Lesions	Extremely randomized trees classifier	Diagnosis	Classification of liver lesions
Ji GW et al. [128]	2019	CT + clinical data + radiological data	HC	HCC	MRMR, RSF, LASSO Cox, unsupervised hierarchical clustering, Cox	Prognosis	Prediction of HCC recurrence after curative resection
Nayak A et al. [129]	2019	CT	HC	HCC	LR, SVM	Segmentation/Diagnosis	Liver segmentation, classification of healthy, cirrhosis, and cirrhosis with HCC livers
Ouhmich F et al. [130]	2019	CT	DL	HCC	CNN	Segmentation	Segmentation of liver parenchyma, active and necrotic tumor
Oyama A et al. [131]	2019	MRI	HC	HCC, metastasis, hemangioma	Texture analysis and LDA, topological data analysis and XGBoost	Diagnosis	Classification of HCC, metastasis, and hepatic hemangioma

Shan QY et al. [132]	2019	CT	HC	HCC	LASSO linear regression	Prognosis	Prediction of early HCC recurrence after curative resection or ablation
Wang CJ et al. [107]	2019	MRI	DL	Lesions	CNN	Diagnosis	Follow-up study to Hamm CA et al. [76] for identification of features contributing to lesion classification, generation of feature maps, and calculation of feature relevance scores
Wang K et al. [133]	2019	CT + MRI	DL	None	CNN	Segmentation	Liver segmentation, computation of liver volume and hepatic proton density fat fraction
Wang K et al. [72]	2019	Ultrasound	DL	Fibrosis	CNN	Diagnosis	Fibrosis stage classification
Wang W et al. [134]	2019	CT + clinical data	DL	HCC	CNN	Prognosis	Prediction of early HCC recurrence after resection
Yang DW et al. [135]	2019	MRI	DL	HCC	CNN	Diagnosis	Diagnosis of HCC pathologic grade
Ahmed Y et al. [136]	2020	MRI	HC	Fibrosis	SVM	Diagnosis	Classification of normal or fibrotic liver
Budai BK et al. [137]	2020	CT	HC	Fibrosis	K-means, hierarchical cluster analysis, linear regression, PCA,, RF, SVM, RFE	Diagnosis	Classification of low-grade and high-grade fibrosis
Cao SE et al. [138]	2020	CT	DL	Focal liver lesions	CNN	Diagnosis	Classification of focal liver lesions
Chen WF et al. [139]	2020	CT	DL	Tumor	CNN	Segmentation	Liver and lesion segmentation
Doman K et al. [140]	2020	CT	DL	Metastasis	Lesion image generation with Poisson blending, CT value distribution, and DCGANs; CNN	Technical Paper/Diagnosis	Detection of liver metastasis
Han A et al.[71]	2020	Ultrasound	DL	NAFLD	CNN	Diagnosis	NAFLD diagnosis and hepatic fat quantification
Hu HT et al. [89]	2020	CT	HC	HCC	LASSO	Prognosis	Prediction of early HCC recurrence after resection or ablation

