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Recent Trends in Biomarker-Based Early Detection of Hepatic Disorders in Clinical Biochemistry

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Abstract: Liver disease remains a major public health challenge worldwide. It not only significantly drives up population-wide morbidity and mortality rates, but also continuously increases the financial burden on global healthcare systems. Early detection is a core, necessary measure to prevent the disease from progressing to advanced liver fibrosis, cirrhosis, liver failure, and ultimately hepatocellular carcinoma (HCC). Conventional liver function tests, the basic diagnostic tools currently used in clinical practice, have clear shortcomings in sensitivity and specificity for identifying early-stage liver disease, which has created demand for the development of new biomarkers. In recent years, multiple categories of candidate biomarkers have emerged in the field, including circulating microRNAs, extracellular vesicles, and cell-free DNA. Technologies such as multi-omics, AI prediction models, innovative biosensors, and point-of-care diagnostic platforms are continuously empowering early diagnosis. Existing validation data confirms that integrated biomarker sets have higher diagnostic accuracy than single biomarkers. This review will critically assess recent progress in these early diagnostic biomarkers, organize their clinical significance, diagnostic performance, limitations, and future prospects, discuss challenges related to their clinical translation, and outline how technologies such as precision medicine can advance the early diagnosis and management of liver disease.

Keywords: *Hepatic Disorders; Liver Biomarkers; Clinical Biochemistry; MicroRNA; Exosomes; Cell-free DNA; Metabolomics; Proteomics; Hepatocellular Carcinoma; Liver Fibrosis.*

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I. INTRODUCTION

The liver carries out six core physiological functions including metabolism, detoxification, and protein synthesis. Abnormal liver function exerts far-reaching impacts on systemic health, and liver diseases have emerged as a major global public health challenge, continuously driving up the global incidence, mortality, and healthcare expenditures related to liver diseases. The spectrum of liver diseases, whose prevalence has kept rising in recent years, covers seven categories: metabolic dysfunction-associated steatotic liver disease (MASLD), viral hepatitis, alcoholic liver disease, autoimmune liver disease, liver fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC), generating an urgent clinical need for effective early diagnosis and disease monitoring solutions. The core clinical pain point of liver diseases is the absence of obvious symptoms in the early stages. Delayed onset of clinical symptoms often leads to diagnostic delay, which in turn triggers various severe complications, making early diagnosis the core prerequisite for implementing timely interventions andimproving patient prognosis. The seven biochemical markers commonly used in traditional liver disease diagnosis include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), bilirubin, albumin, and prothrombin time. Yet these methods have clear limitations: biochemical indicators cannot accurately reflect disease severity, and some patients with confirmed significant liver pathology still show normal test results. Additionally, liver biopsy, the gold standard for liver disease diagnosis, has inherent flaws including its invasive nature, high cost, risk of bleeding, and susceptibility to sampling errors. Recent technological advances in clinical biochemistry and molecular diagnostics have spawned a batch of new biomarkers. Among these, six types with strong application prospects include circulating microRNA, extracellular vesicles, cell-free DNA, proteomic signatures, metabolomic profiles, and fibrosis-related proteins, which can detect liver diseases before clinical symptoms appear and fill the gaps in traditional diagnostic approaches.

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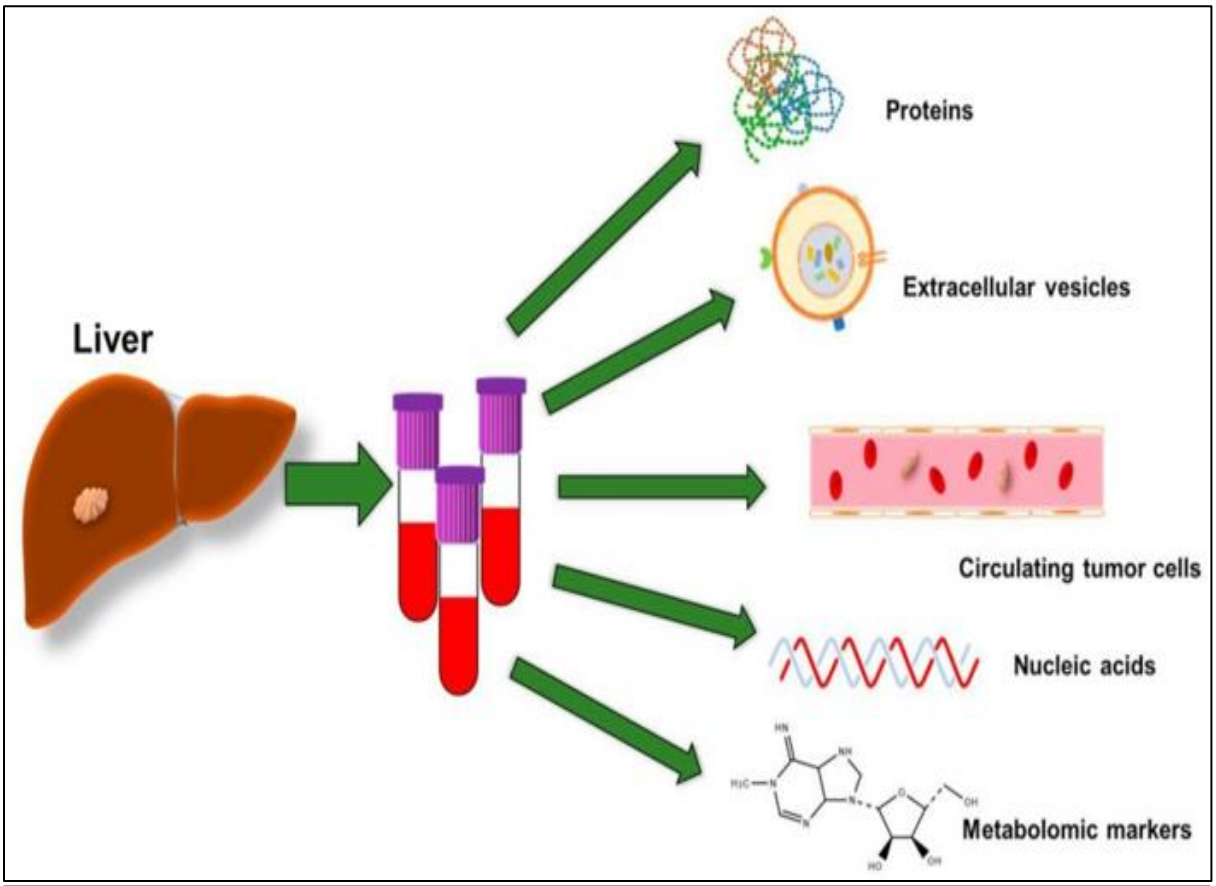

