Transforming Screening, Risk Stratification, and Treatment Optimization in Chronic Liver Disease Through Data Science and Translational Innovation

Tamer A. Addissouky [1,2,3], Majeed M. A. Ali [1], Ibrahim El Tantawy El Sayed [2], Yuliang Wang [4]

[1]Al-Hadi University College, Baghdad, Iraq.
[2]Department of Biochemistry, Science Faculty, Menoufia University, Menoufia, Egypt
[3]MLS ministry of health, Alexandria, Egypt.
[4]Joint International Research Laboratory of Metabolic and Developmental Sciences, Key Laboratory of Urban Agriculture (South) Ministry of Agriculture, Plant Biotechnology Research Center, Fudan-SJTU-Nottingham Plant Biotechnology R&D Center, School of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai, China

Corresponding Author:
Tamer A. Addissouky, Al-HADI University College, Baghdad. Iraq. - Department of Biochemistry, Science Faculty, Menoufia University, Egypt. - MLS ministry of health, Alexandria, Egypt. - MLS, ASCP, USA. Email: tedesoky@gmail.com; tedesoky@science.menofia.edu.eg; https://orcid.org/0000-0003-3797-9155

ABSTRACT

Background: *Chronic liver diseases like hepatocellular carcinoma (HCC) and primary biliary cholangitis (PBC) continue to face challenges in prognosis, treatment optimization, and understanding of mechanisms. Innovations in data integration and analytics could address these gaps. This review synthesizes innovative research improving prediction, understanding, detection, treatment, and translation in chronic liver disease.*

Method: *Multiple studies leveraged approaches like machine learning and genomics. MAPS-CRAFITY integrates clinical variables, imaging, and AFP to predict immunotherapy/TKI response in HCC. Transformer modeling of RFA data improves outcome prediction to guide management. Genome-wide association analysis revealed IL21R as a PBC susceptibility gene in Chinese cohorts. Quantifying childhood MAFLD informs screening needs. Supporting the use of G6PD-deficient liver donors enables transplantation access expansion through risk stratification. Updating Baveno criteria enhances PBC prognosis. An HCC prognostic score identifies optimal RFA candidates.*

Conclusion: *Recent research leverages diverse data types, genetics, imaging, and machine learning to develop integrated predictive systems that allow more personalized therapy selection. Elucidating molecular pathways provides therapeutic targets and prognostic biomarkers. Evidence-based screening and risk models facilitate delivering tailored interventions. Optimization of current modalities through prognostic validation and patient selection improves real-world effectiveness. Multifaceted modern research approaches promise to address unmet needs and transform hepatology care.*

Keywords: *Artificial intelligence; Endothelial dysfunction; Immunogenetics; Metabolomics; Personalized medicine*

INTRODUCTION

Recent years have witnessed remarkable progress in hepatology, but significant challenges and unmet needs persist. [1] Chronic liver diseases impose a major public health burden, with hepatocellular carcinoma (HCC) ranking as the fourth leading cause of cancer mortality worldwide. [2] Deficiencies in risk evaluation, screening, prognosis, and therapy optimization contribute to suboptimal patient care. However, the hepatology field stands ready to make major strides given emerging research and new tools enabling enhanced comprehension of liver disease mechanisms, superior prognostic accuracy, and more tailored treatment delivery. Translating these innovations from bench to bedside will be key to improving clinical management and outcomes in patients with liver disorders. [3] One of the most pressing hepatology needs is boosting prognostic precision and treatment selection for HCC. As the most common primary liver cancer, HCC accounts for substantial cancer mortality. [4] Optimizing and individualizing HCC therapies necessitates accurately predicting treatment response and overall prognosis. [5] Studies have shown prognostic utility for biomarkers like alpha-fetoprotein (AFP) and imaging characteristics, yet combining multiple modalities could further refine outcome prediction. One example is the MAPS-CRAFITY score, which assimilates clinical variables, AFP levels, and CT/MRI findings into a system predicting immunotherapy and targeted therapy response in advanced HCC. Machine learning approaches including transformer models also exhibit promise for dissecting complex datasets to determine HCC prognosis after locoregional treatments such as radiofrequency ablation (RFA). [6-10]

