Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

CHRONIC LIVER DISEASE: AN INTEGRATED REVIEW OF HISTOPATHOLOGICAL, IMMUNOHISTOCHEMICAL, BIOCHEMICAL AND EPIDEMIOLOGICAL EVIDENCE

Alina Dumitrache (Păunescu) [1,2*], Monica Ileana Baniță [1], Cătălina Gabriela Pisoschi [1], Monica Marilena Țânțu [2], Ana Cătălina Țânțu [1], Nicoleta Anca Șuțan [2], Liliana Cristina Soare [2], Maria Cristina Ponepal [2]

[1]Doctoral School of University and Pharmacy of Craiova, Petru-Rareș Street no.2, 200349 Craiova, Romania
[2] Department of Natural Sciences, National University of Science and Technology POLITEHNICA Bucharest, Pitești University Centre, 1st Targul din Vale Street, 110040 Pitești, Romania

Abstract
Chronic liver disease represents a major global health burden characterized by progressive evolution from inflammation to fibrosis, cirrhosis and hepatocellular carcinoma. Accurate evaluation of liver damage is essential for diagnosis, prognosis and clinical management. This review summarizes current evidence regarding the role of histopathological and immunohistochemical indices in the assessment of liver disease.
Attention is given to key biomarkers such as alpha-smooth muscle actin (α-SMA), transforming growth factor beta 1 (TGF-β1), glial fibrillary acidic protein (GFAP) and CD5L which reflect hepatic stellate cell activation, inflammation and fibrogenesis. In addition, non-invasive methos including serum-based indices (APRI, FIB-4, GPR) and imaging technique are increasingly used in clinical practice.
Although non-invasive approaches offer significant advantages, histopathological evaluation remains the reference standards. The integration of these methods may improve diagnostic accuracy and patient monitoring, although further validation of emerging biomarkers is required for clinical implementation and improved patient outcomes.

Keywords: biochemical indices, epidemiological evidence, immunohistochemical parameters, histopathological observation

1. INTRODUCTION

Chronic liver diseases represent a major global health burden characterized by progressive structural and functional alteration that may culminate in fibrosis, cirrhosis and hepatocellular carcinoma (GBD, 2019; Griffin et al., 2021). The complexity of hepatic pathology requires a multidimensional approach for accurate diagnosis, staging and prognosis assessment. In this context histopathological and immunohistochemical analyses remain essential tools for understanding the mechanism underlying liver injury and fibrogenesis (Casari et al., 2023; Sterling et al., 2025).
Recent advances have highlighted the importance of specific molecular markers such as alpha-smooth muscle actin (α-SMA), transforming growth factor beta 1 (TGF-β1), glial fibrillary protein (GFAP) and CD5L in reflecting key processes including hepatic stellate cell activation, inflammation and extracellular matrix remodelling (Akpolat et al., 2005; Bàrcena et al., 2019;

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Carpino et al., 2005; Flisiak et al., 2005; Gairing et al., 2023; Morini et al., 2005). Along these, biochemical and hematological indices and non-invasive diagnostic methods have gained relevance in clinical practice for the evaluation of liver fibrosis and disease progression (Bibi et al., 2024; Janulaityte et al., 2025; Sterling et al., 2025).
The review aims to synthesize current knowledge regarding the role of histopathological markers and non-invasive parameters in the evaluation of liver disease with particular emphasis on their diagnostic, prognostic and clinical utility.

2. MATERIALS AND METHODS

Study design

This paper represents a systematic literature review focused on histopathological, immunohistochemical and biochemical markers involved in liver fibrosis and cirrhosis based on the PRISMA guidelines (Moher et al., 2009)

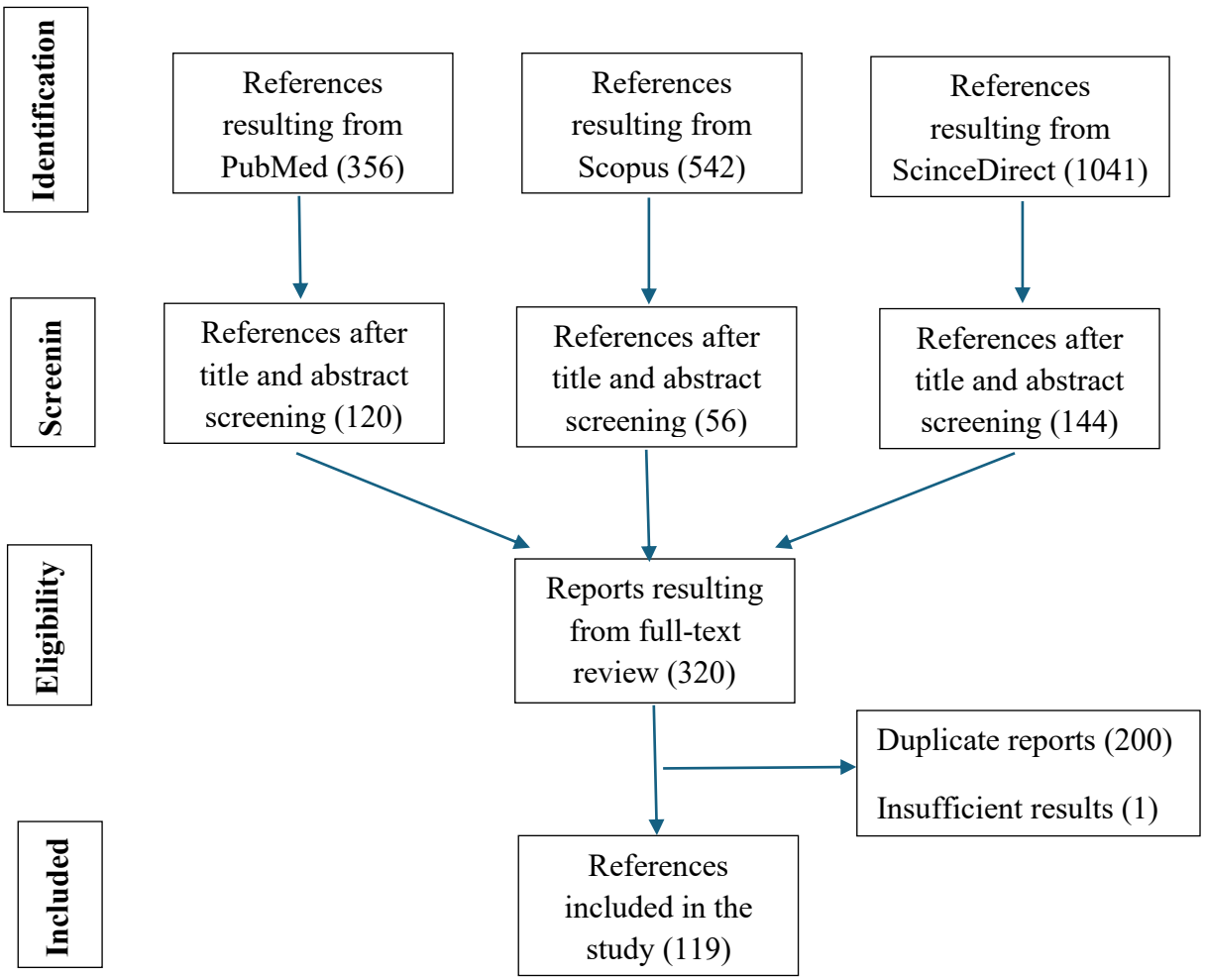

Figure 1. PRISMA Flowchart of studies selection methos

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Search strategy
A comprehensive literature search was performed in electronic databases including PubMed, Scopus and ScienceDirect.
The search covered studies published between 2000-2025 mostly. Keywords included: ″liver fibrosis″, ″cirrhosis″, ″alpha-SMA″, ″TGF-β1″, ″GFAP″, ″CD5L″, ″biomarkers″, ″FibroScan″, ″non-invasive markers″, ″chronic hepatitis B″, ″chronic hepatitis C″.
Inclusion and exclusion criteria
Inclusion criteria: original research articles, clinical studies and review; studies involving patients with chronic liver diseases; studies evaluating histopathological, immunohistochemical, biochemical or hematological markers in chronic liver disease
Exclusion criteria: case reports, editorials, conference abstracts without full text, non-English articles, studies lacking relevant data on fibrosis or biomarkers.
Study selection
Articles were screened based on title and abstract followed by full-text evaluation. Only studies meeting the inclusion criteria were retained. Duplicate records were removed.
Data extraction
Relevant data extracted from the studies included: author and year of publication, study design and population, type of liver disease, biomarkers analysed (α-SMA, TGF-β1, GFAP, CD5L), main findings regarding diagnosis, staging and prognosis.
Data synthesis
The selected studies were analysed qualitatively with emphasis on the role of histopathological and immunohistochemical markers, the utility of biochemical and hematological indices, the diagnostic and prognostic value of non-invasive methods. Findings were grouped and discussed comparatively to highlight similarities, differences and clinical relevance.

3. RESULTS AND DISCUSSIONS

3.1 Histopathological and immunohistochemical analysis of liver lesions, with emphasis on the importance of alpha-SMA (α-SMA), TGF beta1 (TGF-β1), GFAP and CD5L markers
In liver fibrosis, due to the replacement of healthy tissue by (myo)fibroblasts depositing large amounts of extracellular matrix proteins, there is loss of hepatocyte function, portal hypertension, variceal bleeding and increased susceptibility to infections (Casari et al., 2023). Although in the early stage, liver fibrosis is a dynamic and reversible process, from the cirrhotic stage there is significant progression to hepatocellular carcinoma. Defining the stage of fibrosis is very important for the prognosis and monitoring of liver disease in patients with chronic hepatitis. Various histological scoring systems to stage fibrosis and grade inflammation and steatosis have been used: Ishak system, Scheuer METAVIR score, Brunt classification (Ishak et al., 1995; Kleiner et al., 2005; Knodell et al., 1981).
Transient elastography and platelet-to-spleen ratio as the better noninvasive predictors of variceal development and bleeding (Marasco et al., 2019). The clinical study conducted by Răcășan et al. (2016) on patients with chronic hepatitis B and C using the noninvasive assessment method of liver fibrosis FibroScan showed a very low error rate (an accuracy of 79.16%, respectively 80% compared to PBH in patients with HCV, respectively HBV), the method being simple and reproducible.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Staging of liver cirrhosis is predominantly performed by the Child-Pugh score (three stages: A to C), which was created in the 1970 s, the first popular scoring systems for cirrhosis, which takes into account laboratory parameters such as serum bilirubin, albumin levels, INR but also clinical parameters (presence of ascites and hepatic encephalopathy) (Bibi et al., 2024). The Child-Pugh score also has disadvantages such as the subjectivity of the classification of ascites and encephalopathy and the ceiling effect resulting from a low score range (Peng et al., 2016).
To overcome the limitations of the Child-Pugh score, the MELD score was developed, which estimates 3-month mortality based on laboratory parameters: serum bilirubin, creatinine, and INR (Kamath et al., 2001). The MELD-Na score was created by adding serum sodium to the initial MELD equation, as hyponatremia highly correlates with poor outcomes in cirrhosis (Biggins et al., 2006). The model for end-stage liver disease (MELD) score, and its sodium-adjusted variant MELD Na has been implemented for liver transplant prioritization (Naik & Moorthy, 2025). The ability of Child-Pugh and MELD scores to predict individual complications of cirrhosis – ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and hepatocellular carcinoma (HCC) – is still under investigation (Naik & Moorthy, 2025).

