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REVIEW

Insights into ALD and AUD diagnosis and prognosis: Exploring AI and multimodal data streams

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Abstract

The rapid evolution of artificial intelligence and the widespread embrace of digital technologies have ushered in a new era of clinical research and practice in hepatology. Although its potential is far from realization, these significant strides have generated new opportunities to address existing gaps in the delivery of care for patients with liver disease. In this review, we discuss how artificial intelligence and opportunities for multimodal data integration can improve the diagnosis, prognosis, and management of alcohol-associated liver disease. An emphasis is made on how these approaches will also benefit the detection and management of alcohol use disorder. Our discussion encompasses challenges and limitations, concluding with a glimpse into the promising future of these advancements.

INTRODUCTION

Alcohol use disorder and the hepatotoxicity that can result in alcohol-associated liver disease (ALD) represent a dual pathology with increasing prevalence, marked heterogeneity, and several unmet needs in diagnosis and management. These characteristics make AUD and ALD apt for the application of AI solutions, which can leverage large amounts of data to unravel intricate patterns and correlations in disease. AI algorithms have the capacity to process diverse data sources to aid in the earlier detection of ALD, more accurate prognostic assessments, and the development of personalized treatment strategies.

Globally, 5.1% (283 million) of the population has a diagnosis of AUD. It is estimated that 35% of individuals with AUD will develop liver disease,[1] further cementing the gravity of this intertwined health concern. However, it remains less clear for whom the risk of ALD is greatest and what predisposing factors exist in addition to alcohol use. ALD encompasses a spectrum of diseases from asymptomatic stages of hepatic steatosis to quality of life-limiting presentations of decompensated cirrhosis and HCC. Alcohol-associated hepatitis (AH) is a severe inflammatory phenotype of ALD that has been extensively studied as a discrete entity due to its disproportionate contribution to hospitalizations and high mortality. Therapies for AH remain confined to corticosteroids[2] and early liver transplantation (LT),[3] with limitations in their effectiveness and accessibility, respectively.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACCELERATE-AH, American Consortium of Early Liver Transplantation for Alcohol-Associated Hepatitis; AH, alcohol-associated hepatitis; ALCHAIN, ALCoholic Hepatitis Artificial INtelligence; ALD, alcohol-associated liver disease; GLM, generalized linear model; IRC, immune-related cells; LASSO, least absolute shrinkage and selection operator; LLM, large language model; LR, linear regression; LT, liver transplantation; MAIN-ART, Michigan Alcohol Improvement Network-Alcohol Reduction and Treatment; MASLD, metabolic dysfunction-associated steatotic liver disease; MIMIC-III, The Million Veteran Program and the Medical Information Mart for Intensive Care III; MLA, machine-learning algorithm; MLP, multilayer perceptron; NIALC, normogram for intensive care unit patients with ALD-C; NLP, natural language processing; NLU, natural language understanding; PBMC, peripheral blood mononuclear cell; RFE-RF, recursive feature elimination using random forest; TAM2, Technology Acceptance Model 2; VR, virtual reality; XAI, explainable AI.

In recent years, the epidemiological landscape of ALD has changed, with a marked surge in incidence among women, minority individuals, and younger demographics.[4] Simultaneously, the revised nomenclature for metabolic dysfunction-associated steatotic liver disease (MASLD) comes with a recognition that ALD falls within this larger classification of steatotic liver disease as a spectrum with a coexisting impact of both processes ("MetALD").[5,6] These trends signal the pressing need for advanced diagnostic and prognostic tools to effectively address the heterogeneity within AUD-ALD and the complexities of its management.[7] Existing approaches have traditionally used clinical, biochemical, radiographical, and histological data to diagnose ALD, predict disease outcomes, and deliver synchronous treatment in conventional physician-patient interactions. Despite advances in each of these individual data-generating areas, there remain limitations in accurately evaluating and prognosticating ALD.

To address these challenges, there is a growing interest in harnessing the diverse sources of data and power of AI to synergistically transform high-volume data into meaningful solutions that enhance clinical research and patient care. Multimodal data integration involves synthesizing diverse data streams, including mobile and wearable technology. From machine learning to natural language processing, AI has the ability to analyze and compute varied inputs of data with great speed and accuracy. Advanced computing methods and the availability of digital technologies can also forge a path closer to personalized medicine. However, the current utilization of AI in ALD remains in its nascent stages.

In this review, we explore how AI and multimodal data integration add substantial value to the understanding and management of ALD, with an emphasis on their concurrent impact on the management of AUD. We include a futuristic view of how AI, in combination with digital technology, may revolutionize AUD-ALD care at a patient and population level, acknowledging areas in which AI remains undeveloped and in need of improvement.

RELEVANT DEFINITIONS AND BENEFITS OF AI TO ALD

Recent in-depth reviews have supplied the essential background information, definitions, and context pertaining to AI in hepatology[8,9] and, thus, will not be discussed here. We summarize key terms and concepts in Table 1.

CURRENT STATE OF AI IN ALD

Search strategy

To understand the depth of current publications in AI and ALD, we performed a comprehensive search on PubMed using Medical Subject Heading (MeSH) terms. Multiple keywords for AI were paired with "alcohol" and classifiers of liver disease. Examples included, but were not limited to, "machine learning," "deep learning," "neural networks," "natural language processing," "digital," "sensors," and "computing." Publications were reviewed in detail and included in this review based on their relevance.

A total of 12 studies were identified that used machine-learning algorithms (MLAs) with the aim of enhancing diagnostic and prognostic capabilities in ALD. Five of these studies focused specifically on AH[10–13] (Table 2).

When searching particularly for investigations of digital technologies in ALD, 5 additional studies were found.[14–18] These efforts are primarily in the proof-of-concept stages (Table 3).

Diagnosis of ALD

Unmet need: Early detection of ALD

Patients diagnosed with ALD often present at advanced stages of liver disease and exhibit faster progression compared to other etiologies.[19,20] In comparison to patients with MASLD, those with ALD are more likely to develop liver-related decompensation with a higher MELD scores, resulting in an overall worse transplant-free survival.[19] Moreover, a cross-sectional analysis involving 3453 patients across 17 international centers revealed that ALD was less likely to be diagnosed at early, reversible stages when compared to etiologies such as hepatitis C.[20]

Various factors contribute to this trend. Individuals at high risk of liver-related complications due to AUD may not commonly seek care in primary care or hepatology clinics where screening tools for alcohol misuse are available. Instead, their presentations may be related to other consequences of alcohol use, such as complicated withdrawal or other end-organ damage (eg, alcohol-associated pancreatitis, peripheral neuropathy, cardiomyopathy, etc). This perspective suggests the existence of multiple time points and missed opportunities for early intervention.

