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REVIEW

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Artificial intelligence in nonalcoholic fatty liver disease

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) has led to serious health-related complications worldwide. NAFLD has wide pathological spectra, ranging from simple steatosis to hepatitis to cirrhosis and hepatocellular carcinoma. Artificial intelligence (AI), including machine learning and deep learning algorithms, has provided great advancement and accuracy in identifying, diagnosing, and managing patients with NAFLD and detecting squeal such as advanced fibrosis and risk factors for hepatocellular cancer. This review summarizes different AI algorithms and methods in the field of hepatology, focusing on NAFLD.

Methods: A search of PubMed, WILEY, and MEDLINE databases were taken as relevant publications for this review on the application of AI techniques in detecting NAFLD in suspected population

Results: Out of 495 articles searched in relevant databases, 49 articles were finally included and analyzed. NASH-Scope model accurately distinguished between NAFLD and non-NAFLD and between NAFLD without fibrosis and NASH with fibrosis. The logistic regression (LR) model had the highest accuracy, whereas the support vector machine (SVM) had the highest specificity and precision in diagnosing NAFLD. An extreme gradient boosting model had the highest performance in predicting non-alcoholic steatohepatitis (NASH). Electronic health record (EHR) database studies helped the diagnose NAFLD/NASH. Automated image analysis techniques predicted NAFLD severity. Deep learning radiomic elastography (DLRE) had perfect accuracy in diagnosing the cases of advanced fibrosis.

Conclusion: AI in NAFLD has streamlined specific patient identification and has eased assessment and management methods of patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Artificial intelligence, Machine learning, Deep learning, Electronic health records, Automated image analysis, Elastography, Hepatocellular cancer

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder affecting globally. The presence of steatosis in more than 5% of hepatocytes without considerable alcohol intake is used to diagnose it. The term NAFLD refers to conditions ranging from benign nonalcoholic fatty liver (NAFL) to the more severe non-alcoholic steatohepatitis (NASH). Despite the fact that NAFLD may affect patients of any weight, more than 80% of NAFLD patients are obese, with a body mass index (BMI) of greater than 30 kg/m^2. The prevalence of NAFLD and many metabolic disorders such as obesity have lately increased globally. In less than a decade, NAFLD is likely to overtake cirrhosis as the leading cause of liver transplantation. It affects anywhere from 6% to 35% of the world's population, with NAFLD affecting around 30% of Americans [26].

With a global incidence of 25.2%, non-alcoholic fatty liver disease (NAFLD) is one of the most frequent chronic liver disorders. Nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma are all possible outcomes of NAFLD [13]. NAFLD is also closely linked to insulin resistance, metabolic

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syndrome, diabetes, and cardiovascular disease, suggesting that it is a multisystem illness with extra hepatic consequences. NAFLD raises the risk of end-stage liver disease, hepatocellular carcinoma (HCC), and liver-related and all-cause mortality compared to the general population of the same age and gender. However, the bulk of fatalities among people with NAFLD, are due to cardiovascular disease and cancer, according to most experts [17]. The majority of research studies so far have focused on associations between NAFLD and CVD, type 2 diabetes (T2DM), chronic kidney disease (CKD), and colorectal cancer (presented in Table 1).

Currently available serological and imaging techniques cannot distinguish between steatosis and NASH, so diagnosing NAFLD is difficult. A liver biopsy allows for an accurate diagnosis. Unfortunately, because of the increased risk of severe bleeding and life-threatening consequences, it is rarely advised in clinical practice. The recently developed imagistic methods of magnetic resonance imaging (MRI) with proton density fat fraction (PDFF) and proton magnetic resonance spectroscopy, which have high diagnostic accuracy, offer an alternative to liver biopsy (1 H-MRS) [9, 18]. According to Chen et al., the presence of NAFLD was linked to an elevated risk of colorectal adenoma and colorectal cancer in later stages [7].

Malignancy is the second-most common cause of mortality in individuals with NAFLD after cardiovascular disease. According to recent research, NAFLD with intermediate or advanced fibrosis remained associated with cardiovascular disease (OR 1.36), extrahepatic cancer (OR 1.24), and chronic kidney disease (OR 1.18) [24].

Cross-sectional study found that individuals with NAFLD, particularly those with NASH, are more likely than healthy controls to acquire advanced colorectal neoplasms. Although earlier research has found a link between NAFLD and the development of colorectal malignancies, no such link has been established over a long period of time. Furthermore, the link between NAFLD and other extra hepatic malignancies has received minimal investigation [34].

