Liver Function Tests and Liver Scores

Relevance, Interpretation, Algorithms, and Disease Specifics

Univ. Prof. Dr. Ali Canbay
Asst. Prof. Dr. Jan Best
Asst. Prof. Dr. Mustafa Özçürümez

Falk FOUNDATION e.V.

Publisher

FALK FOUNDATION e.V.

Leinenweberstr. 5
79108 Freiburg
Germany

www.falkfoundation.org

Illustrations: Katja Heller

5th updated and revised edition 2021

Liver Function Tests and Liver Scores

Relevance, Interpretation, Algorithms, and Disease Specifics

Univ. Prof. Dr. Ali Canbay
Asst. Prof. Dr. Jan Best
Asst. Prof. Dr. Mustafa Özçürümez
University Medical Center Knappschaftskrankenhaus Bochum, Germany

Address for correspondence

Univ. Prof. Dr. Ali Canbay
Ruhr-Universität Bochum
Medical Clinic
University Medical Center Knappschaftskrankenhaus Bochum GmbH
In der Schornau 23–25
44892 Bochum, Germany
Tel. +49 234 299-80100
E-Mail: ali.canbay@rub.de

Co-authors

Asst. Prof. Dr. Jan Best
Ruhr-Universität Bochum
Medical Clinic
Director of the Center for Hepatobiliary Disorders
University Medical Center Knappschaftskrankenhaus Bochum GmbH
In der Schornau 23–25
44892 Bochum, Germany

Asst. Prof. Dr. Mustafa Özçürümez
Ruhr-Universität Bochum
Medical Clinic
Director of Laboratory Medicine
University Medical Center Knappschaftskrankenhaus Bochum GmbH
In der Schornau 23–25
44892 Bochum, Germany

Conflict of Interest

The authors declare no conflicts of interest.

Table of Contents

Summary

Liver diseases – both acute and chronic – are common issues in clinical practice that often pose a major burden for public health systems. In addition to acute liver diseases (toxicity-related acute liver failure, acute viral hepatitis, etc.), chronic liver diseases such as viral hepatitis and, increasingly, fatty liver disease (alcohol-related/ALD and non-alcoholic/NAFLD) are a frequent cause of fibrosis, which can in turn lead to cirrhosis and hepatocellular carcinoma (HCC). An enlarged liver and/or spleen are also findings which require further diagnosis. The spectrum of differential diagnoses ranges from primary liver diseases, myeloproliferative and lymphoproliferative disorders, infiltrative diseases, and infections to a number of hereditary metabolic conditions. Given these risks, early detection of liver diseases is gaining increasing importance, with the goal of initiating treatment early and modifying any predisposing factors.

As the body's central metabolic organ, the liver is highly active with a broad spectrum of functions and synthesized factors that also directly interact with other organs such as the gut (microbiome), heart, muscles, fatty tissue, and kidneys.

Elevated liver enzymes are common findings in clinical practice yet represent a challenge for physicians. While timely detection of a treatable hepatic disorder can improve outcomes, avoiding overdiagnosis is also an important goal. Delayed or absent detection of liver diseases as well as unjustified diagnostic procedures both represent major burdens for patients and for public health care systems. The primary aim must therefore be to detect liver diseases in their early stages in order to prevent long-term complications such as HCC or cirrhosis and its associated disorders using modern therapeutic options.

This booklet is intended to present a diagnostic algorithm that is designed to facilitate efficient diagnosis of liver diseases. It will describe both important liver diseases as well as their typical patterns of laboratory test results and additional tests – both blood and imaging tests – required to further clarify a diagnosis. Scores currently used to evaluate NAFLD and NASH will also be presented.

The contents of this booklet are based on the most up-to-date literature as well as experience from clinical practice. Since research and clinical practice are constantly evolving, this booklet makes no claim to completeness.

Introduction

It is estimated that more than 5 million people suffer from a liver disease in Germany, although the number of undiagnosed cases is likely much higher. Among persons between the ages of 35 and 59, alcohol-related liver disease is the second-highest cause of death in men and the third-highest in women.[1] Many of these patients are not diagnosed with an advanced liver disease until a late stage of disease, despite having abnormally elevated liver enzymes for many years. Although elevated ALT (alanine aminotransferase) levels can be detected in about one-fourth of the German population,[2] they are frequently interpreted to be harmless due to a lack of symptoms or are erroneously thought to be linked to medications or another systemic disorder.

This can be problematic for many types of patients, as even non-alcoholic fatty liver disease (NAFLD) – which is indeed frequently diagnosed – can lead to cirrhosis and its complications such as portal hypertension, liver failure, or HCC in a sizeable percentage of patients. Any initial diagnosis of elevated liver enzymes should always be followed up by further diagnostic procedures. In addition to a patient's medical history and physical examination, laboratory markers of hepatocellular injury, cholestasis, and the synthetic function of the liver represent the basic pillars of initial diagnosis of liver diseases.