While noninvasive modalities like the Fibrosis-4 index have been developed to predict advanced fibrosis,[21] there is still a lack of models designed for ALD prediction. Therefore, there is a pressing need for the development of automated, proactive approaches to enhance early detection and intervention for ALD.

AI-driven solutions. In a national study using the Danish Health Registry Data from 1996 to 2014, MLAs were applied to uncover relevant upstream diagnoses in patients who developed alcohol-associated fibrosis and cirrhosis.[22] Of 33,391 patients identified with ALD in this national registry, the vast majority had alcohol-associated cirrhosis (69.7% or 23,271), and only a small cohort of 499 were identified at an earlier and potentially reversible stage of alcohol-associated fibrosis. Six categories of comorbid diagnoses emerged from a case-control

TABLE 1 Key terms and concepts related to AI

AI: is an inclusive term to describe the ability of machines to perform tasks that otherwise require human reasoning or problem-solving skills. Subsets of AI, like machine learning and deep learning, have been made possible by advances in computing power over the last several decades. Their development and use have been, in part, a response to an exponential increase in data sources along this timeline. **Explainable AI (XAI)** refers to AI systems' ability to provide understandable explanations for their decisions, enhancing transparency and user trust. **Generative AI** refers to a category of AI systems with the ability to produce new content such as text, images, or other media, often based on given prompts or input data.
Data streams: increasingly available, high-dimensional, and complex data has driven the need and use of AI in research and patient care. The EHR has been a primary source of both structured data—such as patient demographics, diagnostic codes, laboratory, and imaging results—as well as unstructured data generated from clinical notes. In addition, advances in sequencing have enhanced the granularity of data with the ability to analyze multiple "omes" (including, but not limited to the genome, proteome, microbiome, metabolome, lipidome, epigenome, and metabolome) at a single-cell level.
Deep learning: involves the use of neural networks containing complex layers of functions. Multiple algorithms are woven together and arranged in layers from which infinite patterns can be generated. Deep learning has been particularly used to process and analyze images and, thus, has been adopted more readily by radiology and pathology.[8]
Digital technologies are innovative and increasingly used sources of data. These technologies include, but are not limited to telemedicine, remote monitoring, mobile phones, wearables, sensors, and virtual reality.[10] Mining data from social media platforms or online forums can also provide unstructured information on patient experiences, perceptions, and population-level patterns. The process of using data from digital sources to better understand individuals' behaviors and improve their health is called **digital phenotyping.**
Machine learning: describes AI techniques in which algorithms build mathematical models from sample data. Supervised learning allows for predictive modeling, exploiting annotated data sets to train algorithms and predict outcomes. Unsupervised learning methods uncover patterns and structures from data without predefined labels. In this review, we emphasize the benefits of pairing machine-learning techniques with complex data derived from diverse data sources.
Machine-learning pipeline: refers to the process of creating and using a machine-learning algorithm (MLA). Available data are typically split into a training set and a testing set. Data are extracted and prepared to be fed into MLAs. From these, the best fit of the data is determined, and a model is created that is then further optimized. Next, a testing set, often an external data set, is used to validate the model. Finally, the performance of the model is evaluated such as through calculating the AUC-receiver operating characteristic, often with comparison to established scores or tools already in clinical use.
Multimodal data integration: refers to combining single-stream data modalities toward the goal of deep phenotyping and personalized medicine. Mimicking how clinicians seamlessly incorporate data across modalities in clinical decision-making, AI can take outputs from multiomics data, imaging, and EHR data that contain patterns otherwise uninterpretable by humans/clinicians to create diagnostic biomarkers or identify therapeutic targets.[11]
Natural language processing (NLP): is a subset of AI focused on enabling computers to understand, interpret, and generate human language in a way that is both meaningful and contextually appropriate.
Natural language understanding (NLU): specifically focuses on the ability of computers to comprehend and interpret human language input, extracting meaning and context from text or speech data.
Neural networks: are computational models inspired by the human brain, composed of interconnected nodes organized into layers. They process information through these layers to learn patterns from data and perform tasks like classification and pattern recognition.
Sensors: devices or components that detect and respond to physical stimuli from the environment, converting them into measurable signals or data.

analysis powered by AI clustering techniques that may predict for later development of ALD.[22] Certain categories, such as those associated with liver dysfunction and alcohol overuse, were predictable, while others, like malnutrition, trauma, and upper intestinal mucosal issues (such as esophagitis), represented diagnoses to which ALD is not automatically linked. This study was powerful in successfully extracting meaningful predictive information with the assistance of AI from a country-wide database.

Unmet need: Distinguish ALD and AH from similar presenting etiologies

In current practice, standard biochemical assessments are used to both suspect and confirm recent alcohol use and alcohol-associated liver injury. To quantify alcohol AUD consumption, biomarkers, such as urine ethyl glucuronide and serum phosphatidylethanol, are routinely measured.[23,24] Elevations in serum gamma-glutamyl transpeptidase, mean corpuscular volume, and elevations in the ratio of aspartate transferase: alanine transferase signal toward either recent alcohol use or alcohol as etiology for liver injury.[25]

However, biochemistries alone have been limited in the ability to characterize early versus later stages of ALD, as well as distinguishing between other hepatobiliary disease entities.[10] Furthermore, radiographic modalities such as ultrasound, elastography, and cross-sectional imaging are helpful in the evaluation of advanced liver fibrosis, though they are not currently used to determine etiology.

TABLE 2 AI and ALD studies: summary table for studies to date using AI approaches, mainly through MLAs, to improve diagnosis and prognosis in ALD

