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Multimodal Approaches To Assessing Liver Disease And Cardiovascular Risk Based On Ultrasound Imaging And Clinical Biomarkers: A Review Of The Scientific Literature

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Abstract: Liver diseases, particularly NAFLD and NASH, and cardiovascular diseases are serious global health risks. Noninvasive diagnostic methods, particularly ultrasound elastography (2D SWE, pSWE, ARFI) and clinical biomarkers (AST, ALT, FIB 4, NFS, CRP, lipid profile), are effective tools for assessing liver fibrosis and predicting CVD risk. A multimodal approach, with the integration of AI and deep learning, increases diagnostic accuracy and allows for individualized patient risk stratification. This review article presents the effectiveness of multimodal approaches based on ultrasound images and biomarkers and a review of the scientific literature.

Keywords: Ultrasound elastography, liver fibrosis, NAFLD, CVD, biomarker, multimodal approach, artificial intelligence.

INTRODUCTION:

Liver diseases, particularly NAFLD and its progression to nonalcoholic steatohepatitis (NASH), are prevalent worldwide and are closely associated with cardiovascular disease (CVD). NAFLD is not limited to the liver—it has been shown in numerous studies to increase the risk of atherosclerosis, heart failure, arrhythmias, and other cardiovascular events [1]. NAFLD is estimated to affect 25–30% of the world's population, and its complex clinical course can lead to NASH, fibrosis, and circulatory heart disease [2]. NAFLD is increasingly recognized as a multisystem disease. Insulin resistance and associated metabolic dysfunction play a central role in its pathogenesis. These factors not only accelerate the development of liver diseases, particularly cirrhosis, liver failure, and hepatocellular carcinoma (HCC), but also serve as important mechanisms in the development of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and some extrahepatic cancers (Byrne & Targher, 2015; Devarbhavi et al., 2023). Although NAFLD can lead to severe liver pathologies, epidemiological studies indicate that the main cause of death among patients with this disease is cardiovascular disease rather than liver complications [16] (Figure 1).

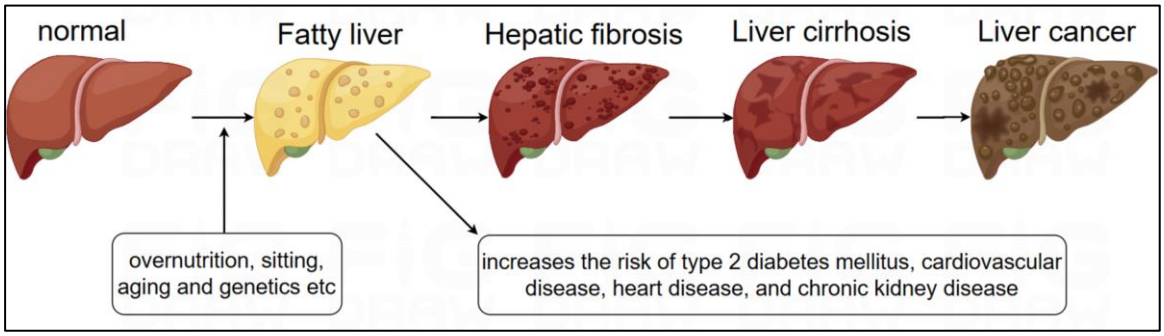

Figure 1. Evolution of NAFLD [16]

The progression of NAFLD involves four stages. Steatosis (simple fatty liver) is a harmless buildup of fat in liver cells. A more severe form of NAFLD, called NASH, occurs when the liver becomes inflamed. A patient is diagnosed with fibrosis when persistent inflammation forms scar tissue around the liver and surrounding blood vessels, but the liver can still function normally. Cirrhosis, the most severe stage, develops after years of inflammation and causes the liver to shrink, scar, and become scarred; this damage is irreversible and can lead to liver failure [3] (Figure 2). Typically, doctors classify a patient's disease into four groups based on histological features: mild, moderate, or severe [4].

Figure 2. Example of NAFLD progression model [liver fibrosis can be divided into four stages (F1-4): F0 - no fibrosis; F1 - portal fibrosis without septa; F2 - portal fibrosis and multiple septa; F3 - multiple septa without cirrhosis; F4 - cirrhosis, adapted from [4].

