Scientific Journal for Damietta Faculty of Science **15**(2) 2025, 129-139
Doi: 10.21608/sjdfs.2025.393515.1237
ISSN Print 2314-8594
ISSN Online 2314-8616

*https://sjdfs.journals.ekb.eg/*

# Prevalence Trends and Diagnostic Biomarkers in Chronic Liver Diseases

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Received: 11 June 2025 /Accepted: 25 July 2025

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## Abstract

Chronic liver disease (CLD) significantly contributes to global morbidity and mortality, covering a spectrum of disorders with diverse etiologies. Hepatocellular damage in cirrhosis leads to hypoalbuminemia, increased bilirubin and extended prothrombin time. Accurate diagnosis, prognosis, and monitoring of chronic liver disease depend profoundly on the assessment of several biomarkers. This review provides a focused overview of key biochemical and hematological biomarkers utilized in the evaluation of major chronic liver disease types, covering viral hepatitis, non-alcoholic fatty liver disease (NAFLD). For each disease category, we discuss the clinical utility of traditional liver function tests (ALT, AST, bilirubin, albumin), markers of fibrosis (platelet count, APRI score, FIB-4 index), and other relevant hematological parameters. By synthesizing current evidence on the diagnostic and prognostic value of these biochemical and hematological indicators across different CLD etiologies, this review aims to provide a practical resource for clinicians and researchers in the field of hepatology.

***Keywords***: Chronic liver diseases (CLD), Biomarkers, Hepatitis B virus (HBV), Hepatitis C virus (HCV).

## Introduction

Chronic Liver Disease (CLD) presents a significant universal health challenge, a particularly high prevalence and impact in Egypt, where cirrhosis stands as a main reason of morbidity and mortality. Globally, CLD were the twelfth primary cause related to death in the United States in 2013, accounting for a substantial number of annual fatalities. While compensated cirrhosis often presents asymptomatically or with subtle signs in a considerable proportion of cases (30-40%), decompensated cirrhosis is typically characterized by severe clinical manifestations such as ascites, portal hypertension, variceal hemorrhage, and hepatic encephalopathy **(Asrani et al.,2019).**

CLD incorporates a comprehensive range of underlying etiologies, including viral infections, schistosomiasis, alcohol abuse, and

various genetic and metabolic disorders. These diverse insults ultimately converge on a common pathway leading to progressive hepatic dysfunction and cirrhosis **(Boon-Yasidhi & Karnsakul,2025).** The incidence of different reasons and the overall burden of cirrhosis and CLD exhibit geographical variations. Notably, the distribution of CLD etiologies within specific regions requires further investigation **(Younossi et al.,2017).**

Existing data regarding the prevalence, incidence, and natural history of CLD have largely been derived from retrospective studies **(Asrani et el.,2019).** Historically, CLD in Egypt has been strongly associated with schistosomiasis, Furthermore, a significant proportion of the Egyptian population (approximately 15%) is seropositive for Hepatitis C Virus (HCV), and a frequent association between schistosomiasis and HCV infection has been reported **(Abdelhamed and Elkassas,2024).** Given these factors and the potential for changing patterns of CLD etiology in Egypt, prospective studies are warranted to assess the etiological modes, clinical presentation, morbidity, and shifting patterns of CLD among Egyptian patients in this endemic area.

**Prevalence of Chronic liver disease:**

Liver disorders are one of the main worldwide health problems, associated with two million deaths per year as a result of cases such as cirrhosis, viral hepatitis, and liver cancer, and accounting for approximately 4% of all global mortality—equivalent to one in every 25 deaths. Notably, one-third of these liver-related deaths occur in females. Liver cancer contributes to an estimated 600,000 to 900,000 deaths per year. Although currently ranked as the eleventh leading cause of death globally, the actual mortality of liver disease burden may be underestimated **(Asrani et al.,2019).**

Cirrhosis ranks among the top causes of death in several regions, it is the tenth leading cause in Africa, ninth in Europe and in both South East Asia. The global health impact of cirrhosis is further emphasized by its substantial contribution to disability-adjusted life-years, where it ranks fifteenth overall. Among individuals aged 25 to 49, liver disease is the twelfth leading cause of disability -adjusted life-years, highlighting its disproportionate effect on younger demographics. Consequently, in Europe, the potential years of life lost due to cirrhosis are likely even higher **(WHO,2022).**