Diagnostic imaging, laboratory data, electro-diagnosis, electronic health records, and recordings from wearable devices are the primary fields in which artificial intelligence (AI) technologies are being employed in healthcare. As a result, the goal of our review is to offer a thorough overview of key AI research that may aid clinicians in the management of NAFLD and assess its diagnostic accuracy, diseases screening, specificity, and sensitivity to machine diagnosis methods.

Materials and methods

A search of PubMed, WILEY, and MEDLINE databases was taken as relevant publications for this review on the application of artificial intelligence techniques in detecting NAFLD in association with cancer. The search terms included: NAFLD, Artificial intelligence OR Machine learning OR Deep learning OR electronic health records OR Automated Diagnosis OR Automated Computer Tomography AND NAFLD OR Nonalcoholic Fatty Liver Disease in association with Cancer OR Carcinoma. Exclusion Criteria are Case Reports, Letters to Editors, Abstracts, Power point Presentations presented in conferences, Studies written in languages other than English, Paediatric Studies.

Data extraction and quality assessment

Data extraction and quality assessment was independently performed by two authors. In case of disagreement, discussion was conducted with the third author. Data extracted included the author, publication year, number of NAFLD patients, type of study, objective of study, and outcome or conclusion by author. Different AI techniques were evaluated, and comparison was stated. AI techniques predicting risk factors, diagnosing NAFLD, staging NASH and its severity, AI used in imaging techniques, AI in electronic health records, automated diagnosis, and AI used to in NAFLD and its association with cancer were analyzed.

Results and discussion

The bifurcation of artificial intelligence is mainly into its two divisions, namely machine learning and deep learning (Fig. 1). A total of 475 articles were extracted from the database. The inclusion criteria included original articles, case studies, review articles, and systematic reviews. Pre-clinical/non-clinical articles, case reports, letters to editors, and pediatric studies were excluded. The number of articles included for analysis was 95 (Fig. 2).

AI in predicting risk factors of NAFLD

In a study by Garcia-Carretero et al., the prevalence of NASH in 2239 hypertensive patients and assessed the relevant features related to hypertension and metabolic syndrome (MS) using supervised machine learning algorithms such as least absolute shrinkage and selection operator (LASSO) and random forest classifier was assessed [16]. LASSO is a regression analysis algorithm that uses an L1 regularization technique, that is, it adds a penalty term to the regression function. A random forest algorithm was used to assess feature importance in regression model produced by LASSO. In univariate analyses, it was associated with metabolic syndrome, type 2 diabetes, insulin resistance, and dyslipidemia.

Table 1 Important studies defining AI in NAFLD

Study	Country	Study cohort	Diagnostic method	AI classifier	Development cohort (*n*)	Validation cohort (*n*)	Validation methods	Sensitivity	Specificity	TP	FP	TN	FN
Aim: AI-assisted ultrasonography to diagnose NAFLD					**NAFLD/total, % Steatosis**	**NAFLD/total, % Steatosis**							
Kuppili et al.	Portugal	Retrospective	Liver biopsy (not defined)	ELMa, SVM	36/63 N/A	N/A	*k*-fold cross-validation	0.913	0.921	33	2	25	3
Byra, et al.	Poland	Prospective	Liver biopsy (> 5% hepatocyte steatosis)	CNN	38/55 50% had steatosis < 30%	N/A	5-fold cross-validation	1	0.882	38	3	15	0
Biswas et al.	Portugal	Retrospective	Liver biopsy (not defined)	CNNa, SVM, ELM	36/63 N/A	N/A	10-fold cross-validation	1	1	36	0	27	0
Shi et al.	China	Prospective	MRI (> 5% hepatic fat content)	RT	34/60 92% had steatosis < 20%	N/A	10-fold cross-validation	0.875	0.9286	30	2	24	4
Han et al.	US	Prospective	MRI (> 5% hepatic fat content)	CNN	70/102 Average 11 ± 9%	70/102 Average 11 ± 8%	Validation cohort	0.97	0.94	68	2	30	2
Zamanian et al.	Poland	Prospective	Liver biopsy (> 5% hepatocyte steatosis)	CNN + SVM	38/55 50% had steatosis < 30%	N/A	10-fold cross-validation	0.972	1	70	0	74	2
Aim: AI-assisted clinical data sets to diagnose NAFLD					**NAFLD/total**	**NAFLD/total**							
Ma et al.	China	Prospective	Ultrasonography	BNa, kNN, SVM, LR, NB, RF, BN, AdaBoost, HNB, Bagging, AODE	2522/10,508	N/A	10-fold cross-validation	0.675	0.878	1702	974	7012	820
Islam et al	Taiwan	Retrospective	Ultrasonography	LRa, RF, SVM, ANN	593/994	N/A	10-fold cross-validation	0.741	0.649	439	141	260	154
Wu et al.	Taiwan	Retrospective	Ultrasonography	RFa, LR, ANN, NB	377/577	N/A	10-fold cross-validation	0.872	0.859	329	28	172	48
Atabaki-Pasdar et al.	United Kingdom	Retrospective	MRI (⩾ 5% hepatic fat content)	RF	640/1514	1011/4617	Validation cohort	0.67	0.74	677	838	2668	334
Chen et al	China	Retrospective	Ultrasonography	ANN	Total 10,354	2218/4436	Validation cohort	0.837	0.804	1857	435	1783	361
Liu et al.	China	Retrospective	Ultrasonography	XGBoosta, LR, SVM, SGD, CNN, MLP, LSTM	4018/10,373	1860/4942	Validation cohort	0.611	0.909	1136	280	2802	724