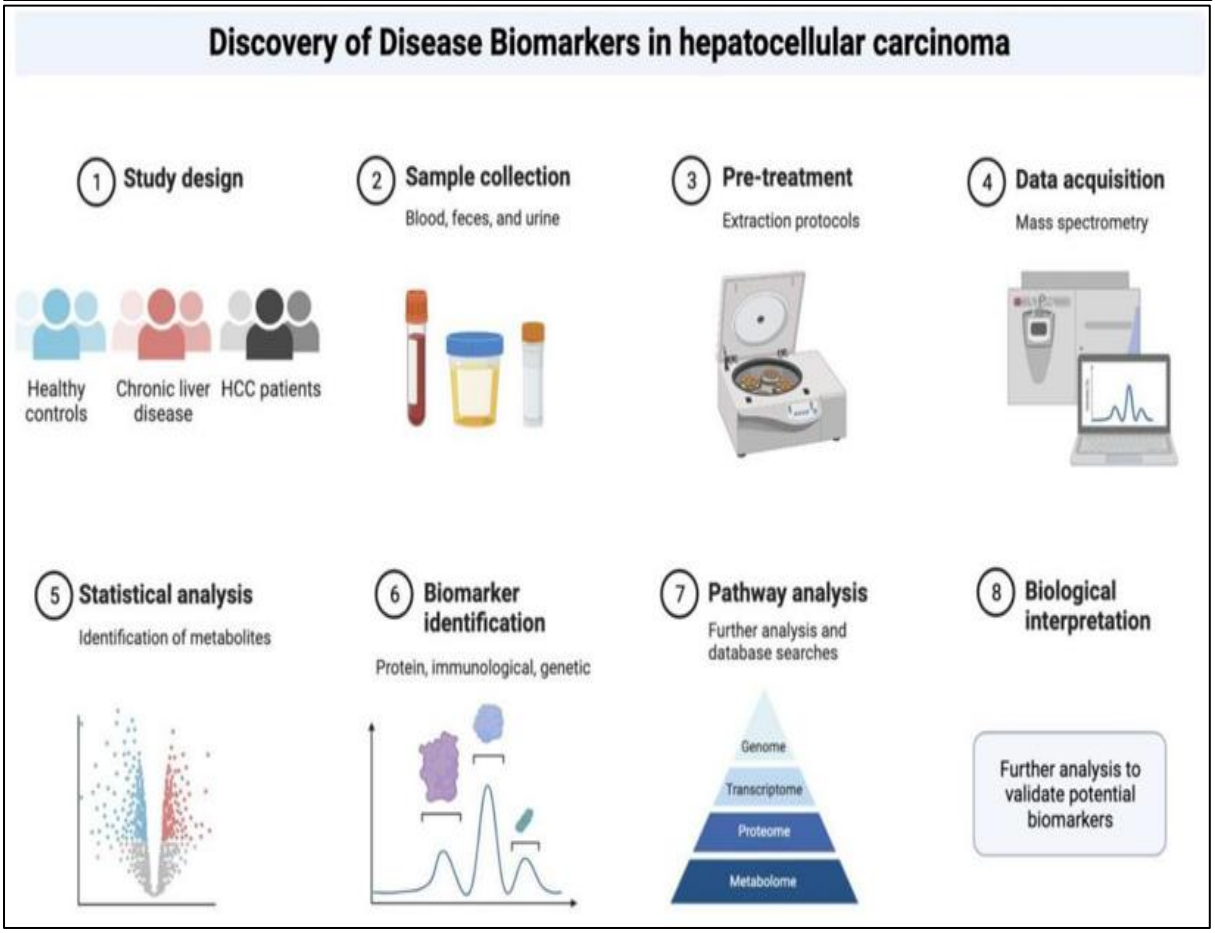

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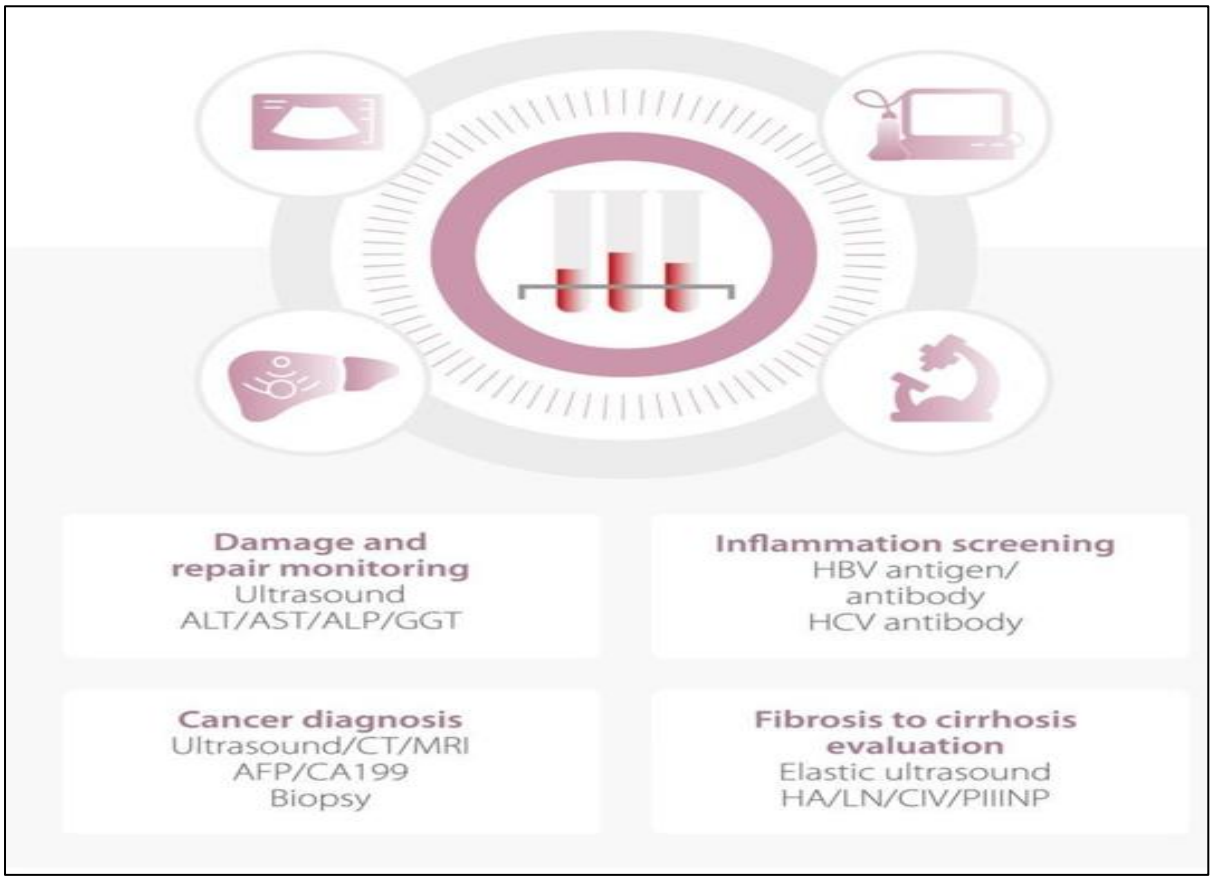

Fig 1 Overview of Conventional and Emerging Biomarkers Used in the Early Detection of Hepatic Disorders, Including Liver Enzymes, Micrornas, Exosomes, Cell-Free DNA, Proteomic and Metabolomic Biomarkers.

➢ *Common MicroRNAs Associated with Hepatic Disorders*

Table 1 Common MicroRNAs Associated with Hepatic Disorders

MicroRNA	Associated Liver Disease	Clinical Significance
miR-122	Viral hepatitis, MASLD, HCC	Early hepatocyte injury marker
miR-21	Liver fibrosis, HCC	Fibrogenesis and tumor progression
miR-34a	MASLD/MASH	Disease severity indicator
miR-155	Chronic inflammation	Immune regulation
miR-221	HCC	Tumor progression and prognosis

- Reference: Frontiers in Molecular Biosciences; Tessitore et al., 2024, Genes.

The development of high-throughput technologies including genomics, transcriptomics, proteomics, metabolomics, and lipidomics has further accelerated biomarker discovery. These advanced analytical platforms facilitate comprehensive evaluation of molecular alterations associated with hepatic injury, inflammation, fibrosis, and carcinogenesis. In addition, artificial intelligence (AI) and machine learning algorithms are increasingly being incorporated into biomarker research to identify complex disease patterns and improve diagnostic accuracy.

II. CONVENTIONAL LIVER BIOMARKERS

Conventional liver biomarkers remain the cornerstone of clinical assessment and diagnosis of hepatic disorders. These biomarkers are routinely measured through liver function tests (LFTs) and provide valuable information regarding hepatocellular injury, cholestasis, synthetic liver function, and overall hepatic health. Despite the emergence of novel molecular biomarkers, conventional biochemical markers continue to play a crucial role due to their accessibility, affordability, and widespread clinical acceptance.

Alanine aminotransferase (ALT) is one of the most commonly used biomarkers for detecting liver injury. ALT is primarily localized within hepatocytes, and its release into circulation occurs following cellular damage. Elevated ALT levels are frequently observed in conditions such as viral hepatitis, MASLD, alcoholic liver disease, and drug-induced liver injury. Because ALT is relatively liver-specific, it is often considered a sensitive indicator of hepatocellular damage. However, normal ALT levels do not necessarily exclude significant liver disease, particularly in patients with advanced fibrosis or cirrhosis.

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➢ *Direct Serum Biomarkers of Liver Fibrosis*

Table 2 Direct Serum Biomarkers of Liver Fibrosis

Biomarker	Biological Function	Clinical Utility
Hyaluronic Acid (HA)	ECM turnover	Detection of advanced fibrosis
PIIINP	Collagen synthesis	Fibrogenesis assessment
TIMP-1	Matrix degradation inhibitor	Fibrosis progression
Type IV Collagen	ECM deposition	Advanced fibrosis
Pro-C3	Collagen formation	Active fibrogenesis

- Reference: Neuman et al., *Clinical Biochemistry* and 2026 MASLD fibrosis review.