A comprehensive meta-analysis encompassing data from 38 countries estimated the global rate of NAFLD at 30.2%, with regional variations ranging from 16.1% in Australia to 34% in South America. The widespread presence of NAFLD is notably frequent in obese individuals, reaching 57.5%. Viral hepatitis, particularly hepatitis B and C, remains a significant contributor to CLD, with hepatitis B affecting approximately 254 million people globally **(WHO,2023)**. In 2022, hepatitis B and C were responsible for 1.3 million deaths each, underscoring their impact on global mortality. Alcohol-related liver disease (ARLD) also contributes to the global CLD burden, with a worldwide prevalence of 4.8%. The increasing presence of metabolic risk factors, such as obesity, has led to a rise in metabolic-associated fatty liver disease (MAFLD), with global prevalence escalating from 25.3% between 1990–2006 to 38.0% between 2016–2019 **(Riazi et al.,2022)**. These trends highlight the shifting etiology of CLD and emphasize the need for targeted public health response to handle the evolving risk factors associated with liver disease.

Economically, cirrhosis represents a considerable financial burden. In the United States alone, liver health services costs totaled $32.5 billion in 2016, with the majority of expenditures linked to inpatient and emergency services. Over the past two decades, healthcare spending related to liver disease has grown at an annual rate of 4%, largely due to increased use of hospital-based care. The following sections will detail the burden associated with specific etiologies of liver disease, followed by an exploration of complications commonly arising across different liver conditions **(Ghamari et al.,2022).**

Table 1. Global epidemiological overview of hepatitis B and C.

| | **Viral hepatitis C 2019*** | **Viral hepatitis B 2019*** | **Viral hepatitis C 2015-2020**** |
|---|---|---|---|
| Incidence | About 1.5 million (1.1-2.6 million) people newly infected with HBV | An estimated 1.5 million (1.3-1.8 million) people were newly infected with HCV | 1.43 million |
| Prevalence | Around 296 million (228-423 million) people living with chronic HBV infection | 58 million (46-76 million) people living with chronic HCV infection | 56.8 million (UI 55.2-67.8 |
| Prevalence in the general population | 3.8% (3-5%) | 0.8% (0.6-1%) | 0.7% (95% UI 0.7-0.9) |
| Prevalence in children | 0.9% (0.7-1.6%) rate of HBV infection among children <5years | | 0.13% (UI 0.08-0.16) |
| Mortality (number) | 820,000 (450,000-950,000) people dying from hepatitis B-related causes | 290,000 (230,000-580,000) people dying from hepatitis C-related causes | 257,816 |
| Source, WHO - 2021 Screening and diagnosis | 30.4 million (24.3-38 million) people with hepatitis B knew their hepatitis B status at the end of 2019 | 15.2 million (12.2-13 million) people with hepatitis C knew their hepatitis C status at the end of 2019 | |
| Treatment | 6.6 million people (5.3-8.3 million) people diagnosed with hepatitis B received treatment in 2019 | 9.4 million (7.5-11.7 million) people diagnosed with hepatitis C received treatment from 2015 to 2019 | 10.1 million From 2015-2020 |

*Data adjusted from WHO, 2021 (Global progress report on HIV, viral hepatitis, and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016-2021: actions for impact).
**Adapted from Lancet Gastroenterol Hepatol 2022; 7: 396-415.

*Viral hepatitis*

Viral hepatitis remains a major global health concern, with a significant mortality burden—contributes to roughly 1.34 million mortalities in 2015 alone Several viruses, particularly hepatotropic types labeled A through E, are known to trigger liver inflammation. While many of these infections are acute, self-resolving hepatitis B (HBV), C (HCV), D (HDV), and E (HEV) have the potential to progress to chronic disease. Additionally, systemic infections caused by viruses such as Cytomegalovirus and Epstein-Barr virus can also lead to hepatic inflammation **(Chen et al.,2019).**

Hepatitis A and E are primarily spread via the fecal-oral route, frequently by oral intake of contaminated food or water **(Blach et al.,2021).** Conversely, hepatitis B, C, and D are transmitted through exposure to infected bodily fluids. Chronic hepatitis is characterized by a persistent inflammatory response in the liver, typically indicated by abnormal liver function tests and histological findings lasting at least six months. Chronic forms of hepatitis B, C, D, and E are diagnosed based on the detection of viral presence in the blood—or in stool for HEV—for more than six months following initial infection **(Asrani et al.,2019).**