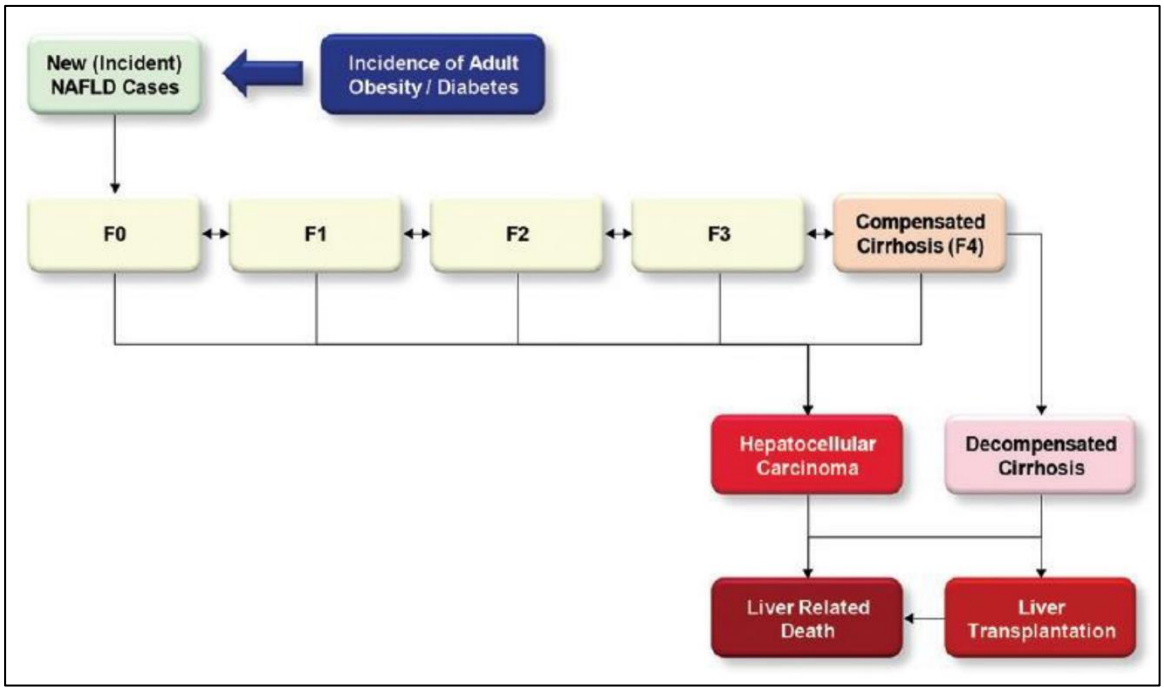

Figure 2. NAFLD progression model [4]

In most cases, abdominal ultrasound is used to diagnose NAFLD [5]. Ultrasonography is an inexpensive, safe, rapid, and uncomplicated procedure available in most healthcare settings [6]. Noninvasive tests or liver biopsies are used to determine the severity of liver disease. Hepatic steatosis, inflammation, and fibrosis are all assessed by liver biopsy. However, liver biopsy is an intrusive procedure that can lead to hemoperitoneum or hemothorax. Liver biopsy is also ineffective as a method of monitoring liver disease due to its invasive nature [7]. Alternative approaches to diagnosing NAFLD, such as clinical/laboratory scores, have been developed, but their effectiveness is questionable. Magnetic resonance imaging proton density fat fractionation (MRI-PDFF) has higher accuracy but is limited in cost and availability [8]. Compared with late-stage NAFLD, transient elastography and several biomarkers have shown better performance in early

stages. Various diagnostic approaches are being combined with artificial intelligence (AI) to improve diagnostic efficiency [9].

Traditional liver biopsy is invasive and associated with pain, bleeding, and infection risks. Therefore, noninvasive methods, such as ultrasound elastography and clinical biomarkers, are increasingly being used to assess liver health and predict cardiovascular risk [10].

In addition, AI and multimodal approaches are integrating liver imaging and biomarker data to improve individual diagnosis and risk prediction [11].

