Artificial Intelligence in

Gastroenterology

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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

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Machine learning approaches using blood biomarkers in non-alcoholic fatty liver diseases

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Abstract

The prevalence of nonalcoholic fatty liver disease (NAFLD) is an important public health concern. Early diagnosis of NAFLD and potential progression to nonalcoholic steatohepatitis (NASH), could reduce the further advance of the disease, and improve patient outcomes. Aiming to support patient diagnostic and predict specific outcomes, the interest in artificial intelligence (AI) methods in hepatology has dramatically increased, especially with the application of less-invasive biomarkers. In this review, our objective was twofold: Firstly, we presented the most frequent blood biomarkers in NAFLD and NASH and secondly, we reviewed recent literature regarding the use of machine learning (ML) methods to predict NAFLD and NASH in large cohorts. Strikingly, these studies provide insights into ML application in NAFLD patients' prognostics and ranked blood biomarkers are able to provide a recognizable signature allowing cost-effective NAFLD prediction and also differentiating NASH patients. Future studies should consider the limitations in the current literature and expand the application of these algorithms in different populations, fortifying an already promising tool in medical science.

Key Words: Artificial intelligence; Liver diseases; Healthcare; Hepatology; Prognosis; Diagnostics

Core Tip: The ability of machine learning approaches to process multiple variables, map linear and nonlinear interactions, ranking the most important features, in addition to the capability of building accurate prediction models, sets a future direction to its application in complex diseases such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Future studies should consider the limitations in the current literature and expand the application of these algorithms in different populations, fortifying an already promising tool in medical science.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects an expressive part of the population worldwide and is a major cause of liver-disease related morbidity[1]. The most common cause of death in NAFLD patients is related to cardiovascular diseases, which is partially explained by the presence of metabolic comorbidities, such as obesity, type 2 diabetes, dyslipidemia, and hypertension[2]. Recently, there was concordance that the term NAFLD cannot represent the multisystemic metabolic disruption associated with the disease, resulting in the novel term MAFLD - metabolic associated fatty liver disease. Moreover, MAFLD considers the hepatic manifestation of a multimodal disease that is heterogeneous in its causes, symptoms, progression, and outcomes[3]. Nevertheless, the progression of liver fibrosis could lead to Nonalcoholic steatohepatitis (NASH), a condition characterized by histological lobular inflammation and hepatocyte ballooning[2]. Hence, detecting possible elements related to a worse prognosis in these conditions in the early stages of the disease could improve the treatment and its efficiency. Considering the significance of advanced fibrosis in NAFLD patients, differentiating NASH from steatosis is vital, reinforcing the need for cost-effective methods for risk stratification in this population [4]. Although liver biopsy is widely considered the gold standard in liver diseases investigation, it is also invasive, expensive, and prone to sampling error. In this context, the use of non-invasive biomarkers gains considerable importance[5].

The interest in artificial intelligence (AI) methods in different medical specialties, including hepatology, has dramatically increased during the last decade[6]. Advances in technology and data acquisition have simplified the collection and storage of large data sets with long time series, leading to increasingly varied fields of application, including biomedical areas. In this context, large-volume data mining evaluations had been showing promising results in recent clinical studies using machine learning methods[7-9]. More specifically, supervised machine learning (SML), can automatically detect patterns in existing training data and then use the detected patterns to predict future data[6]. Rather than considering differences between groups (as traditional statistical comparisons do), SML methods address individual differences, classifying individuals in ways that contribute to the clinical decision-making process.

The commonly late diagnosis of liver disorders contributes to suboptimal treatment and poor results. More specifically, as the prevalence of NAFLD is an important public health concern, early diagnosis of NAFLD and potential progression to NASH, could reduce the further advance of the disease, and improve patient outcomes. Using SML methods allows for collecting patient data and identifying their profile regarding the risk of developing comorbidities associated with liver damage, such as the development of metabolic syndrome or even predicting the patient's prognosis. Several recent reviews highlighted the application of artificial intelligence in hepatology, while broadly discussing how different approaches present potential applications in several areas of hepatology[10-12]. However, specific discussion of machine learning approaches using cost-effective biomarkers could help to guide future studies towards the improvement of NAFLD diagnosis. Therefore, the objective of this mini-review is to discuss the application of SML approaches using biomarkers for the diagnosis of NAFLD and the prediction of NASH presence.