*HBV*

Approximately 30% of the global population has serological evidence of current or past hepatitis B virus (HBV) infection. The majority of transmissions occur through vertical (mother-to-child) or early years exposure, which remain the predominant routes of infection worldwide. Chronic HBV infection progresses through five distinct clinical phases, each with unique characteristics. The initial phase, previously termed the "immune-tolerant" stage, features high HBV-DNA levels exceeding $10^6$ IU/mL, normal or mildly elevated alanine aminotransferase (ALT), and minimal hepatic inflammation. This is followed by an HBeAg-positive chronic hepatitis phase characterized by fluctuating viral loads, elevated ALT, and moderate to severe liver inflammation that may persist for extended periods **(Zhai et al.,2021).** The third phase represents an inactive carrier state with low HBV-DNA levels, normal ALT, and reduced inflammation of liver, though fibrosis severity depends on previous disease activity. Subsequently, some patients progress to HBeAg-negative chronic hepatitis, demonstrating variable viral replication, elevated ALT, and ongoing liver inflammation, with only about 1% achieving spontaneous clearance annually. The final phase involves

occult infection, where hepatitis B surface antigen becomes undetectable although there are core antibodies, often with very minimal or undetectable viral DNA and normal liver enzymes **(Younossi et al.,2021).** Clinical outcomes are significantly influenced by the timing of HBsAg clearance, with loss of surface antigen before cirrhosis development associated with favorable prognosis and reduced risk of complications. However, patients in any phase remain vulnerable to HBV reactivation under immunosuppressive conditions, necessitating careful monitoring in clinical practice. The typical pattern of HBV infection underscores the impact of early detection and appropriate management to prevent disease progression and improve long-term outcome **(Cao et al.,2022).**

*HCV*

Hepatitis C virus (HCV) remains a critical international health burden, with nearly 1.75 million new infections reported in 2015. It is recognized as the most prevalent bloodborne infection in the United States and other Western nations. Approximately 90% of individuals infected with HCV develop chronic liver disease. Intravenous drug use constitutes the primary mode of transmission, responsible for around 80% of cases, while transfusion of blood products accounts for approximately 10.8%. Other, less frequent transmission pathways include organ transplantation, and non-sterile tattooing procedures **(Younossi et al.,2019).**

The World Health Organization reported that an estimated 71 million people were living with chronic HCV infection in 2015. However, this prevalence is not mirrored in diagnosis rates; in 2016, only 20% of infected individuals were diagnosed, and merely 13% of those diagnosed received treatment with direct-acting antivirals **(Younossi et al.,2019).**

A disproportionate burden of HCV infections—approximately 80%—is concentrated in just 31 of the 194 WHO member states, with the highest incidence rates reported in the Eastern Mediterranean and Eastern European regions. Despite a declining incidence of new infections, mortality associated with HCV continues to rise due to its progression to End-stage hepatic disorders, comprising fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) **(Cacoub et al.,2018).**

*Non-alcoholic fatty liver disease (NALFD)*

NAFLD has a global prevalence of approximately 32.4%. The share of deaths attributable to NAFLD from all causes has risen from 0.1% to 0.17% **(Devarbhavi et al., 2023)**. NAFLD is highly connected to metabolic comorbidities, and the increasing burden of these conditions has contributed to the rising prevalence of NAFLD, placing affected individuals at greater risk for progression to advanced liver disease. Lately, NAFLD has emerged as one of the leading causes of hepatocellular carcinoma (HCC) and has become a major indication for liver dysfunction in the United States **(Younossi et al., 2019).**

*Liver fibrosis*

Hepatic fibrosis represents a dynamic and progressive pathological complications of chronic liver injury, recognized by the abnormal accumulation and remodeling of extracellular matrix (ECM) constituents, predominantly collagen. This fibrogenic response is a convergent pathway arising from diverse etiological insults, for example, viral hepatitis, chronic alcohol intake, non-alcoholic fatty liver disease (NAFLD), and autoimmune liver conditions. The main cellular mediator of this mechanism is the hepatic stellate cell (HSC), which undergoes activation into proliferative, contractile myofibroblast-like cells with a heightened capacity for ECM protein synthesis. Beyond HSCs, contributions to the fibrotic milieu originate from bone marrow-derived mesenchymal stem cells, portal fibroblasts, and the process of epithelial-to-mesenchymal transition (EMT) involving both hepatocytes and cholangiocytes. The perpetuation of hepatic insult and the attendant inflammatory signaling cascades sustain fibrogenesis, culminating in the potential development of cirrhosis, portal hypertension, hepatic insufficiency, and an elevated risk of hepatocellular carcinoma **(Bataller & Brenner, 2005).**