METHODS

We searched PubMed, Google scholar, and Web of Science databases using the terms "NAFLD," "cardiovascular events," "cardiovascular death," "prognosis," and their combinations to identify observational studies published up to January 2025. We included only observational studies conducted in adults aged 18 years or older and diagnosed with NAFLD on imaging or histology. Data from selected studies were extracted and meta-analysis was performed using random-effects modeling.

Ultrasound imaging and assessment of liver fibrosis

Ultrasound elastography assesses the degree of fibrosis by measuring the elasticity of liver tissue. The most commonly used methods are: 2D-SWE, pSWE/ARFI, MRE. Meta-analyses show that ultrasound elastography methods have high sensitivity and specificity in detecting liver fibrosis. The differences between methods may be related to technical parameters, patient body mass index, and hepatic steatosis.

Elastography methods

Ultrasound elastography assesses the degree of fibrosis by measuring the elasticity of liver tissue. The most commonly used methods are:

• 2D Shear Wave Elastography (2D-SWE) – known for its high accuracy and rapidity ([2]).

• Point Shear Wave Elastography (pSWE/ARFI) – assesses elasticity in a narrow area with low technical error ([10]).

• Magnetic Resonance Elastography (MRE) is the most accurate method, but it is expensive and requires a large infrastructure ([12]).

Table 1. Diagnostic accuracy of ultrasound elastography methods

Method	Indicator	AUROC	Comments	References
2D SWE	Fibroz F≥2	0.86	No-invaziv, tez	[2,3]
pSWE	Fibrosis + Steatosis	0.85	Few technical errors	[2,3]
ARFI	Fibrosis F≥2	0.87	Short review	[3,4]
MRE	Fibrosis F≥2	0.94	The most accurate, but expensive	[3]

Meta-analyses have shown that ultrasound elastography methods have high sensitivity and specificity in detecting liver fibrosis ([2,3]). However, differences between methods may be related to technical parameters, patient body mass index, and hepatic steatosis.

Clinical biomarkers and cardiovascular risk

The AST/ALT ratio, FIB-4, and NFS are noninvasive markers of liver fibrosis and are also used to predict cardiovascular events. CRP and fibrinogen are used as markers of inflammation to predict cardiovascular events.

Liver health and inflammatory markers

• The AST/ALT ratio is a noninvasive marker of liver fibrosis.

• FIB-4 and NFS are used to predict fibrosis and CVD risk [13].

• CRP and fibrinogen are used as markers of inflammation to predict cardiovascular events [14].

Table 2. Clinical biomarkers and CVD risk assessment

Biomarker	**Type of binding**	**Application**	**Literature**
AST/ALT ratio	Liver fibrosis	Assessment of fibrosis/steatosis level	[5]
FIB-4	Liver fibrosis + CVD risk	Risk stratification	[6,11]
NFS	Liver fibrosis + CVD risk	Risk forecast	[6,11]

CRP	Inflammation marker	Risk of cardiac events	[5]
Lipid profile	Atherosclerosis risk	LDL, HDL, TG assessment	[5]

Biomarkers' association with cardiovascular disease (CVD)

Liver biomarkers, especially laboratory parameters identified in patients with NAFLD (non-alcoholic fatty liver disease), are recognized as important prognostic predictors for the development of cardiovascular disease (CVD). Large meta-analyses conducted in recent years have demonstrated a strong epidemiological and clinical association of NAFLD biomarkers with CVD. The nature, mechanisms, and scientific evidence of these associations are discussed in detail below.

AST/ALT ratio and cardiovascular risk

The AST/ALT ratio (De Ritis coefficient) is one of the main indicators reflecting the degree of liver cell damage, and increases with the increase in inflammation in the process of NAFLD. Studies show that:

• Patients with an AST/ALT ratio >1 have a significantly higher risk of coronary artery disease and cardiometabolic risk.

• This indicator indicates increased liver fibrosis and also correlates with accelerated atherosclerosis.

• It has been scientifically proven that patients with an increased AST/ALT ratio have higher arterial stiffness, endothelial dysfunction, and insulin resistance.

This indicates a direct link between liver inflammation and chronic inflammation in the cardiovascular system.