Table 1 (continued)

Study	Country	Study cohort	Diagnostic method	AI classifier	Development cohort (*n*)	Validation cohort (*n*)	Validation methods	Sensitivity	Specificity	TP	FP	TN	FN
Aim: AI-assisted diagnosis of NASH in patients at-risk for NASH													
Gallego-Duran et al	Spain	Prospective	Liver biopsy	LR	NASH/NAFLD 21/39	NASH/NAFLD 44/87	Validation cohort	0.87	0.6	38	17	26	6
Naganawa et al.	Japan	Retrospective	Liver biopsy	LR	Total 53	NASH/non-NASH 28-Jul	Validation cohort	No suspicion of fibrosis: 1.00 Suspicion of fibrosis: 1.00	No suspicion of fibrosis: 0.92 Suspicion of fibrosis: 0.31	4 3	1 11	11 5	0 0
Uehara et al.	Japan	Retrospective	Liver biopsy	Rule extraction algorithm	NASH/non-NASH 79/23	NASH/non-NASH 65/12	Validation cohort	0.862	0.417	56	7	5	9
Garcia-Carretero et al.	Spain	Retrospective	Ultrasonography with LFTs	Lasso regression	NASH/non-NASH 204/1587	NASH/non-NASH 51/397	Validation cohort	0.7	0.79	36	83	314	15
Docherty et al.	USA	Retrospective	Liver biopsy	kNN, RF, XGBoosta	NASH/NAFLD 270/152	NASH/NAFLD 180/102	Validation cohort	0.81	0.66	146	34	68	34
AI-assisted diagnosis of liver fibrosis in NAFLD													
Pournik et al.	Iran	Retrospective	Liver biopsy	ANN	Cirrhotic/non-cirrhotic 52/248	Cirrhotic/non-cirrhotic 15/65	Validation cohort	0.657	0.987	44	4	309	23
Gallego-Duran et al.	Spain	Prospective	Liver biopsy	LR	F0-1/F2-4 20/19	F0-1/F2-4 56/31	Validation cohort	F2-4 0.77	F2-4 0.80	24	11	45	7
Shahabi et al.	Iran	Retrospective	Elastography	ANN	F0/F1/F2/F3/F4 415/151/132/23/5	15% of data set (same proportion)	Validation cohort	F1 0.993 F2 0.939 F3 1.000 F4 1.000	F1 0.757 F2 0.938 F3 0.993 F4 1.000	-	-	-	-
Okanoue et al.	Japan	Retrospective	Liver biopsy and ultrasonography	ANN	Normal/F0/F1/F2/F3/F4 48/106/74/56/65/23	F0/F1/F2/F3-F4 17/18/15/24	Validation cohort	NAFLD (F0) vs. NASH (F1-4) 0.877	NAFLD (F0) vs. NASH (F1-4) 0.941	50	7	1	16

Table 1 (continued)