The clinical trajectory of liver fibrosis is critically dependent on its stage, with early fibrotic changes exhibiting potential for reversibility upon successful etiological treatment. However, unchecked progression to cirrhosis is accompanied by significant incidence and mortality, underscoring the

clinical imperative for timely diagnosis and therapeutic intervention. Histopathological assessment of liver biopsies, utilizing standardized scoring systems such as METAVIR and Ishak, remains a cornerstone in the staging of fibrosis and informing clinical management strategies. Complementary to invasive biopsy, non-invasive tools, encompassing serum-based biomarkers (APRI, FIB-4) and advanced imaging techniques like transient elastography, are increasingly employed for the non-invasive fibrosis severity assessment **(Castera et al., 2005)**. These advancements facilitate enhanced patient surveillance and risk stratification within both clinical and research paradigms.

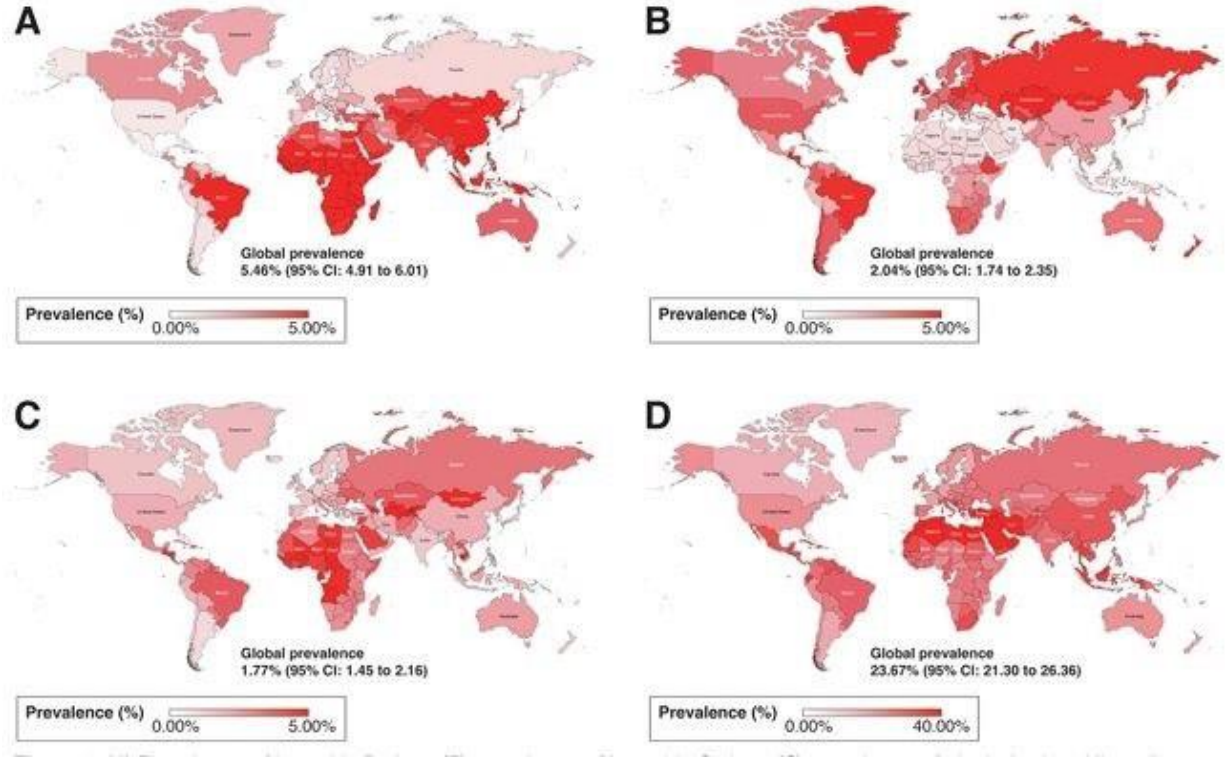


Figure 1. (A) Rate of hepatitis B virus, (B) Rate of hepatitis C virus, (C) Rate of alcohol-related liver disease, and (D) Rate of nonalcoholic fatty liver disease (in individuals age >20 years).