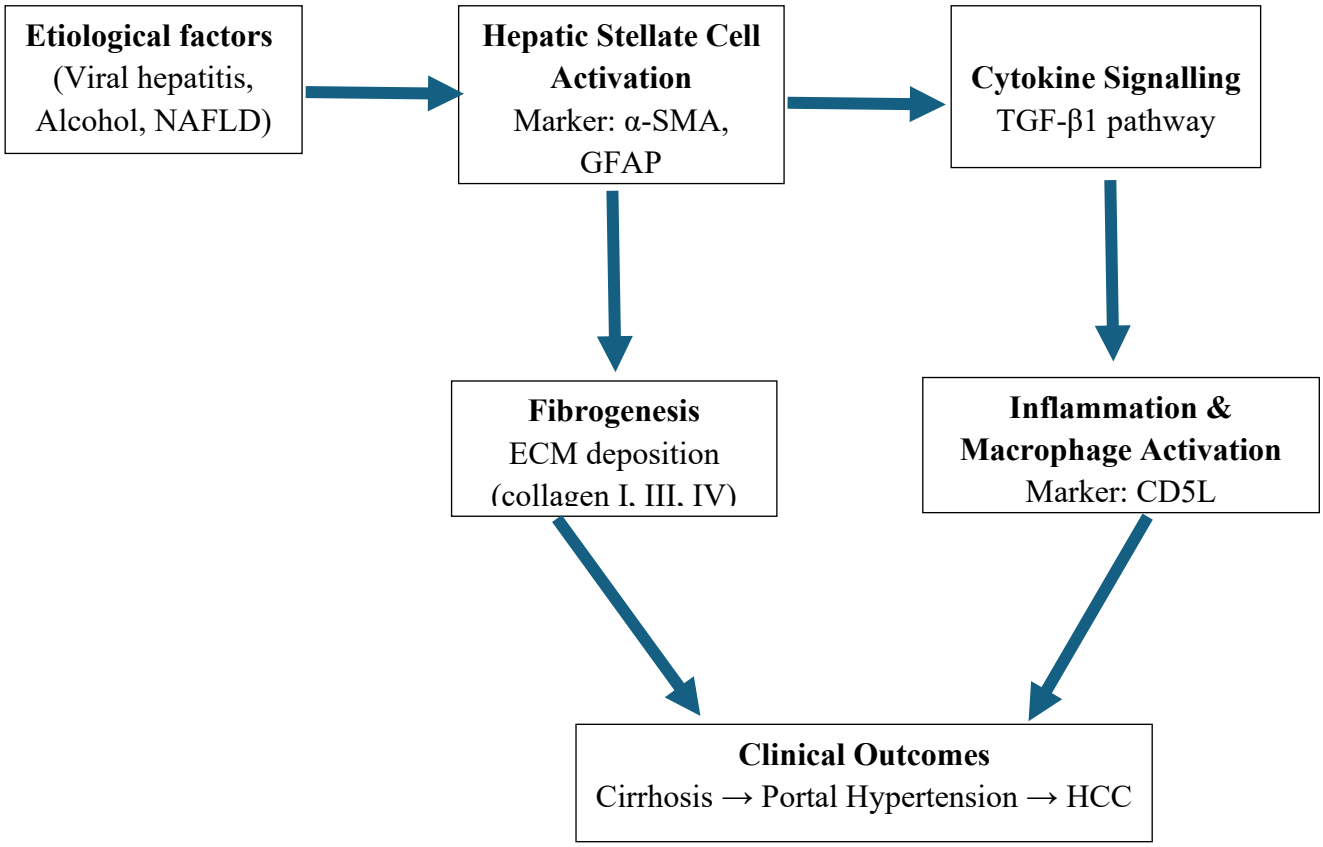

Figure 2. Mechanism of liver fibrogenesis and progression to cirrhosis and hepatocellular carcinoma (HCC)

The main complication of decompensated cirrhosis is ascites, caused by portal hypertension and sodium retention. In a study on the effectiveness of the MELD score, MELD-Na and Child-Pugh score (CPS) in predicting complications in patients with cirrhosis conducted in 2025 by Naik &

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Moorthy, the authors found that the CPS was more accurate in predicting ascites (Angeli et al., 2018), while the MELD and MELD-Na scores predicted hepatic encephalopathy and hepatorenal syndrome more reliably.

Current noninvasive assessments are developed in relation to cross-sectional, histopathologic scores and do not account for the dynamic progression of fibrogenesis (Sterling et al., 2025). The "direct" markers used for staging liver fibrosis are mostly complex macromolecules derived from myofibroblasts and extracellular matrix remodeling (glycoproteins - hyaluronate, laminin, procollagen 3, collagen type 4, collagenases and their inhibitors, cytokines related to the fibrinogenic process: alpha-SMA, TGF-beta 1, TNF-alpha), while the "indirect" markers reflect inflammation and/or portal hypertension (Sterling et al., 2025).

In the case of liver damage (viruses, alcohol, steatosis), stellate cells become activated, lose their vitamin A storage capacity and differentiate into myofibroblasts, starting to produce large amounts of **alpha-SMA**. Stellate cell transcription has been claimed to be controlled by α-SMA (Mann & Smart, 2002). Activation of hepatic stellate cells represents the initial stage in the development of fibrosis (Friedman, 1993), and the appearance of alpha-SMA positive cells often precedes the visible deposition of collagen (structural fibrosis). Alpha-SMA (alpha-smooth muscle actin) is considered a reliable marker of hepatic stellate cell (HSC) activation – (Akpolat et al., 2005; Carpino et al., 2005; Morini et al., 2005), being useful for identifying early stages of fibrosis, although α-SMA positivity in a few stellate cells of the liver is normal.

Akpolat et al., (2005) investigated the predictive importance of alpha-SMA and concluded that in liver biopsy samples, α-SMA may represent a valuable marker in the evaluation of stellate cell activation and fibrosis progression and an early indicator of the development of fibrosis. Alpha-SMA is a reliable marker of hepatic stellate cell activation, which precedes the deposition of fibrous tissue even in the context of chronic recurrent HCV hepatitis after liver transplantation (Carpino et al., 2005).

In male Wistar rats with experimentally induced fibrosis, Cardoso-Lezama et al. (2024) found that serum α-SMA levels were significantly correlated with hepatic α-SMA levels as well as with the severity of hepatic fibrosis, suggesting that serum α-SMA can be considered a potential reliable and noninvasive biomarker for early hepatic fibrosis. Alpha-SMA is therefore a highly accurate tool in liver biopsy to confirm that fibrosis is active and progressive, reflecting the number of myofibroblasts producing extracellular matrix.

Chronic liver inflammation leads to the activation of Kupffer cells that locally release proinflammatory cytokines such as TNF-α and interleukins (IL) 1β and 6 (Capuron & Miller, 2011; Laye et al., 2000). Transforming growth factor (**TGF-β**) is a multifunctional protein in the cytokine family, which activates hepatic stellate cells to deposit extracellular matrix and stimulates fibrosis formation (Gressner et al., 1993). The natural source of TGF-β is platelets, from which the cytokine is released immediately because of their degranulation and occurs directly after injury or because of immunological reactions (Braczkowski et al., 2024).

TGF-β strongly suppresses hepatocyte proliferation, stimulates the production of extracellular matrix proteins by stellate cells, and mediates apoptosis, unbalanced TGF-β activity during regeneration can lead to liver fibrosis (Sanderson et al., 1995). Dysfunctional TGF-β signaling can play key roles in numerous pathological processes, including fibrotic diseases and inflammatory diseases, as well as tumors (Deng et al, 2024). Fibrotic diseases are closely associated with the hyperactivity of TGF-β signaling (Deng et al., 2024). The effects of TGF-β signaling tissue fibrosis (Border et al., 1990) have been studied shortly after the discovery of the cytokine.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

TGF-β1 has an important role in the pathogenesis of viral hepatitis, being considered the main mediator of fibrogenesis in the liver, with increased levels being correlated with disease severity (Brenner, 2009; Flisiak et al, 2005). In fibrotic livers, TGF-β1 expression increases markedly with fibrogenic activity (Sakaguchi et al., 2002). Flisiak et al. (2005) underlines the role of TGF-beta1 in the pathogenesis of acute viral hepatitis, which seems to be related to the degree of hepatocyte damage, but not to its mechanism or etiology. TGF-β can enhance viral infection through certain pathogen-specific mechanisms as in cases of hepatitis C virus (HCV) infection (Lin et al., 2008).
In the early stages of tumor formation, TGF-β acts as a tumor suppressor during but turns into a tumor promoter at later stages of tumor development (Deng et al., 2024).
The role of TGF-β and PDGF-mediated signaling pathways in both fibrogenesis and tumorigenesis, following the activation of hepatic stellate cells (HSCs), was highlighted by Beno et al. (1995). To rectify the dysfunction of TGF-β in different kinds of diseases, a series of methods for regulating TGF-β activity have been developed by intervening at the level of biosynthesis, activation, and signaling (Border, 1990). A series of studies using inhibitors and antagonists of the TGF-β-mediated signaling pathway (LY2109761, Smad7, tyrosine kinase inhibitor PTK/ZK, pentoxifylline) have shown a decrease in connective tissue growth factor (CTGF) synthesis and a reduction in tumor growth (Beno et al., 1995; Hernández et al., 2007; Mikula et al., 2006; Narmada et al., 2013).
Serum and tissue levels of TGF-β have shown potential as predictors or indicators of the development, complication, response, recurrence, and outcomes of various kinds of diseases, but TGF-β or related factors as clinical biomarkers still need further development and assessment (Deng et al., 2024).
TGF-β has been shown to play a key role in many physiological and pathological processes of the liver, and its concentration may be a potential diagnostic and prognostic marker in liver diseases (Braczkowsky et al., 2024).
GFAP (Glial Fibrillary Acidic Protein) is a cell structural protein with a role in various physiological processes such as the maintenance of the blood–brain barrier, and astrocyte migration and proliferation (Gairing et al., 2023). Although GFAP expression is a key step in the astrocytes differentiation and constitutes the hallmark response of astrocytes to injury, it is also used in the study of liver diseases as a marker of early activation of hepatic stellate cells (Gairing et al., 2023).
GFAP expression has been correlated with vascular remodeling and fibrosis progression, being unevenly distributed in the liver depending on the stage of the disease, GFAP-positive stellate cells are distributed in the earlier stages and confined to the periphery of the hepatic lobule in the advanced ones, and is a marker related with the acquisition of contractile properties in a subpopulation more closely associated with precocious stages of the fibrosis. (Carotti et al., 2008). GFAP could represent a useful marker for early hepatic stellate cells activation (Abdelhak et al., 2018).
Gairing et al. (2023) observed that GFAP levels are associated with hepatic encephalopathy in patients with cirrhosis, suggesting that astrocyte injury may already occur in patients with cirrhosis and subclinical cognitive deficits and that's GFAP could be explored as a novel biomarker. GFAP may be useful for detecting early fibrosis in patients with chronic hepatitis C (CHC), helping to identify mild stages before cirrhosis develops (Carotti et al., 2008). Today, even very low GFAP levels in the blood can be detected using high-sensitivity assays (Abdelhak et al., 2018).
CD5L (CD5 antigen-like)/AIM (apoptosis inhibitor of macrophage) is a member of the scavenger receptor cysteine-rich (SRCR) family (Gebe et al., 1997; Miyazaki et al., 1999) and is secreted

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

primarily by macrophages (including Kupffer cells in the liver). CD5L is predominantly found in the blood in a form combined with immunoglobulin (Ig) M (Takimoto-Sato et al., 2023). CD5L is a marker of inflammation and macrophage activation, intervening not only in the regulation of inflammation (Kim et al., 2021; Sánchez-Rodríguez et al., 2022; Yang et al., 2023) but also in the regulation of lipid metabolism (Miyazaki et al., 2011; Sanchez-Moral et al., 2021) and in the pathogenesis of hepatocellular carcinoma (Luo et al., 2021; Shimizu et al., 2022; Yamazaki et al., 2014). Thus, CD5L plays an essential role in the development of conditions determined by acute or chronic inflammation, including infectious, metabolic and autoimmune diseases (Sanchez-Moral et al., 2021).