Aim	Study	Patient cohorts	Data stream(s)	AI classifier	Findings
Identify upstream diagnoses for earlier detection/prediction of ALD	Grissa et al[22]	Danish health registry data 1999–2014 ALD (N = 33,391) ALD-fibrosis (ALD-F) (n = 499) ALD-Cirrhosis (ALD-C) (n = 22,271)	Clinical data	MLAs: SVM, RF, LightGBM, Naïve Bayes	• Comparison of ALD-C versus non-ALD controls identified 6 categories of statistically significant upstream diagnoses (liver dysfunction, alcohol overuse, malnutrition, trauma and injuries, upper intestinal mucosal, other) • MLAs tested prediction of ALD based on upstream diagnoses: in training model ALD-C AUC 0.89. In ALD-F AUC dropped to 0.67.
Distinguish ALD from MASLD; distinguish ALD-C from ALD-NC	Sowa et al[26]	MASLD (n = 31) ALD-C (n = 51) ALD-NC (n = 51)	Laboratory data	MLAs: LR, DT, SVM, RF	• High ALT/AST ratio and low levels of adiponectin, TNF-alpha distinguished MASLD from ALD • MLAs distinguished MASLD vs. ALD-NC (AUC = 0.92), ALD-C vs. ALD-NC (AUC = 0.98)
Distinguish AH from acute cholangitis	Ahn et al[10]	Training cohort: N = 459 AH (n = 265) Acute cholangitis (n = 194) External cohort: MIMIC-III database (N = 305) AH (n = 92) Acute cholangitis (n = 213)	Clinical and laboratory data	8 Supervised MLAs: LR, DT, SVM, RF, GBM, Naïve Bayes, ANN, kNN	• Best 5-variable subset by MLAs AUC 0.994 vs. physicians (tested by survey) with AUC 0.790 in distinguishing AH from acute cholangitis • MLAs had accuracy up to 0.932 and AUC up to 0.986 on the training data set, external validation had accuracy up to 0.909 and AUC up to 0.970
Identify imaging features that can accurately diagnose AH	Tana et al[11]	AH (n = 34) No ALD controls (n = 35)	Imaging data (CT)	Texture features RFE-RF Deep learning—CNN	• RFE-RF identified 23 top features to classify AH images, producing a model with an accuracy of 82.4% in the test set • Deep learning CNN had an accuracy of 70% in test sets
Identify imaging features to diagnose ALD-C from other etiologies of cirrhosis	Luetkens et al[28]	N = 465 ALD-C (n = 221) Other cirrhosis (n = 244)	Imaging data (MRI) T2-weighted single-slide images at caudate lobe split for training and validation	Deep learning—CNN	• Two different CNN architectures—ResNet50 and DenseNet121 were evaluated on testing data • ResNet50 with unfrozen pretrained parameters had the highest classification performance for ALD-C with AUC 0.82
Identify alcohol relapse risk after early LT for AH	Lee et al[12]	ACCELERATE-AH (after LT for AH) Training cohort: n = 91, 8 centers Validation cohort: n = 25, 2 centers	Clinical data	MLAs: LR, RF, XGBoost	• Training set had an AUC of 0.930, PPV 0.891 • External validation set had an AUC of 0.692, PPV 0.82 • Variables related to social support and substance use correlated with prediction of post-LT harmful alcohol use
Creation of NIALC	Zheng et al[38]	Training cohort: N = 394 ICU patients from MIMIC-III database Validation cohort: ICU patients with ALD-C Internal (n = 394) External (n = 501)	Clinical data	MLAs: Regression analysis method, LASSO	• Development of NIALC score with AUCs in validation cohort: 0.767 and 0.760 • NIALC score outperformed existing scores for liver disease severity and prognosis such as MELD, MELD-Na, CPC, and CLIF-SOFA

Develop an AI-generated model to predict 90-day mortality in AH superior to MELD	Dunn et al[13]	GlobalAlcHep network N = 1720 (22 centers, 9 countries)	Clinical Data	MLAs	• MLAs helped produce the ALCHAIN score (age, BUN, albumin, bilirubin, Cr, INR, NLR) with AUC 0.79 for predicting AH 90-day mortality • ALCHAIN score superior when compared to MELD, MELD-Na, MELD 3.0, MDF, ABIC, and Glasgow-AH
Create a model to predict 90-day mortality for AH with stool "omics" data.	Gao et al[34]	AH (n = 210), 10 centers	Clinical data Laboratory data Stool samples-micro/mycobiome/virome "omics"	MLAs: LR, RF, SVM, GBM	• Gradient boosting achieved the highest AUC of 0.87 for 30-day mortality prediction using the bacteria and metabolic pathways data set, and AUC of 0.87 for 90-day mortality prediction using the fungi data set • MLA-produced model had better prediction than MELD (AUC 0.78 for 30-day mortality and AUC 0.82 for 90-day mortality)
Create a model using proteomic biomarkers to predict alcohol-associated fibrosis	Niu et al[36]	Training cohort N = 596 Early ALD (n = 459) Healthy controls (n = 137) Validation cohort (n = 63)	Laboratory data Liver biopsy samples Plasma samples	MS-based proteomics MLAs—LR	• MLAs identified proteomics biomarkers panels that detected fibrosis (AUC 0.92, accuracy 0.82) and mild inflammation (AUC, 0.87, accuracy, 0.79) • Biomarker panels predicted future liver-related events (C-index 0.90) and all-cause mortality (C-index 0.79)
Identify gene signatures that can distinguish ALD	Listopad et al[35]	AH (n = 32) ALD-C (n = 8) Other liver disease (n = 19) Healthy controls (n = 8) Validation RNA-sequency data set: AH (n = 10) ALD-C (n = 6)	Laboratory data Liver biopsy samples PBMCs	RNA sequencing MLAs—LR, SVM, kNN	• Liver tissue RNA-seq data, when analyzed with MLAs, yielded a model with 33 genes that were able to distinguish between AH, ALD-C, and healthy conditions with an accuracy of 90% (internal data set) and 82% (external validation sets)
Develop an IRC-based machine-learning model to aid in the diagnosis and prognosis of ALD	Zhang et al[37]	ALD (n = 207) Healthy controls (n = 234)	Laboratory data Immune-related cells	MLAs—RF, GBM, MLP, GLM	• RF models have the greatest performance of MLAs tested for ALD diagnosis and prognosis • Combination of 8–13 variables (gender and measures of IRCs) predicted the greatest risk for ALD progression with AUC between 0.9 and 1.00 in the testing and training data sets

Abbreviations: AH, alcohol-associated hepatitis; ALCHAIN, ALCoholic Hepatitis Artificial INtelligence; ALD, alcohol-associated liver disease; ANN, artificial neural network; CNN, convoluted neural network; DT, decision tree; GBM, gradient boosting machine; GLM, generalized linear model; IRC, immune-related cells; kNN, k-nearest neighbor; LASSO, least absolute shrinkage and selection operator; LR, linear regression; MASLD, metabolic dysfunction–associated steatotic liver disease; MDF, Maddrey's discriminant function; MIMIC-III, Million Veteran Program and the Medical Information Mart for Intensive Care III; MLA, machine-learning algorithm; MLP, multilayer perceptron; NIALC, normogram for intensive care unit patients with ALD-C; PBMC, peripheral blood mononuclear cell; RF, random forest; RFE-RF, recursive feature elimination using random forest; SVM, support vector machine.