Aspartate aminotransferase (AST) is another important enzyme involved in amino acid metabolism. Unlike ALT, AST is present in several tissues including the liver, heart, skeletal muscles, kidneys, and brain. Consequently, elevated AST levels may occur in both hepatic and non-hepatic conditions. The AST/ALT ratio is frequently used in clinical practice to differentiate various liver disorders. For example, an AST/ALT ratio greater than two is often associated with alcoholic liver disease, whereas lower ratios are more commonly observed in viral hepatitis and MASLD.

Alkaline phosphatase (ALP) serves as a key marker of cholestatic liver disease. This enzyme is primarily found in bile duct epithelial cells, bone tissue, and the placenta. Elevated ALP levels may indicate biliary obstruction, primary biliary cholangitis, primary sclerosing cholangitis, or infiltrative liver diseases. However, interpretation of ALP requires caution because increased levels may also originate from non-hepatic tissues, particularly bone.

Gamma-glutamyl transferase (GGT) is widely used as a complementary biomarker for assessing hepatobiliary disorders. Elevated GGT levels are commonly observed in alcohol-related liver disease, cholestasis, and drug-induced liver injury. When interpreted alongside ALP, GGT can help confirm whether elevated ALP originates from hepatic rather than skeletal sources.

Serum bilirubin is another important marker that reflects the liver's ability to metabolize and excrete bilirubin. Elevated bilirubin concentrations may indicate hepatocellular dysfunction, biliary obstruction, or hemolytic disorders. Clinically, increased bilirubin levels often manifest as jaundice and are associated with advanced liver disease.

➢ *Emerging Biomarkers*

The limitations associated with conventional liver biomarkers have driven the search for more sensitive and specific indicators of hepatic injury. Recent advances in molecular biology, clinical biochemistry, and high-throughput analytical technologies have led to the identification of numerous emerging biomarkers that can detect liver disease at earlier stages and provide insights into disease mechanisms. These biomarkers have the potential to transform clinical practice by enabling non-invasive diagnosis, improved risk stratification, and personalized therapeutic interventions.

Emerging biomarkers encompass a diverse range of molecules, including circulating microRNAs, extracellular vesicles, cell-free DNA, proteins, metabolites, lipids, and inflammatory mediators. Unlike traditional liver enzymes that primarily indicate cellular injury, these novel biomarkers often reflect specific molecular pathways involved in disease initiation and progression. Consequently, they may offer greater diagnostic accuracy and prognostic value.

One of the most promising areas of biomarker research involves circulating nucleic acids. These molecules can be detected in blood samples and provide valuable information regarding gene expression patterns associated with liver disease. Alterations in specific microRNA profiles have been linked to inflammation, fibrosis, steatosis, and carcinogenesis. Similarly, cell-free DNA released from damaged hepatocytes has emerged as a potential marker for monitoring liver injury and cancer development.

Extracellular vesicles, including exosomes, have gained significant attention due to their role in intercellular communication. These vesicles carry proteins, lipids, and nucleic acids that reflect the physiological state of their cells of origin. Changes in exosomal content have been associated with various liver disorders and may serve as highly informative diagnostic biomarkers.

Advances in metabolomics have enabled comprehensive analysis of small molecules involved in metabolic pathways. Because the liver is central to metabolic regulation, alterations in metabolite profiles can provide early indications of hepatic dysfunction. Similarly, proteomic technologies have facilitated the identification of disease-specific protein signatures that may improve diagnostic precision.

Another emerging trend involves the development of biomarker panels rather than reliance on individual markers. Combining multiple biomarkers can enhance sensitivity and specificity while capturing the complex biological processes underlying liver disease. Such panels are particularly valuable for distinguishing between different stages of fibrosis, predicting disease progression, and identifying patients at high risk of hepatocellular carcinoma.

The integration of artificial intelligence and machine learning further enhances the potential of emerging biomarkers. Advanced computational approaches can analyze large datasets, identify hidden patterns, and generate predictive models with superior diagnostic performance. As a result, biomarker research is increasingly moving toward

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precision medicine approaches tailored to individual patient characteristics.

Despite their promise, many emerging biomarkers remain in the validation phase and require large-scale clinical studies before widespread implementation. Standardization of analytical methods, establishment of reference ranges, and evaluation of cost-effectiveness are essential for successful clinical translation. Nevertheless, these biomarkers represent a rapidly evolving field with substantial potential to improve the early detection and management of hepatic disorders.

➢ *MicroRNAs*

MicroRNAs (miRNAs) have emerged as one of the most promising biomarker classes for the early detection and monitoring of hepatic disorders. MicroRNAs are small, non-coding RNA molecules consisting of approximately 18–25 nucleotides that regulate gene expression at the post-transcriptional level. They play critical roles in numerous biological processes including cell proliferation, differentiation, apoptosis, metabolism, inflammation, and immune responses. Dysregulation of specific microRNAs has been implicated in the pathogenesis of various liver diseases, making them valuable candidates for non-invasive diagnostic applications.

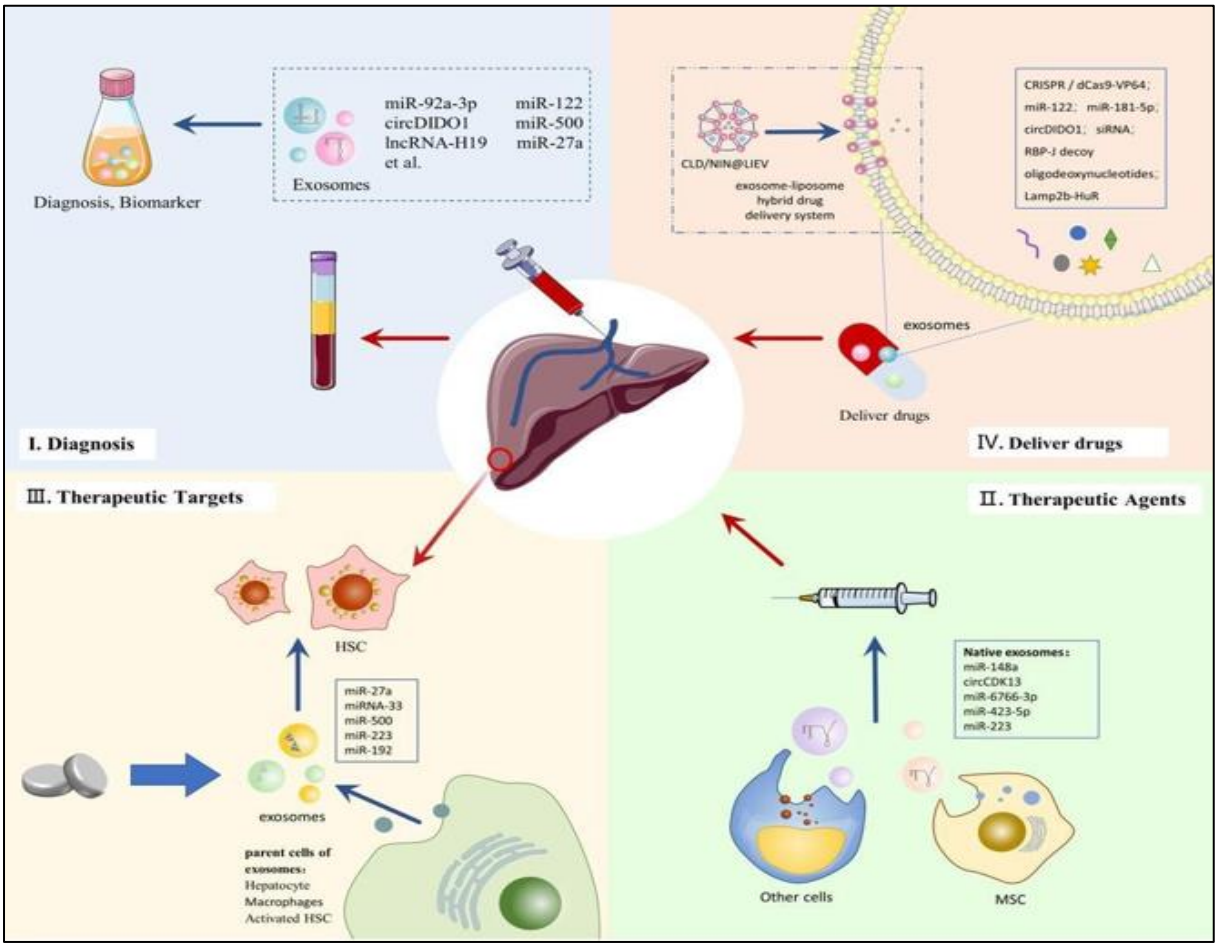

Fig 2 Mechanisms through which circulatingMicro RNAs and Exosomes Regulate Inflammation, Fibrosis, and Hepatocellular Carcinoma Development.