By harnessing diverse data sources, robust predictive systems can be developed to direct treatment decisions and follow-up care. In addition to prediction, elucidating disease mechanisms is fundamental for identifying therapeutic targets and improving models. Primary biliary cholangitis (PBC), an autoimmune liver disease with unclear etiology, represents a prime example. Though human studies are lacking, emerging preclinical evidence implies certain vaccines may mitigate aspects of metabolic dysfunction underlying MAFLD pathology. Warranting future exploration as MAFLD therapeutic strategies are targeted vaccination approaches aiming to beneficially modulate gut microbiota, hepatic and systemic inflammation, and insulin resistance. [11] Genome-wide association studies and genetic screening have revealed variants potentially governing susceptibility, including IL21R as a candidate PBC gene in Chinese cohorts. Characterizing genetic contributors furnishes clues into molecular pathways subject to pharmaceutical manipulation. Moreover, investigating pathological processes like portal hypertension endothelial dysfunction provides insights into disease progression. Dysregulated von Willebrand factor processing and elevated antigen levels likely mediate cirrhosis and portal hypertension complications through impaired angiogenesis. Knowledge gained by probing molecular aberrations in liver diseases like PBC and cirrhosis can ultimately inform management strategies. [12] Another active hepatology research area involves optimizing care delivery through screening and risk stratification. For example, growing recognition exists that metabolic-associated fatty liver disease (MAFLD) can manifest in childhood and cause substantial morbidity if untreated. [13] Studies quantifying MAFLD prevalence and associated factors in pediatric cohorts underscore the necessity of early identification and intervention. Adult liver condition management could also benefit from enhanced risk models to expand treatment access [14-16]. In liver transplantation, appropriate categorization of donor graft quality enables the utilization of extended criteria donors without compromising recipient outcomes. Propensity score matching has verified comparable outcomes with grafts from glucose-6-phosphate dehydrogenase deficient donors, enabling donor pool expansion through evidence-based acceptance criteria. [17]

Finally, a fundamental aim of hepatology research is refining available therapies through rigorous optimization. Although novel agents remain desirable, fine-tuning current modalities can also improve outcomes. For PBC, recent work validated that liver stiffness cutoffs in Baveno VI criteria accurately identify patients at increased risk of adverse events, supporting broader liver elastography implementation for dynamic PBC prognostication. Determining optimal candidates for interventions is also impactful, as demonstrated in HCC studies identifying tumor factors associated with RFA success. By pinpointing patients likely to have a complete response, appropriate patient selection eases treatment burdens. With limited curative options still characterizing the field, any strategy expanding therapy eligibility and efficacy offers immense advantages. [18]

Despite progress made, critical voids remain in prognosis, therapy optimization, and mechanistic understanding of chronic liver diseases. This review synthesizes recent innovative research leveraging diverse data types and analytics to address these needs through predictive modeling, genetic analysis, novel screening methodologies, treatment refinements, and

pathological pathway elucidation. It furnishes an updated perspective on translational efforts poised to transform clinical management if thoughtfully implemented while steering future research toward addressing remaining knowledge gaps using similar multifaceted approaches.

PREDICTIVE MODELS IN HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is a major contributor to cancer mortality worldwide. As the most common primary liver malignancy, HCC represents a global health threat. The asymptomatic nature of early HCC coupled with limited curative therapeutic options contribute to high mortality rates. However, the prognosis and treatment response for HCC patients can be heterogeneous based on tumor characteristics and liver function. Accurately prognosticating outcomes and predicting therapy response would allow individualization of care to improve survival. Recent advances in integrating clinical data through the use of predictive models hold promise for guiding the management of HCC. One major focus has been the development of tools to anticipate treatment efficacy and optimize first-line therapy selection. [19-20]