TABLE 3 Digital technologies and ALD studies: summary table for studies to date evaluating the use of digital data streams in ALD management

Aim	Study	Patients	Digital technology	Findings
Feasibility: Quantitative and qualitative assessment of patients with ALD using alcohol biosensor	DiMartini et al[14]	ALD (n = 27)	Wrist Transdermal Alcohol Sensor	• Quantitative data TAM2 13-item assessment + qualitative assessment • Limitations: Minor inconveniences causing participants to not consistently wear the biosensor; technological challenges (devices lost/damaged, data lost) • Patients with severe AUD and the heaviest alcohol consumption (n = 2 in this study with >20 drinks/d) hardly used the biosensor 7% and 13%
Proof of concept: App with behavioral change techniques and digital breathalyzer with primary outcome alcohol use reduction	Mehta et al[15]	ALD (n = 41)	AlcoChange Mobile application Novel digital therapeutic with validated behavior change techniques and a digital alcohol breathalyzer	• Adherence to app usage correlated with a significant reduction in alcohol use $p = 0.029$, higher rate of abstinence at 3 mo, and reduced risk of alcohol-associated readmission in 12 mo ($p = 0.008$)
Feasibility: Primary outcome was the acceptability of the app along with the recruitment/retention rate; the aim was to increase AUD treatment	Mellinger et al[16]	ALD (n = 60) Randomized 1:1 to intervention vs. usual care	MAIN-ART Online/phone application Single session of two modules	• Primary outcome: Recruitment rate (46%) and retention rate (65% at 6 mo), acceptability of App (>90%) • Secondary outcomes: Increased AUD treatment at 6 mo in intervention group • Limitations: Survey fatigue
Mixed methods: Qualitative study to see if app can motivate ALD patients to seek treatment	Park et al[17]	ALD (n = 11)	mHealth digital health mobile application	• App useable and viewed favorably among participants • Preliminary results suggest ALD is a motivator for patients to seek treatment for AUD
Proof of concept: Ability of passive sensor data to correlate with EMAs for alcohol cravings and risk of relapse	Wu et al[18]	ALD (n = 24) (50% retention rate)	AWARE mobile application with collection of passive sensor data and delivery of EMAs	• Associations between alcohol craving and mood (positive association with negative moods; negative correlations with positive mood) • Less movement/less change in location entropy associated with an increase in craving score • Accelerometer magnitude higher in those who experienced alcohol relapse

Abbreviations: ALD, alcohol-associated liver disease; EMA, ecological momentary assessments; MAIN-ART, Michigan Alcohol Improvement Network-Alcohol Reduction and Treatment; TAM2, Technology Acceptance Model 2.

AI-driven solutions. Among the earliest adoptions of MLAs to ALD research was by Sowa and colleagues in 2014, who investigated the ability of various cytokines to distinguish ALD from MASLD. The ratio of alanine transferase:aspartate transferase favored a specificity for MASLD over ALD. Additional cytokine analysis showed that adiponectin and TNF-alpha levels were lower in MASLD compared to ALD, while cell death markers were higher in ALD.[26] By combining laboratory data and cytokine analysis, the authors demonstrated a basic multimodal strategy for improving the diagnosis of ALD.

AH is a severe clinical manifestation within ALD that relies on the combination of substantial recent alcohol use, cholestatic liver injury, and signs of acute inflammation.[27] The biochemical features have similarities to acute cholangitis, which, on initial presentation to emergency rooms or critical care settings, can cause diagnostic confusion and delays. Ahn and colleagues developed an AI model from MLAs capable of discerning acute cholangitis from AH using 5 standard laboratory values with an accuracy of $>90\%$. When compared to surveyed physicians, the 5-variable subset statistically outperformed clinical judgment (AUC: 0.790 vs. 0.994). An important element of this study was its direct comparison to the current standard of care, highlighting the super-human or "super-physician" capabilities of AI modeling outputs.[10]

Deep learning methods with convoluted neural networks have been employed in 2 radiology studies to assess whether cross-sectional imaging can accurately diagnose AH[11] as well as alcohol-associated cirrhosis.[28] In their analysis of CT studies in 34 patients with AH and 25 controls, Tana et al[11] found that a machine-learning technique of recursive feature elimination could effectively discriminate between radiographic features most and least relevant for ALD diagnosis. The radiographic features identified by convoluted neural network involved intricacies of pixel distributions and intensities that would not have been possible by human interpretation alone.[11] Similarly, a deep learning approach of T2-weighted MRI images from 465 patients with cirrhosis was able to construct a convoluted neural network architecture that could distinguish alcohol-associated cirrhosis from other etiologies of cirrhosis with an AUC up to 0.82.[28]

These preliminary studies have demonstrated the diagnostic potential of AI in ALD and reinforced that the success of machine-learning approaches depends on the quality of input data. Further research in ALD also stands to benefit from insights gained from research in MASLD and HCC. Studies employing machine-learning models for MASLD have already exhibited superiority over traditional noninvasive tests like FibroScan, Fibrosis-4 Index, FibroScan-aspartate transferase (FAST), and NAFLD Fibrosis Score.[29] Deep learning applications have already achieved advanced uses in HCC among other primary liver malignancies with combinations of different types of imaging such as ultrasound, CT, and MRI being used simultaneously for increasing diagnostic accuracy.[30]

Prognosis

Unmet needs: Biomarkers for predicting outcomes in ALD and AH

ALD is a heterogenous process, and the influence of ongoing alcohol use, genetic predispositions, and epigenetic contributions can significantly affect an individual's rate of liver disease progression.[31] These characteristics of ALD contribute to the difficulties in finding reliable biomarkers for risk stratification.[32]

There has been significant interest in predictive models, particularly for AH. MELD and its subsequent versions, like MELD 3.0, have been validated for use in ALD and AH.[33] They have adequate performance for predicting short-term mortality and appropriate allocation for those listed for LT. These existing models were created using logistic regression, which is a supervised machine-learning approach; however, they lack incorporation of nuances specific to ALD pathogenesis.