Study	Country	Study cohort	Diagnostic method	AI classifier	Development cohort (*n*)	Validation cohort (*n*)	Validation methods	Sensitivity	Specificity	TP	FP	TN	FN
AI-assisted diagnosis of liver fibrosis in NAFLD													
Okanoue et al.	Japan	Retrospective	Liver biopsy	ANN	F0/F1/F2/F3/F4	F0/F1/F2/F3-F4	Validation cohort	F0 vs. F1-4: 0.85	F0 vs. F1-4: 0.867	68	4	26	12
					106/74/56/65/23	30/27/24/29		F0-1 vs. F2-4: 0.755	F0-1 vs. F2-4: 0.877	40	7	50	13
								F0-2 vs. F3-4: 0.828	F0-2 vs. F3-4: 0.877	24	10	71	5
Aim: AI-assisted steatosis quantification of pathological specimen													
Vanderbeck et al.	USA	Retrospective	Pathologist	SVM	Macrosteatosis/other features	N/A	10-fold cross-validation	0.98	0.94	1072	48	859	28
					1100/859								
Liu et al.	China	Prospective	Pathologist	Linear regression	Steatosis grade 0: 0	Steatosis grade 0: 1	Validation cohort	Steatosis	Steatosis	71	0	1	0
					Grade 1: 77	Grade 1: 41		grade 0 vs. ⩾ 1: 0.99	grade 0 vs. ⩾ 1: 1.00	28	6	36	3
					Grade 2: 45	Grade 2: 22		grade ⩽ 1 vs. ⩾ 2: 0.91	grade ⩽ 1 vs. ⩾ 2: 0.85	6	1	63	3
					Grade 3: 24	Grade 3: 9		grade ⩽ 2 vs. 3: 0.67	grade ⩽ 2 vs. 3: 0.98				
Sun et al.	USA	Prospective	Pathologist	CNN	30	66	Validation cohort	⩾ 30% steatosis	⩾ 30% steatosis	15	2	73	6
								0.714	0.973				
Teramoto et al.	Japan	Retrospective	Pathologist	Logistic regression	Matteoni classification46	Matteoni classification	Validation cohort	type 1 vs. NASH: 0.879	type 1 vs. NASH: 1.00	29	0	66	4
					Type 1/type 2/type 3-4 (NASH)	Type 1/type 2/type 3-4 (NASH)		type 2 vs. NASH: 0.909	type 2 vs. NASH: 0.909	30	6	60	3
					33/33/33	33/33/33							

ANN artificial neural network, *AODE* aggregating one-dependence estimators, *BN* Bayesian network, *CNN* convolutional neural networks, *ELM* extreme learning machine, *F0-4* METAVIR fibrosis staging, *FLD* fatty liver disease, *HNB* hidden naïve Bayes, *kNN* k-nearest network, *LFTs* liver function tests, *LR* logistic regression, *LSTM* long short-term memory, *MLP* multilayer perceptron, *MRI* magnetic resonance imaging, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *NB* naïve Bayes, *RF* random forest, *RT* regression tree, *SGD* stochastic gradient descent, *SVM* support vector machine, *XGBoost* extreme gradient boosting

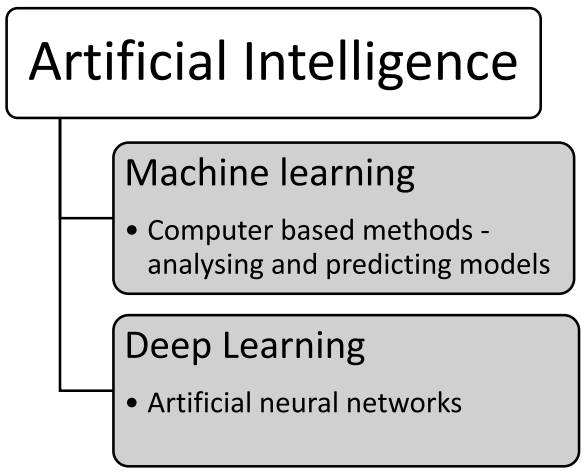

Fig. 1 Bifurcation of artificial intelligence into two main types—machine learning and its subset, deep learning [19]

Serum ferritin and insulin were selected with high sensitivity and specificity using the LASSO approach with a sensitivity of 70%, specificity of 79%, and area under the curve of 0.79 [16]. Another study by Garcia-Carretero et al. used random forest (RF) models for predicting patients at risk of developing NASH in 1525 patients [15]. The electronic health records were used to assess the presence of NASH. The random forest model correctly classified patients with NASH with an accuracy of 0.87 in the best model and to 0.79 in the worst one. Four features that were the most relevant included insulin resistance, ferritin, serum levels of insulin, and triglycerides. Random forest-based modeling demonstrated that machine learning could be used to improve interpretability, produce an understanding of the modeled behavior, and demonstrate how far certain features can contribute to predictions [15].