BLOOD BIOMARKERS IN NAFLD

Biomarkers are a "defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention". This includes a plethora of possible assessments commonly investigated in NAFLD, such as blood profile, imaging (histo-logical/radiographic) exams, specific anthropometric characteristics (body composition), and also phase angle derived from bioimpedance[13]. Noteworthy, blood biomarkers are a less invasive approach from a biological point of view and could complement imaging techniques to improve disease monitoring. In clinical settings, liver biopsy is the diagnostic gold standard for NAFLD, allowing the assessment of lipid content, inflammation, hepatocellular ballooning, and fibrotic alterations, which can also determine NASH diagnostics[14]. However, non-invasive techniques provide limited inflammation and hepatocellular ballooning determination, making objective biomarker panels for the assessment and monitoring of NAFLD or NASH a current challenge[14,15].

Nevertheless, abnormal liver function is often initially identified by nonspecific hepatocellular damage through elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in addition to alkaline phosphatase and gamma-glutamyl transferase (GGT)[16]. However, ALT and AST can present normal levels while GGT can present a 1.5 - fold elevation, and this response does not reflect hepatic inflammation, fibrosis, or patient metabolic risks[17,18]. Recently, cytokeratin (CK)-18 gained attention as a more specific approach for hepatocyte apoptosis since CK-18 is a major intermediate filament protein cleaved by caspases creating fragments during the apoptotic processes[19]. Assays of CK-18 fragments provide moderate accuracy due to high variability between cut-offs and respective diagnostic accuracy among studies[19]. More specifically, M30 measures caspase-cleaved CK18 produced during apoptosis, and M65 measures the total levels of (both cleaved and intact) CK18[20]. The CK-18 fragments could independently predict NAFLD severity and detect the presence of NASH with a specificity close to 90%[21,22]. In a large and heterogeneous cohort, the blood concentration of CK-18 fragments of patients with NAFLD was higher when compared with healthy volunteers and correlated to several biomarkers of liver damage and steatosis[22]. Moreover, several "biomarker panels" to grade NAFLD patients' steatosis and fibrosis through specific scores comprise different biomarker combinations, summarized in Table 1. Notably, the *FibroTest*, *Fibrometer*, *Hepascore*, and *Enhanced Liver Fibrosis* scores are patented and commercially available panels. Nevertheless, most of the biomarker panels for the diagnosis of NAFLD and NASH, lack validation in specific cohorts, such as bariatric patients and patients with varying ethnicities[23,24]. Further, recent evidence reinforces that a combination of different commonly assessed blood-based biomarkers in addition to direct fibrogenesis markers can provide higher diagnostic accuracy in detecting advanced fibrosis when compared to current protocols. The study of Vilar-Gomez *et al*[25], reviewed the diagnostic accuracy of several blood-based biomarkers, suggesting an algorithm to diagnose NAFLD patients at risk of fibrosis development. Additionally, the European guidelines recommend the combination of different tests to assess NAFLD, stating that the *Fibrometer* is a non-invasive alternative to liver biopsy, albeit the guidelines are not clear regarding which specific version of the *FibroMeter* is preferred[26]. Also, the commercially available biomarker panels and other complementary methods are not accessible for most health services, justifying the search for alternative approaches[25].

The validation study by Wu *et al*[27] compared different panels of biomarkers in 417 NAFLD patients (156 with advanced fibrosis), showing that when predicting liver fibrosis scores Fibrosis-4 (FIB-4), NAFLD Fibrosis Score (NFS), AST to Platelet Ratio Index (APRI) and BARD score (BARD), it is possible to obtain a prediction of moderate fibrosis based on the receptor operator area under the curve (AUROC; 0.724, 0.671 and 0.609, respectively). The authors argued that FIB-4 and NFS performed better compared to both APRI and BARD scores, which resulted in high false-positive rates. Importantly, this study evaluated NAFLD patients based on the new definition of MAFLD, highlighting that the invest-igated biomarker panels provided poor performance in this setting[27]. In conclusion, the fact that the aforementioned biomarkers come from different types of procedures makes it hard for human experts to jointly analyze all this information, which motivates the use of machine learning techniques. These models can work with different types of data and discovering the relationship between them to obtain a better prediction.