➢ *Conventional and Emerging Biomarkers in Hepatocellular Carcinoma*

Table 3 Conventional and Emerging Biomarkers in Hepatocellular Carcinoma

Biomarker	Sensitivity (%)	Specificity (%)	Clinical Application
AFP	41–65	80–94	HCC screening
DCP/PIVKA-II	48–62	81–98	Prognosis and diagnosis
SCCA	84	49	Early diagnosis
GP73	75	69	HCC diagnosis

One of the major advantages of circulating microRNAs is their remarkable stability in biological fluids such as serum, plasma, saliva, and urine. Unlike many conventional biomarkers that degrade rapidly, microRNAs are protected from enzymatic degradation through encapsulation within extracellular vesicles or binding to carrier proteins. This stability allows reliable detection and quantification using advanced molecular techniques such as

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quantitative real-time polymerase chain reaction (qRT-PCR), next-generation sequencing, and microarray analysis.

Numerous studies have demonstrated altered microRNA expression profiles in patients with liver diseases. Among these, miR-122 has received particular attention because it accounts for nearly 70% of total hepatic microRNA content and is highly liver-specific. Elevated circulating levels of miR-122 have been reported in acute liver injury, viral hepatitis, drug-induced hepatotoxicity, and metabolic dysfunction-associated steatotic liver disease (MASLD). Importantly, increases in miR-122 may occur before significant elevations in conventional liver enzymes such as ALT and AST, suggesting its utility as an early biomarker of hepatocellular damage.

Several other microRNAs have also been associated with hepatic disorders. For example, miR-21 is frequently linked to liver fibrosis and inflammation, whereas miR-34a is associated with lipid metabolism abnormalities and steatohepatitis. Increased expression of miR-155 has been observed in inflammatory liver conditions, while miR-29 family members are closely involved in extracellular matrix regulation and fibrosis progression. These findings indicate that distinct microRNA signatures may reflect specific pathological processes occurring during liver disease development.

MicroRNAs have also shown significant promise in the diagnosis and prognosis of hepatocellular carcinoma (HCC). Altered expression of miR-21, miR-221, miR-224, and miR-199 has been reported in HCC patients. Several studies suggest that combinations of multiple microRNAs can achieve higher sensitivity and specificity than traditional tumor markers such as alpha-fetoprotein (AFP). Consequently, microRNA panels are being investigated as potential tools for early cancer detection and risk stratification.

III. EXOSOMES

Exosomes have recently gained considerable attention as innovative biomarkers for the early detection of hepatic disorders. These small extracellular vesicles, typically ranging from 30 to 150 nanometers in diameter, are secreted by various cell types and play a crucial role in intercellular communication. Exosomes carry a diverse cargo of proteins, lipids, messenger RNA, microRNAs, DNA fragments, and other bioactive molecules that reflect the physiological and pathological status of their cells of origin.

The liver actively releases exosomes under both normal and pathological conditions. During liver injury, inflammation, fibrosis, and carcinogenesis, hepatocytes and other liver-associated cells such as hepatic stellate cells, Kupffer cells, and cholangiocytes produce exosomes with altered molecular compositions. These disease-specific changes provide valuable insights into ongoing pathological processes and make exosomes attractive candidates for biomarker development.

One of the primary advantages of exosome-based biomarkers is their exceptional stability in circulation. The lipid bilayer membrane surrounding exosomes protects their molecular contents from degradation, allowing accurate detection in blood and other biological fluids. Furthermore, exosomes can be obtained through minimally invasive liquid biopsy approaches, making them suitable for repeated monitoring and large-scale screening applications.

Research has identified several exosomal components associated with liver diseases. Exosomal microRNAs, particularly miR-122, miR-192, miR-21, and miR-34a, have been linked to liver injury, fibrosis, and metabolic dysfunction-associated steatotic liver disease (MASLD). Elevated levels of these molecules in circulating exosomes may indicate early pathological changes before the appearance of clinical symptoms or significant abnormalities in conventional liver function tests.

Exosomes also play an important role in liver fibrosis. Activated hepatic stellate cells release exosomes containing fibrogenic molecules that contribute to extracellular matrix deposition and fibrosis progression. Consequently, fibrosis-associated exosomal markers may facilitate early detection of fibrotic changes and help assess disease severity.

In hepatocellular carcinoma, exosomes have demonstrated significant diagnostic potential. Tumor-derived exosomes contain specific proteins, nucleic acids, and signaling molecules that reflect malignant transformation. Several studies have reported that exosomal biomarkers may achieve higher sensitivity and specificity than conventional markers such as alpha-fetoprotein. Moreover, exosome analysis may help identify aggressive tumor phenotypes, predict therapeutic responses, and monitor disease recurrence following treatment.

Recent advances in proteomic and genomic technologies have accelerated the discovery of exosome-based biomarker panels. By combining multiple exosomal components, researchers aim to improve diagnostic accuracy and overcome the limitations associated with single biomarkers. Integration of exosomal biomarkers with machine learning algorithms further enhances their potential for precision medicine applications.

- *Cell-Free DNA*

Cell-free DNA (cfDNA) has emerged as a promising non-invasive biomarker for the early detection, monitoring, and prognosis of hepatic disorders. Cell-free DNA refers to short fragments of DNA that are released into the bloodstream following cellular apoptosis, necrosis, or active secretion. Under normal physiological conditions, small amounts of cfDNA circulate in the blood; however, increased levels are often observed in pathological conditions involving tissue injury, inflammation, fibrosis, and cancer. Since liver diseases are characterized by continuous hepatocyte damage and regeneration, cfDNA has attracted considerable attention as a potential indicator of hepatic pathology.

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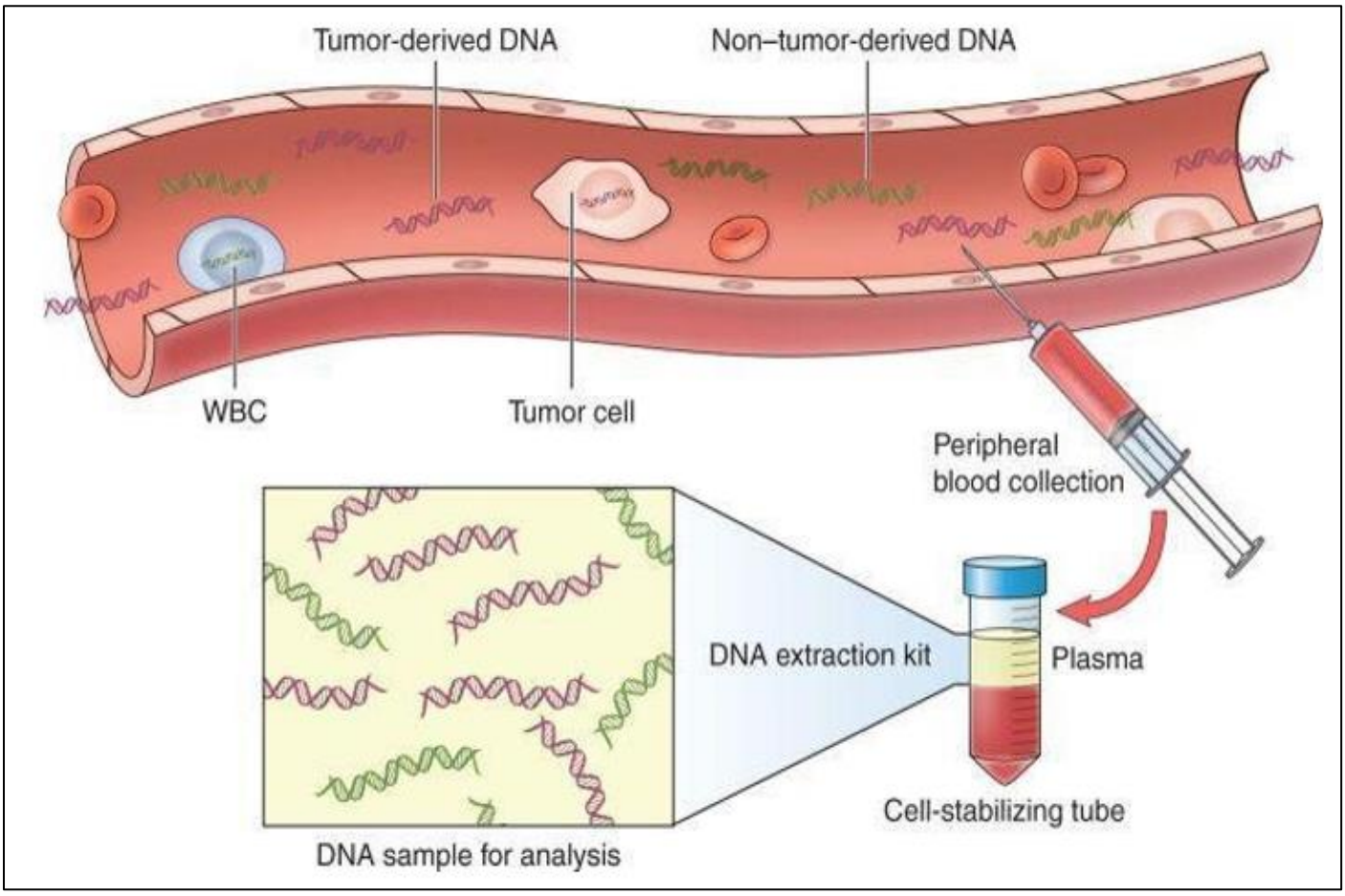