The MAPS-CRAFITY model highlights the potential of assimilating diverse data types into integrated predictive systems. Machine learning offers opportunities to analyze multifaceted datasets and identify complex patterns. A recent application involved training transformer models on HCC cohorts who underwent radiofrequency ablation (RFA). By processing information on tumor number, size, location, and other features, the system could accurately predict 3-year overall survival post-RFA. This could facilitate selecting patients likely to have a durable response, as incomplete thermal ablation is associated with local recurrence and poor outcomes. Beyond treatment selection, predictive models like these can also aid post-procedure monitoring, providing individual risk estimates to guide follow-up intensity. [21]

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UNDERSTANDING DISEASE MECHANISMS

Metabolic dysfunction underlies the pathogenesis of metabolic-associated fatty liver disease (MAFLD), encompassing interlinked factors like aberrant lipid metabolism, insulin resistance, and diabetes. [24] Its development implicates numerous interlinked factors including oxidative stress, derangements in lipid metabolism, insulin resistance, inflammation, gut microbiota imbalance, and immune dysregulation. The interplay of these molecular aberrations and systemic metabolic abnormalities contributes to hepatic lipotoxicity, activation of fibrogenic pathways, and cumulative liver damage as depicted in **Figure 1**. [25]

Hepatic steatosis demonstrated through biomarkers, imaging, or histology, is characteristic of both MAFLD and NAFLD when alcohol and other liver diseases are excluded. [26] However, MAFLD can be differentiated from NAFLD by additional indicators of metabolic dysregulation like central adiposity, hypertension, dyslipidemia with low HDL and high triglycerides, elevated fasting blood glucose or hemoglobin A1c, insulin resistance as measured by HOMA-IR, and increased inflammatory markers like C-reactive protein. [27] As depicted in **Figure 2**, the presence of overweight/obesity and/or type 2 diabetes specifically points to an MAFLD diagnosis as opposed to plain NAFLD. [28]

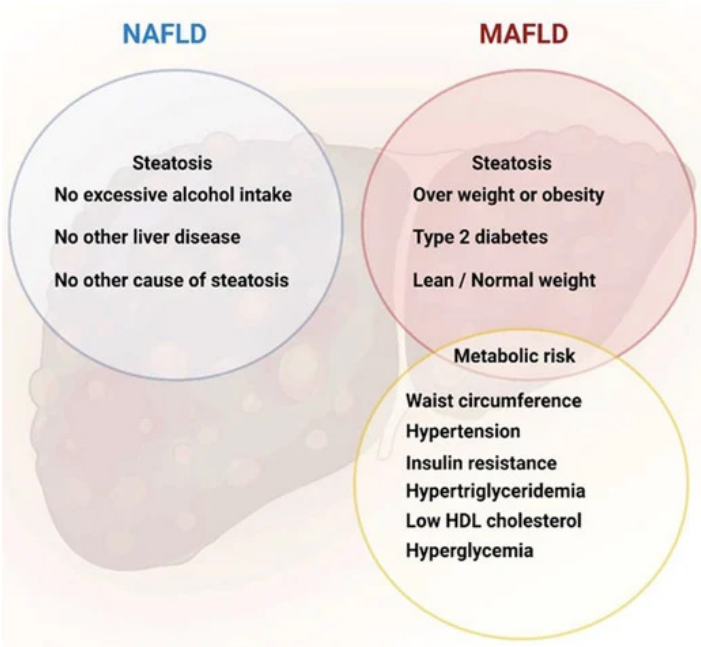

Fig. 1. Distinguishing features of NAFLD and MAFLD [25]