Several established clinical indices serve as adjuncts in the evaluation of hepatic physiology and the estimation of fibrosis burden. Child-Pugh score, a widely adopted clinical classification system, provides a prognostic assessment in chronic liver disease, specifically cirrhosis, by integrating five clinical and biochemical elements, serum bilirubin, serum albumin, prothrombin time, the occurrence and severity of ascites, and the presence and grade of hepatic encephalopathy, thereby categorizing patients from Class A (well-compensated) to Class C (decompensated) **(Pugh et al., 1973).** Furthermore, the APRI and FIB-4 indices represent readily applicable non-invasive models derived from routine hematological and biochemical analyses. APRI, estimated from aspartate aminotransferase (AST) levels and platelet count, with values exceeding 1.5 suggestive of significant fibrosis **(Wai et al., 2003**). FIB-4, which incorporates age, AST, alanine aminotransferase (ALT), and platelet count, provides a stratified risk assessment for advanced fibrosis, with values above 3.25 indicating a higher probability and values below 1.45 generally excluding it **(Sterling et al., 2006).** These non-invasive tools contribute significantly to reducing reliance on invasive procedures and facilitating earlier detection and management of liver fibrosis.

Contemporary therapeutic methods are directed towards addressing the underlying etiological factors, mitigating hepatic inflammation, and inhibiting key signaling pathways involved in fibrogenesis. The growth of antifibrotic agents targeting pivotal molecules including transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF) continuous an active area of research, although no agents have yet received regulatory approval for liver fibrosis. Lifestyle modifications, targeted antiviral therapies for viral hepatitis, and meticulous

metabolic control in the context of NAFLD constitute essential components of current management. Experimental animal models, including chemically induced fibrosis using carbon tetrachloride ($CCl_4$) and mechanical injury models like bile duct ligation (BDL) in rodent systems, continue to be indispensable for elucidating the intricate mechanisms of fibrogenesis and evaluating the efficacy of novel therapeutic interventions **(Kisseleva & Brenner, 2021).**

*Liver Cirrhosis*

Liver diseases, primarily resulting from adverse outcomes including, cirrhosis, hepatocellular carcinoma (HCC), and viral hepatitis, account for approximately two million deaths annually. While cirrhosis remains the principal cause of liver-related mortality worldwide, liver cancer represents the principal contributor of death within this category. Globally, the predominant reasons of cirrhosis consist of hepatitis, alcohol abuse, and non-alcoholic fatty liver disorders (NAFLD). An estimated two billion individuals consume alcohol, many of whom are affected by alcohol-use disorders and are therefore at elevated risk for alcohol-related liver disease. Additionally, around two billion adults are classified as overweight or obese, and approximately 400 million have diabetes—both conditions that significantly promote the development of NAFLD and HCC. Acute liver diseases are commonly triggered by hepatitis, although a substantial proportion also result from drug-induced liver injury. This global overview reflects updated insights from the 2019 revised framework and emphasizes key areas of advancement in the understanding of liver disease, especially in terms of HCC, hepatitis, alcohol liver disease, and NAFLD **(Asrani et al., 2019; Devarbhavi et al., 2023).**

*Hepatocellular Carcinoma (HCC)*

Liver tumor represents the fourth chief cause of tumor-related mortality globally and ranks second among men. The widespread occurrence of chronic HBV infection in places like Sub-Saharan Africa and Eastern Asia contributes to over 80% of hepatocellular carcinoma (HCC) cases worldwide. In recent decades, the epidemiological and etiological landscape of HCC has undergone significant changes. Although HBV was responsible for more than 50% of HCC cases globally in 1990, this figure declined to 42% by 2019. In contrast, the occurrence of hepatitis C virus (HCV)-associated HCC has markedly decreased in regions like Japan and Europe, primarily stemming from the widespread adoption of direct-acting antiviral therapies. The share of HCC cases attributed to nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis has escalated, with NASH rising from 5% to 6% and alcoholic steatohepatitis from 13% to 18% **(Kim, 2024).** Chronic HBV and HCV infections are major contributors to cirrhosis, which is frequently observed in HCC patients and forms a significant casual factor in HCC irrespective of its underlying etiology **(El-Serag, 2012).** In 2018, Egypt ranked as the country with the second-highest liver cancer risk globally, following Mongolia, where the incidence among men was approximately four times higher than that observed in China and South Korea. The age distribution of hepatocellular carcinoma cases worldwide is influenced by the dominant type of viral hepatitis and the age at which the infection is acquired. In regions with high HCC incidence, hepatitis B virus HBV, typically transmitted perinatally, is the top reason. Consequently, HCC tends to be diagnosed at a younger age in these areas compared to regions where hepatitis HCV often contracted later in life—is more prevalent **(Mittal and El-Serag,2013).**