Fig 3 Liquid Biopsy Approach Utilizing Cell-Free DNA, Circulating Tumor DNA, and Epigenetic Biomarkers for Early Detection of Liver Fibrosis and Hepatocellular Carcinoma.

The biological basis of cfDNA as a biomarker lies in its ability to reflect ongoing cellular events within affected tissues. During liver injury, damaged hepatocytes release DNA fragments into circulation, resulting in elevated plasma cfDNA concentrations. These circulating DNA fragments can be detected through highly sensitive molecular techniques such as quantitative PCR, digital PCR, and next-generation sequencing. Such approaches allow not only quantification of cfDNA levels but also detailed analysis of genetic and epigenetic alterations associated with liver disease.

Several studies have demonstrated increased cfDNA concentrations in patients with acute liver injury, chronic hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Elevated cfDNA levels often correlate with disease severity and may provide valuable prognostic information. Unlike conventional liver enzymes, which primarily indicate hepatocellular damage, cfDNA offers insight into molecular changes occurring at the genomic level, thereby enhancing diagnostic precision.

An important advancement in cfDNA research is the analysis of methylation patterns. DNA methylation is a key epigenetic modification involved in gene regulation, and abnormal methylation profiles are frequently observed during liver disease progression. Specific methylation signatures detected in circulating cfDNA have shown potential for distinguishing healthy individuals from patients with fibrosis, cirrhosis, and liver cancer. These epigenetic markers may enable earlier diagnosis compared to traditional diagnostic methods.

➢ *Blood-Based Biomarkers for HCC Detection*

Table 4 Blood-Based Biomarkers for HCC Detection

Biomarker Category	Examples	Clinical Significance
Protein Biomarkers	AFP, AFP-L3, DCP, GP73	Early detection
Genetic Biomarkers	ctDNA	Tumor mutation profiling
Epigenetic Biomarkers	DNA methylation markers	Early diagnosis
RNA Biomarkers	miRNAs, lncRNAs	Disease monitoring
Exosomal Biomarkers	Exosomal RNAs	Non-invasive diagnosis

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Cell-free DNA has also demonstrated considerable promise in hepatocellular carcinoma detection. Tumor-derived cfDNA, commonly known as circulating tumor DNA (ctDNA), contains genetic mutations and epigenetic alterations specific to malignant cells. Analysis of ctDNA allows identification of cancer-associated mutations, monitoring of tumor progression, assessment of treatment response, and detection of minimal residual disease following therapy. Consequently, liquid biopsy approaches based on cfDNA are increasingly being investigated as alternatives to invasive tissue biopsies.

Furthermore, cfDNA may contribute to personalized medicine by enabling real-time monitoring of disease dynamics. Repeated blood sampling can provide continuous information regarding disease progression and therapeutic efficacy without exposing patients to invasive procedures. This advantage is particularly valuable for chronic.

➢ *Metabolomic Biomarkers*

Metabolomics has emerged as a powerful approach for identifying novel biomarkers associated with hepatic disorders. Metabolomics refers to the comprehensive study of small-molecule metabolites present within biological systems, including amino acids, lipids, sugars, organic acids, and other metabolic intermediates. Because the liver serves as the central organ of metabolism, alterations in hepatic function are often reflected by measurable changes in metabolite profiles. Consequently, metabolomic biomarkers offer significant potential for the early detection and characterization of liver diseases.

The liver regulates numerous metabolic pathways involving carbohydrate metabolism, lipid synthesis, amino acid metabolism, detoxification, and energy production. Hepatic injury disrupts these processes, leading to distinct metabolic alterations that can be detected in blood, urine, and other biological samples. Advanced analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS) have facilitated comprehensive profiling of these metabolic changes.

- *Advantages and Limitations of Emerging Hepatic Biomarkers*

Table 5 Advantages and Limitations of Emerging Hepatic Biomarkers

Biomarker	Advantages	Limitations
miRNAs	High sensitivity, stable	Lack of standardization
Exosomes	Reflect cellular communication	Isolation challenges
cfDNA	Non-invasive, real-time monitoring	High analytical cost
Proteomics	Functional disease information	Complex analysis
Metabolomics	Comprehensive metabolic profile	Biological variability

One of the most extensively studied applications of metabolomics is in metabolic dysfunction-associated steatotic liver disease (MASLD). Patients with MASLD frequently exhibit altered lipid metabolism characterized by increased free fatty acids, triglycerides, and specific phospholipid species. Changes in amino acid profiles, particularly branched-chain amino acids and aromatic amino acids, have also been associated with disease progression. These metabolic signatures may help distinguish simple steatosis from more advanced stages such as metabolic dysfunction-associated steatohepatitis (MASH).

Metabolomic biomarkers have also shown promise in identifying liver fibrosis and cirrhosis. Progressive fibrosis is associated with disruptions in energy metabolism, oxidative stress pathways, and amino acid turnover. Several metabolites involved in the tricarboxylic acid cycle, bile acid metabolism, and mitochondrial function have been proposed as indicators of fibrotic progression. Such biomarkers may complement existing fibrosis assessment tools and improve early diagnosis.

In viral hepatitis, metabolomic analyses have revealed characteristic alterations in lipid metabolism, bile acid synthesis, and inflammatory pathways. These metabolic changes may provide insights into disease activity and therapeutic response. Similarly, alcohol-related liver disease is associated with distinct metabolomic patterns reflecting oxidative stress, mitochondrial dysfunction, and impaired fatty acid metabolism.

Metabolomics is particularly valuable in hepatocellular carcinoma research. Cancer cells undergo extensive metabolic reprogramming to support rapid growth and proliferation. Consequently, specific metabolic signatures associated with altered glucose utilization, lipid synthesis, and amino acid metabolism have been identified in HCC patients. These biomarkers may facilitate early cancer detection and improve prognostic evaluation.

A major strength of metabolomics is its ability to provide a comprehensive snapshot of physiological and pathological processes occurring within the body. Unlike single biomarkers, metabolomic profiles capture complex biochemical interactions and may reveal subtle changes that precede clinical manifestations of disease. Integration of metabolomics with genomics, proteomics, and machine learning approaches further enhances its diagnostic potential.

Nevertheless, challenges remain regarding standardization, reproducibility, and interpretation of metabolomic data. Variability in sample collection, analytical platforms, and statistical methodologies can influence results. Additionally, metabolite concentrations may be affected by

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diet, lifestyle, medications, and environmental factors. Addressing these limitations will be essential for successful clinical translation.

IV. BIOMARKERS IN MASLD/MASH

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH) have become the most prevalent chronic liver diseases worldwide. These conditions are closely associated with obesity, insulin resistance, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome. While simple hepatic steatosis may remain relatively benign, progression to MASH can lead to fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. Therefore, identifying reliable biomarkers for early detection and risk stratification is of considerable clinical importance.

Traditional liver function tests such as ALT and AST are commonly used to evaluate MASLD. However, these enzymes often fail to accurately reflect disease severity, and many patients with advanced fibrosis may exhibit normal enzyme levels. Consequently, researchers have focused on identifying more sensitive and specific biomarkers capable of detecting disease progression at earlier stages.

Among emerging biomarkers, cytokeratin-18 (CK-18) has received significant attention. CK-18 is released during hepatocyte apoptosis, a key feature of MASH pathogenesis. Elevated serum CK-18 levels have been associated with increased liver inflammation, ballooning degeneration, and fibrosis. Several studies suggest that CK-18 may help differentiate simple steatosis from steatohepatitis.