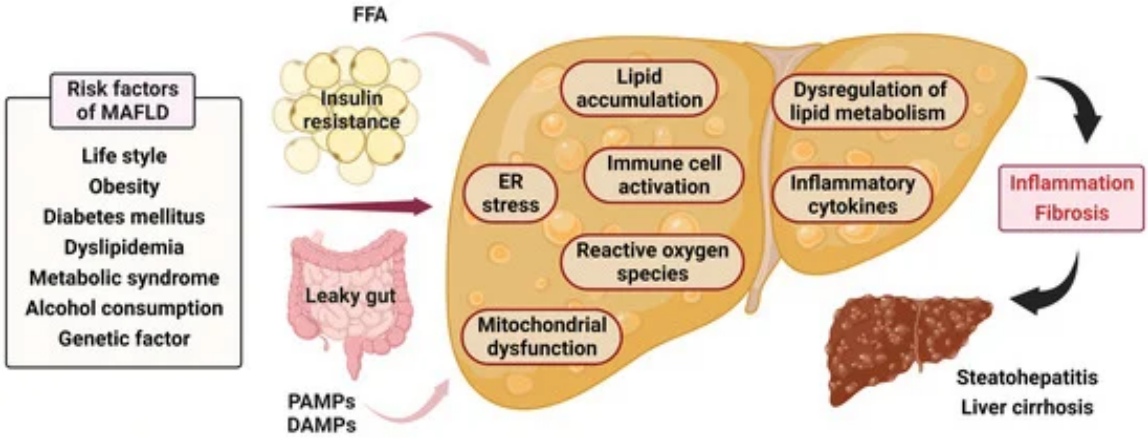

Fig. 2. Pathophysiology of MAFLD [28]

Emerging evidence suggests H. pylori infection may contribute to the pathogenesis and progression of non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) through induction of insulin resistance, inflammation, and dysbiosis of gut microbiota, but more research is warranted to elucidate the mechanisms linking this common bacteria to hepatic steatosis and confirm the efficacy of H. pylori eradication for ameliorating metabolic liver injury. [29] Careful phenotypic characterization thus facilitates distinguishing these related but distinct fat-accumulation liver conditions.

Elucidating the fundamental mechanisms underlying liver diseases is essential to guide the development of targeted therapies and improve prognostic models. Research on the genetic drivers of primary biliary cholangitis and the role of endothelial dysfunction in portal hypertension has uncovered molecular processes that contribute to pathogenesis. Characterizing these aberrant pathways provides potential therapeutic targets and biomarkers that could transform disease management. [30] Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease characterized by the destruction of small intrahepatic bile ducts. Although environmental triggers likely play a role, gene variants that disrupt immune tolerance are hypothesized to be major PBC susceptibility factors. Genome-wide association studies have uncovered dozens of genetic loci associated with PBC, including human leukocyte antigen (HLA) genes regulating antigen presentation. Confirming causative variants has proven challenging, however, as risk loci often contain multiple genes. Nevertheless, the identification of high-confidence PBC genes could clarify pathogenesis and suggest modifiable targets. A recent Chinese genome study implicated interferon regulatory factor

2 binding protein 2 (IRF2BP2) and interleukin 21 receptor (IL21R) as likely PBC susceptibility genes. IL21R is notable as the receptor for cytokine IL-21, which promotes B and T cell activation. The study confirmed increased IL21R expression in PBC liver samples, suggesting aberrant IL-21 signaling drives autoimmunity. These genetic clues provide molecular context to inform the development of future immunomodulatory treatments. [31]

Beyond elucidating PBC pathogenesis, genetics may also predict prognosis. PBC displays heterogeneous progression, with some patients experiencing rapid declines in liver function. Variants in genes regulating immune activation like IL12RB could modulate disease severity. In a Chinese cohort, an IL12RB polymorphism correlated with earlier PBC onset, higher alkaline phosphatase levels, and increased risk of adverse outcomes. Genotyping thus could help prognosticate clinical course at diagnosis. [32] Furthermore, the genetic underpinnings of PBC complications like hepatic osteodystrophy require a better definition. Associations between disease severity and vitamin D pathway gene polymorphisms support a genetic component in osteopenia pathogenesis. Overall, analyses of genetic contributors to PBC susceptibility, progression markers, and complications will continue illuminating biological pathways that dictate outcomes. [33-37]

While immune dysregulation is implicated in PBC, endothelial dysfunction is a key mediator of portal hypertension and its complications. Portal hypertension arises from architectural distortions and increased resistance to portal blood flow. Hemodynamic forces trigger angiogenesis to shunt portal blood into the systemic circulation, perpetuating complications like variceal hemorrhage and ascites. However, the aberrant new vessel formation is dysfunctional, likely due to endothelial impairment. A critical mediator is the von Willebrand factor (VWF), a multimeric glycoprotein that controls clot formation and modulates angiogenesis. In cirrhosis, reduced ADAMTS13 activity leads to the accumulation of ultra-large VWF multimers that paradoxically induce abnormal angiogenesis. [38]