In liver pathology, CD5L is expressed primarily by macrophages (including Kupffer cells) and hepatocytes under stress conditions, such as chronic inflammation, fibrosis, and tumor (Aran et al., 2018). CD5L is overexpressed in HCC tumor tissue compared to adjacent non-tumor tissue. CD5L activates the UPR and autophagy mechanisms in the liver cancer lines Huh7, thereby providing a novel molecular link between the unfolded protein response (UPR) and autophagy in liver cancer (Aran et al., 2018).

Table 1 Immunohistochemical markers involved in liver fibrogenesis

MARKER	CELLULAR TYPE / SOURCE	MAIN BIOLOGICAL ROLE	SIGNIFICANCE IN FIBROSIS	CLINICAL UTILITY/ DIAGNOSTICS
α-SMA (alpha-smooth muscle actin)	Activated stellate cells (HSCs), myofibroblasts (Akpolat et al., 2005; Carpino et al., 2005; Morini et al., 2005)	Myofibroblast differentiation marker; involved in contractility and extracellular matrix synthesis	Early indicator of HSC activation; precedes collagen deposition	Evaluation of fibrogenic activity; sensitive marker for early stages (Akpolat et al., 2005; Cardoso-Lezama et al., 2024)
TGF-β1 (Transforming Growth Factor beta 1)	Platelets (Braczkowski et al., 2024), stellate cells, macrophages	Major profibrogenic cytokine; stimulates ECM synthesis and inhibits hepatocyte regeneration	Correlated with fibrosis severity (Deng et al., 2024); central mediator of fibrosis progression (Brenner, 2009; Flisiak et al, 2005)	Potential prognostic biomarker (Braczkowsky et al., 2024; Deng et al., 2024); therapeutic target
GFAP (Glial Fibrillary Acidic Protein)	Subpopulation of hepatic stellate cells (Carotti et al., 2008)	Structural protein involved in early HSC activation (Gairing et al., 2023)	Increased expression in early stages of fibrosis	Marker for early detection of fibrosis (Carotti et al., 2008; Abdelhak et al., 2018); possible serum biomarker (Gairing et al.,

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

				2023)
CD5L (CD5 antigen-like/AIM)	Macrophages (Kupffer cells), hepatocytes under stress (Aran et al., 2018)	Regulates inflammation (Kim et al., 2021; Sánchez-Rodríguez et al., 2022; Yang et al., 2023), lipid metabolism (Miyazaki et al., 2011; Sanchez-Moral et al., 2021) and cell survival	Levels increase with severity of fibrosis and inflammation (Bárcena et al. (2019)	Marker of inflammation and disease progression; useful in monitoring (Bárcena et al., 2019; Caussy et al., 2018; Gangadharan et al., 2007; Gray et al, 2009; Yamazaki et al., 2014)
TNF-α	Macrophages	Proinflammatory cytokine that initiates the inflammatory cascade	Contributes to HSC activation and fibrosis progression	Indirect marker of liver inflammation
Laminin	Extracellular matrix	Component of the basement membrane	Increases in advanced fibrosis	Direct marker of fibrosis (Sterling et al., 2025)
Hyaluronic	Extracellular matrix	Glycoprotein involved in tissue remodeling	Correlated with the degree of fibrosis	Non-invasive serum biomarker

Bárcena et al. (2019) explored the role of CD5L in hepatic inflammation and fibrosis with human samples from hepatitis and cirrhotic patients and the widely used rodent model of CCl4-induced fibrosis and reported that serum levels of CD5L significComponent of the basement membraneand correlated to the stage of liver fibrosis (which suggests that serum CD5L is strongly associated with liver disease severity). Also, by immunohistochemistry in liver tissues, some correspondence has been identified between circulating CD5L and its hepatic protein expression levels. Therefore, CD5L is a useful immunohistochemical marker to assess macrophage activation, liver fibrosis and the presence of hepatocellular carcinoma, closely correlated with the progression and severity of chronic liver damage.

Gangadharan et al. (2007) studied the possibility of using new serological biomarkers for the diagnosis of liver fibrosis in patients diagnosed with hepatitis C, including CD5L. The increase in CD5L levels reflects active liver inflammation, a central mechanism in most liver diseases (hepatitis, NASH, cirrhosis). Thus, in patients with advanced liver damage, increased levels of CD5L were recorded (regardless of the nature of the disease) significantly correlated with other parameters characteristic of liver function (Bárcena et al., 2019; Caussy et al., 2018; Gangadharan et al., 2007; Gray et al, 2009; Yamazaki et al., 2014)

Numerous studies have shown that serum CD5L levels increase progressively with the degree of liver damage (Bárcena et al., 2019) and correlate with histological scores (Bárcena et al., 2019) and tissue expression (Bárcena et al., 2019), being useful not only for diagnosis but also for staging. However, Sánchez-Rodríguez et al. (2022) found significant reductions in plasma extracellular vesicles (EVs) in patients with cirrhosis, regardless of its severity, with considerable changes in the

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

content of CD5L and lipid mediators as the disease progressed. Due to its simple methodology and reproducibility, CD5L is a promising candidate for expanded clinical use in the screening and monitoring of liver diseases (Sanchez-Moral et al., 2021).
Non-invasive methods have become an important tool in clinical practice, with an increasing number of such methods now available, methods validated especially in patients with chronic hepatitis C. The future of cirrhosis management is focused on personalized prediction, integrating objective scoring models with patient-level variables—comorbidities, nutrition, quality of life, and inflammatory status.

3.2 Analysis of biochemical and hematological indices in chronic hepatitis B, C, alcoholic and non-alcoholic cirrhosis

Due to the pathological complexity of liver diseases and high mortality, it is necessary to use blood biomarkers that accurately reflect the state of liver damage, with increasing emphasis on the use of non-invasive tests in the diagnosis and staging of fibrosis (Dumitrache et al., 2025).
The defining element in the detection and monitoring of viral hepatitis is the detection and measurement of liver fibrosis (Răcășan et al., 2016). In addition to liver biopsy (invasive method), non-invasive methods are also widely used (serum methods - single parameters or scores that combine several parameters - and imaging methods - FibroScan, FibroMax). In recent years, emphasis has been placed on the development of multiple noninvasive blood biomarkers and imaging modalities or tests to determine the presence and severity of liver fibrosis, steatosis and clinically significant portal hypertension (Sterling et al., 2025).
The use of biochemical and hematological indices is essential for the early diagnosis and monitoring of the progression of liver diseases (hepatitis B, C, alcoholic and non-alcoholic cirrhosis). Although there are overlaps in the clinical picture, each etiology presents changes in the level of liver enzymes, synthesis proteins and blood figured elements. The analysis of biochemical and hematological indices allows the differentiation between inflammation (hepatitis) and severe degradation of the organ (cirrhosis), as well as the identification of the etiological cause. Indirect markers of liver fibrosis are increasingly used, markers that reflect changes in liver function: platelet count, AST, ALT, GGT, gamma globulins, albumin, prothrombin time (Friedman, 2003; Sebastiani & Alberti, 2006). Routine hematological, biochemical and coagulation tests provide vital information about liver health, indirectly reflecting immune activity, fibrotic progression and the extent of liver cell damage (Janulaityte et al., 2025). Fibrosis assessment based on blood tests has the advantage of investigating the interaction between inflammatory response and fibrogenesis (Sterling et al., 2025).
Hepatocyte injury can be assessed by measuring alanine aminotransferase ALT (ALT) and aspartate aminotransferase AST (AST), which increases rapidly in the blood when liver cells are inflamed or damaged (viral hepatitis, fatty liver, alcohol) and are essential for assessing liver health and diagnosing liver disease (Bibi et al., 2024). ALT is the most specific liver enzyme, with elevations directly indicating liver damage, while AST is elevated not only in liver disease but also in heart or muscle damage. Both liver enzymes showed elevated expression in HCV infected individuals, but ALT is a more specific biomarker compared to AST of HCV infection and liver damage (Amjad et al., 2021). The AST/ALT ratio (AAR) was one of the first non-invasive markers used, values > 1, due to increased AST release, decreased AST clearance and/or impaired ALT synthesis, being indicative of liver cirrhosis (a disadvantage is that it cannot be used for fibrosis) (Lai et al., 2024).

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Cholestasis (blockage of the bile ducts) can be assessed by measuring alkaline phosphatase (ALP) and γ-glutamyltransferase GGT (Gamma-GT), with elevations of these markers indicating bile duct obstruction, cholestatic hepatitis, or alcohol consumption. Calvopina et al. (2022) demonstrated utility of the gamma-glutamyl transpeptidase-to-platelet ratio (GPR) in predicting fibrosis severity in children with cystic fibrosis-related liver disease.

Non-invasive indices from routine tests (hematological, biochemical, and coagulation tests) and derived indices (FIB-4, APRI, AST/ALT ratio, PLR, NLR, SII, AISI, PNI, HALP, PAR, NAR) provide valuable information about the inflammatory and nutritional status of patients with hepatitis C, the values differing depending on sex and degree of viremia (Janulaityte et al., 2025).

Recent research (Xuan et al., 2025) highlights the elevated GGT to HDL-C ratio (GHR) as a powerful, novel, non-insulin-based marker for identifying metabolic dysfunction, particularly in the prediction of Non-Alcoholic Fatty Liver Disease (NAFLD), GHR being considered a better predictor of these conditions than GGT or HDL-C alone. GPR generally outperforms older markers like APRI and FIB-4 in detecting significant advanced fibrosis.

Differentiation by scores is also currently used. Numerous studies have demonstrated the prognostic value of indices such as the fibrosis-4 index (FIB 4) and AST to platelet ratio index (APRI) in assessing fibrosis (Sterling et al., 2006).

The AST/platelet ratio (APRI) is used to classify fibrosis and cirrhosis, but approximately 50% of cases remain undiagnosed (Sebastiani & Alberti, 2006; Wai et al., 2003). APRI has been proposed as a noninvasive and readily available tool for the assessment of liver fibrosis in chronic hepatitis C (Loaeza-del-Castillo et al., 2008). FIB-4 is an index that uses platelets, ALT, AST and age, and has good performance in detecting severe fibrosis and cirrhosis in chronic hepatitis C (Vallet-Pichard et al., 2007).

The Forns index is a score that provides information about significant fibrosis (but not cirrhosis) resulting from the combination of age, GGT and platelets, with an accuracy between 50% and 85% reported in hepatitis C (Forns et al., 2002; Sebastiani & Alberti, 2006).