Diagnosis of NAFLD using AI

In literature, various diagnostic models for NAFLD were studied. Some of the algorithms were logistic regression (LR), k-nearest neighbor (kNN), support vector machine (SVM), naive Bayes, Bayesian network (BN), and decision tree and K2 algorithm including adaptive boosting (AdaBoost), bootstrap aggregating (bagging), and random forest and extensions to the algorithm like hidden naive Bayes (HNB) and aggregating one-dependence estimators (AODE) [23]. Ma H et al. investigated these 11 machine learning algorithms in 10508 patients to predict the best diagnostic model of NAFLD [23]. They reported that 83.41% accuracy was detected with the logistic regression (LR) model, whereas the highest specificity and precision was achieved by the SVM model with values of 0.946 and 0.725, respectively. AODE model was the most sensitive, with a value of 0.680. In this study, *F*-measure was used to analyze the classification for building these prediction models, with the highest *F*-measure being 0.655 for BN model and the lowest was for fatty liver index (FLI) with a value of 0.318. The authors determined that the best performance was shown by the BN model with a 9.17% improvement in the *F*-measure score [23].

Yip et al. included 922 patients to compare logistic regression, AdaBoost, and ridge regression. Finally, the logistic regression model achieved an accuracy of 87–88% and six relevant features, such as insulin resistance, triglycerides, or alanine aminotransferase [33]. Sorino et al. compared eight different machine learning algorithms, namely Boosting Tree Classifier (using Adaboost Classifier), Decision Tree Classifier, Naive Bayes Classifier, K-Nearest Neighbors Classifier, Neural Network Classifier, Random Forest Classifier, Regularized Multinomial Classifier (use Logistic regression), and Support Vector Machine Classifier. Using the Meta learner approach, three models consisting (1) FLI plus GLUCOSE plus SEX plus AGE, (2) abdominal volume index (AVI) plus GLUCOSE plus gamma-glutamyl transpeptidase (GGT) plus SEX plus AGE, and (3) body roundness index (BRI) plus GLUCOSE plus GGT plus SEX plus AGE were created. The authors reported SVM algorithm (Support Vector Machine in Python) was the most appropriate and had better performance in the analyzed models [28]. Model 3 had the highest accuracy of 77% compared to models 2 and 1, with an accuracy of 68% each. As model 2 had lesser prediction errors, it was considered the best model [28]. Cheng et al. developed several models using KNN, RF, and support vector machines (SVM) to detect NAFLD. They observed that SVM had 86.9% accuracy in men, and RF had 80% in women. Both models selected some relevant features, including cholesterol-related and insulin resistance-related factors [8].

Docherty et al. developed a machine learning (ML) model to predict NASH, using confirmed NASH and non-NASH based on liver histology results in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) dataset to train the model [11]. An extreme gradient boosting model (XGBoost) consisting of 14 features exhibited high performance as measured by area under the curve (0.82), sensitivity (81%), and precision (81%) in predicting NASH [11]. Slightly reduced performance was observed with an abbreviated feature set of 5 variables (0.79, 80%, and 80%, respectively) [11]. The full model demonstrated good performance (AUC 0.76) to predict NASH in Optum data [11]. The proposed model, named NASH map, is the first ML model developed with confirmed NASH and non-NASH cases as