Studies suggest VWF processing could be a valuable prognostic marker in advanced chronic liver disease. In cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt procedures, those with PVT had significantly higher VWF antigen levels. This implies measuring VWF can help predict the risk of thrombosis, a feared complication that can preclude transplantation. VWF also independently predicted the development of clinical decompensation events like ascites and variceal bleeding. Assessing endothelial dysfunction via VWF thus may enable dynamic prognostication and earlier intervention. Moving forward, a better understanding of portal hypertension pathophysiology could identify combined biochemical, imaging, and clinical predictors of decompensation amenable to machine learning models. [39] **Table 1** summarizes key genetic associations reported for primary biliary cholangitis (PBC).

SCREENING AND RISK STRATIFICATION

Optimizing the delivery of hepatology care requires accurately screening patients to identify those requiring intervention, as well as properly stratifying risks to select appropriate management. Research on defining metabolic-associated fatty liver disease (MAFLD) prevalence and associations in children demonstrates the importance of early screening. Meanwhile, studies supporting the safety of G6PD-deficient liver donors highlight how evidence-based risk criteria allow care personalization. Applying insights from recent advances could greatly enhance screening and risk

Table 1. Key genetic associations for primary biliary cholangitis (PBC):

Gene/Locus	Polymorphism(s)	Proposed Functional Role	Impact on PBC
IL12RB	rs3790567	Cytokine receptor subunit regulates IL-12 induced IFN-γ production	Associated with earlier PBC onset and higher disease severity
IL21R	rs907715	Cytokine receptor for IL-21 activates lymphocytes	Implicated as PBC susceptibility gene in Chinese cohorts
HLA region	Various HLA alleles	Antigen presentation, immune activation	Linked to PBC susceptibility, specific alleles associated with prognosis
IRF2BP2	rs11556355	Transcriptional corepressor regulates interferon signaling	Candidate PBC susceptibility gene in Han Chinese
CLEC16A	rs12444268	C-type lectin domain family 16 member A, immunomodulatory	PBC susceptibility, validated across cohorts
STAT4	rs7574865	Signal transducer and activator of transcription 4, mediates IL-12 signaling	Associated with PBC susceptibility and more rapid progression
DENND1B	rs12085620	DENN domain containing 1B, trafficking regulatory protein	PBC risk locus requires further functional validation

stratification paradigms to improve outcomes. [40] MAFLD has emerged as the most common chronic liver disorder in children, paralleling rising pediatric obesity rates. However, estimates of MAFLD prevalence have been hindered by a lack of definitive diagnostic criteria, with reported rates of 2-17% based largely on ultrasound or liver enzyme elevation. More concerning is that pediatric MAFLD can advance to non-alcoholic steatohepatitis (NASH), fibrosis, and even end-stage liver disease requiring transplantation. Longitudinal cohorts have proven instrumental in elucidating the burden of MAFLD and its hepatic and metabolic consequences in at-risk youth. For instance, a Shanghai study quantified MAFLD incidence at 7% by MRI-proton density fat fraction. Importantly, new cases already displayed cardiometabolic aberrations like dyslipidemia and hyperinsulinemia, affirming the need for prompt diagnosis and intervention. [41]

Characterizing the relationships between MAFLD and metabolic traits in pediatric populations also highlights pathways contributing to pathogenesis. A European registry analysis verified strong associations between MAFLD and indexes of adiposity like waist circumference and visceral fat. The disproportionate rise in MAFLD prevalence relative to obesity rates suggests a complex interplay between lifestyle factors, fat distribution, and inherent susceptibility. Hispanic youth may have a higher risk, so monitoring based on ethnicity could enhance screening sensitivity. Just as screening aims to optimize patient identification, accurate risk stratification is imperative when assessing donors and recipients for liver transplantation. Model for end-stage liver disease (MELD) scoring for organ allocation has allowed equitable access by stratifying risk. Still, room for improvement remains, as highlighted by recent work on outcomes utilizing grafts from glucose-6-phosphate dehydrogenase deficient (G6PD) donors. G6PD deficiency impairs response to oxidative stress, raising concerns about transplantation suitability. [42-45]