To quantify fibrosis and steatosis, the FibroMax/FibroScan scores are used, which analyze complex sets of markers (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1). The most validated non-invasive procedure for fibrosis of various etiologies is Fibrotest, which combines GGT, total bilirubin, haptoglobin, alpha-2-macroglobulin, apolipoprotein A1, age and sex (Imbert-Bismut et al., 2001). There are also other fibrosis markers such as: Pohl Score, FIBROspect II, European Liver Fibrosis Group Algorithm (ELFGA), and Hepascore. Ekin et al. (2023) evaluated the efficiency of nine non-invasive markers for predicting liver fibrosis in patients with chronic Hepatitis B: Aspartate aminotransferase to Platelet Ratio Index (APRI), Fibrosis-4 score (FIB-4), Aspartate aminotransferase to Alanine aminotransferase Ratio (AAR), AAR to Platelet Ratio Index (AAPRI), Gamma glutamyl transpeptidase to Platelet Ratio (GPR), King's Score, Fibro quotient (Fibro-Q), S Index and Platelet to Lymphocyte Ratio (PLR) and concluded that GPR ((GGT/ upper limit of normal for GGT) / PLT (109/L) x 100), King's Score ((Age (years) x AST x INR) / PLT (109/L)) and S-Index ((1000 x GGT) / (PLT (109/L) x Albumin^2)) have the best diagnostic values for fibrosis staging, providing a valuable non-invasive alternative on liver biopsy.

The evaluation of the liver's synthetic function can be performed by determining albumin (its level decreases when the liver is severely affected, as occurs in cirrhosis) and prothrombin time (INR/PT) – if it increases, the liver no longer synthesizes coagulation factors. INR alone cannot portray the complex interaction of pro- and anticoagulants in cirrhosis (Intagliata et al., 2021). APP (albumin platelet product) can diagnose fibrosis stage, especially (Fujita et al., 2021).

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Table 2. Non-invasive biomarkers and scores for liver disease assessment

Marker/ Score	Parameters included	Clinical Significance	Advantages	Limitations	References
APRI	AST, PLT	Assesses fibrosis and cirrhosis	Simple, inexpensive	Limited sensitivity (~50% missed cases)	Wai et al, 2003; Sebastiani& Alberti, 2006
FIB-4	Age, AST, ALT, PLT	Detects advanced fibrosis	Widely validated	Influenced by age	Vallet-Pichard et al., 2007
GPR	GGT, PLT	Predictor of significant fibrosis	Better than APRI/FIB-4 in some studies	Limited standardization	Ekin et al, 2023; Sterling et al., 2025
GHR	GGT, HDL-C	Predictor of NAFLD and metabolic dysfunction	Nove land promising	Requires further validation	Xuan et al., 2025
Forns Index	Age, GGT, PLT	Detects significant fibrosis	Moderate accuracy (50-85%)	Cannot detect cirrhosis	Forns et al., 2002; Sebastiani & Alberti, 2006
FibroTest	Multiple biomarkers	Accurate fibrosis assessment	Highly validated	Expensive, less accessible	Imbert-Bismut et al., 2001
Inflammatory indices NLR, PLR, SII	Hematological parameters	Reflect systemic inflammation	Easily derived	Non-specific	Janulaityte et al., 2025; tang et al, 2025

The evaluation of detoxification and metabolism function can be performed by means of bilirubin levels (total, direct or indirect); its increase leads to jaundice (yellowing of the skin/eyes) and indicates the inability of the liver to process the degradation products of hemoglobin. Hyperbilirubinemia is a known marker of liver and bile alterations and has prognostic value in certain liver diseases (hepatic cirrhosis can be accompanied by progressive bilirubin elevations) (Guerra Ruiz et al., 2021).

Chronic liver diseases leading to advanced fibrosis and cirrhosis are associated with bleeding disorders and thrombocytopenia due to splenomegaly and impaired hepatocyte synthesis (Rautou et al., 2023). Platelets have been observed to play an important role in fibrosis (Mandel et al., 2022). Low platelet levels (thrombocytopenia) correlate with the severity of liver dysfunction, fibrosis, portal hypertension, and splenomegaly (Van der Meer et al., 2012), some patients also display platelet functional defects (Lambert, 2016). Patients with acute or chronic liver diseases frequently present with complex alterations in the hemostatic system (Lisman et al., 2002) including reduced levels of coagulation factors and changes in platelet count (Casari et al., 2023).

Anemia also occurs frequently in liver disease due to bleeding (esophageal varices), nutritional deficiencies, or hemolysis. Changes in white blood cell count (leukopenia/leukocytosis) may

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

indicate infection or bone marrow suppression. Changes in leukocyte, erythrocyte, and platelet-related markers may indicate immune dysregulation and early fibrotic changes (Tang et al., 2025). Clinical studies have shown that higher platelet count is associated with less fibrosis (Wang et al, 2018).

For predicting liver fibrosis and cirrhosis in patients with chronic hepatitis B, Chen et al. (2013) recommends the use of RDW to Platelet Ratio (RPR). Ding et al. (2021) recommends the INR-to-platelet ratio (INPR) as a novel, non-invasive index for predicting liver fibrosis in patients with chronic hepatitis B (CHB). Hypercoagulability and thrombosis illustrate the impact that hepatic imbalances can have on tightly controlled effector cascades in hemostasis (Rautou et al., 2023).

The combined determination of biochemical and hematological indices provides an image of liver "health", the severity of fibrosis and disease progression without the need for invasive or costly procedures, being indispensable indices for rapid diagnosis and correct risk management (Tang et al., 2025). Dumitrache et al. (2026) conducted a single-center cross-sectional study that highlighted the prognostic utility in staging liver fibrosis of some serological biomarkers (AST, ALT, TBIL, ALB, PLT, INR, GGT, CD5L and TGFβ1) and non-serological indices (AST/ALT ratio, ALBI score, GPR, APRI, FIB-4, INPR and FibroQ) in four etiologies (including CHB, CHC, ALC and NALC)

HCV infection modifies hematological, biochemical and coagulation parameters in a gender- and viremia-dependent manner (Janulaityte et al., 2025).

There are no validated blood biomarker thresholds that correlate with fibrosis stage in HCV patients, and they are associated with high rates of false-negative results for advanced fibrosis after antiviral therapy in patients with HBV or HCV (Sterling et al., 2025).

3.3 Incidence of chronic liver diseases B, C, alcoholic and non-alcoholic cirrhosis in the population, highlighting comorbidities and mortality risk

Worldwide, in 2017, approximately 1.5 billion people suffered from chronic liver disease (CLD): non-alcoholic fatty liver disease (NAFLD) - 60%, chronic hepatitis B virus (HBV): 29%, hepatitis C virus (HCV): 9% and alcohol-related liver disease (NAFLD): 2% (GBD, 2019).

Chronic infections with hepatitis B (HBV) and C (HCV) viruses are major public health problems, associated with a series of liver comorbidities, which can frequently progress to liver cirrhosis, liver cancer (hepatocellular carcinoma) and require careful monitoring. Liver disease is considered the 11th leading cause of death worldwide, with figures likely underestimated (Griffin et al., 2021).

Europe has the highest burden of liver disease in the world, with an increasing trend in many countries (Pimpin et al., 2018). The etiology of liver disease in Europe follows a geographical pattern, with alcohol being predominant in Western countries, while in Eastern countries viral hepatitis B and C are the most common causes, with a higher prevalence of hepatitis C (Pimpin et al., 2018).

People infected with the hepatitis C virus are often asymptomatic for many years, but it slowly damages the liver, leading to cirrhosis, hepatocellular carcinoma (HCC) (Cooke et al., 2024). According to data from the World Health Organization (2024), globally in 2022 there were approximately 304 million people living with chronic HBV or HCV infection (254 million with HBV and 50 million with HCV) and 2.2 million new infections during the same period. WHO estimates that over 6,000 new infections with viral hepatitis B and C occur daily, and approximately 1.3 million deaths occur annually due to liver complications, such as cirrhosis and liver cancer (WHO, 2024). Although the World Health Organization (WHO) aims to achieve 90% vaccination

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

coverage at birth by 2030, global coverage of birth doses is only 46% overall (Al-Busafi & Alwassief, 2024).

Despite the availability of effective interventions to prevent and treat hepatitis B and C, these diseases remain the leading causes of cirrhosis, especially in low- and middle-income countries (GBD, 2019).

The incidence and prevalence of HBV vary substantially between different geographical regions, reflecting the diverse impact of socio-economic factors, health policies and preventive measures (Gnyawali et al., 2024). Thus, in Sub-Saharan Africa and East Asia, HBV prevalence rates exceed 8% (due to perinatal transmission and horizontal transmission during early childhood (Fofana et al., 2023), while countries in Western Europe and North America have significantly lower HBV prevalence rates, often below 2% (Al-Busafi & Alwassief, 2024).

In WHO reports, the cumulative incidence of HBV and HCV globally decreased slightly in 2022 compared to 2019 (2.2 million compared to 2.5 million new cases), reflecting advances in HBV vaccination and HCV treatment (WHO, 2024). However, the same report shows that only a small proportion of infected people had access to treatment; thus, in 2022, only about 13% of people with chronic HBV infection and about 36% of those with HCV had been diagnosed, and antiviral treatment was received by only about 3% (HBV) and about 20% (HCV) (WHO, 2024).The European Centre for Disease Prevention and Control has estimated that there are 2.4 million individuals with chronic HCV infection in the EU/EEA (GBD, 2019).

However, Eastern European countries, including Romania, report higher HBV prevalence rates compared to Western countries (Bivegete et al., 2023), cost-effective interventions are needed to continue the prevention and treatment of viral hepatitis (Iacob et al., 2024). Based on 4 studies conducted on 1048 patients with cirrhosis in Romania, between 2000 and 2018, the incidence of HBV infections was approximately 21% and that of HCV approximately 29% (data processed by Alberts et al., 2022).

The screening program LIVE(RO)2 results show significant demographic and epidemiological patterns of HBV prevalence in Romania showed an overall prevalence rate of chronic HBV infection of 1.67% (Iacob et al., 2024). In Romania, HBVs prevalence was higher among males than females. Risk factors associated with HBsAg seropositivity in this study were male sex, rural residence, contact with infected individuals, and certain medical procedures (e.g., hemodialysis, blood transfusions).

The global incidence of HCV infection in 2020 was 1.43-1.5 million individuals (0.7% of the population) – a decrease compared to 2015 of 0.9%, like HBV. The highest prevalence in 2020 in eastern Europe (2.9%) – Polaris Observatory HCV Collaborators, 2022.

Specialized studies show that there are significant gender differences in the epidemiology and clinical characteristics of HBV infections (Liu et al., 2022). The prevalence of chronic HBV infection is higher in men compared to women, as shown by numerous specialized studies (Iacob et al., 2024; Su et al., 2007).

Also, the possibility of progression to more severe forms is higher in men compared to women (Stroffolini et al., 2015). Sanai et al., (2019) conducted a retrospective observational study showing that CHB patients in Saudi Arabia were older in 2015 compared to 2010 and 2012 and more likely to develop comorbidities, including cirrhosis.