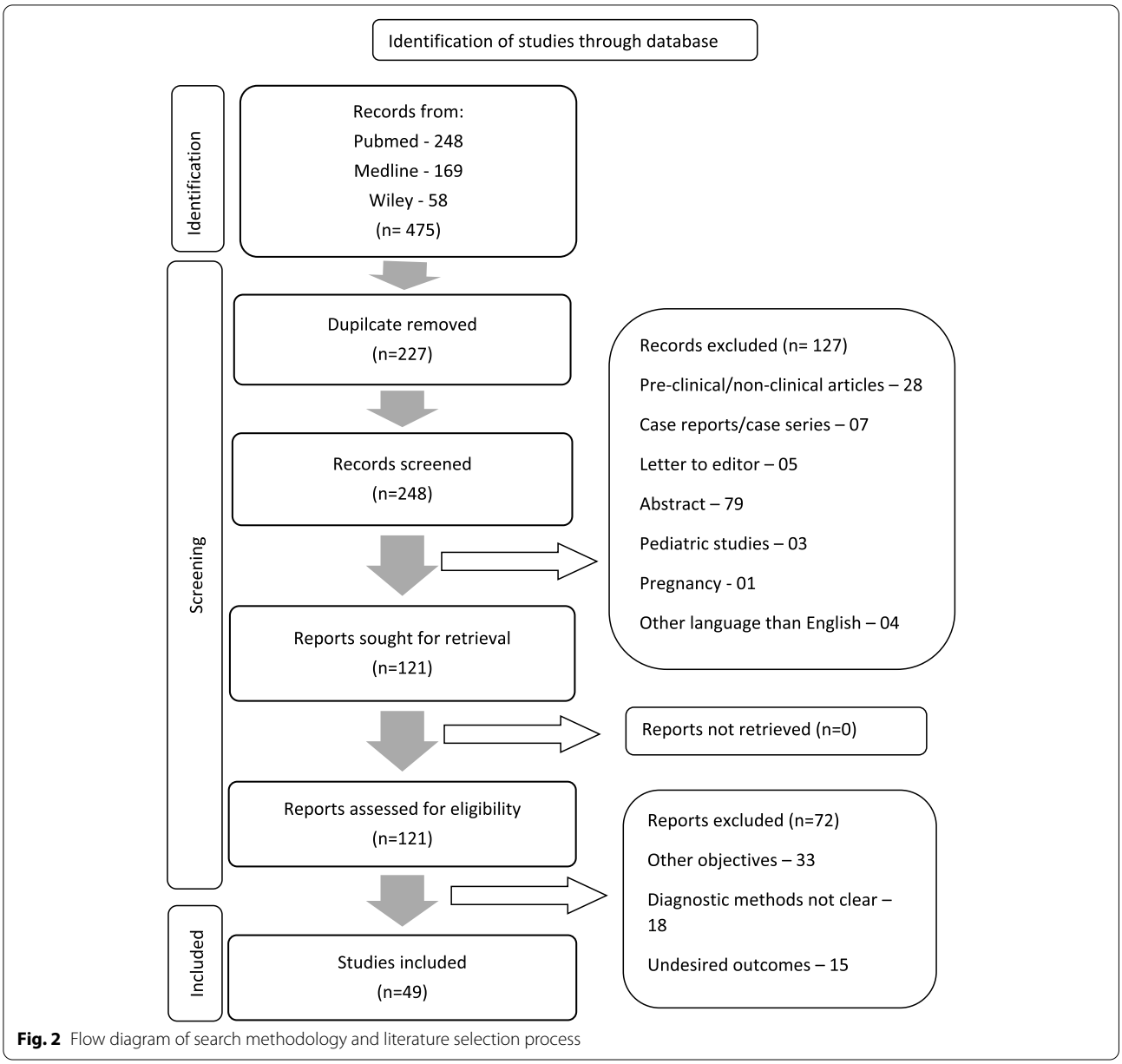

Fig. 2 Flow diagram of search methodology and literature selection process

determined through liver biopsy and validated on a large, real-world patient dataset [11].

AI in predicting the severity and staging of NASH

For the assessment of severity of nonalcoholic fatty liver disease (NAFLD) and identification of patients with nonalcoholic steatohepatitis (NASH), a novel machine learning approach, ensemble feature selection (EFS), was devised by Canbay et al. [5]. Non-invasive parameters were selected by an ensemble feature selection (EFS) from a retrospectively collected training cohort of 164 obese individuals (age: 43.5 ± 10.3 years; BMI: 54.1 ± 10.1kg/m^2) to develop a model able to predict the histological assessed NAFLD activity score (NAS) [5]. Advantages of this score are a continuous distribution allowing disease assessment apart from a dichotomous classification as NAFL or NASH and thus could possibly be used to monitor disease progression or resolution over time. Additional parameters, i.e., transient elastography or controlled attenuation parameter, could be added, given sufficiently large reference datasets [5]. Okanoue et al. developed novel non-invasive test with the help of an AI/neural network system called NASH-Scope, and the model could accurately distinguish between NAFLD