Kagadis GC et al. [141]	2020	Ultrasound	DL	CLD	CNN	Diagnosis	Fibrosis stage classification
Kim J et al. [142]	2020	MRI	DL	HCC	CNN	Diagnosis	HCC detection
Li Q et al. [143]	2020	CT	DL	Fibrosis	CNN	Diagnosis	Fibrosis stage classification
Liang W et al. [144]	2020	CT + MRI + clinical data	HC	HCC, hepatic epithelioid angiomyolipoma, FNH	Mutual information, RF, LR	Diagnosis	Classification of hepatic epithelioid angiomyolipoma from HCC and FNH
Liu QP et al. [145]	2020	CT + clinical data + radiological data	HC, DL	HCC	RF, SVM, DAE, time-varying DL algorithm, Cox	Diagnosis/Prognosis	Predictions for MVI, Edmondson-Steiner grade, and prognosis/survival after TACE
Mao B et al. [146]	2020	CT + clinical data	HC	HCC	RFE, XGBoost	Diagnosis	HCC pathologic grade prediction
Mokrane FZ et al. [147]	2020	CT	HC	HCC	KNN, RF	Diagnosis	HCC diagnosis in a cirrhotic background with indeterminate liver nodules on, HCCrisk stratification
Nebbia G et al. [148]	2020	MRI	HC	HCC	LASSO, SVM	Diagnosis	MVI prediction
Oezdemir I et al. [149]	2020	Ultrasound	HC	HCC	Distance-weighted discrimination method	Prognosis	Prediction of response to TACE
Peng J et al. [87]	2020	CT	DL	HCC	CNN	Prognosis	Prediction of response to TACE
Ponnoprat D et al. [150]	2020	CT	DL, HC	HCC, CCC	CNN, SVM	Segmentation/Diagnosis	Classification of HCC and intrahepatic cholangiocarcinoma
Schawkat K et al. [151]	2020	MRI	HC	Fibrosis	PCA, SVM	Diagnosis	Fibrosis stage classification
Shi W et al. [152]	2020	CT	DL	HCC	CNN	Diagnosis	Classification of HCC from other focal liver lesions
Son JH et al. [153]	2020	CT	DL	CLD	CNN	Segmentation/Diagnosis	Fibrosis stage classification, correlation of liver and spleen volumetrics with fibrosis stage

Wei L et al. [154]	2020	CT + PET + dosimetry data	HC	Lesions	LASSO LR, LASSO Cox	Prognosis	Prediction of lesion-level response to radioembolization and lesion-level progression
Wu Y et al. [155]	2020	MRI	DL	HCC	CNN	Diagnosis	Classification of LI-RADS grade 3 from LI-RADS grade 4 and 5 lesions
Yang Q et al. [156]	2020	Ultrasound + clinical data + radiological data	DL	Lesions	CNN, LR	Diagnosis	Classification of benign and malignant focal liver lesions
Zhang L et al. [157]	2020	CT + clinical data	DL	HCC	CNN, MRMR, Elastic Net, Cox	Prognosis	Overall survival prediction in HCC patients treated with TACE and sorafenib
Zhen SH et al. [108]	2020	MRI + clinical data	DL	Tumor	CNN	Diagnosis	Classification of liver tumors
Bousabarah K et al. [65]	2021	MRI	DL + HC	HCC	CNN, RF	Segmentation	Segmentation of liver and HCC
Byra M et al. [158]	2021	Ultrasound	DL	NAFLD	CNN, LR, LASSO	Diagnosis	Diagnosis of fatty liver and advanced steatosis, quantification of proton density fat fraction
Che H et al. [159]	2021	Ultrasound	DL	NAFLD	CNN	Diagnosis	NAFLD classification
Chen W et al. [160]	2021	CT	HC	HCC	LASSO, SVM	Diagnosis	Differentiation between low-grade and high-grade HCC
Chen Y et al. [161]	2021	MRI	DL	HCC	CNN, GDBT, Cox	Segmentation/Diagnosis /Prognosis	Preoperative prediction of cytokeratin 19 expression and analysis of recurrence-free survival
Chen Y et al. [162]	2021	MRI	HC	HCC	LASSO, KNN, SVM, LR, XGBoost	Diagnosis	MVI prediction
Das A et al. [163]	2021	Ultrasound	HC	NAFLD	SVM, multi-layered perceptron NN, XGBoost, ensemble learning	Diagnosis	Classification of NAFLD from normal liver
Gao F et al. [164]	2021	MRI	DL + HC	HCC	CNN, LASSO LR, ensemble learning	Diagnosis	MVI prediction