Most studies show a higher prevalence of chronic hepatitis C in men, especially in middle-aged men (Bhattarai et al., 2022), with lower levels of education, unemployed and often unmarried, living predominantly in urban areas. Some studies show an increased prevalence of chronic hepatitis C in

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

women (Pennap, 2010; Imran et al., 2012) - often linked to unsafe medical or obstetric procedures. Key risk factors include intravenous drug use (IVDU), blood transfusions, and unsafe medical procedures, with Genotype 1 being the most common (Posuwan et al., 2024; Talić Drlje et al., 2025).

The demographic profile of patients with chronic hepatitis C (HCV) has evolved significantly with the advent of new antiviral therapies (DAAs) and varies depending on the geographical region and dominant risk factors (Devarbhavi et al., 2023; Stasi et al., 2024).

The most common comorbidities among patients with hepatitis C include type 2 diabetes, cardiovascular disease, and liver cirrhosis (Tsai et al., 2023). The risk of developing cirrhosis over the next 20 years in patients with chronic hepatitis C is estimated at 15-30% (2). The fact that worldwide about 42% of patients with cirrhosis are infected with HBV suggests the significant role HBV plays in liver disease progression (Iacob et al., 2024). Although the mortality of chronic liver disease caused by HBV and HCV has decreased from 1990 to 2019, the number of deaths will continue to increase until 2030 (Ou et al., 2024).

Mortality from liver diseases is approximately 2 million deaths annually, (4% of all deaths), one in three deaths being female (WHO, 2017). Chronic HBV and HCV infections were responsible for 96% of the 1.3 million deaths caused by hepatitis viruses worldwide in 2015, 720,000 of which occurred in the cirrhosis stage (WHO, 2017). The trend reported by (Ciardullo et al., 2024) for the last 10 years regarding the relative contribution of different liver diseases to the development of end-stage liver disease was a reduction in chronic viral hepatitis and an increase in deaths related to alcoholic liver disease ALD and metabolic dysfunction–associated steatotic liver disease MASLD.

The EASL-HEPAHEALTH (2018) – Burden of liver disease in Europe report from 2018 states that over 150,000 of the deaths recorded annually in Europe are determined by complications of chronic liver disease; the same report emphasizes that Romania has the highest mortality (36 deaths per 100,000 inhabitants) due to chronic liver disease.

Chronic hepatitis B (CHB) affected approximately 296 million people globally in 2019, leading to approximately 820,000 deaths, while chronic hepatitis C (CHC) affected approximately 58 million people and led to 290,000 deaths (WHO, 2024).

In 2022, viral hepatitis was one of the leading causes of death worldwide after COVID-19 - chronic hepatitis B (CHB) caused about 820,000 deaths, while chronic hepatitis C (CHC) caused 290,000 deaths (WHO, 2024).

It is estimated that 21% of patients diagnosed with chronic HCV infection, about 66% had been treated with direct-acting antivirals (DAAs) by the end of 2019 (Devarbhavi et al., 2023; Stasi et al., 2024).

Worldwide, in 2017, approximately 1.5 billion people suffered from chronic liver disease (CLD): non-alcoholic fatty liver disease (NAFLD) - 60%, chronic hepatitis B virus (HBV): 29%, hepatitis C virus (HCV): 9% and alcohol-related liver disease (NAFLD): 2% (GBD, 2017). In a large review published by Alberts et al. (2022) the authors report a prevalence of 42% of HBV infection and 21% of HCV infection in patients with cirrhosis registered worldwide. The authors report significant differences between regions: a lower rate of HBV infection in patients with cirrhosis in Europe, America and Oceania compared to Asia and Africa.

Excessive alcohol consumption, obesity, and liver virus infections are the main etiological factors of chronic liver diseases (Pimpin et al., 2018).

Type 2 diabetes is a major risk factor for metabolic steatohepatitis and doubles the risk of developing advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma (Ciardullo et al., 2024).

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

However, mortality among patients with type 2 diabetes caused by liver disease decreased from 1.13 to 0.64 deaths per 1000 person-years from 2010 to 2019 (Ciardullo et al., 2024). The prevalence of obesity and type 2 diabetes has increased worldwide (Sunt et al., 2022). It is estimated that approximately 43% of the population consumes alcohol (Devarbhavi et al., 2023), with an estimated annual consumption of 6.4L of alcohol/person aged at least 15 years (Rossow & Makela, 2021). Alcohol consumption and metabolic-associated fatty liver disease are increasingly recognized as contributing factors to cirrhosis (Iacob et al., 2024). Alcohol is the main cause of cirrhosis worldwide (approximately 60% of cirrhosis cases in Europe, North America and Latin America are caused by alcohol consumption (Avila et al., 2020; Pimpin et al., 2018; Stein et al., 2016). The contribution of alcohol consumption to the determinism of cirrhosis is higher at European level (country range 16-78%) and lower in Asia (0-41%) (Alberts et al., 2022). In recent years, there has been an increase of the incidence of alcoholic hepatitis in young people (15-44 years) and women (WHO, 2017; Singal et al., 2021). A slight global decrease in the age-standardized incidence rate for alcoholic cirrhosis among women was reported during the period 1992-2021 by Zhang et al. (2025), with significant variations depending on the socio-demographic index.

There is an important link between the strength of alcohol consumed and the progression to cirrhosis; most patients with alcohol-related liver disease who progress to cirrhosis are heavy drinkers (Sheron et al., 2014). Alcohol acts synergistically with other risk factors for liver disease, such as obesity and viral infections (for a BMI above 35 kg/m2, alcohol hepatotoxicity doubles (Hart et al., 2010). Obesity and metabolic syndrome may synergistically potentiate the severity of alcoholic cirrhosis (Aberg et al., 2018).

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, with an increasing prevalence of up to 10–30% in the general population (Younossi et al., 2018). It is estimated that between 7–30% of patients with NAFLD may develop an inflammatory disease called nonalcoholic steatohepatitis, which appears to be a more aggressive form of the disease, which more frequently progresses to advanced fibrosis and cirrhosis. Nonalcoholic fatty liver disease, the hepatic manifestation of metabolic syndrome, is already the leading cause of chronic liver disease worldwide and of cirrhosis considered to be cryptogenic (Andronesc et al., 2018; Li et al., 2018).

The average prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide was estimated at 38% in 2016, a significantly increased value compared to 2005 (26%) (Teng et al., 2023). NAFLD has a different distribution depending on geographical region, ethnicity, genetic variants and lifestyle (135, 139), with the prevalence being higher in men (40%) compared to women – 26% (138).

At the European level, the prevalence of NAFLD has been estimated at 23-33% of the population, with important differences depending on the category in which the study is carried out (Younossi et al., 2018; Riazi et al., 2022), with lower values, of around 20%, in Hungary and Romania (Tarnoki et al., 2012). Much higher prevalences of NAFLD have been reported among obese individuals (69%) and diabetic patients (69.5%) (Pimpin et al., 2018).

NAFLD can also occur in the absence of obesity or clinical criteria for metabolic syndrome. As a result of the increasing incidence of metabolic risk factors and the aging population, the burden of this condition is estimated to double by 2030 compared to 2016 (Younossi et al., 2018; Estes et al., 2018).

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

4. CONCLUSIONS

Chronic liver disease remains a major global health concern with a progressive evolution from inflammation to fibrosis, cirrhosis and hepatocellular carcinoma requiring accurate and early diagnostic approaches.

Histopathological and immunohistochemical evaluation continues to represent the gold standard for assessment of liver fibrosis providing essential insights into disease mechanism. Among the studied markers α-SMA, TGF-β1, GFAP, CD5L play key roles in reflecting hepatic stellate cell activation, inflammatory processes and fibrogenesis proving their value as potential diagnostic and prognostic tools.

At the same time, non-invasive methods including biochemical and hematological indices and composite score (APRI, FIB-4, GPR) have gained increasing importance due to their accessibility, reproducibility and clinical applicability. However, these methods still present limitations particularly in accurately distinguishing intermediate stages of fibrosis and in reflecting the dynamic nature of disease progression.

The integration of histopathological markers with non-invasive parameters represents a promising direction for improving the accuracy of liver disease assessment and patient stratification. A combined, personalized approach that incorporates molecular biomarkers, clinical scores and patient-specific factors may significantly enhance early diagnosis, monitoring and therapeutic decision-making.

Despite significant advances further studies are needed to validate novel biomarkers, standardize diagnostic thresholds and improve the predictive value of non-invasive methods across different etiologies of liver disease.

6. REFERENCES

Abdelhak, A., Huss A, Kassubek, J., *et al.* (2018). Serum GFAP as a biomarker for disease severity in multiple sclerosis. *Sci Rep, 8*, 14798. https://doi.org/10.1038/s41598-018-33158-8.

Aberg, F., Helenius-Hietala, J., Puukka, P., Farkkila, M., Jula, A. (2018) Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology*, *67*, 2141–2149.

Akpolat, N., Yahsi, S., Godekmerdan, A., Yalniz, M., Demirbag, K. (2005) The Value of α-SMA in the Evaluation of Hepatic Fibrosis Severity in Hepatitis B Infection and Cirrhosis Development: A Histopathological and Immunohistochemical Study. *Histopathology*, *47*, 276–280, doi:10.1111/j.1365-2559.2005.02226.x.

Alberts, C.J., Clifford, G.M., Georges, D., Negro, F., Lesi, O.A., Hutin, Y.J., de Martel, C. (2022). Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: A systematic review. *Lancet Gastroenterol.Hepatol*, *7*, 724–735.

Al-Busafi, S.A., Alwassief, A. (2024). Global Perspectives on the Hepatitis B Vaccination: Challenges, Achievements, and the Road to Elimination by 2030. *Vaccines*, *9*, 288.

Amjad, S., Akram, A., Iqbal, M., Hussain, M., Khan, M. (2021). Analysis of ALT and AST Levels in HCV Infected Patients. *Adv. Life Sci*, *8,* 349–354.

Andronescu, C.I., Purcărea, M.R., Babeș, P.A. (2018). Nonalcoholic fatty liver disease: Epidemiology, pathogenesis and therapeutic implications. *J. Med. Life*, *11(1)*, 20–23.

Angeli, P., Bernardi, M., Villanueva, C., Francoz, C., Mookerjee, R.P., Trebicka, J. et al. (2018). EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*, *69(2)*, 406–460.

Aran, G., Sanjurjo, L., Bárcena, C., Simon-Coma, M., Téllez, É., Vázquez-Vitali, M., Garrido, M., Guerra, L., Díaz, E., Ojanguren, I., Elortza, F., Planas, R., Sala, M., Armengol, C., Sarrias, M.R. (2018). CD5L is upregulated in hepatocellular carcinoma and promotes liver cancer cell proliferation and antiapoptotic responses by binding to HSPA5 (GRP78). *FASEB J.*, *32(7)*, 3878-3891. doi: 10.1096/fj.201700941RR.

Asrani, S.K., Devarbhavi, H., Eaton, J., Kamath, P.S. (2019). Burden of Liver Diseases in the World. *J. Hepatol, 70*, 151–171. doi.org/10.1016/j.jhep.2018.09.014.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Avila, M.A., Dufour, J.F., Gerbes, A.L., Zoulim, F., Bataller, R., Burra, P., et al. (2020). Recent advances in alcohol-related liver disease (ALD): summary of a Gut round table meeting. *Gut*, *69*, 764–780.