AI-driven solutions. "Omics" sciences—including, but not limited to genomics, lipidomics, metabolomics, proteomics, and transcriptomics—have allowed for the study of ALD at an immuno-molecular level and have produced vast quantities of data that are well suited for the use of AI. In a study of serum and fecal samples from 210 patients with AH, Gao et al[34] were able to use MLAs to narrow considerable amounts of viral and bacterial pathway data produced by metabolomics and lipidomics into an 11-variable model that exceeded the MELD score in 30-day and 90-day mortality predictions. To aid in the discovery of relevant genetic biomarkers for ALD, Listopad and colleagues fed data obtained from RNA-sequencing performed on peripheral and liver tissue samples into a machine-learning pipeline. They discovered a set of 33 gene biomarkers that differentiated alcohol-associated cirrhosis and AH from other liver diseases and healthy controls with an accuracy of 90% within their internal data set and 82% in the external validation cohort.[35] In a similar approach of using peripheral and liver tissue samples from patients with early ALD, Niu et al located proteomic markers with MLAs tested on data from mass-spectrometry–based, high-throughput proteomic analysis. The biomarker panels developed outperformed existing noninvasive fibrosis tests, including Fibrosis-4 Index, enhanced liver fibrosis, and aspartate transferase to Platelet Ratio Index scores. Furthermore, there was a significant overlap seen between liver and plasma proteomes, suggesting that a liquid biopsy approach using proteomic biomarkers is reliable for ALD.[36]

Although these studies were limited by a small sample size, they illustrate the synergy and translational power of pairing AI with multiomics in developing noninvasive prognostic biomarkers for ALD.

While the cost of "omics" tools has fallen considerably over the last 2 decades, novel biomarkers from these methods face considerable obstacles to adoption in routine clinical use. Thus, the use of AI to produce highly specific models from readily available, low-cost laboratory parameters is a desirable strategy. In a study by Zhang and colleagues, immune-related cells such as neutrophils and lymphocytes were included in a nomogram alongside other variables such as sex, age, and components of the complete blood count in patients with ALD in comparison to healthy controls. IRC-based MLAs were then analyzed with a sophisticated AI statistical tool called the least absolute shrinkage and selection operator (LASSO). This regression analysis method enhanced prediction accuracy and interpretability in ALD onset, progression, and prognosis.[37] The models also were able to correlate with a MELD score cutoff >20 that has been established for ALD severity. A recent global study focusing on AH also incorporated neutrophil to lymphocyte ratio in the AI-produced ALCHAIN score (other components were age, international normalized ratio, bilirubin, creatinine, albumin, and blood urea nitrogen), which better selected patients who would survive and respond to corticosteroids than MELD based scores and Maddrey's discriminant function.[13]

In addition to generating general biomarkers for ALD, predictive modeling using AI can assist decision-making in specific patient scenarios. The nomogram for intensive care unit patients with alcohol-associated cirrhosis (NIALC) was created using LASSO feature selection by Zheng et al[38] to improve estimates of mortality in hospitalized, critically ill patients with ALD. The NIALC was compared to Child-Pugh and the acute-on-chronic liver failure (CLIF-ACLF) scores and facilitated more individualized predictions.

The studies discussed here show that ALD biomarkers can be produced through AI-powered analyses of "omics" data in combination with other clinical, histological, and laboratory parameters.

Unmet need: Identify the risk of return to alcohol use

Sustained remission of alcohol use has repeatedly been shown to be a strong predictor for survival and recompensation in ALD.[39,40] The ability to identify which patients are most vulnerable to alcohol relapse and at which time points along their disease continuum would have far-reaching benefits, from preventing cirrhosis-related hospital readmissions, to preserving allograft survival in patients undergoing LT for ALD.

AI-driven solutions. Disease recurrence is common after LT for most indications and is a major concern in ALD if patients return to harmful alcohol use. Thus, efforts to identify intervenable psychosocial and behavioral risk factors for relapse are of great importance to liver graft and overall survival. A recent study sought to achieve this aim using the multicenter American Consortium of Early Liver Transplantation for Alcohol-Associated Hepatitis (ACCELERATE-AH) database and MLAs derived from narrative psychosocial evaluations recorded in these patients. Variables related to social support and concomitant substance use emerged as the strongest predictors for post-LT return to alcohol use. The intended uses of these findings are to ensure timely interventions to patients in danger of recidivism and optimize LT selection practices. To this latter end, AI algorithms have already been proposed with deep learning techniques to automize LT listing decisions to which psychosocial parameters could be added.[41]

Novel digital data sources could further aid in real-time prediction and prevention of return to alcohol use. A recent study illustrating this concept by Wu and colleagues showed that smartphone sensors may serve as surrogate measures of alcohol craving as it relates to mood. Through digital phenotyping, the authors identified that various mood types and sensor features related to location and mobility were associated with alcohol cravings. Certain sensor features were also noted to be associated with relapse at 90 days, though none of the features achieved statistical significance after adjusting for multiple sensor features. Nevertheless, this signal between smartphone data and relapse demonstrated the feasibility of using novel data from readily available digital technologies as potential markers of disease and prediction of outcomes.[18]

The studies described highlight how AI has already contributed to enhancing prognostication in ALD. An even greater opportunity lies with multimodal integration. For example, an MLA simultaneously incorporates genomics data and smartphone-derived sensor data or a comprehensive molecular signature composing multiomics data. These are combinations of data and patterns impossible to ascertain without AI computing power (Figure 1).

Management

Unmet need: Achievement of AUD remission and prevention of relapse

An area in which we remain the most limited is the management of ALD. While we appropriately recognize that AUD treatment is an essential component, there has been little advancement in pharmacological agents approved to help patients combat cravings. Existing medications for AUD, such as naltrexone and

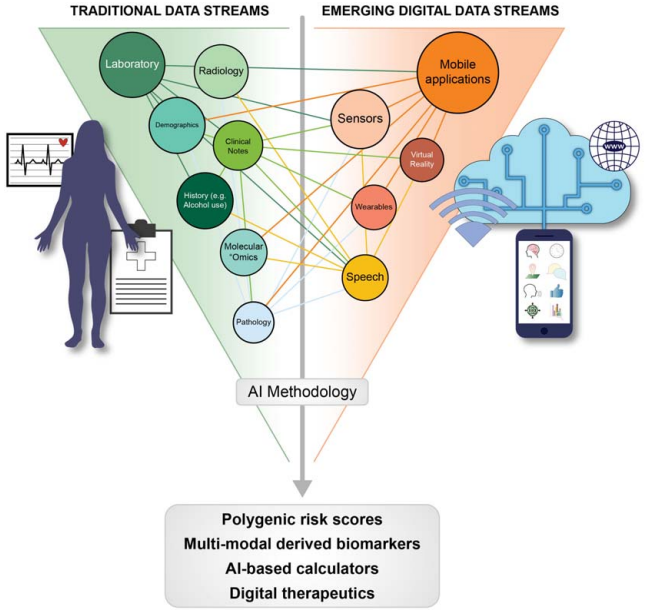

FIGURE 1 Multimodal data integration: Multiple sources of data aid in the diagnosis and prognosis of ALD. Traditional data sources, depicted on the left panel, typically require patients to be seen in physical encounters either during a hospitalization or clinic visit. Emerging digital data sources, depicted on the right panel, transform this paradigm by enabling continuous monitoring and remote data collection, offering insights into patient health outside of conventional clinical settings. Maximizing the integration of data streams across diverse sources enhances our diagnostic and prognostic abilities significantly, highlighting the importance of combining information from various modalities for more comprehensive insights into ALD. Abbreviation: ALD, alcohol-associated liver disease.

acamprosate, can prevent return to harmful drinking and progression of ALD,[42] though they are consistently underprescribed.[43] Behavioral interventions, either paired with medications for AUD or used independently, are more effective, but our current delivery systems make accessibility and scalability difficult for populations with limited access to care. Recently, multidisciplinary clinics have been developed involving psychiatry and addiction specialists alongside hepatologists. These models center on colocalization of AUD-ALD care and there has been published success in the patients served by these clinics.[44,45] One major obstacle to their wider implementation is the degree of resources and work force they require. Furthermore, our existing pharmacotherapies and behavioral interventions adhere to a generic, one-size-fits-all model, lacking a personalized approach.