Circulating microRNAs have also shown promise in MASLD diagnosis. MicroRNAs such as miR-122, miR-34a, and miR-192 are frequently elevated in affected individuals and correlate with disease severity. These molecules reflect underlying molecular changes related to lipid metabolism, inflammation, and hepatocyte injury, making them valuable non-invasive biomarkers.

Metabolomic biomarkers have provided additional insights into MASLD pathophysiology. Altered levels of free fatty acids, branched-chain amino acids, bile acids, and lipid metabolites have been associated with disease progression. These metabolic signatures may help distinguish between different stages of liver involvement and identify individuals at increased risk of developing advanced disease.

Fibrosis-related biomarkers are particularly important because fibrosis stage is the strongest predictor of clinical outcomes in MASLD. Serum markers such as hyaluronic acid, Pro-C3, tissue inhibitor of metalloproteinases (TIMP-1), and enhanced liver fibrosis (ELF) score components have demonstrated utility in assessing fibrotic progression. These biomarkers may reduce the need for invasive liver biopsy in many patients.

Recent studies have also explored exosomes and cell-free DNA as potential biomarkers for MASLD. Exosomal cargo containing specific proteins and microRNAs may reflect disease activity, while cfDNA levels may indicate ongoing hepatocellular injury. These novel approaches offer promising opportunities for non-invasive disease monitoring.

The integration of multiple biomarkers into diagnostic panels has further improved accuracy. Composite scores such as FIB-4, NAFLD Fibrosis Score, and ELF score combine biochemical and clinical parameters to enhance risk assessment. Artificial intelligence-based algorithms are increasingly being used to analyze complex biomarker datasets and generate personalized predictions regarding disease progression.

- *Biomarkers of Liver Fibrosis*

Liver fibrosis is a wound-healing response that develops following chronic liver injury caused by viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease, autoimmune hepatitis, and other hepatic disorders. It is characterized by excessive accumulation of extracellular matrix (ECM) proteins, particularly collagen, leading to progressive scarring of liver tissue. If left untreated, fibrosis may progress to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Since fibrosis progression is often asymptomatic, early detection through reliable biomarkers is essential for timely intervention and improved patient outcomes.

Traditionally, liver biopsy has been considered the gold standard for assessing fibrosis. However, biopsy is invasive, costly, associated with procedural risks, and subject to sampling variability. Consequently, considerable research has focused on developing non-invasive biomarkers capable of accurately evaluating fibrosis severity and monitoring disease progression.

Fibrosis biomarkers can generally be classified into direct and indirect markers. Direct biomarkers reflect extracellular matrix turnover and fibrogenesis, whereas indirect biomarkers indicate alterations in liver function associated with fibrosis. Direct biomarkers are particularly valuable because they provide information regarding the biological processes driving fibrotic progression.

Hyaluronic acid (HA) is one of the most extensively studied direct fibrosis biomarkers. It is a glycosaminoglycan produced by hepatic stellate cells and degraded by liver sinusoidal endothelial cells. Elevated serum HA levels indicate increased extracellular matrix deposition and reduced hepatic clearance, making it a useful marker of advanced fibrosis and cirrhosis.

Procollagen type III N-terminal peptide (PIIINP) is another important fibrosis biomarker. This peptide is released during collagen synthesis and reflects active fibrogenesis. Increased serum PIIINP levels have been associated with progressive fibrosis across various chronic liver diseases. Similarly, type IV collagen and laminin are extracellular matrix components that increase during fibrotic remodeling and can serve as indicators of fibrosis severity.

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The Enhanced Liver Fibrosis (ELF) score combines three direct biomarkers—hyaluronic acid, PIIINP, and tissue inhibitor of metalloproteinase-1 (TIMP-1). The ELF score has demonstrated excellent diagnostic performance for identifying advanced fibrosis and is increasingly used in clinical practice as a non-invasive alternative to liver biopsy.

Indirect fibrosis markers include routine laboratory parameters such as platelet count, AST, ALT, albumin, and bilirubin. These variables are incorporated into composite indices such as the Fibrosis-4 Index (FIB-4), AST-to-Platelet Ratio Index (APRI), and NAFLD Fibrosis Score. These scoring systems are inexpensive, widely available, and useful for initial risk stratification, although their accuracy may be lower in intermediate disease stages.

- *Biomarkers for Early Hepatocellular Carcinoma Detection*

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents one of the leading causes of cancer-related deaths worldwide. The majority of HCC cases develop in individuals with chronic liver diseases, including viral hepatitis, cirrhosis, MASLD, and alcohol-related liver disease. Early detection is critical because curative treatment options such as surgical resection, liver transplantation, and local ablative therapies are most effective when tumors are diagnosed at an early stage. Consequently, the identification of sensitive and specific biomarkers for early HCC detection has become a major research priority.

Alpha-fetoprotein (AFP) is the most widely used serum biomarker for HCC screening and surveillance. AFP is a fetal glycoprotein that is normally expressed during embryonic development but becomes elevated in many HCC patients. However, AFP has significant limitations, including low sensitivity for detecting early-stage tumors and false-positive elevations in chronic hepatitis and cirrhosis. As a result, AFP alone is insufficient for reliable early diagnosis.

To overcome these limitations, several additional biomarkers have been investigated. Des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), is produced by malignant hepatocytes and has demonstrated improved specificity for HCC detection. Elevated DCP levels are often associated with tumor aggressiveness, vascular invasion, and poor prognosis.

Golgi protein 73 (GP73) has emerged as another promising biomarker. GP73 is a Golgi membrane protein that is overexpressed in liver disease and HCC. Several studies have reported that GP73 may achieve higher diagnostic sensitivity than AFP, particularly in patients with early-stage tumors.

Osteopontin, a multifunctional glycoprotein involved in inflammation and tumor progression, has also shown potential as an HCC biomarker. Elevated serum osteopontin levels have been observed in HCC patients and may facilitate earlier detection when combined with AFP.

Recent advances in molecular diagnostics have expanded the search for novel biomarkers. Circulating microRNAs such as miR-21, miR-122, miR-221, and miR-224 are frequently dysregulated in HCC and may serve as highly sensitive indicators of malignant transformation. Similarly, circulating tumor DNA (ctDNA) and methylation-based biomarkers provide valuable information regarding genetic and epigenetic alterations associated with cancer development.

- *Multi-Omics Approaches*

The complexity of liver diseases involves numerous molecular pathways, genetic factors, metabolic alterations, and environmental influences. Therefore, relying on a single biomarker often fails to capture the full spectrum of pathological changes occurring during disease progression. To address this limitation, researchers have increasingly adopted multi-omics approaches, which integrate data from multiple biological disciplines including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics. These comprehensive strategies provide a deeper understanding of disease mechanisms and facilitate the discovery of highly accurate biomarker panels for hepatic disorders.

Genomics focuses on the study of genetic variations and mutations associated with liver disease susceptibility and progression. Specific genetic polymorphisms, such as those involving the PNPLA3, TM6SF2, and MBOAT7 genes, have been linked to increased risk of MASLD, fibrosis, and hepatocellular carcinoma. Identifying these genetic factors can help predict disease risk and guide personalized preventive strategies.