ARTIFICIAL INTELLIGENCE APPLICATION IN NAFLD

Briefly, AI is an umbrella term, referring to a structured utilization of software and algorithms that analyze a wide range of data, ultimately simulating human cognition and intelligence[6]. Machine learning (ML) is one of the subdisciplines of AI, focusing on learning from data and associating specific patterns with different outcomes. An important advantage of ML techniques is that they allow the modeling of complex problems that depend on multiple input variables, justifying the application of ML methods to potentially fill several gaps in the study of complex diseases, such as NAFLD[6]. This is especially important in the case of NAFLD, which is closely related to metabolic disturbances associated with obesity and metabolic syndrome[28]. Given its complexity, NAFLD presents in different forms,

Table 1 Blood biomarker panels for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Blood biomarker panels for steatosis

Panel	Patient	Anthropometry	Blood biomarkers
FLI	-	BMI, Waist circumference	GGT and TG
HSI	Presence of DM	BMI	AST:ASL
Steatotest	Sex	BMI	ALT, GGT, TG, A2M, ApoA1, haptoglobin, bilirubin,cholesterol, and glucose
LAP	Sex	Waist circumference	TG
ION	Sex	Waist to hip ratio	ALT, TG
NAFLD LFS	Presence of DM and MS	-	AST:ALT, Insulin

Blood biomarker panels for fibrosis

Panel	Patient	Anthropometry	Blood biomarkers
APRI	-	-	Platelet count, AST
FIB-4	Age	-	Platelet count, AST, ALT
FibroTest	Age, sex	BMI	GGT, A2M, ApoA1, haptoglobin, and total bilirubin
Fibrometer	Age	Body weight	Platelet count, AST, ALT, glucose, ferritin
ELF	-	-	Hyaluronic acid, PIIINP and TIMP-1
Hepascore	Age, sex	-	GGT, Hyaluronic acid, PIIINP and TIMP-1
BARD	Presence of DM	BMI	AST:ALT
NFS	Age, sex, Presence of DM	-	Platelet count, AST:ALT, Albumin

A2M: Alpha-2-macroglobulin; ALT: alanine aminotransferase; ApoA1: Apolipoprotein A1; AST: Aspartate aminotransferase; BMI: body mass index; DM: Diabetes mellitus; GGT: gamma-glutamyl transpeptidase; MS: Metabolic syndrome; NAFLD: Nonalcoholic fatty liver disease; PIIINP: Amino-terminal propeptide of type III procollagen; TG: Triglycerides; TIMP1: tissue inhibitor of matrix metalloproteinases-1.

from simple asymptomatic lipid accumulation to symptomatic non-alcoholic steatohepatitis (NASH) characterized by several factors, including steatosis, hepatocellular ballooning, lobular inflammation, and often fibrosis[28]. Machine learning methods are becoming increasingly popular, which has also motivated an increase in the complexity of these models. Particularly, deep learning (DL) models, like convolutional neural networks (CNN), showed promising results in hepatology, especially with high-resolution data such as images and spectrograms[29]. Likewise, CNN models encompass several layers that involve operations like convolution, pooling, and nonlinear activations, making their decisions difficult to understand. Therefore, they represent black-box models, as opposed to interpretable (white-box) techniques, such as regression/decision trees and Bayesian networks[30,31]. Hence, ML could identify patients at risk and guide clinical treatments, whilst considering that the clinical manifestations of NAFLD appear in advanced disease status and the availability and cost of screening methods for the clinicians. Also, ML can help to rank and categorize specific biomarkers and help to elaborate specific "disease signatures", contributing not only to clinical diagnostics, but also provide mechanistic insights for the study of the disease and the development of specific treatments.