Bàrcena, C., Aran, G., Perea, L., Sanjurjo, L., Téllez, É., Oncins, A., et al. (2019). CD5L is a Pleiotropic Player in Liver Fibrosis Controlling Damage, Fibrosis and Immune Cell Content. *EBioMedicine, 43*, 513–24. doi: 10.1016/j.ebiom.2019.04.052.

Beno, D.W., Mullen, J., Davis, B.H. (1995). Lipoxygenase inhibitors block PDGF-induced mitogenesis: a MAPK-independent mechanism that blocks fos and egr. *Am J Physiol*, *268*, 604-610.

Bhattarai, S., Bhatta, D. R., & Gautam, B. (2022). Demographic, clinical and virological profile of patients with chronic hepatitis C virus infection. *Journal of Chitwan Medical College*, *12(1),* 34–38.

Bibi, A., Farhan, M., Inam, Q., Rehman, S., Zehra, S.R., Shoaib, A., Saghit, N.A. (2024). Analysis of Hepatic Function Markers in Chronic Liver Disease Patients According to Child-Pugh Classifications. *J. Xi'an Shiyou Univ. Nat. Sci. Ed., 67*, 118–123. https://doi.org/10.5281/zenodo.10953167.

Biggins, S.W., Kim, W.R., Terrault, N.A., Saab, S., Balan, V., Schiano, T. et al. (2006). Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology, 130(6),* 1652–1660.

Bivegete, S., McNaughton, A.L., Trickey, A., Thornton, Z., Scanlan, B., Lim, A.G., Nerlander, L., Fraser, H., Walker, J.G., Hickman, M. et al. (2023). Estimates of hepatitis B virus prevalence among general population and key risk groups in EU/EEA/UK countries: A systematic review. *Eurosurveillance*, *28*, 2200738.

Border, W.A., Okuda, S., Languino, L.R., Sporn, M.B., Ruoslahti, E. (1990). Suppression of experimental glomerulonephritis by antiserum against transforming growth factor beta 1. *Nature, 346*, 371–374.

Braczkowski, M.J., Kufel, K.M., Kulińska, J., Czyż, D.Ł., Dittmann, A., Wiertelak, M., Młodzik, M.S., Braczkowski, R., Soszyński, D. (2024). Pleiotropic Action of TGF-Beta in Physiological and Pathological Liver Conditions. *Biomedicines, 12,* 925. https://doi.org/10.3390/biomedicines12040925.

Brenner, D.A. (2009). Molecular pathogenesis of liver fibrosis. *Trans Am Clin Climatol Assoc*, *120,* 361-8.

Calvopina, D.A., Lewindon, P.J., Ramm, L.E., Noble, C., Hartel, G.F., Leung, D.H., Ramm, G.A. (2022). Gamma-glutamyl transpeptidase-to-platelet ratio as a biomarker of liver disease and hepatic fibrosis severity in paediatric Cystic Fibrosis. *J Cyst Fibros, 21(2),* 236-242. doi: 10.1016/j.jcf.2021.10.014.

Capuron, L., Miller, A.H. (2011). Immune system to brain signalling: Neuropsychopharmacology implications. *Pharmacology and Therapeutics*, *130*, 226-238.

Cardoso-Lezama, I., Ramos-Tovar, E., Arellanes-Robledo, J., Vargas-Pozada, E.E., Vásquez-Garzón, V.R., Villa-Treviño, S., Muriel, P. (2024). Serum α-SMA is a potential noninvasive biomarker of liver fibrosis. *Toxicology Mechanisms and Methods*, *34(1),* 13–19. https://doi.org/10.1080/15376516.2023.2244061.

Carotti, S., Morini, S., Corradini, S.G., Burza, M.A., Molinaro, A., Carpino, G., Merli, M., De Santis, A., Muda, A.O., Rossi, M., Attili, A.F., Gaudio, E. (2008). Glial fibrillary acidic protein as an early marker of hepatic stellate cell activation in chronic and posttransplant recurrent hepatitis C. *Liver Transpl, 14(6),* 806-14. doi: 10.1002/lt.21436.

Carpino, G., Morini, S., Ginannicorradini, S., Franchitto, A., Merli, M., Siciliano, M., Gentili, F., Onettimuda, A., Berloco, P., Rossi, M. (2005). Alpha-SMA Expression in Hepatic Stellate Cells and Quantitative Analysis of Hepatic Fibrosis in Cirrhosis and in Recurrent Chronic Hepatitis after Liver Transplantation. *Digestive and Liver Disease*, *37*, 349–356, doi:10.1016/j.dld.2004.11.009.

Casari, M., Siegl, D., Deppermann, C., Schuppan, D. (2023). Macrophages and platelets in liver fibrosis and hepatocellular carcinoma. *Front. Immunol.*, *14*, 1277808. doi: 10.3389/fimmu.2023.1277808

Caussy, C., Ajmera, V.H., Puri, P., Hsu, C.L., Bassirian, S., Mgdsyan, M., et al. (2018). Serum metabolites detect the presence of advanced fibrosis in derivation and validation cohorts of patients with non-alcoholic fatty liver disease. *Gut, 68(10),* 1884-1892. https://doi.org/10.1136/gutjnl-2018-317584.

Chen, B., Ye, B., Zhang, J., Ying, L., Chen, Y. (2013). RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. *PLoS One, 8(7),* e68780. doi: 10.1371/journal.pone.0068780.

Ciardullo, S., Morabito, G., Rea, F., Savaré, L., Perseghin, G., Corrao, G. (2024). Time Trends in Liver-Related Mortality in People with and Without Diabetes: Results from a Population-Based Study. *J Clin Endocrinol Metab, 109(10),* 2513-2519. doi:10.1210/clinem/dgae182.

Cooke, G.S., Flower, B., Cunningham, E., Marshall, A.D., Lazarus, J.V., Palayew, A., Jia, J., Aggarwal, R., Al-Mahtab, M., Tanaka. (2024). Progress towards elimination of viral hepatitis: A Lancet Gastroenterology & Hepatology Commission update. *Lancet Gastroenterol.Hepatol*, *9*, 346–365.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Deng, Z., Fan, T., Xiao, C. *et al.* (2024). TGF-β signaling in health, disease and therapeutics. *Sig Transduct Target Ther, 9,* 61, doi.org/10.1038/s41392-024-01764-w.

Devarbhavi, H., Asrani, S.K., Arab, J.P., Nartey, Y.A., Pose, E., Kamath, P.S. (2023). Global Burden of Liver Disease: 2023 Update. *J. Hepatol, 79*, 516–537. https://doi.org/10.1016/j.jhep.2023.03.017.

Ding, R., Zheng, J., Huang, D., Wang, Y., Li, X., Zhou, X., Yan, L., Lu, W., Yang, Z., Zhang, Z. (2021). INR-to-Platelet Ratio (INPR) as a Novel Noninvasive Index for Predicting Liver Fibrosis in Chronic Hepatitis B. *Int. J. Med. Sci, 18*, 1159–1166. https://doi.org/10.7150/ijms.51799.

Dumitrache (Păunescu), A., Ionescu (Șuțan), N.A., Țânțu, M.M., Ponepal, M.C., Soare, L.C., Țânțu, A.C., Atamanalp, M., Baniță, I.M., Pisoschi, C.G. (2025). Evaluating the Discriminative Performance of Noninvasive Biomarkers in Chronic Hepatitis B/C, Alcoholic Cirrhosis, and Nonalcoholic Cirrhosis: A Comparative Analysis. *Diagnostics*, *15*, 1575, doi:10.3390/diagnostics15131575.

Ekin, N., Ucmak, F., Ebik, B., Tugba-Tuncel, E., Kacmaz, H., Arpa, M., Engin-Atay, A. (2022). GPR, King's Score and S-Index are superior to other non-invasive fibrosis markers in predicting the liver fibrosis in chronic Hepatitis B patients. *Acta Gastroenterol Belg*, *85(1),* 62-68. doi: 10.51821/85.1.9156.

Estes, C., Razavi, H., Loomba, R., Younossi, Z., Sanyal, A.J. (2018). Modelling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*, *67,* 123–133.

Flisiak, R., Prokopowicz, D., Jaroszewicz, J., Flisiak, I. (2005). Plasma transforming growth factor-beta (1) in acute viral hepatitis. *Med Sci Monit*, *11(6),* CR304-308.

Fofana, D.B., Somboro, A.M., Maiga, M., Kampo, M.I., Diakité, B., Cissoko, Y., McFall, S.M., Hawkins, C.A., Maiga, A.I., Sylla, M., et al. (2023). Hepatitis B Virus in West African Children: Systematic Review and Meta-Analysis of HIV and Other Factors Associated with Hepatitis B Infection. *Int. J. Environ. Res. Public Health*, *20,* 4142.

Forns, X., Ampurdanes, S., Llovet, J.M., et al. (2002). Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology, 36,* 986-92.

Friedman, S.L. (2003). Liver fibrosis – from bench to bedside. *J Hepatol, 38,* Suppl 1: S38-S53.

Friedman, S.L. (1993). The cellular basis of hepatic fibrosis: mechanisms and treatment strategies. *N. Engl. J.Med*, *328,* 1828-1835.

Fujita, K., Yamasaki, K., Morishita, A., Shi, T., Tani, J., Nishiyama, N., Kobara, H., Himoto, T., Yatsuhashi, H., Masaki, T. (2021). Albumin platelet product as a novel score for liver fibrosis stage and prognosis. *Sci Rep*, *11(1),* 5345. doi:10.1038/s41598-021-84719-3.

Gairing, S.J., Danneberg, S., Kaps, L., Nagel, M., Schleicher, E.M., Quack, C., Engel, S., Bittner, S., Galle, P.R., Schattenberg, J.M. et al. (2023). Elevated Serum Levels of Glial Fibrillary Acidic Protein Are Associated with Covert Hepatic Encephalopathy in Patients with Cirrhosis. *JHEP Reports*, *5*, 100671, doi:10.1016/j.jhepr.2023.100671.

Gangadharan, B., Antrobus, R., Dwek, R.A., Zitzmann, N. (2007). Novel Serum Biomarker Candidates for Liver Fibrosis in Hepatitis C Patients. *Clin. Chem*, *53,* 1792–1799. https://doi.org/10.1373/clinchem.2007.089144.

GBD. (2017). Disease and Injury Incidence and Prevalence Collaborators.

GBD. (2019). Europe Hepatitis B & C Collaborators. Hepatitis B and C in Europe: An update from the Global Burden of Disease Study 2019. *Lancet Public Health*, e701–e716. doi: 10.1016/S2468-2667(23)00149-4.

Gebe, J.A., Kiener, P.A., Ring, H.Z., Li, X., Francke, U., Aruffo, A. (1997). Molecular cloning, mapping to human chromosome 1 q21-q23, and cell binding characteristics of Spalpha, a new member of the scavenger receptor cysteine-rich (SRCR) family of proteins. *J Biol Chem*, *272(10*), 6151–8.

Gnyawali, B., Pusateri, A., Nickerson, A., Jalil, S., Mumtaz, K. (2022). Epidemiologic and socioeconomic factors impacting hepatitis B virus and related hepatocellular carcinoma. *World J. Gastroenterol, 28,* 3793–3802.

Gray, J., Chattopadhyay, D., Beale, G.S., Patman, G.L., Miele, L., King, B.P., Stewart, S., Hudson, M., Day, C.P., Manas, D.M. et al. (2009). A Proteomic Strategy to Identify Novel Serum Biomarkers for Liver Cirrhosis and Hepatocellular Cancer in Individuals with Fatty Liver Disease. *BMC Cancer, 9,* 271. https://doi.org/10.1186/1471-2407-9-271.