AI-driven solutions. Digital technologies are growing in usage through patient-facing health care applications and are uniquely equipped to help patients seeking to quit alcohol use. From mobile health apps and wearable devices to telehealth platforms, these technologies have the potential to empower patients with real-time data collection and delivery of treatment interventions. Recently, studies have evaluated the feasibility and usability of such devices (Table 3). In a study by DiMartini and colleagues, 27 patients with ALD were enrolled and provided with a wrist transdermal alcohol biosensor to wear for 3 months. While the study was not powered for adequate subanalysis, the authors showed that 2 individuals with the highest severity of AUD and heaviest alcohol consumption had the lowest adherence rate when wearing the biosensor.[14]

In the study previously described by Wu and colleagues, smartphones were demonstrated to offer an innovative solution for collecting markers of behavior in ALD. Understanding such digital biomarkers can further guide the collection of real-time data and delivery of treatment interventions to connect individuals to care before they experience a return to drinking.[14,18]

Early efforts are in the process of using digital applications to help patients with ALD seek AUD treatment[16,17] (Table 3). Overall, recruitment and retention rates have been modest in pilot studies, though participants have consistently viewed web and mobile applications as useable and favorable. In a feasibility study of a single session online or mobile application to improve engagement in AUD treatment ("MAIN-ART" Michigan Alcohol Improvement Network-Alcohol Reduction and Treatment), the recruitment rate was 46%, and the retention rate was 65% at 6 months[16]; however, acceptability was rated at over 90%.

Only one study thus far has attempted to quantify the ability of digital technology to reduce alcohol use among patients with ALD. Mehta and colleagues trademarked a custom-built mobile application called AlcoChange that uses nudge behavioral therapy techniques to promote alcohol cessation. In a proof-of-concept study of 41 patients with ALD, adherence to app usage correlated with a significant reduction in alcohol use ($p = 0.029$), a higher rate of abstinence at 3 months, and a reduced risk of alcohol-associated readmission in 12 months ($p = 0.008$).[15]

Digital technologies offer numerous advantages in terms of patient engagement and empowerment. In contrast to conventional pharmacotherapies, they pose fewer physical adverse effects. However, it is essential to note that digital tools carry the potential for technological malfunctions and unintended secondary consequences. As reflected in the retention rates of recent studies, the requirement of frequent active participation assessments, for example, can lead to response fatigue.

SPECIAL CONSIDERATIONS

Researchers, clinicians, developers, and implementors of AI-driven solutions for ALD have the moral imperative to ensure their reliability, equity, and practicality. Accordingly, it is crucial to recognize that AI will not replace the need for human involvement as physicians and researchers; instead, AI will primarily serve as an

adjunct to enhance patient care in ALD. A human presence remains vital throughout this process, ensuring ethical use and interpretation of AI-generated insights. ALD inherently includes a behavioral component where provider empathy plays a significant role in establishing trust and connection with patients, an area where human capacity remains superior to AI. The many challenges and limitations brought by AI are not novel to ALD. However, by appropriately acknowledging potential disparities and operationalizing strategies to overcome them, ALD could inform and improve AI in a reciprocal fashion (Table 4).

Bias

The advancement of study in diseases affected by alcohol and substance use disorders has historically faced discrimination and neglect, reflected in ALD specifically through the sustained use of stigmatizing language,[46] underfunding, and the scarcity of patient-centered resources.[47] Seeking out and cultivating AI and digital approaches to diagnose and treat AUD-ALD is itself a powerful form of advocacy as it assigns research priority to issues that affect many underserved populations.[48] However, there is also the undesirable prospect of big data approaches perpetuating existing biases on a larger scale.

Relationships between social determinants of health and alcohol consumption have been neither linear nor predictable.[49] Certain minority populations carry a disproportional burden with ALD, such as Hispanic, American Indian, and Alaska Native groups.[50] Genetic predispositions, typified by polymorphisms in patatin-like phospholipase domain-containing protein 3 (PNPLA3), further contribute to the rapid progression of steatosis and overall ALD risk, especially in Hispanic individuals.[51] Through the COVID-19 pandemic, alcohol consumption increased the most among Black individuals and females,[52] the same 2 subgroups that have the least access to LT for ALD.[53] There are also sex differences in alcohol metabolism that contribute to females presenting with ALD despite lower overall alcohol consumption.[54]

Given these differences, prediction models and decision tools built by AI need to consider the impact of conceivable modifiers such as sex, gender, established genetic polymorphisms, race, and ethnicity. The ideal AI-developed model for the diagnosis and prognosis of ALD would be able to balance biological susceptibility and social determinants of health. At a minimum, transparency of how AI algorithms are created, tested, and disseminated is crucial. As AI prognostic models seek routine use in ALD, possible biased outcomes should be evaluated at every step of the machine-learning pipeline, both before and after deployment. Follow-up studies examining outcomes such as access to care and LT will be important, with adjustments inevitably required to ensure equity across sex and ethnicity.