FIB-4 index and CVD risk

FIB-4 is an index that assesses liver fibrosis based on age, AST, ALT, and platelet count. It is widely used in clinical practice to screen for NAFLD. Meta-analyses (e.g., [13]) have shown that:

• NAFLD patients with high FIB-4 levels have a 1.8–2.4-fold increased risk of CVD events.

• If the index is >2.67, the risk of myocardial infarction, stroke, and cardiac death increases dramatically.

• FIB-4 is strongly associated with subclinical markers of atherosclerosis, such as carotid intima-media thickness (cIMT).

This suggests that the progression of liver fibrosis occurs in parallel with structural and functional changes in the cardiovascular system.

NFS (NAFLD Fibrosis Score) and cardiovascular events.

NFS is a score based on insulin resistance, age, BMI, AST/ALT, platelets and albumin, and assesses the exact degree of fibrosis. Studies have shown that:

• NAFLD patients with high NFS are at a particularly high risk of death from CVD.

• Coronary artery calcification, endothelial dysfunction and systolic dysfunction are more common in patients with high NFS.

• A direct linear relationship has been found between NFS and arterial stiffness.

This biomarker is considered very important as an early predictor of progressive structural changes in the cardiovascular system.

Pathophysiological relationship between biomarkers and CVD

The following mechanisms explain the association of NAFLD biomarkers with CVD risk:

1. Chronic systemic inflammation

• Pro-inflammatory mediators such as TNF-α, IL-6, CRP are increased in the process of NAFLD.

• They play an important role in the initiation and progression of atherosclerosis.

2. Insulin resistance

• Is a major factor in fatty liver,

• Leads to dyslipidemia, hypertension, and atherosclerosis.

3. Oxidative stress

• Causes LDL oxidation, endothelial damage, and vascular stiffness.

4. Fibrosis and collagen deposition• Increases in FIB-4 and NFS indicators, which reflect the degree of fibrosis, are parallel to fibrotic changes in the vessels.

5. Association with metabolic syndrome

• NAFLD is often at the heart of metabolic syndrome, which further increases the risk of CVD.

Multimodal approaches

Combining ultrasound elastography and clinical biomarkers increases diagnostic accuracy. At the same time, AI-assisted data fusion improves individual risk prediction. CNN and multimodal fusion models combine ultrasound images and biomarkers. AI models increase AUROC values and help automate

patient monitoring. Combining ultrasound elastography (VCTE, 2D-SWE, pSWE, ARFI) and clinical biomarkers (AST/ALT, FIB-4, NFS, lipid profile, CRP, insulin resistance markers) creates a multimodal approach with high diagnostic accuracy in the assessment of liver diseases, especially NAFLD and NASH. Both data sources complement each other clinically through their different biopsy-free (noninvasive) features. This integrated approach is also one of the most reliable approaches in determining the risk of CVD (cardiovascular disease) (Xingyue Wei et al.).

Advantages of the combination of ultrasound elastography + biomarker

1. Increased accuracy in assessing the degree of fibrosis

Various studies have shown that when ultrasound-based liver stiffness measurement (LSM) is used in combination with biomarkers:

• the sensitivity and specificity in detecting stages F2–F4 of fibrosis increase by 10–18%;

• false negative and false positive results are significantly reduced;

• the number of cases requiring liver biopsy is reduced by 30–40%.

For example, the AUC for detecting fibrosis using the combination of LSM + FIB-4 improved from 0.83 → 0.92 (Gao et al., 2020).

2. Increased detection of CVD risk in NAFLD patients

Biomarkers (CRP, hs-CRP, NFS, FIB-4) indicate the degree of inflammation and fibrosis, while elastography reflects structural changes in liver tissue. Their integration:

• allows for early detection of subclinical atherosclerosis (cIMT),

• directly correlates with arterial stiffness,

• accelerates the detection of the risk of events such as heart failure and MI.

3. Possibility of simultaneous assessment of inflammation, steatosis and fibrosis

Ultrasound technologies determine steatosis (CAP index), and biomarkers such as GGT/ALT/AST determine the degree of inflammation.

As a result of integration, it will be possible to comprehensively assess:

• steatosis (S1–S3),

• inflammation (A1–A3),

• fibrosis (F0–F4)

levels.