In Egypt, recent studies have shown a shift in the etiology of liver cancer, with HCV now contributing to approximately 40–50% of HCC cases. In contrast, the impact of HBV and combined HBV/HCV infections has declined, accounting for about 25% and 15% of cases, respectively **(El-Zayadi et al.,2005).** HCC is currently the most frequently diagnosed cancer among Egyptian men, the second most prevalent in women, and the leading cancer overall when considering both sexes combined **(Ferlay et al.,2018).** HCC share rose to 19.7% of all cancer cases in 2018, with 25,399 new cases reported. These figures were based on data from the Aswan, Damietta, and Minia cancer registries. Furthermore, HCC represents the primary cause of cancer-related mortality in Egypt, constituting 32.35% of all cancer deaths, as reported by the World Health Organization (WHO) **(Ferlay2019).**

*Aspartate aminotransferase (AST)*

Aspartate aminotransferase (AST) is an enzyme chiefly existing in the liver and heart, with lower concentrations found in the kidneys and muscles. It is released into the bloodstream following liver injury. The normal serum AST range is typically between 0 and 35 IU/L. Elevated levels of mitochondrial AST are observed in conditions such as myocardial infarction involving extensive tissue necrosis, as well as in chronic liver diseases marked by hepatic degeneration and necrosis. The diagnostic significance of the ratio of mitochondrial AST to total AST lies in its ability to distinguish between liver cell necrosis and alcoholic hepatitis. AST is commonly assessed in conjunction with alanine aminotransferase (ALT), another liver enzyme, as both tend to increase in response to hepatic damage. The AST/ALT ratio is a valuable tool for differentiating the basic origin of liver injury **(Anderson et al.,2000).**

*Alanine aminotransferase ALT*

ALT is an enzyme primarily located in the liver, with lower concentrations present in the kidneys. It is fundamental to protein metabolism and energy production by aiding in the breakdown of food. The normal range for serum ALT levels fall between 7 and 56 IU/L. Hepatic cells injury leads to an increase in ALT levels in the bloodstream. ALT levels up to 300 IU/L are typically classified as indetermined, while elevations exceeding 500 IU/L are commonly associated with conditions that directly impact hepatocytes, such as viral hepatitis, ischemic liver failure, or toxic liver damage. Elevated aminotransferase levels are indicative of hepatitis infections. In hepatitis C, ALT elevation results from liver cell death due to both apoptosis and necrosis. Persistent ALT elevation lasting over six months in cases of acute hepatitis is a diagnostic marker for chronic hepatitis **(Anderson et al.,2000).**

*Markers of liver synthetic function*

Albumin, a major serum protein constituting approximately 50%–60% of total plasma protein, is synthesized exclusively by the liver, making it a key indicator of hepatic synthetic capacity. While albumin levels are a useful reflection of liver function, they may also be affected by extraneous factors such as systemic inflammation—given its nature as a negative acute-phase reactant—as well as inadequate protein intake, nephrotic syndrome, fluid retention, or protein-losing enteropathies. Albumin serves several functional roles, including the maintenance of plasma oncotic pressure and the transport of both endogenous substances (bilirubin) and external compounds (pharmaceutical agents). The normal serum albumin concentration typically ranges between 3.5 and 5 g/dL **(Tufoni et al.,2020).**

Prothrombin time (PT) and international normalized ratio (INR) perform as functional assessments of the extrinsic pathway of the coagulation cascade, for which the liver is responsible through the synthesis of several coagulation factors, as well as natural anticoagulants like protein C, protein S, and antithrombin. PT and INR are generally higher than activated partial thromboplastin time (aPTT) in liver disease due to compensatory production of factor VIII and von Willebrand factor in extrahepatic tissues, which can mask aPTT prolongation in vitro. However, due to concurrent deficiencies in both pro-coagulant and anticoagulant pathways, PT/INR and aPTT are not robust indicator of hemorrhage risk in individuals with cirrhosis. Furthermore, these parameters assess only pro-coagulant activity and do not account for disruptions in anticoagulant systems. In patients with CLD or cirrhosis, thrombocytopenia is frequently observed as a result of splenic sequestration and minimized synthesis of thrombopoietin, compounding the risk of hemorrhagic complications **(Harrison,2018).**