TABLE 4 Benefits, risks, and mitigation strategies for the use of AI in ALD

	Benefits	Risks	Mitigation Strategies
Diagnostic accuracy	AI can enhance the detection of AUD/ALD by analyzing complex patterns in large data sets, leading to earlier and more accurate diagnoses.	AI models may replicate or amplify existing biases in data, potentially leading to misdiagnosis.	Use diversified training data sets that include a wide range of demographic and clinical characteristics. Regularly update and audit AI models to ensure accuracy and fairness.
Personalized treatment	AI enables the customization of treatment plans based on individual patient data, improving treatment efficacy and patient outcomes.	There is a risk of privacy breaches with the use of personal data in AI systems.	Implement robust data encryption and access controls. Ensure compliance with data protection regulations like GDPR or HIPAA.
Cost efficiency	By automating routine tasks and improving resource allocation, AI can reduce health care costs associated with AUD/ALD and increase scalability.	Dependence on AI could lead to reduced involvement of health care professionals.	Develop policies that promote the complementary use of AI and human expertise, ensuring AI supports rather than replaces human expertise.
Clinical research	AI can accelerate research by efficiently processing and analyzing large data sets, identifying new potential therapeutic targets.	Complex AI models may produce “black box” decisions that are difficult to interpret, complicating clinical decision-making.	Incorporate explainability frameworks in AI development. Train health care professionals in AI usage and interpretation. Recommend AI systems be “glass box” and not “black box”
Long-term monitoring	AI systems can continuously monitor patients, providing real-time insights into patient health and early warnings of disease progression.	Continuous monitoring raises concerns about patient privacy and the potential misuse of surveillance data.	Clearly communicate the purpose and extent of monitoring to patients and obtain informed consent. Use anonymization techniques to protect patient identities.

Abbreviations: ALD, alcohol-associated liver disease; GDPR General Data Protection Regulation.

Infrastructure

Decisions to focus research efforts on AI and digital technologies in ALD are accompanied by a commitment to building the necessary infrastructure. Willingness among individual researchers and institutions to collaborate and share access to data will accelerate the speed and impact AI is able to have on the field. In ALD, consortiums for AH, such as AlcHepNet[55] and GlobalAlcHep,[33] have already been formed with large repositories to aggregate and harmonize large-scale data. The Million Veteran Program and the Medical Information Mart for Intensive Care III (MIMIC-III) are other examples of national, multimodal data sets. The digitization of histopathological and radiological data has further facilitated the ease of making data available that can be used simultaneously for different purposes. Strategic investments and policy changes can also assist in funding and fostering efforts to improve data sharing, data storage, and advanced analytic platforms.

Clinicians dually trained in addiction medicine and hepatology have a unique skill set to bring to AUD-ALD.[56] Similarly, academic hepatologists well versed in computational science and informatics will be positioned well for earlier implementation of AI to ALD research. In addition, there will remain a need for dedicated data scientists and biostatisticians to be part of the inter-disciplinary team.

Standardization and interpretability

There is a current lack of standardization in the use of AI in clinical research, posing challenges for comparison and reproducibility across studies. Without a unified framework or set of benchmarks for AI platforms in ALD studies, questions remain unanswered regarding what should be established as the "gold standard" in ALD for diagnostic or prognostic comparators.

While machine-learning models offer high accuracy, their nonlinear relationships often lack explainability. Addressing the "curse of dimensionality,"[57] particularly in risk prediction scores, is crucial for building trust and overcoming inherent barriers. Balancing simplicity and convenience against the complexity of decision-making is a challenge that requires careful navigation.

To address these issues, collaborative initiatives aimed at establishing guidelines similar to those set for clinical trial endpoints will be invaluable. These efforts can help ensure consistency and comparability across studies, enhance the interpretability of AI-driven insights, and ultimately improve patient care outcomes in ALD.

Implementation and regulation

Ethical and privacy concerns, particularly in the context of user-generated data from digital technologies not subject to regulations like the HIPAA, represent

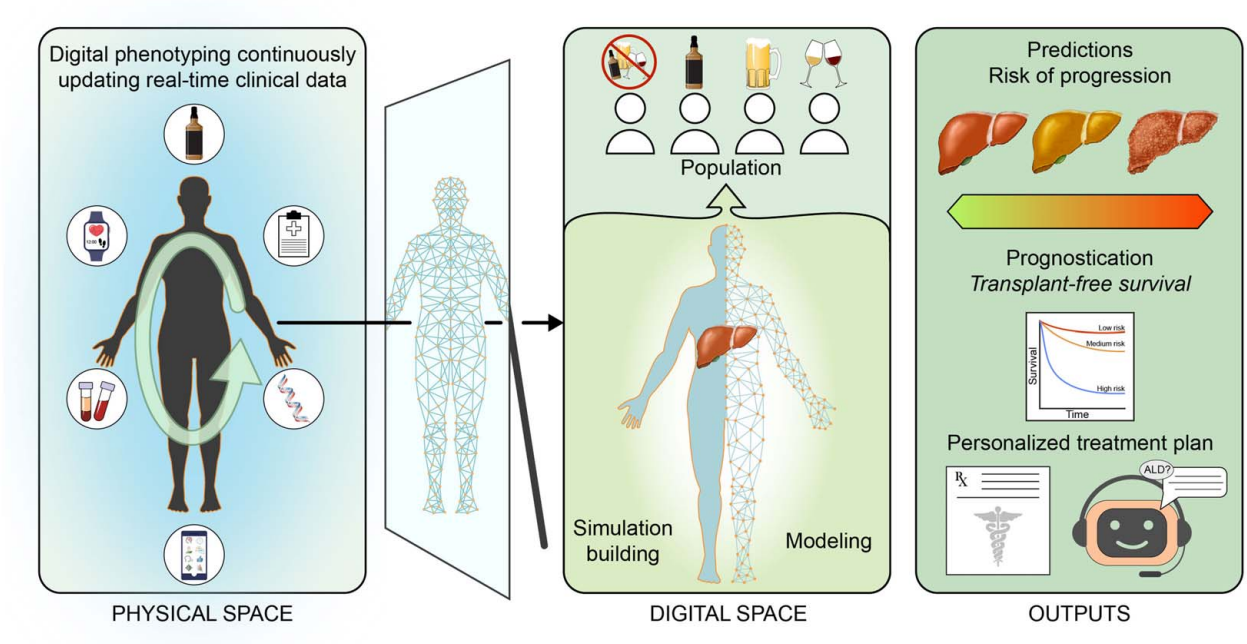

FIGURE 2 Conceptual framework of digital twin for ALD. The image illustrates the process of collecting digital phenotyping data from a model patient with alcohol-associated liver disease in a physical space, which is then integrated into the digital space. AI analyzes these data alongside information from other patients at various disease stages. The digital twin interface uses these data to predict the patient's risk of disease progression, transplant-free survival, and to tailor personalized treatment plans for managing AUD and preventing relapse. Portrayed are three examples of digital twin–derived simulations. Abbreviation: ALD, alcohol-associated liver disease.

uncharted territory. Securing patient safeguards and Federal Drug Administration (FDA) approvals for digital technologies are imperative steps for the responsible implementation of AI in ALD research.[58] There are further legal and commercial implications of using increasingly granular patient data that will mandate robust legislation. For example, transparent data use agreements that require patient consent can provide clear information on how data will be used, stored, and distributed.