However, recent cohorts adjusting for confounders showed no impact of G6PD status on recipient survival. Though G6PD deficiency may still increase risks of dysfunction or non-anastomotic biliary strictures, with close monitoring it need not preclude donation. [46] This illustrates how prognostic research refines risk categories to safely expand options. For example, donor age over 60-65 years and steatosis over 30% are relative contraindications to donation, but machine perfusion systems could expand utilization through better organ assessment and repair. Ongoing trials and observational studies will clarify evidence-based criteria to optimize donor-recipient pairing. Transplantation inherently requires weighing risks like infection and graft failure against benefits. However careful, dynamic risk stratification enables delivering the best outcomes through proper organ allocation. [47]

OPTIMIZING THERAPEUTICS IN PBC AND HCC

Realizing the full potential of available interventions requires identifying patients most likely to benefit and fine-tuning treatment protocols to maximize efficacy. Recent research validating the utility of Baveno VI criteria for prognostication in primary biliary cholangitis (PBC) demonstrates the value of refining care guidelines. Studies selectivity of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) highlight the importance of appropriate patient selection to improve outcomes. Though the discovery of novel agents continues, optimal utilization of current modalities through evidence-based optimization can increase therapeutic success. PBC is an autoimmune cholestatic liver disease that can progress to cirrhosis and liver failure without treatment. Ursodeoxycholic acid is standard therapy, but some patients experience inadequate response or a decline in liver function. Prognostic assessment is thus crucial for dynamic risk stratification to guide care. Serum biochemical measures of cholestasis like alkaline phosphatase (ALP) and bilirubin predict outcomes, but liver stiffness correlates best with the histologic stage. This motivated the recent expansion of stiffness thresholds in the Baveno VI criteria to better identify patients at higher risk of adverse events. [48]

Validation of the enhanced Baveno VI criteria in independent PBC cohorts has confirmed improved performance for prognostic prediction. In compensated patients, liver stiffness ≥10 kPa identified cases at increased 5-year risk of decompensation, variceal bleeding, and death. Stiffness also correlated with biochemical non-response, indicating potential utility for guiding the need for second-line agents. Serial elastography could allow dynamic risk assessment to prompt timely intervention in patients with rising stiffness. The analysis substantiates the incorporation of liver stiffness evaluation into PBC care guidelines to determine the intensity of monitoring. Still, stiffness alone lacks perfect accuracy, so combining with prognostic algorithms like GLOBE and UK-PBC may further optimize prognostic utility. [49] Selecting appropriate patients is equally important when delivering localized therapies like RFA for HCC. [50]

Table 1. Prediction of metabolic associated fatty liver disease (MAFLD).

Screening Approach	Sensitivity/Specificity	Cost	Risk Factors Assessed	Age Considerations
Liver biochemistry (ALT, AST)	Low sensitivity, can be elevated due to other causes	Low	Nonspecific	Can be used in children >10 years
Imaging - Ultrasound	Moderate sensitivity, user-dependent	Low	Fatty liver changes	Recommended first-line for ages 2-18 years
Imaging - MRI-PDFF	High sensitivity and specificity	High	Quantifies hepatic steatosis	Research use, validated down to age 5 years
Imaging - MRE	High sensitivity and specificity	High	Quantifies fibrosis	Research use, validated down to age 6 years
Pediatric NAFLD Fibrosis Score	Moderate accuracy	Low	ALT, AST, BMI, age	Validated for ages 7-18 years
Screening tools (HAIR, PedsQL)	Low-moderate accuracy	Low	Family history, associated conditions	Questionnaire-based for ages 8+ years