Gressner, A.M., Lotfi, S., Gressner, G., et al. (1993). Synergism between hepatocytes and Kupffer cells in the activation of fat storing cells (perisinusoidal lipocytes). *J Hepatol*, *19,* 117-32.

Griffin, C., Agbim, U., Ramani, A., Shankar, N., Kanwal, F., Asrani, SK. (2021). Under estimation of cirrhosis-related mortality in the medicare eligible population, 1999-2018. *Clin Gastroenterol Hepatol*, *21(1),* 223–225.

Guerra-Ruiz, A.R., Crespo, J., López-Martínez, R.M., Iruzubieta, P., Casals-Mercadal, G., Lalana-Garcés, M., Lavin, B., Morales-Ruiz, M. (2021). Measurement and Clinical Usefulness of Bilirubin in Liver Disease. *Adv. Lab. Med./Av. Med. Laboratorio*, *2,* 352 361. https://doi.org/10.1515/almed-2021-0047.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Hart, C.L., Morrison, D.S., Batty, G.D., Mitchell, R.J., Davey, S.G. (2010). Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ, 340,* c1240.

Hassan, S., Syed, S., Kehar, S.I. (2014). Glial Fibrillary Acidic Protein (GFAP) as a Mesenchymal Marker of Early Hepatic Stellate Cells Activation in Liver Fibrosis in Chronic Hepatitis C Infection. *Pak J Med Sci*, *30*, doi:10.12669/pjms.305.5534.

Hernández, E., Bucio, L., Souza, V., et al. (2007). Pentoxifylline downregulates alpha (I) collagen expression by the inhibition of I kappa b alpha degradation in liver stellate cells. *Cell Biol Toxicol*, *24(4),* 303-14.

Iacob, S., Csiki, I., Iacob, R., Ghioca, M., Constantinescu, I., Chiper, B., Huiban, L., Muzica, C., Girleanu, I., Tiuca, N. et al. (2024). Hepatitis B Prevalence and Referral Rates in Vulnerable Populations Undergoing Community-Based Screening—Results from the LIVE(RO)2 Program. *Viruses*, *16,* 1318. doi.org/10.3390/v16081318.

Imbert-Bismut, F., Ratziu, V., Pieroni, L., et al. (2001). Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet, 357*, 1069-75.

Imran, S., Maham, N.A., Umar, M. (2012). Demographic Profile of Patients with Chronic Hepatitis C. *Journal of Rawalpindi Medical College*, *16(2),* 106-108.

Intagliata, N.M., Davitkov, P., Allen, A.M., Falck-Ytter, Y.T., Stine, J.G. (2021). AGA technical review on coagulation in cirrhosis. *Gastroenterology, 161(5),* 1630–1656.

Ishak, K., Baptista, A., Bianchi, L., Callea, F., De Groote, J., Gudat, F., Denk, H., Desmet, V., Korb, G., MacSween, R.N.M, et al. (1995). Histological Grading and Staging of Chronic Hepatitis. *Journal of Hepatology*, *22*, 696–699, doi:10.1016/0168-8278(95)80226-6.

Janulaityte, I., Petkute, G., Maciuliene, A., Borodiciene, J., Kareiva, J., Vitkauskiene, A. (2025). Evaluation of Hematological, Biochemical, and Coagulation Tests in Patients with Hepatitis C. *Medicina*, *61*, 2049.

Kamath, P.S., Wiesner, R.H., Malinchoc, M., Kremers, W., Therneau, T.M., Kosberg, C.L. et al. (2001). A model to predict survival in patients with end–stage liver disease. *Hepatology*, *33(2),* 464.

Kim, T.H., Yang, K., Kim, M., Kim, H.S., Kang, J.L. (2021). Apoptosis inhibitor of macrophage (AIM) contributes to IL-10-induced anti-inflammatory response through inhibition of inflammasome activation. *Cell Death Dis*, *12(1),* 19.

Kleiner, D.E., Brunt, E.M., Van Natta, M., Behling, C., Contos, M.J., Cummings, O.W., et al. (2005). Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*, *41,* 1313–21.

Knodell, R.G., Ishak, K.G., Black, W.C., Chen, T.S., Craig, R., Kaplowitz, N., et al. (1981). Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*, *1,* 431–5.

Lai, X., Chen, H., Dong, X., Zhou, G., Liang, D., Xu, F., Liu, H., Luo, Y., Liu, H., Wan, S. (2024). AST to ALT Ratio as a Prospective Risk Predictor for Liver Cirrhosis in Patients with Chronic HBV Infection. *Eur. J. Gastroenterol. Hepatol*, *36*, 338–344. https://doi.org/10.1097/MEG.0000000000002708.

Lambert, M.P. (2016). Platelets in liver and renal disease. *Hematol Am Soc Hematol Educ Program*, *1*, 251–5. doi: 10.1182/asheducation-2016.1.251.

Laye, S., Gheusi, G., Cremona, S., et al. (2000). Endogenous brain IL-1 mediates LPS induced anorexia and hypothalamic cytokine expression. *Am J Physiol Regulatory Integrative Comp Physiol*, *279,* R93-8.

Li, B., Zhang, C., Zhan, Y.T. (2018). Nonalcoholic Fatty Liver Disease Cirrhosis: A Review of Its Epidemiology, Risk Factors, Clinical Presentation, Diagnosis, Management, and Prognosis. *Can J. Gastroenterol. Hepatol*, *550(1),* 1-8.

Lin, W., Weinberg, E., Tai, A., Pend, L., Brockman, M., Kim, K., Kim, S.S., Borges, C., Shao, R.X., Chung, R. (2008). HIV increases HCV replication in a TGF-beta1-dependent manner. *Gastroenterology*, *134,* 803–811.

Lisman, T., Leebeek, F.W., de Groot, P.G. (2002). Haemostatic abnormalities in patients with liver disease. *J Hepatol*, *37(2),* 280–7. doi: 10.1016/S0168-8278(02)00199-X.

Liu, M., Li, L., Zhao, J., Ungvari, G.S., Ng, C.H., Duan, Z., Zheng, S.J., Xiang, Y.T. (2022). Gender differences in demographic and clinical characteristics in patients with HBV-related liver diseases in China. *PeerJ*, *10*. doi: 10.7717/peerj.13828.

Loaeza-del-Castillo, A., Paz-Pineda, F., Oviedo-Cárdenas, E., Sánchez-Avila, F., Vargas-Voráckova, F. (2008). AST to Platelet Ratio In dex (APRI) for the Noninvasive Evaluation of Liver Fibrosis. *Ann. Hepatol*, *7*, 350–357.

Luo, Y., Huang, X., Zhan, J., Zhang, S. (20121). Role of CD5L and SRD5A2 as prognostic biomarkers for Hepatocellular Carcinoma. *Int J Gen Med*, *14,* 9247–60.

Mandel, J., Casari, M., Stepanyan, M., Martyanov, A., Deppermann, C. (2022). Beyond hemostasis: platelet innate immune interactions and thromboinflammation. *Int J Mol Sci*, *23(7),* 3868. doi: 10.3390/ijms23073868.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Mann, D.A., Smart, D.E. (2002). Transcriptional regulation of hepatic stellate cell activation. *Gut*, *50,* 891–899.

Marasco, G., Colecchia, A., Colli, A., Ravaioli, F., Casazza, G., Bacchi-Reggiani, M.L. et al. (2019). Reply to correspondence concerning: "role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection." *J Hepatol, 70(4),* 809–810.

Mikula, M., Proell, V., Fischer, A.N., et al. (2006). Activated hepatic stellate cells induce tumor progression of neoplastic hepatocytes in a TGF-beta dependent fashion. *J Cell Physiol, 209*, 560-7.

Miyazaki, T., Hirokami, Y., Matsuhashi, N., Takatsuka, H., Naito, M. (1999). Increased susceptibility of thymocytes to apoptosis in mice lacking AIM, a novel murine macrophage-derived soluble factor belonging to the scavenger receptor cysteine-rich domain superfamily. *J Exp Med*, *189(2),* 413–22.

Miyazaki, T., Kurokawa, J., Arai, S. (2011). AIMing at metabolic syndrome. Towards the development of novel therapies for metabolic diseases via apoptosis inhibitor of macrophage (AIM). *Circ J, 75(11),* 2522–31.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med, 6(7),* e1000097.

Morini, S., Carotti, S., Carpino, G., Franchitto, A., Corradini, S.G., Merli, M., Gaudio, E. (2005). GFAP expression in the liver as an early marker of stellate cells activation. *Ital J Anat Embryol*, *110(4),* 193-207.

Naik, A.R., Moorthy, S. (2025). A Comparative Analysis between Model for End-Stage Liver Disease Score (MELD), Modified Model for End-Stage Liver Disease Score (MELD-Na), and Child–Pugh Score (CPS) in Predicting Complications among Cirrhosis Patients. *Egypt. J. Intern. Med.*, *37*, 99. https://doi.org/10.1186/s43162-025-00478-x.

Narmada, B.C., Chia, S.M., Tucker-Kellogg, L., Yu, H. (2013). HGF regulates the activation of TGF-β1 in rat hepatocytes and hepatic stellate cells. *J. Cell Physiol*, *228*, 393–401.

Ou, T.Y., Huy, L.D., Mayne, J., Shih, C.L., Mai, X.H., Nguyen, N.T.H., Linh, N.H., Bui, L.T.M., Chang, Y.M., Abdi, A.A. et al. (2024). Global mortality of chronic liver diseases attributable to Hepatitis B virus and Hepatitis C virus infections from 1990 to 2019 and projections to 2030. *J. Infect. Public Health*, *17,* 102443.

Peng, Y., Qi, X., Guo, X. (2016). Child–Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. *Medicine*, *95*, e2877. https://doi.org/10.1097/MD.0000000000002877.

Pennap, G.R. (2010). Prevalence of hepatitis B and C virus infection among people of a local community in Keffi, Nigeria. *African Journal of Microbiology Research*, *4,* 274-78.

Pimpin, L., Cortez-Pinto, H., Negro, F., Corbould, E., Lazarus, J.V., Webber, L., Sheron, N. (2018). Burden of Liver Disease in Europe: Epidemiology and Analysis of Risk Factors to Identify Prevention Policies. *J. Hepatol*, *69*, 718–735. https://doi.org/10.1016/j.jhep.2018.05.011.

Posuwan, N., Wasitthankasem, R., Pimsing, N., Phaengkha, W., Ngamnimit, S., Vichaiwattana, P., Klinfueng, S., Raksayod, M., Poovorawan, Y.(2024). Hepatitis B Prevalence in an Endemic Area of Hepatitis C Virus: A Population-Based Study Implicated in Hepatitis Elimination in Thailand. *J. Virus Erad*, *10*, 100577. https://doi.org/10.1016/j.jve.2024.100577.

Rautou, P.E., Caldwell, S.H., Villa, E. (2023). Bleeding and thrombotic complications in patients with cirrhosis: A state-of-the-art appraisal. *Clin Gastroenterol Hepatol*, *21(8),* 2110–23. doi: 10.1016/j.cgh.2023.04.016.