Although bilirubin is not a direct marker of hepatic synthetic function, its metabolism is closely associated with the liver's capacity for conjugation and excretion. Bilirubin is a terminal product of heme catabolism and circulates in the bloodstream bound to albumin. Hepatic processing involves conjugation and subsequent biliary excretion. Elevated serum levels of bilirubin are categorized as conjugated or unconjugated hyperbilirubinemia. Direct hyperbilirubinemia typically results from impaired hepatic excretion, such as in cholestatic conditions or inherited syndromes like Dubin-Johnson and Rotor. Conversely, indirect hyperbilirubinemia may arise from hepatocellular injury or increased hemolysis **(Ramirez-Mejia et al.,2024).**

*Red blood cells indices*

Chronic liver disease (CLD) often leads to alterations in red blood cell (RBC) indices due to multifactorial mechanisms, including nutritional deficiencies, hypersplenism, and chronic inflammation. Common findings include decreased hemoglobin (HGB) levels, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), reflecting microcytic or normocytic anemia, often associated with iron deficiency or anemia of chronic disease (ACD) **(Gonz-Casas et al., 2009**). Additionally, macrocytic anemia may occur because of folate or vitamin B12 deficiency, frequently observed in alcoholic liver disease (ALD) or advanced cirrhosis **(O'Leary & Friedman, 2017).** Hypersplenism, a consequence of portal hypertension **(Lata, 2012).**

The RBC distribution width (RDW) is often elevated in CLD, indicating increased variability in RBC size (anisocytosis), which correlates with disease severity and prognosis **(Li et al., 2015).** Furthermore, impaired hepatic synthesis of erythropoietin and hepcidin dysregulation contribute to anemia pathogenesis **(Girelli et al., 2016).** These hematological changes are critical markers for monitoring CLD progression and guiding therapeutic interventions, such as nutritional supplementation or splenectomy in select cases **(Verma et al., 2018**).

*White blood cells indices*

Chronic liver disease (CLD) is frequently linked to alterations in white blood cell (WBC) parameters, driven by systemic inflammation, portal hypertension, and compromised immune function. Leukopenia, particularly neutropenia, is commonly observed in advanced stages of cirrhosis, largely attributed to hypersplenism-induced sequestration and destruction of leukocytes **(Giannini et al., 2003).** Moreover, diminished bone marrow activity and reduced synthesis of granulocyte colony-stimulating factor (G-CSF) further contribute to neutrophil depletion **(López-Karpovitch et al., 2016).** In contrast, leukocytosis may occur in response to acute bacterial infections or hepatic inflammation, with an elevated NLR serving like prognostic indicator for severity of disease and complications such as spontaneous bacterial peritonitis (SBP) **(Kalra et al., 2018).**

Lymphopenia is also prevalent in CLD, often resulting from chronic immune dysfunction and malnutrition, thereby increasing vulnerability to infections **(Albillos et al., 2014).** In addition, monocyte dysfunction characterized by aberrant cytokine production contributes to the persistence of systemic inflammation **(Zimmermann et al., 2011).** Elevated NLR and PLR have been linked to adverse prognoses in hepatocellular carcinoma cases (HCC) and decompensated cirrhosis, underscoring their utility in risk stratification **(Chen et al., 2015).** Therefore, continuous monitoring of WBC indices is crucial for the early identification of infectious complications and the implementation of immunomodulatory interventions in CLD management.