RFA induces tumor necrosis through thermal ablation, but recurrence is common. Risk factors like larger size, multifocality, vascular invasion, and location near vessels limit complete ablation. However, guidelines often recommend RFA based on tumor stage alone. Identifying factors associated with RFA failure or success could improve patient selection to maximize benefit. A Hong Kong study derived and validated a prognostic score for RFA using tumor number, size, platelet count, and albumin. The model discriminates patients with 5-year disease-free survival over 70% who stand to gain greatly from RFA. [51] External validation of predictive systems like this RFA model in diverse settings is essential before routine clinical adoption. Prospective evaluation is also warranted to determine if guided patient selection improves therapeutic efficacy and efficiency. Other locoregional therapies like transarterial embolization and stereotactic body radiation could also benefit from predictive modeling to identify optimal candidates. Even for systemic agents, prognostic indicators may help anticipate a response, as AFP dynamics during immunotherapy predict HCC outcomes. Ongoing trials will also clarify how combining modalities like checkpoint inhibitors with RFA or transarterial approaches alters resectability and prognosis. [52] Table **1** compares screening modalities and risk factors for pediatric metabolic-associated fatty liver disease (MAFLD).

PRACTICE AND FUTURE DIRECTIONS

Translating therapeutic optimizations like updated PBC guidance and tools for HCC patient selection follows similar principles. Pilot studies should precede endorsement in care standards. Monitoring for unintended consequences is also critical as modifications alter referral and treatment patterns. The benefits of expanded screening or therapies must be weighed against risks and costs at the system level. Advanced machine learning algorithms applied to diverse omics data show promise for elucidating mechanisms of metabolic dysfunction-associated fatty liver disease pathogenesis, enabling noninvasive disease prediction through the integration of clinical information and imaging features. [53] Sophisticated deep learning models may also aid in optimizing and personalizing treatment strategies and facilitating translational efforts to improve clinical outcomes of metabolic dysfunction-associated fatty liver disease. [54] However, model interpretability, prospective validation in diverse patient populations, and assessment of clinical utility remain critical priorities before the widespread adoption of artificial intelligence tools for guiding the management of this condition in clinical practice. [55]

Making the most of emerging technologies will require modernizing infrastructure, including through expanded data interoperability. Electronic health records and regional repositories need to become more dynamic to capitalize on growing sources of clinical data. Natural language processing and quality checks are needed to ensure reliable data inputs for large-scale analytics. Molecular profiling of conditions like PBC could uncover novel drug targets and biomarkers for precision medicine. Environmental triggers of liver disease also warrant study, particularly in light of rising rates of MAFLD. [56] To enhance predictive modeling, combining deep clinical data with transcriptomics, metabolomics, and imaging features through AI algorithms may allow more granular outcome projections. [57] Separately, the development of therapies targeting pathways implicated in liver diseases remains imperative to expand the limited treatment arsenal. [58] Improved animal models that better recapitulate human pathophysiology could aid drug discovery. [59]

CONCLUSIONS

Recent advances in hepatology research show great promise for improving prognostic accuracy, elucidating disease mechanisms, optimizing screening and risk stratification, and enhancing available therapies in conditions like HCC, PBC, and MAFLD. Integrating diverse clinical data into predictive models like MAPS-CRAFITY and machine learning algorithms can facilitate personalized treatment selection and monitoring. Elucidating genetic factors, dysfunctional molecular pathways, and biomarkers provides insights into pathogenesis to guide drug development. Refining screening paradigms and risk criteria through studies enables earlier intervention and safe expansion of care access. Optimizing management via validation of prognostic thresholds and predictive scores maximizes the efficacy of current modalities. Translation into clinical practice necessitates further validation and evaluation to ensure value. Meanwhile, research should continue unraveling disease mechanisms, improving risk stratification, and developing novel therapies to sustain advancement in hepatology**Availability of Data and Materials:** All data and sharing, as well as publication, are available.

Competing Interests: The authors hereby say that they have no competing interests.

Funding: The corresponding author supplied all study materials. There was no further funding for this study.

Authors' Contributions: All authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript. All authors reviewed and confirmed the final version of the manuscript.

Acknowledgments: The authors thank all the researchers, editors, reviewers, and the supported universities that have made great efforts in their studies. Moreover, we are grateful to this journal's editors, reviewers, and readers.

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