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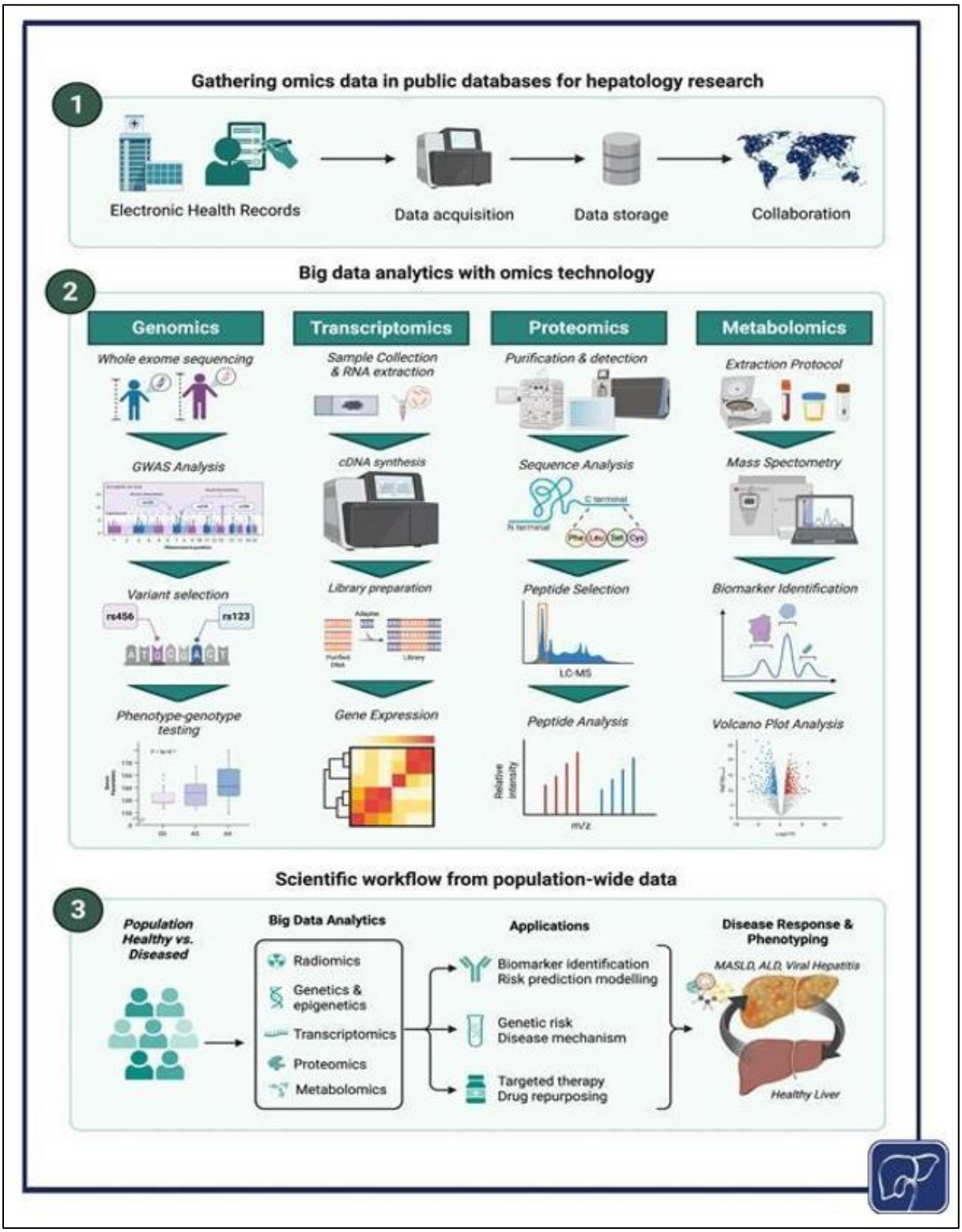

Fig 4 Integration of Genomics, Transcriptomics, Proteomics, Metabolomics, and Artificial Intelligence for Biomarker Discovery and Personalized Management of Hepatic Disorders.

Transcriptomics examines gene expression patterns by analyzing messenger RNA (mRNA) and non-coding RNA molecules. Changes in transcriptomic profiles provide valuable information regarding cellular responses to injury, inflammation, and fibrosis. For example, altered expression of specific microRNAs and long non-coding RNAs has been associated with various stages of liver disease progression.

Proteomics complements genomic and transcriptomic analyses by investigating protein expression and function. Since proteins directly mediate biological activities, proteomic alterations often provide a closer representation of disease pathology. Simultaneously, metabolomics evaluates changes in metabolic pathways and identifies small molecules reflecting physiological and pathological

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processes occurring within the liver.

The integration of these omics datasets offers significant advantages over single-platform analyses. Multi-omics approaches enable researchers to identify interactions among genes, proteins, metabolites, and environmental factors, thereby providing a more comprehensive understanding of disease biology. Such integration often leads to the discovery of biomarker signatures with superior sensitivity and specificity for early diagnosis.

In hepatic disorders, multi-omics analyses have demonstrated remarkable potential for distinguishing between different disease stages, predicting progression, and identifying therapeutic targets. For example, combining metabolomic and proteomic biomarkers has improved the differentiation of simple steatosis from steatohepatitis. Similarly, integrated genomic and epigenomic analyses have enhanced early detection of hepatocellular carcinoma.

Advanced computational tools and bioinformatics platforms play a crucial role in managing the vast amount of data generated by multi-omics studies. Machine learning algorithms can identify complex molecular patterns and generate predictive models that facilitate personalized medicine approaches. These models may assist clinicians in selecting appropriate interventions based on an individual's unique molecular profile.

- *Artificial Intelligence and Machine Learning in Biomarker Discovery*

Artificial intelligence (AI) and machine learning (ML) have emerged as powerful tools in modern biomedical research, significantly transforming biomarker discovery and disease diagnosis. The increasing availability of large-scale biological datasets generated through genomics, proteomics, metabolomics, and clinical studies has created opportunities for advanced computational methods to identify complex patterns that may not be detectable through traditional statistical approaches. In hepatic disorders, AI and ML are increasingly being applied to improve biomarker identification, disease prediction, risk stratification, and clinical decision-making.

Machine learning refers to a subset of artificial intelligence that enables computer systems to learn from data and make predictions without explicit programming. These algorithms analyze large datasets, recognize hidden relationships among variables, and generate predictive models capable of supporting clinical diagnosis. Such capabilities are particularly valuable in liver disease research, where multiple molecular pathways contribute to disease development and progression.

One of the primary applications of AI in hepatology is biomarker discovery. Traditional biomarker identification methods often focus on individual molecules, whereas machine learning algorithms can simultaneously analyze thousands of biological variables. This comprehensive approach facilitates the identification of biomarker combinations that provide superior diagnostic accuracy compared with single markers. As a result, researchers have successfully developed predictive models for liver fibrosis, cirrhosis, MASLD, and hepatocellular carcinoma.

AI-based analyses have demonstrated significant potential in the early detection of hepatocellular carcinoma. By integrating clinical parameters, imaging findings, genetic information, and molecular biomarkers, machine learning models can identify high-risk individuals and detect subtle disease-associated patterns. Several studies have reported that AI-assisted biomarker panels outperform conventional screening methods based solely on alpha-fetoprotein measurements.

In fibrosis assessment, machine learning algorithms have been used to analyze serum biomarkers, imaging data, and clinical characteristics to predict fibrosis severity. These models may reduce reliance on invasive liver biopsy procedures and facilitate earlier intervention. Similar approaches have been applied in MASLD, where AI systems can predict disease progression and identify patients at risk of developing advanced fibrosis or cirrhosis.

Artificial intelligence also plays an important role in multi-omics data integration. The enormous complexity of genomic, transcriptomic, proteomic, and metabolomic datasets requires sophisticated computational tools for meaningful interpretation. Machine learning algorithms can identify interactions among multiple biological pathways and generate personalized risk profiles based on individual molecular signatures.

- *Point-of-Care and Biosensor Technologies*

The growing demand for rapid, accurate, and non-invasive diagnostic methods has accelerated the development of point-of-care (POC) testing and biosensor technologies for hepatic disorders. Traditional laboratory-based diagnostic approaches often require specialized equipment, trained personnel, and prolonged processing times, which may delay clinical decision-making. Point-of-care diagnostics aim to overcome these limitations by providing immediate results at or near the patient's location. These technologies have the potential to improve early disease detection, facilitate timely treatment, and enhance healthcare accessibility, particularly in resource-limited settings.

Point-of-care testing involves the use of portable devices capable of analyzing biological samples such as blood, serum, plasma, saliva, or urine without the need for centralized laboratory infrastructure. In liver disease management, POC devices are increasingly being developed to measure conventional biomarkers including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and albumin. Rapid assessment of these biomarkers can support clinical screening, treatment monitoring, and disease surveillance.

Biosensors represent one of the most promising innovations in point-of-care diagnostics. A biosensor is an analytical device that combines a biological recognition

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element with a signal transducer to detect specific target molecules. Depending on the detection mechanism, biosensors may be classified as electrochemical, optical, piezoelectric, or nanotechnology-based systems. These devices offer high sensitivity, specificity, portability, and cost-effectiveness.

Electrochemical biosensors have gained particular attention in liver disease diagnostics. These sensors can detect biomarkers through electrical signal changes generated by biochemical interactions. Recent studies have demonstrated successful detection of liver enzymes, alpha-fetoprotein (AFP), microRNAs, and fibrosis-associated proteins using electrochemical biosensor platforms. Their rapid response times and low sample requirements make them attractive for clinical applications.

Nanotechnology has further enhanced biosensor performance by improving sensitivity and detection limits. Nanomaterials such as gold nanoparticles, graphene, carbon nanotubes, and quantum dots provide large surface areas and enhanced signal amplification capabilities. These features enable detection of extremely low concentrations of biomarkers, which is essential for identifying liver disease at early stages.