MACHINE LEARNING APPROACHES USING BLOOD BIOMARKERS IN HEPATOLOGY

As stated above, the interest in using AI approaches to support clinical decision-making processes in hepatology has increased, albeit current literature is still scarce. Table 2 summarizes the specific studies addressing NAFLD and NASH classification. Initially, the study of Sowa *et al*[32] showed no differences in the investigated biomarkers (ALT, AST, and apoptotic signaling) between patients with a fibrosis score of 1 or 2. However, combining these parameters using random forests (RF) reached 79% accuracy in fibrosis prediction with a sensitivity of more than 60% and specificity of 77%. Moreover, RF identified the cell death markers M30 and M65 as more important for the decision than the classic liver parameters. Similarly, Yip *et al*[33] built a model to predict steatosis in a study including 922 individuals with assessment for NAFLD. The four models developed presented good diagnostic precision for steatosis (AUROC was 0.87-0.9), albeit the authors claimed that the "NAFLD ridge score" offered the best balance between efficacy and simplicity. This model included six parameters (serum triglycerides, alanine aminotransferase, high-density lipoprotein cholesterol, hemoglobin A1c, white cell count, and

Table 2 Machine learning studies in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis patients

Ref.	Patients	Investigated biomarker	Model with best performance	Results
Sowa *et al* [32], 2013	126 patients	Alanine aminotransferase; Aspartate aminotransferase; M30; M60; Hyaluronic acid	Randon forest	79% Accuracy in fibrosis prediction; 60% sensitivity; 77% specificity
Yip *et al* [33], 2017	922 patients	Alanine aminotransferase; High-density lipoprotein cholesterol; Triglycerides; HbA1c; White blood cells; Hypertension	Ridge score	88% Accuracy in steatosis prediction; 92% sensitivity; 90% specificity
Ma *et al* [34], 2018	10.508 patients; 2522 NAFLD patients	Age; Sex; Body mass index; Alanine aminotransferase; Aspartate aminotransferase; Alkaline phosphatase; Gamma-glutamyl transpeptidase; Triglycerides; Blood urea nitrogen; Bilirubin; Cholesterol; Creatinine; Fasting glucose; Uric acid	Bayesian network model	83% Accuracy in NAFLD prediction; 68% sensitivity; 94% specificity
Canbay *et al* [35], 2019	164 patients; 122 (validation)	Age; HbA1c; Gamma-glutamyl transpeptidase; M30; Adiponectin	Logistic regression	70% Accuracy in separate NAFLD and NASH
Liu *et al* [36], 2021	15.315 patients 5878 with NAFLD	Body mass index; Waist circumference; Waist-to-height ratio; Alanine aminotransferase; Fasting blood glucose; Gamma-glutamyl transpeptidase; Very-low-density lipoprotein cholesterol; Low-density lipoprotein cholesterol; High-density lipoprotein cholesterol; Systolic blood pressure; Alkaline phosphatase; Diastolic blood pressure	XGBoost model	79% Accuracy in NAFLD prediction; 61% sensitivity; 90% specificity
Pei *et al* [37], 2021	3.419 patients; 845 with fat liver diseases	Age; Height; Hemoglobin; Aspartate aminotransferase; Glucose; Uric acid; Low-density lipoprotein; Alpha-fetoprotein; Triglycerides; High-density lipoprotein; Carcinoembryonic antigen	XGBoost model	94% accuracy of prediction; 90% sensitivity; 95% specificity

NAFLD: Nonalcoholic fatty liver disease; XGBoost: Extreme gradient boosting.