In addition to ethical considerations, effective implementation of AI in ALD research requires addressing technical challenges, such as data interoperability and integration with existing health care systems. A multistakeholder approach will help encourage innovation while ensuring patient safety, privacy, and equitable access to AI-enabled health care services.[58,59]

PROMISE OF AI IN ALD

It is evident that machine-learning approaches are poised to become the standard for statistical approaches in clinical research, ALD included. Digital technologies are gaining traction as well in their adjunctive use to face-to-face clinical care. High-level machine intelligence is evolving with considerable speed, such that reviews like this one can capture only momentary snapshots of its progress. A significant benefit to both AI and digital technologies has been their ability to foster creativity, enabling the discovery of unconventional approaches and unexpected tools to solve health care problems. We will next discuss AI domains that will be extremely beneficial to, but remain unexplored, in ALD. We make predictions based on knowledge of how AI is being used within other medical subspecialties as well as in sectors outside of medicine.

POPULATION-LEVEL RESEARCH IN AUD-ALD

ALD stands apart from infectious causes of liver disease like hepatitis B and C as a noncommunicable etiology. However, as a leading preventable contributor to death, there is utility in understanding geographic areas and populations that are more at risk, whether due to proximity of alcohol outlets, targeted advertising, or long-standing structural and systematic discriminations predisposing to higher rates of substance use and addiction. Similar to how it was used for COVID-19 tracking, wastewater-based epidemiology[60,61] is a unique strategy to uncover community trends and hotspots in alcohol consumption. Population-level trends related to AUD-ALD can also be ascertained through the mining of social media. In the addiction literature, for instance, language phenotypes from social media posts have been able to predict short-term outcomes of abstinence, relapse, and treatment dropout.[62] As AI-based linguistic capabilities become more sophisticated, so could the automation of assessment and intervention tools with social media as the primary input data. Together, real-time population-level data from sources such as wastewater-based epidemiology or social media could inspire local, state, and national health alcohol policy changes guided and monitored through AI-powered platforms.

LARGE LANGUAGE MODELS

Large language models (LLMs), exemplified by models like OpenAI's Chat Generative Pre-trained Transformer (ChatGPT), demonstrate remarkable aptitude for generating creative content. Their proficiency extends to natural language processing, a crucial aspect in the extraction of structured data elements from unstructured sources like clinical notes, radiology reports, or pathology images.

Traditional research methods using national databases or probing electronic health records frequently encounter the limitations of diagnostic coding systems, such as the *ICD-9* and *ICD-10*. This challenge is no different in ALD, particularly in AH.[63] LLMs could also help ALD research contend with nomenclature changes and terminology inconsistencies.

Ge et al have developed a liver-disease–specific LLM called "LiVersa" that was trained on clinical practice guidelines from the American Association for the Study of Liver Diseases (AASLD) pertaining to HCC.[64] An analogous LLM for ALD could help with information retrieval, summarizing research findings, and guidelines for clinicians.

For patients, LLMs can become personal assistants, providing a user-friendly dynamic interface that can answer questions about a diagnosis of ALD or transform into a virtual health coach/addiction counselor.

Despite their impressive abilities, LLMs have present limitations like "parroting," where they generate convincing text without genuine comprehension, and "hallucinations," producing incorrect or nonsensical output. LLMs created to help educate or instruct patients with AUD-ALD will need to be adequately tested and verified before widespread use. Inaccurate outputs with LLMs in medical use could have detrimental legal and clinical consequences.

VIRTUAL REALITY

Virtual reality (VR) is a technology that immerses users in a simulated environment. VR itself is an entity for digital therapeutics. One type of VR therapy is through cue-exposure. Patients are repeatedly exposed to disease-relevant, realistic life scenes with multiple sensory inputs

with the goal of conditioning a psychophysiological response. A recent study looked into the ability of VR Cue-exposure therapy to reduce alcohol cravings in patients with AUD.[5] The intervention was VR-Cue-exposure therapy in the form of a video that simulated a scenario where close friends were drinking alcohol for a celebratory occasion. Patients watched the video while receiving olfactory stimulation with real alcohol and while a biofeedback device collected vital signs and skin conductance information. With repeated VR-Cue-exposure therapy sessions, the study group ultimately had fewer cravings and physiological responses to alcohol.[65] Further applications of VR into ALD may offer innovative avenues for patient education, behavior modification, and therapeutic interventions.

DIGITAL TWIN

The concept of a "digital twin," though remaining an abstract idea in medicine, has found practical application in other industries like aerospace. In health care, a digital twin involves constructing a virtual replica of an individual patient by vertically integrating their available lifestyle, clinical, and laboratory data.[57] Through horizontal integration, digital twins from thousands to millions of patients with similar disease processes and demographics can be analyzed collectively. AI algorithms can continuously update and simulate a digital twin's health status based on personal and comparative factors, potentially offering highly individualized insights into disease progression and/or risk assessments.[66,67]

In ALD, digital twins could facilitate the recalibration of individual risk profiles, knowing that underlying AUD can be a relapsing-remitting process. For example, in a patient achieving sustained alcohol remission, the digital twin–powered simulation could accurately predict recompensation of liver disease. A separate patient's digital twin may alert a higher risk of pending alcohol relapse using passive sensor data that is then used to deploy timely interventions, which may involve communication with the hepatology health care team or engagement of digital technology like a virtual health coach (Figure 2).

Digital twin represents the cumulative supremacy of multimodal data integration, digital technologies, and AI-powered analytics for real-time, continuous, high-precision outputs (Figure 2). Yet, the digital twin represents still one part of a larger digital medical revolution that includes digital clinical trials, personalized chatbots, and the conceivable digitization of the patient experience from home to hospital.

CONCLUSIONS

In this review, we summarized the current landscape of the application of AI and digital technologies for the care of patients with ALD. Early work in this space has used AI methodologies for single or mixed streams of data. As the field progresses, we anticipate multimodal data integration with the application of advanced computing technologies will improve the diagnosis, prediction, and management of ALD and AUD. While AI methodologies —spanning advanced machine-learning applications, LLMs, and digital therapeutics—hold tremendous promise, their successful implementation will require addressing biases, technical challenges, regulatory frameworks, and ensuring ethical data practices.

AUTHOR CONTRIBUTIONS

Praveena Narayanan: conceptualization, investigation, visualization, writing—original draft, and writing—review and editing; Tiffany Wu: visualization, conceptualization, and writing—review and editing; Vijay H. Shah: supervision and writing—review and editing; Brenda L. Curtis: conceptualization, supervision, and writing—review and editing.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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