Biosensor technologies are also being applied to emerging biomarkers such as circulating microRNAs, exosomes, and cell-free DNA. Advanced biosensing platforms can rapidly analyze these molecular markers with high precision, supporting early diagnosis and personalized disease monitoring. Such approaches may eventually complement or replace more complex laboratory-based techniques.

Wearable biosensors represent another exciting development in the field. These devices can continuously monitor physiological and biochemical parameters through minimally invasive sampling methods. Although still in early stages of development, wearable biosensors may provide real-time monitoring of liver disease progression and treatment response in the future.

V. CLINICAL CHALLENGES AND LIMITATIONS

Despite remarkable advances in biomarker research, several challenges and limitations continue to hinder the routine clinical implementation of biomarker-based diagnostics for hepatic disorders. While numerous conventional and emerging biomarkers have demonstrated promising results in research settings, translating these discoveries into everyday clinical practice remains a complex process requiring extensive validation and standardization.

One of the major limitations is the lack of disease specificity associated with many biomarkers. Conventional liver enzymes such as ALT, AST, ALP, and GGT may be elevated in a variety of hepatic and non-hepatic conditions. Consequently, abnormal biomarker levels do not always accurately identify the underlying cause of liver injury. Similarly, some emerging biomarkers may be influenced by inflammatory processes, metabolic disorders, or other systemic diseases, reducing their diagnostic specificity.

Another significant challenge involves biological variability among individuals. Factors such as age, sex, ethnicity, dietary habits, lifestyle, medication use, and comorbid conditions can influence biomarker concentrations. This variability complicates the establishment of universal reference ranges and may affect diagnostic accuracy across diverse populations.

Standardization represents a critical issue in biomarker research. Different studies often employ varying sample collection procedures, storage conditions, analytical platforms, and data processing methods. Such methodological differences can lead to inconsistent findings and limit reproducibility. For example, quantification of microRNAs, exosomes, and cell-free DNA may vary significantly depending on the techniques used for extraction and analysis.

The majority of emerging biomarkers also require validation in large multicenter clinical trials before widespread adoption. Many studies have been conducted using relatively small patient cohorts, limiting the generalizability of findings. Robust validation across different populations and healthcare settings is necessary to confirm clinical utility and establish evidence-based guidelines.

Cost and accessibility present additional barriers. Advanced technologies such as next-generation sequencing, mass spectrometry, and multi-omics analyses often require expensive equipment and highly trained personnel. These requirements may restrict availability in low-resource healthcare settings, where liver disease burden is often greatest.

Interpretation of complex biomarker data poses another challenge. Emerging biomarkers frequently generate large amounts of molecular information that require sophisticated bioinformatics tools and specialized expertise. Clinicians may face difficulties integrating such data into routine decision-making processes without appropriate computational support.

Ethical and regulatory considerations must also be addressed. The use of genomic and multi-omics data raises concerns regarding patient privacy, data security, informed consent, and equitable access to precision medicine technologies. Regulatory agencies require extensive evidence regarding safety, accuracy, and clinical effectiveness before approving new diagnostic tools.

VI. FUTURE PERSPECTIVES

The field of biomarker-based diagnostics for hepatic disorders is rapidly evolving, and future advancements are expected to significantly transform the early detection, monitoring, and management of liver diseases. With

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increasing understanding of molecular mechanisms underlying hepatic injury, fibrosis, cirrhosis, and hepatocellular carcinoma, researchers are moving toward more precise, personalized, and non-invasive diagnostic strategies. The integration of emerging technologies with clinical biochemistry is likely to redefine the future of hepatology and improve patient outcomes.

One of the most promising future directions is the development of highly sensitive multi-biomarker panels. Since liver diseases involve complex interactions among genetic, metabolic, inflammatory, and fibrotic pathways, reliance on a single biomarker often provides limited diagnostic information. Future diagnostic approaches will likely combine multiple biomarkers, including microRNAs, exosomes, cell-free DNA, proteins, metabolites, and fibrosis markers, to achieve superior sensitivity and specificity. Such integrated biomarker panels may facilitate earlier disease detection and more accurate risk stratification.

Advances in multi-omics technologies are also expected to play a central role in future biomarker discovery. The integration of genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics provides a comprehensive understanding of disease pathogenesis at multiple biological levels. These approaches can identify novel molecular signatures associated with disease initiation and progression, thereby supporting the development of precision medicine strategies tailored to individual patients.

Artificial intelligence and machine learning are anticipated to further revolutionize liver disease diagnostics. As healthcare systems generate increasingly large and complex datasets, AI-based algorithms will become essential for analyzing biomarker information and identifying clinically relevant patterns. Future predictive models may integrate laboratory results, imaging data, genetic profiles, and clinical parameters to provide personalized disease risk assessments and treatment recommendations.

Liquid biopsy technologies represent another important area of future development. Analysis of circulating microRNAs, exosomes, cell-free DNA, and circulating tumor DNA offers a minimally invasive approach for detecting liver disease and monitoring disease progression. These technologies may eventually reduce dependence on invasive procedures such as liver biopsy while enabling real-time evaluation of treatment responses.

Point-of-care diagnostic platforms are expected to become increasingly sophisticated and widely available. Advances in biosensor technology, nanotechnology, and portable analytical devices will facilitate rapid, cost-effective testing outside traditional laboratory settings. Such innovations may improve access to liver disease screening in remote and underserved populations, contributing to earlier diagnosis and intervention.

Personalized medicine is likely to become a major focus of future hepatology practice. Biomarker-guided therapeutic strategies may enable clinicians to identify patients who are most likely to benefit from specific treatments while minimizing adverse effects. This individualized approach has the potential to improve treatment efficacy and optimize healthcare resource utilization.

VII. CONCLUSION

Hepatic disorders continue to represent a major global healthcare challenge, contributing substantially to morbidity, mortality, and economic burden worldwide. The increasing prevalence of metabolic dysfunction-associated steatotic liver disease, viral hepatitis, alcohol-related liver disease, liver fibrosis, cirrhosis, and hepatocellular carcinoma highlights the urgent need for effective strategies for early diagnosis and disease monitoring. Early detection remains one of the most critical factors influencing treatment success, disease progression, and patient survival.

Conventional liver biomarkers such as ALT, AST, ALP, GGT, bilirubin, and albumin remain fundamental components of clinical evaluation. These markers provide valuable information regarding liver injury and function; however, their limited sensitivity and specificity restrict their effectiveness in detecting early-stage disease. Consequently, considerable research efforts have focused on identifying novel biomarkers capable of reflecting molecular alterations that occur before the onset of significant clinical manifestations.

Emerging biomarkers including microRNAs, exosomes, cell-free DNA, metabolomic signatures, and proteomic markers have demonstrated significant potential for improving diagnostic accuracy. These biomarkers offer several advantages, including non-invasive assessment, enhanced sensitivity, and the ability to provide insights into specific pathological processes such as inflammation, fibrosis, and carcinogenesis. Their application in conditions such as MASLD, liver fibrosis, and hepatocellular carcinoma has generated encouraging results and may significantly improve future clinical practice.

The incorporation of multi-omics approaches has further expanded opportunities for biomarker discovery by enabling comprehensive analysis of genetic, transcriptomic, proteomic, and metabolic alterations. Combined with artificial intelligence and machine learning technologies, these approaches facilitate the identification of complex molecular patterns and support the development of highly accurate predictive models. Such innovations are driving the transition toward precision medicine in hepatology.

Point-of-care testing and biosensor technologies have also emerged as valuable tools for rapid and accessible liver disease diagnosis. These innovations may enhance healthcare delivery by enabling early detection in diverse clinical settings, including resource-limited environments where access to advanced diagnostic facilities is restricted.

Despite substantial progress, several challenges remain before widespread clinical implementation can be achieved. Issues related to biomarker standardization, validation,

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reproducibility, cost, and regulatory approval require further investigation. Large-scale multicenter studies are essential to confirm diagnostic performance and establish evidence-based clinical guidelines. Overall, biomarker-based diagnostics represent a transformative advancement in clinical biochemistry and hepatology. Continued research, technological innovation, and interdisciplinary collaboration will be critical for translating emerging biomarkers into routine clinical practice. As these developments continue to evolve, biomarker-driven approaches have the potential to significantly improve the early detection, prognosis, and personalized management of hepatic disorders, ultimately enhancing patient outcomes and reducing the global burden of liver disease.

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