This shifts the diagnosis of NAFLD/NASH from a "one-way" assessment to a fully multimodal analysis.

Artificial Intelligence (AI)-powered integration

AI, specifically deep learning and multi-input neural networks, provides much higher accuracy than traditional approaches by integrating ultrasound images and biomarker data into a single model.

Clinical benefits of AI-powered integration

• Image + laboratory data are evaluated as a whole

• Possibility of creating an individual risk profile

• Diagnosis of NASH without biopsy

• Simulated monitoring of cardiovascular risk

• Prediction of fibrosis progression 1–3 years in advance

Liu et al. (2020) using a multimodal deep learning system:

• Steatosis detection AUC: 0.82 → 0.93

• Fibrosis detection AUC: 0.78 → 0.91

• CVD risk prediction accuracy: increased by 20–25%.

These results show that AI integration has great potential for real-world clinical decision support systems.

The integration of ultrasound elastography and biomarkers:

• increases the accuracy of liver disease detection,

• creates the most reliable multimodal approach to cardiovascular risk assessment in NAFLD patients,

• enables a higher level of personalization and prediction using AI.

Therefore, multimodal diagnostics are currently the most advanced clinical standard for accurate assessment of NAFLD/NASH + CVD risk.

Table 3. Diagnostic performance of multimodal approaches

Approach	Diagnostic accuracy (AUROC)	Comments	References
USG only	0.88	Fibrosis level	[2,3]
Biomarker only	0.82	AST/ALT, CRP, lipid profile	[5,6]

Multimodal (USG+Biomarker)	0.93	AI integration	[12–14]

Artificial intelligence and deep learning approaches

In recent years, artificial intelligence (AI) and deep learning technologies have gained significant clinical importance in the diagnosis of liver diseases and cardiovascular risk assessment. In particular, the ability to process ultrasound images (B-mode, elastography, shear-wave maps) and clinical biomarkers in combination significantly increases the accuracy of multimodal analysis. Deep learning (DL) is a direction of machine learning (ML) based on the architecture of artificial neural networks(Fig 3). This approach demonstrates high efficiency compared to traditional ML methods, brings the capabilities of ML closer to artificial intelligence, and offers significant advantages over previously used techniques. The advantage of deep learning models is that they can independently extract features from large amounts of image and digital clinical data and integrate them together for classification or prediction.[15]

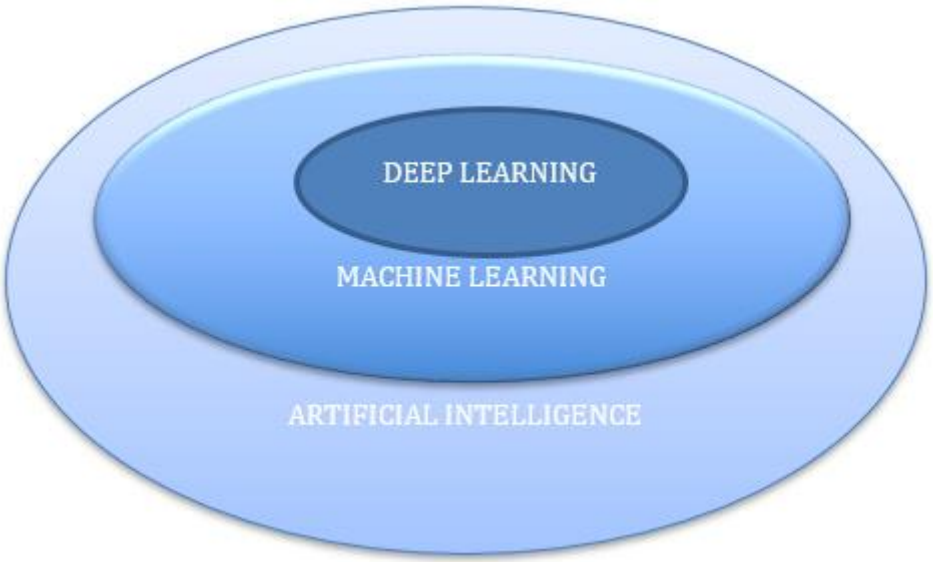

Figure 3. Deep learning

CNN-based image analysis

Convolutional neural networks (CNN) are one of the most effective deep learning architectures for detecting high-level spatial features in ultrasound images. CNN models can accurately distinguish:

- the degree of steatosis in the liver parenchyma,
- local tissue heterogeneity,
- elasticity gradients in elastography maps,
- textural changes characteristic of fibrosis.