*Platelet indices:*

Platelet indices (PIs) are routinely obtained parameters included in automated complete blood count analyses. They serve as potential indicators of platelet morphology, activation status, and production dynamics. With advancements in hematology analyzers, the measurement of PIs has become efficient and standardized. In recent years, PIs have gained attention as emerging biomarkers with diagnostic and prognostic value across a range of acute and chronic diseases. Numerous studies have investigated their clinical relevance in conditions such as sepsis, thrombocytopenia, liver diseases, cardiovascular disorders, surgical trauma, and malignancies. Due to their noninvasive nature, low cost, and easy availability, PIs have become appealing for research on platelet biology over the past decade. Among these parameters, mean platelet volume (MPV) has been the most extensively studied. MPV reflects the average size of circulating platelets, typically ranging from 7.2 to 11.7 femtoliters (fL). Several factors, including ethnicity, age, physical activity, smoking, and alcohol consumption, can influence MPV values. Elevated MPV levels have been associated with poorer outcomes in cases such as pancreatic cancer and myocardial infarction. while reduced MPV has been linked to effective inflammation control in rheumatoid arthritis **(Gouda AM et al., 2024).**

Platelet distribution width (PDW) indicates platelet size variability. It increases upon platelet activation, reflecting platelet

anisocytosis. Plateletcrit (PCT), on the other hand, measures the volume percentage of platelets in the bloodstream, with normal values ranging from 0.22% to 0.24%. The platelet large cell ratio (P-LCR) represents the proportion of large platelets in circulation and normally falls within the 15–35% range. Studies have demonstrated a positive association among P-LCR, PDW, and MPV, and an inverse relationship between P-LCR and platelet count in thrombocytopenic patients. Furthermore, P-LCR has shown greater sensitivity to platelet size variation compared to MPV **(Oral et al.,2019).**

*Glial cell line-derived neurotrophic factor (GDNF)*

GDNF is a glycosylated homodimer stabilized by disulfide bonds and is considered a divergent member of the transforming growth factor-beta (TGF-β) protein family group. Clinical research has demonstrated elevated GDNF levels in both the parietal cortex and plasma of individuals with relapsing major depressive disorder. Furthermore, GDNF expression significantly increases following exposure to various cell-toxic agents **(Lin et al.,1993)**. Elevated GDNF levels have also been observed in certain types of cancer cells. GDNF is increasingly recognized as a promising biomarker in the context of CLD. Evidence indicates that GDNF contributes to liver fibrogenesis by facilitating the hepatic stellate cells activation, a central mechanism in the development of fibrosis. Elevated GDNF expression has been reported in both liver tissue and serum of patients with advanced liver conditions, suggesting its practical use as a noninvasive marker of disease severity. Additionally, GDNF may participate in hepatocarcinogenesis by enhancing cellular survival and proliferation. These findings highlight GDNF's possible dual role as both a detective biomarker and a therapeutic target in CLD **(Hu et al., 2021).** Serum GDNF levels are significantly elevated versus healthy controls and those with chronic hepatitis B (CHB) without cirrhosis. **Yang et al. (2022**) have demonstrated that serum GDNF levels are higher in CHB patients with fibrosis (28.4 pg/ml vs. 11.6 pg/ml in non-fibrotic patients) and even more elevated in those with cirrhosis (33.8 pg/ml vs. 23.5 pg/ml in non-cirrhotic patients).

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## الملخص العربي

### عنوان البحث: الاتجاهات الوبائية والواسمات التشخيصية في أمراض الكبد المزمنة

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تعَدُّ أمراض الكبد المزمنة سبباً رئيسياً للوفيات والاعتلال على الصعيد العالمي، وتشمل طيفاً واسعاً من الاضطرابات ذات المسببات المتنوعة. يعتمد التشخيص الدقيق والإنذار ومراقبة أمراض الكبد المزمنة بشكل كبير على تقييم العديد من المؤشرات الحيوية. يقدم هذا البحث لمحة مركزة عن المؤشرات الحيوية الكيميائية والدموية الرئيسية المستخدمة في تقييم الأنواع الأساسية لأمراض الكبد المزمنة، بما في ذلك التهاب الكبد الفيروسي ومرض الكبد الدهني غير الكحولي (NAFLD). لكل فئة مرضية، نناقش الفائدة السريرية لاختبارات وظائف الكبد التقليدية (مثل ALT, AST، البيليروبين، الألبومين)، ومؤشرات التليف (مثل عدد الصفائح الدموية، درجة APRI، ومؤشر FIB-4)، بالإضافة إلى المعايير الدموية الأخرى ذات الصلة. ومن خلال تجميع الأدلة الحالية حول القيمة التشخيصية والإنذارية لهذه المؤشرات الكيميائية والدموية عبر المسببات المختلفة لمرض الكبد المزمن، يهدف هذا البحث إلى توفير مرجع عملي للأطباء والباحثين في مجال أمراض الكبد.