the presence of hypertension) that are routinely available for individuals undergoing medical checkups, and it does not require anthropometric measures, which are not always available. Although there is evident feasibility of the NAFLD ridge score to screen individuals, it still needs additional validation in other ethnicities. The study of Ma *et al*[34], investigated the predictive power for NAFLD of eleven machine learning techniques, demonstrating that the Bayesian network model had the best performance, revealing that the five most discriminating features (based on information gain scores) to be weight, TG, ALT, GGT, and serum uric acid levels. Thus, in practice, users could focus on these features. Furthermore, Canbay *et al*[35] compared different scores for the non-invasive detection of NASH. Briefly, using an ensemble feature selection approach for biomarker selection, the authors built a logistic regression model and validated in an independent study cohort of 122 patients. The logistic regression model generated from age, GGT, hemoglobin A1c, M30, and adiponectin had a strong correlation with the non-alcoholic steatohepatitis activity score and demonstrated reasonable performance to discriminate between NAFL and NASH. Likewise, Liu *et al*[36] performed a retro-spective cross-sectional study on 15315 Chinese subjects, where 5878 patients presented NAFLD. The biomarker ranking indicated the body mass index as the most valuable indicator to predict NAFLD, followed by waist circumference, triglycerides, waist-to-height ratio, and alanine aminotransferase. Notably, among seven machine learning models, the extreme gradient boosting (XGBoost) model demonstrated the best prediction ability. Similarly, the XGBoost also presented the highest AUC (0.93), accuracy (0.94), and sensitivity value (0.90) in the study of Pei *et al*[37], comparing different models for predicting fatty liver Disease risk in 3419 participants, of which 845 had diagnostic confirmation. Importantly, regarding the biomarkers, uric acid, body mass index, and triglycerides were the most decisive risk factors for the ML models, whilst high-density lipoprotein and hemoglobin also counted as important risk factors for prediction. Strikingly, these studies provide insights into ML application in a complex context such as NAFLD patients' prognostics. Notably, while there are investigations using AI techniques and common biomarkers to predict NAFLD and NASH, approaches using AI and novel proposed biomarkers are scarce. For instance, a recent meta-analysis showed that CK-18 is the only marker for NASH presenting external validation, with an AUROC of 0.82[38]. Conversely, a large study conducted by the multicenter NASH Clinical Research Network demonstrated that the addition of routinely available clinical-laboratory parameters to CK-18 measurement did not significantly improve its diagnostic performance[22]. However, it remains unknown whether the use of AI techniques combining different biomarkers in a large and diverse cohort could provide different results. Taken together, the data suggests that ranked blood biomarkers can provide a recognizable signature allowing cost-effective NAFLD prediction and also differentiating NASH patients.

CURRENT CHALLENGES IN SML APPROACHES IN HEPATOLOGY

The term "AI-Chasm" describes the gap between developing and testing an algorithm and the definitive application of the algorithm in clinical practice[39]. Unequivocally, the AI application in medical sciences is auspicious, and current literature is shading light on a plethora of potential applications; however, many challenges for SML approaches using biomarkers in hepatology still await scrutiny.

Firstly, the collection, curation, and preprocessing of patient data is a major concern, since SML methods are data-driven[10]. Notably, the cited studies in this mini-review provide relatively small data from specific populations which could lead to sampling bias whilst limiting the generalization of the obtained results. Further, data collection should be standardized and precise, but should also be monitored for privacy and data security breaches. Secondly, as recently discussed by Quinn *et al*[40], one of the main aspects of concern in future studies is the understanding that transdisciplinary approaches require cooperation to build a conceptually appropriate framework while also focusing on evaluating the performance of SML algorithms in terms of clinical endpoints and not just predictive accuracy. In addition to these technical challenges, there is also an increasing demand for transparency concerning the predictions of these models, especially in areas that have no computing background. For instance, healthcare professionals and other stakeholders that can benefit from these solutions are still reluctant to the idea of employing these methods, evidencing the necessity of educational programs aimed to explicit information about the involved decision processes. Nevertheless, the field of explainable AI has emerged to address these issues, with the purpose of creating ML techniques that produce explainable models while maintaining a high level of learning performance, enabling humans to understand and trust the predictions to support their decisions[41].

CONCLUSION

Recent advances in the field of biosciences applying machine learning algorithms resulted in promising results for the diagnosis of disease and biomarker study. The main idea is that SML could overcome the limitations of common statistical techniques. For instance, SML identifies data patterns for classification, considering multiple features at once, allowing the ranking and selection of the available blood biomarkers related to disease pathogenesis for the prediction of NAFLD or NASH, minimizing potential errors between the predicted values and the real data. Although the cited studies provide promising results, there are specific limitations that future studies should reduce. For example, most of the studies involved the Chinese population, and these algorithms still need additional validation in heterogeneous populations. The strong association between NAFLD and metabolic syndrome, obesity, and alcohol consumption may be a confounding factor in previous studies, and the application of these methods in diabetic patients with and without NAFLD could shed light on the influence of specific treatments on the performance of these ML methods. Nevertheless, the ability of ML approaches to process multiple variables, map linear and nonlinear interactions, and rank the most important features, in addition to the capability of building accurate prediction models, sets a future direction to its application in complex diseases, including NAFLD and NASH. Future studies should consider the limitations in the current literature and expand the application of these algorithms in different populations, fortifying an already promising tool in medical science.

FOOTNOTES

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