Răcășan, A., Voiculescu, M., Iliescu, L. (2016). Evaluarea non-invazivă a fibrozei hepatice cu ajutorul elestografiei hepatice (FibroScan) la pacienţii cu infecţie cronică VHB şi VHC. *Romanian Journal of Infectious Diseases*, *19*, 103-107. 10.37897/RJID.2016.3.9.

Riazi, K., Azhari, H., Charette, J.H., Underwood, F.E., King, J.A., Afshar, E.E., Swain, M.G., Congly, S.E., Kaplan, G.G., Shaheen, A.A. (2022). The Prevalence and Incidence of NAFLD Worldwide: A Systematic Review and Meta-Analysis. *Lancet Gastroenterol. Hepatol*, *7*, 851–861. https://doi.org/10.1016/S2468-1253(22)00165-0.

Rossow, I., Makela, P. (2021). Public health thinking around alcohol-related harm: why does per capita consumption matter? *J Stud Alcohol Drugs, 82,* 9–17.

Sakaguchi, E., Kayano, K., Segawa, M., Okamoto, M., Sakaida, I., Okita, K. (2002). Th1 down-regulation at the single-lymphocyte level in HCV related liver cirrhosis and the effect of TGF-beta on Th1 response: possible implications for the development of hepatoma. *Hepatol. Res, 24,* 282.

Sanai, F., Alghamdi, H., Alswat, K., Babatin, M., Ismail, M., Alhamoudi, W., Alalwan, A., Dahlan, Y., Alghamdi, A., Alfaleh, F., et al. (2019). Greater Prevalence of Comorbidities with Increasing Age: Cross-Sectional Analysis of Chronic Hepatitis B Patients in Saudi Arabia. *Saudi J. Gastroenterol.*, *25*, 194. doi.org/10.4103/sjg.SJG_447_18.

Sanchez-Moral, L., Ràfols, N., Martori, C., Paul, T., Téllez, É., Sarrias, M.R. (2021). Multifaceted Roles of CD5L in Infectious and Sterile Inflammation. *IJMS*, *22,* 4076. https://doi.org/10.3390/ijms22084076. and Proliferation.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Sánchez-Rodríguez, M.B., Téllez, É., Casulleras, M., Borràs, F., Arroyo, V., Clària, J., Sarrias, M.R. (2022). Reduced Plasma Extracellular Vesicle CD5L Content in Patients With Acute-On-Chronic Liver Failure: Interplay with Specialized Pro-Resolving Lipid Mediators. *Front. Immunol*., *24(3),* 282. https://doi.org/10.3389/fimmu.2022.842996.

Sanderson, N., Factor, V., Nagy, P., Kopp, J., Kondaiah, P., Wakefield, L., Roberts, A.B., Sporn, M.B., Thorgeirsson, S.S. (1995). Hepatic expression of mature transforming growth factor beta 1 in transgenic mice results in multiple tissue lesions. *Proc. Natl. Acad. Sci. USA*, *92*, 2572–2576.

Sebastiani, G., Alberti, A. (2006). Non-invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. *World J Gastroenterol,12,* 3682-94.

Sheron, N., Chilcott, F., Matthews, L., Challoner, B., Thomas, M. (2014). Impact of minimum price per unit of alcohol on patients with liver disease in the UK. *ClinMed,14(4),* 396-403.

Shimizu, T., Sawada, T., Asai, T., Kanetsuki, Y., Hirota, J., Moriguchi, M., et al. (2022). Hepatocellular carcinoma diagnosis using a novel electrochemiluminescence immunoassay targeting serum IgM-free AIM. *Clin J Gastroenterol,15(1),* 41–51.

Singal, A.K., Arsalan, A., Dunn, W., Arab, J.P., Wong, R.J., Kuo, Y.F., et al. (2021). Alcohol associated liver disease in the United States is associated with severe forms of disease among young, females and Hispanics. *Aliment Pharmacol Ther*, *54,* 451–461.

Stasi, C., Milli, C., Voller, F., Silvestri, C. (2024). The Epidemiology of Chronic Hepatitis C: Where We Are Now. *Livers*, *4,* 172–181, doi:10.3390/livers4020013.

Stein, E., Cruz-Lemini, M., Altamirano, J., Ndugga, N., Couper, D., Abraldes, J.G., et al. (2016). Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. *J Hepatol, 65*, 998–1005.

Sterling, R.K., Lissen, E., Clumeck, N., Sola, R., Correa, M.C., Montaner, J.S., Sulkowski, M., Torriani, F.J., Dieterich, D.T., Thomas, D.L. et al. (2006). Development of a Simple Noninvasive Index to Predict Significant Fibrosis in Patients with HIV/HCV Coinfection. *Hepatology*, *43*, 1317–1325. https://doi.org/10.1002/hep.21178.

Sterling, R.K., Patel, K., Duarte-Rojo, A., Asrani, S.K., Alsawas, M., Dranoff, J.A., Fiel, M.I., Murad M.H., Leung, D.H., Levine, D., et al. (2025). AASLD Practice Guideline on Blood-Based Noninvasive Liver Disease Assessment of Hepatic Fibrosis and Steatosis. *Hepatology, 81,* 321–357, doi.org/10.1097/HEP.0000000000000845.

Stroffolini, T., Esvan, R., Biliotti, E., Sagnelli, E., Gaeta, G.B., Almasio, P.L. (2015). Gender differences in chronic HBsAg carriers in Italy: evidence for the independent role of male sex in severity of liver disease. *Journal of Medical Virology*, *87*, 1899.

Su, F.H., Chen, J.D., Cheng, S.H., Lin, C.H., Liu, Y.H., Chu, F.Y. (2007). Seroprevalence of Hepatitis-B infection amongst Taiwanese university students 18 years following the commencement of a national Hepatitis-B vaccination program. *Journal of Medical Virology*, *79*, 138.

Sun, H., Saeedi, P., Karuranga, S, et al. (2022). IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract., 183,* 109119.

Takimoto-Sato, M., Suzuki, M., Kimura, H., Ge, H., Matsumoto, M., Makita, H., Arai, S., Miyazaki, T., Nishimura, M., Konno, S. (2023). Apoptosis inhibitor of macrophage (AIM)/CD5L is involved in the pathogenesis of COPD. *Respir Res, 24(1),* 201. doi: 10.1186/s12931-023-02508-0.

Talić-Drlje, I., Šušak, B., Skočibušić, S., Tutiš, B., Jakovac, S., Arapović, J. (2025). Sociodemographic Characteristics, Risk Factors and Genotype Distribution of Hepatitis C Virus in Bosnia and Herzegovina: Single Center Experience. *Clin. Epidemiol. Glob. Health*, *31*, 101845. doi.org/10.1016/j.cegh.2024.101845.

Tang, Y., Deng, Y., Zhang, G., Wang, Y., Wang, J., Wun, J., Gu, M. (2025). Inflammatory markers as predictors of liver fibrosis in type 2 diabetes patients with metabolic dysfunction-associated fatty liver disease. *Front.Endocrinol*.,*16,*1556646.

Tarnoki, A.D., Tarnoki, D.L., Bata, P., Littvay, L., Osztovits, J., Jermendy, G., et al. (2012). Heritability of non-alcoholic fatty liver disease and association with abnormal vascular parameters: a twin study. *Liver Int, 32,* 1287–1293.

Teng, M.L., Ng, C.H., Huang, D.Q., Chan, K.E., Tan, D.J., Lim, W.H., Yang, J.D., Tan, E., Muthiah, M.D. (2023). Global Incidence and Prevalence of Nonalcoholic Fatty Liver Disease. *Clin. Mol. Hepatol.*, *29*, S32–S42. doi.org/10.3350/cmh.2022.0365.

*Corresponding author, E-mail address: alina.paunescu@upb.ro

Current Trends in Natural Sciences
Vol. 14, Issue 28, pp. 06-27, 2025
https://doi.org/10.47068/ctns.2025.v14i28.001
Current Trends in Natural Sciences (on-line)
ISSN: 2284-953X
ISSN-L: 2284-9521
Current Trends in Natural Sciences (CD-Rom)
ISSN: 2284-9521
ISSN-L: 2284-9521

Tsai, P.S., Cheng, Y.M., Wang, C.C., Kao, J.H. (2023). The impact of concomitant hepatitis C virus infection on liver and cardiovascular risks in patients with metabolic-associated fatty liver disease. *Eur J Gastroenterol Hepatol.*, *35(11),* 1278-1283. doi: 10.1097/MEG.0000000000002558.

Vallet-Pichard, A., Mallet, V., Nalpas, B., et al. (2007), FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology*, 46, 32-36.

Van Der Meer, A.J., Veldt, B.J., Feld, J.J., Wedemeyer, H., Dufour, J.F., Lammert, F., et al. (2012). Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*, *308 (24),* 2584. doi: 10.1001/jama.2012.144878.

Wai, C.T., Greenson, J.K., Fontana, R.J., Kalbfleisch, J.D., Marrero, J.A., Conjeevaram, H.S., Lok, A.S.F. (2003). A Simple Noninvasive Index Can Predict both Significant Fibrosis and Cirrhosis in Patients with Chronic Hepatitis C. *Hepatology*, *38,* 518–526. https://doi.org/10.1053/jhep.2003.50346.

Wang, L., Wang, B., You, H., Wu, X., Zhou, J., Ou, X., et al. (2018). Platelets' increase is associated with improvement of liver fibrosis in entecavir-treated chronic hepatitis B patients with significant liver fibrosis. *Hepatol Int*, *12(3),* 237–43. doi: 10.1007/ s12072-018-9864-z.

WHO. (2017). Global hepatitis report. Geneva, Switzerland: World Health Organization.

WHO. (2024). Global hepatitis report *Action for Access in Low- and Middle-Income Countries*, 1st ed.; World Health Organization: Geneva, Switzerland, ISBN 978-92-4-009167-2.

WHO. (2026). HIV and viral hepatitis diagnostic tests in low- and middle-income countries: forecasts of global and regional demand for 2022-2026.

Xuan, Y., He, F., Liu, Q., Dai, D., Wu, D., Shi, D., Yao, Q. (2025). Elevated GGT to HDL ratio as a marker for the risk of NAFLD and liver fibrosis. *Scientific Reports*, *15*, 10, https://doi.org/10.1038/s41598-024-84649-w

Yamazaki, T., Mori, M., Arai, S., Tateishi, R., Abe, M., Ban, M., et al. (2014). Circulating AIM as an indicator of liver damage and hepatocellular carcinoma in humans. *PLoS ONE*, *9(10),* e109123.

Yang, H., Luo, Y., Lai, X. (2023). The Comprehensive Role of Apoptosis Inhibitor of Macrophage (AIM) in Pathological Conditions. *Clinical and Experimental Immunology*, *212*, 184–198, doi:10.1093/cei/uxac095.

Younossi, Z., Anstee, Q.M., Marietti, M., Hardy, T., Henry, L., Eslam, M., et al. (2018). Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*, *15*, 11–20.

Zhang, Z., Xu, C., Chen, W. et al. (2025). Global, regional, and national burdens of alcohol-related cirrhosis among women from 1992 to 2021 and its predictions. *Sci Rep*, *15*, 10959. https://doi.org/10.1038/s41598-025-95563-0

https://easl.eu/wp-content/uploads/**2018**/09/EASL-HEPAHEALTH-Report.pdf

*Corresponding author, E-mail address: alina.paunescu@upb.ro