He K et al. [66]	2021	CT	DL	Tumor	CNN	Segmentation	Segmentation of tumor and ablation zone
Jiang YQ et al. [82]	2021	CT + clinical data+ radiological data	DL + HC	HCC	CNN, XGBoost	Diagnosis	MVI prediction
Jin Z et al. [88]	2021	CT + clinical data + radiological data	HC	HCC	LDA, Bayes, LR	Prognosis	Prediction of extrahepatic spread and macrovascular invasion in HCC patients who underwent TACE
Kim DW et al. [165]	2021	CT	DL	Lesions	CNN	Segmentation/Diagnosis	Detection of primary liver tumors
Li H et al. [166]	2021	MRI + clinical data	DL	CLD	CNN	Diagnosis	Liver stiffness classification
Liu P et al. [167]	2021	CT	HC	HCC	LASSO, LR	Diagnosis	MVI prediction
Liu X et al. [168]	2021	CT + MRI	HC	HCC, CCC	PCA, SVM	Diagnosis	Differentiation of combined HCC and CCC, CCC, as well as CCC
Nakai H et al. [169]	2021	CT	DL	HCC, CCC	CNN	Diagnosis	Differentiation of moderately differentiated HCC, poorly differentiated HCC, and intrahepatic cholangiocarcinoma
Nowak S et al. [170]	2021	MRI	DL	Cirrhosis	CNN	Segmentation/Diagnosis	Diagnosis of cirrhosis
Oestmann PM et al. [77]	2021	MRI	DL	HCC	CNN	Diagnosis	Lesion characterization, classification of typical HCC and atypical HCC from non-HCC
Pickhardt PJ et al. [171]	2021	CT	DL	NAFLD	CNN	Segmentation	Steatosis characterization
Sheng R et al. [172]	2021	MRI	DL	HCC	CNN	Segmentation/Diagnosis	Semi-automation of LI-RADS grading
Song D et al. [83]	2021	MRI + clinical data	DL	HCC	CNN	Diagnosis	MVI status and MVI grade prediction

Tiyarattanachai T et al. [173]	2021	Ultrasound	DL	Lesions	CNN	Diagnosis	Diagnosis of liver lesions
Wan Y et al. [174]	2021	MRI	DL	Lesions	CNN	Diagnosis	Diagnosis of liver lesions
Wang M et al. [175]	2021	CT	DL	HCC	CNN	Diagnosis	Diagnosis of HCC
Wei L et al. [109]	2021	CT + clinical data	DL + HC	HCC	CNN, VAE	Prognosis	Survival in HCC patients treated with SBRT
Zhang Y et al. [176]	2021	MRI	DL	HCC	CNN	Diagnosis	MVI prediction
Zheng R et al. [177]	2021	MRI	DL + HC	Fibrosis	CNN, LASSO LR, Gaussian Naive Bayes, SVM, LR	Segmentation/Diagnosis	Fibrosis stage classification
Zhou B et al. [67]	2021	CT + MRI	DL	HCC	CNN	Segmentation	Multimodal registration and segmentation for TACE
Zhou W et al. [84]	2021	MRI	DL	HCC	CNN	Diagnosis	MVI prediction
He T et al. [14]	2021	MRI + WSI + clinical data	DL	HCC	CNN, NLP, RBF NN, multilayer perceptron NN	Segmentation/Prognosis	Recurrence of HCC after liver transplantation

Table S2. AI studies in liver radiology.

Abbreviations for Supplementary Tables S1 and S2:

CCC = cholangiocellular carcinoma

CLD = chronic liver disease

CNN = convolutional neural network

CT = computed tomography

DAE = deep auto-encoder

DCGAN = deep convolutional generative adversarial networks

DL = deep learning

FLD = fatty liver disease

FNH = focal nodular hyperplasia

GDBT = gradient boosting tree

H&E = hematoxylin and eosin

HC = handcrafted features

HCC = hepatocellular carcinoma

KNN = K-nearest neighbors

LASSO = least absolute shrinkage and selection operator

LDA = linear discriminant analysis

LR = logistic regression

MRI = magnetic resonance imaging

MRMR = maximum relevance minimum redundancy

MVI = microvascular invasion

NAFLD = nonalcoholic fatty liver disease

NASH = nonalcoholic steatohepatitis

NLP = natural language processing

NN = neural network

PCA = principal component analysis

PNN = probabilistic neural network

RBF NN = radial basis function neural network

RF = random forest

RFE = recursive feature elimination

SVM = support vector machine

TACE = transarterial chemoembolization

VAE = variational auto-encoder

XGBoost= eXtreme Gradient Boosting

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