and non-NAFLD and between NAFLD without fibrosis and NASH with fibrosis in 398 histologically diagnosed NAFLD patients [25]. Moreover, a systematic review by Li et al. evaluating AI-assisted diagnosis of liver fibrosis and NAFLD demonstrated promising potential and validation of these models in larger cohorts is required before implementing it into clinical practice [21]. AI (artificial intelligence) application in predicting NAFLD is extensively reviewed elsewhere [32]. The NAFLD ridge score is a machine-learning algorithm and is one of the most effective tools to detect NAFLD [33]. It is based on multiple laboratory parameters that include serum levels of ALT, serum triglycerides, HDL, HbA1c, hypertension, and leukocyte count and has an AUROC value of 0.87 [33] . It uses H-MRS (proton magnetic resonance spectroscopy) as a reference and has a negative predictive value (NPV) of 96% [33]. Despite being an effective scoring system to detect NAFLD, its use is limited to the research setting and fails to risk stratify steatosis progression [3].

AI in imaging modalities

Pasdar et al., in a multicenter prospective cohort study of 3029 European-ancestry adults recently diagnosed with T2D ($n = 795$) or at high risk of developing NAFLD ($n = 2234$). The analyses applied machine learning methods to data from the deep-phenotyped IMI DIRECT cohorts ($n = 1514$) to identify sets of highly informative variables to predict NAFLD. The criterion measure was liver fat quantified from MRI. LASSO (least absolute shrinkage and selection operator) was applied to select features from the different layers of omics data and random forest analysis to develop the models. A total of 18 prediction models were developed. The authors reported that the model including all omics and clinical variables yielded a cross-validated receiver operating characteristic area under the curve (ROCAUC) of 0.84 (95% CI 0.82, 0.86; $p < 0.001$), which compared with a ROCAUC of 0.82 (95% CI 0.81, 0.83; $p < 0.001$) for a model including 9 clinically accessible variables [4].

In a study by Cao et al., two-dimensional hepatic imaging was analyzed by the envelope signal, grey scale signal, and deep-learning index obtained by 3 image-processing techniques in 240 participants with mild, moderate, and severe NAFLD [6]. The authors reported that the 3 methods showed good ability (AUC > 0.7) to identify NAFLD. Meanwhile, the deep-learning index showed superior diagnostic ability in distinguishing moderate and severe NAFLD (AUC = 0.958) [6].

Rapid MRI techniques could be used to predict nonalcoholic steatohepatitis (NASH) noninvasively by measuring liver stiffness with magnetic resonance elastography (MRE) and liver fat with chemical shift-encoded (CSE) MRI [12]. So, Dzyubak et al. validated an automated image analysis technique to maximize the utility of these methods in eighty-three patients with suspected NAFLD [12]. A logistic regression model to predict pathology-diagnosed NASH was trained based on stiffness and proton density fat fraction. The area under the receiver operating characteristic curve (AUROC) was calculated using 10-fold cross-validation for models based on both automated and manual measurements [12]. Liver stiffness and PDFF were also calculated using an automated method. A separate model was trained to predict the NASH severity score (NAS). The model for predicting biopsy-diagnosed NASH had an AUROC of 0.87, and the NAS-prediction model had a *C*-statistic of 0.85. The stiffness and PDFF measurements based on automated ROIs had a higher agreement with the expert reader ($R2 = 0.87$ for stiffness and $R2 = 0.99$ for PDFF) than the expert and experienced readers had with each other ($R2 = 0.85$ for stiffness and $R2 = 0.98$ for PDFF) [12].

In a study by Addeman et al., a novel software package named AdipoQuant for the automated quantification of total adipose tissue (TAT), SAT, and IAAT in the abdomen was used, and similar results were obtained to manual segmentation methods [1].

Electronic health records and NAFLD

Logistic regression, decision trees, RF, extreme gradient boosting (XGBoost), or k-nearest neighbors (KNN) have been used with electronic health records (EHR), while neural networks and deep learning have been used for histology and images [30]. Sowa et al. included EHR of 126 patients to develop a final model with an accuracy of 0.79. However, this model relied on features that are not easily collected or measured, such as apoptosis markers [29]. Genome-wide association studies (GWAS) have identified several risk loci for nonalcoholic fatty liver disease (NAFLD). GWAS of 4761 cases of NAFLD and 373,227 healthy controls without evidence of NAFLD was performed using electronic health records by Fairfield et al. [14]. Loomis et al. conducted large scale electronic health record database studies with The Health Improvement Network (THIN) database ($n = 133,525$) and Humedica EHR database ($n = 148,934$) and established the consistent and strong relationships between body mass index (BMI) and *prospectively* recorded diagnoses of NAFLD/NASH and emphasize the importance of weight reduction strategies for prevention and management of NAFLD [22].