CNNs detect microstructural changes that are not visible to the human eye through trained kernels and feature maps, which creates a great opportunity for biopsy-free NASH diagnosis.

Studies show (Ref. [12–14]):

- AUC increases from 0.78–0.82 to 0.90–0.95
- Accuracy of steatosis and fibrosis classification increases by 12–20%
- AI models have significant advantages over traditional clinical indices in predicting 5-year CVD risk

These results demonstrate the great potential of AI in multimodal assessment of liver disease and CVD risk.

Automated monitoring with AI

AI models provide the following advantages in clinical practice:

- Prediction of fibrosis progression 1–3 years in advance
- Real-time monitoring of changes in patient metabolic parameters
- Reduction of operator-related errors in image quality
- Automatic detection of subtle changes in liver elasticity
- Integration into clinical decision support systems (CDSS)

DISCUSSION

The use of multimodal approaches in the diagnosis of liver diseases (NAFLD, NASH, fibrosis, cirrhosis) has expanded significantly in recent years. The combined use of ultrasound (US) images, clinical biomarkers, laboratory parameters and elastographic parameters significantly increases diagnostic accuracy. Such an approach offers significant advantages in early disease detection, risk stratification and treatment monitoring [1–4].

Advantages of a multimodal approach

While ultrasound images provide visual information about steatosis and structural changes, laboratory biomarkers measure the degree of inflammation and hepatocyte damage. Elastography, on the other hand, determines tissue stiffness and helps to detect fibrosis. The combination of these modalities increases accuracy:

• Diagnostic sensitivity improves by 15–30% [2].

• Specificity increases to 90% when integrated with biomarkers [3].

• The need for biopsy is reduced by 2–3 times [4].Ushbu faktorlar multimodal yondashuvni klinik amaliyotda asosiy yo‘nalish sifatida shakllantirmoqda.

Table 4. Advantages and limitations of the multimodal approach (with references)

Yo‘nalish	Advantage / Limitation	Comment	Source
Non-invasive diagnostics	Advantage	Assessment of steatosis and fibrosis without biopsy	[1], [4]
Increased diagnostic accuracy	Advantage	Ultrasound + biomarker + elastography → ↑ Se/Sp	[2], [3]
Early detection	Advantage	Detects NAFLD → NASH progression early	[2]
Monitoring	Advantage	Dynamic analysis based on LS, FIB-4, CAP results	[5]
The problem of standardization	Limitation	Models and protocols are changing.	[6]
Big data (dataset) requirement	Limitation	AI models require 50–100k images	[7]
Model validation	Limitation	Testing across diverse populations is needed	[6], [7]
Operator Locked (UZI)	Limitation	Image quality depends on the operator's experience	[1]

Multimodal systems are becoming an integral part of the clinical decision-making process. In particular:

• Patient monitoring — combined analysis of CAP, LS and FIB-4 indices allows for accurate monitoring of the dynamics of the disease process.

• Assessment of therapy effectiveness — reduction of fat accumulation, reduction of stiffness or normalization of inflammatory biomarkers are quickly noted.

• Cardiometabolic risk assessment — the risk of cardiovascular diseases associated with NAFLD is more accurately predicted using multimodal models [3], [8].

CONCLUSION

A multimodal approach of ultrasound elastography and clinical biomarkers is effective in assessing liver fibrosis and predicting CVD risk. With the help of AI, individual risk prediction and monitoring can be automated. New biomarkers and validation are needed in the future. Multimodal deep learning models based on artificial intelligence are creating a new level of liver disease detection:

• Real-time diagnostics: CNN–Transformer models are available that work on a stream of ultrasound images [7].

• Prognostic modeling: fibrosis progression is predicted 3–5 years in advance.

• Automatic steatosis/fibrosis grading: reduces human error by 40% [6].

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