Danford et al. developed and validated an electronic health record (EHR) algorithm to accurately identify cases of NASH cirrhosis in the HER ($n = 300$) [10]. Recommendations of the Electronic Medical Records and Genomics (eMERGE) network, a network funded by the

National Human Genome Research Institute, was followed to construct the algorithm [10]. The algorithm with the highest PPV of 100% on internal validation and 92% on external validation consisted of ≥ 3 counts of cirrhosis, no mention of alcohol (571.5, K74.6), and ≥ 3 counts of nonalcoholic fatty liver (571.8–571.9, K75.81, K76.0) codes in the absence of any diagnosis codes for other common causes of chronic liver disease [10].

Nonalcoholic fatty liver disease in association with advanced fibrosis and cancer

The current machine learning approaches have identified type 2 diabetes mellitus (T2DM) as a strongly correlated feature with some degree of liver fibrosis and adverse hepatic outcomes (cirrhosis, malignancy) [30]. In a study by Aggarwal and Alkhouri, the authors reported that machine learning algorithms such as deep learning radiomic elastography (DLRE) have excellent accuracy in diagnosing cases of advanced fibrosis [2]. This finding was based on another study by Wang et al. where 344 patients with nonalcoholic fatty liver disease (NAFLD) underwent 428 liver biopsies (240 had paired transient elastography examination) [31]. The fibrosis stage was scored using the NASH Clinical Research Network system, and automated quantification of fibrosis-related parameters (q-FPs) was measured by dual photon microscopy using unstained slides. At the best cut-offs, the two q-FPs had 88.3–96.2% sensitivity and 78.1–91.1% specificity for different fibrosis stages in the validation cohort [31]. It was noted that automated quantification of fibrosis-related parameters by dual-photon microscopy has high accuracy in diagnosing fibrosis and cirrhosis in NAFLD patients [31].

Lewinska et al. developed a noninvasive surveillance method for NAFLD-hepatocellular carcinoma (HCC) [20]. Using comprehensive ultra-high-performance liquid chromatography mass-spectrometry, they investigated 1295 metabolites in serum from 249 patients. The area under the receiver operating characteristic curve was calculated for all detected metabolites and used to establish their diagnostic potential, and logistic regression analysis was used to establish the diagnostic score [20]. The diagnostic model was constructed using ROC curves generated by Monte-Carlo cross-validation (MCCV) using balanced sub-sampling, and the linear support vector machine (SVM) method was used for sample classification [20]. The authors reported that the combination of 5 metabolites accurately distinguishes NAFLD-HCC patients from healthy individuals (AUC = 0.989), morbidly obese bariatric surgery NAFLD (OB-NAFLD) patients (AUC = 0.997), and patients with alcohol- and viral-associated HCC (AV-HCC) (AUC = 0.999), and this model performed well against a validation set of NAFLD patients (AUC = 0.905) [20]. With the help of machine learning model, the authors speculated that NAFLD-HCC tumors act as sinks for unsaturated fatty acids from the blood and link between increased transport of fatty acids by CD36 and NAFLD-HCC [20, 27].

Conclusion

Artificial intelligence is a growing field that supports the identification, diagnosing, and management of diseases such as NAFLD. Many machine learning algorithms predict the risk factors of NAFLD, and with a lifestyle change, the disease can be prevented. In conclusion, it would appear that AI in NAFLD has streamlined specific patient identification and eased assessment and management methods of patients with NAFLD. Moreover, it has proven logistic regression (LR), k-nearest neighbor (kNN), support vector machine (SVM), naive Bayes, Bayesian network (BN), and decision tree and K2 algorithm effective for diagnosing NAFLD. New imaging processing techniques and interpretation using machine learning such as LASSO, automated imaging analysis, and AdipoQuant have caused rapid development in the field of diagnostic radiology. Methods to stage liver fibrosis based on measurements of liver stiffness with the help of vibration controlled transient elastography (VCTE) and shear wave elastography (SWE) are gaining increasing importance. In future, AI will sharpen accuracy in diagnosing, staging and managing NAFLD without sequelae and will promote early detection of HCC and promptly help in its management.

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Author's contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. The authors read and approved the final manuscript.

Authors' information

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