Laboratory blood tests help classify the pattern of injury (hepato-cellular, cholestatic, toxic, or mixed) to aid in differential diagnosis, and also help evaluate the severity and prognosis of the disease. In-depth diagnostic procedures may progress sequentially from immunological and molecular markers to imaging modalities and biopsies.

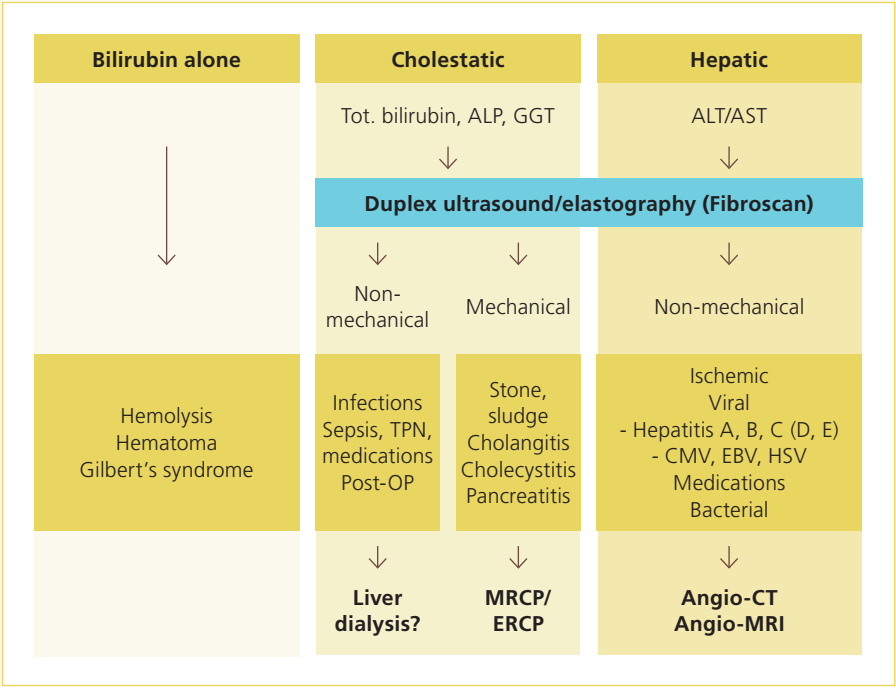


Figure 1: General elevations in liver function tests

1 Clinical approach

Whenever a patient is suspected of having a liver disease, the initial diagnostic procedure should begin with blood tests that include transaminases, GGT (γ-glutamyltransferase), and albumin (fig. 1). Levels of at least one of the three enzymes AST (aspartate aminotransferase, also known as glutamic-oxaloacetic transaminase [GOT]), ALT (alanine aminotransferase, also known as glutamic-pyruvic transaminase [GPT]) or GGT are elevated in 95% of all patients.[3] In-depth diagnosis is mandatory in all cases of elevated liver enzymes should these levels persist (generally longer than 6 months), be associated with clinical symptoms, or durably exceed the upper limit of normal. Queries into the patient's medical history should focus on both the patient's reported history as well as any occupational factors (e.g. chemical exposure, etc.), risk factors (e.g. sexual promiscuity), travel, and medications (including medicinal herbs) over the previous 6 months, as well as any prior medical interventions. The physical examination should check for potential jaundice and abdominal status as well as extrahepatic manifestations of chronic liver disease such as spider angioma, palmar erythema, smooth tongue, glossy lips, temporal wasting (especially in alcohol-related liver disease), etc. and signs of portal hypertension (splenomegaly, caput medusae, etc.) (fig. 2). These core diagnostic examinations may provide initial hints on the etiology and help differentiate between acute and chronic injury, and may also allow the severity of the liver disease to be estimated.

The laboratory parameters measured in core diagnostic tests can also help identify the pattern of liver injury and thus provide valuable insights into the origin of the liver disease. Always remember: **"Liver function tests do not lie!"** Indicators of parenchymal (hepatocellular) injury are AST, ALT, and GLDH (glutamate dehydrogenase). Disorders of biliary excretion, represented by the "cholestatic" pattern, are characterized by elevated levels of ALP (alkaline phosphatase), GGT, and bilirubin. If elevated GGT is most prominent, this is an indication of a toxicity-related injury (fig. 1). Not all liver injuries adhere strictly to this pattern – mixed presentations also occur. Parameters reflecting the synthetic function of the liver are the INR (international normalized ratio), albumin,

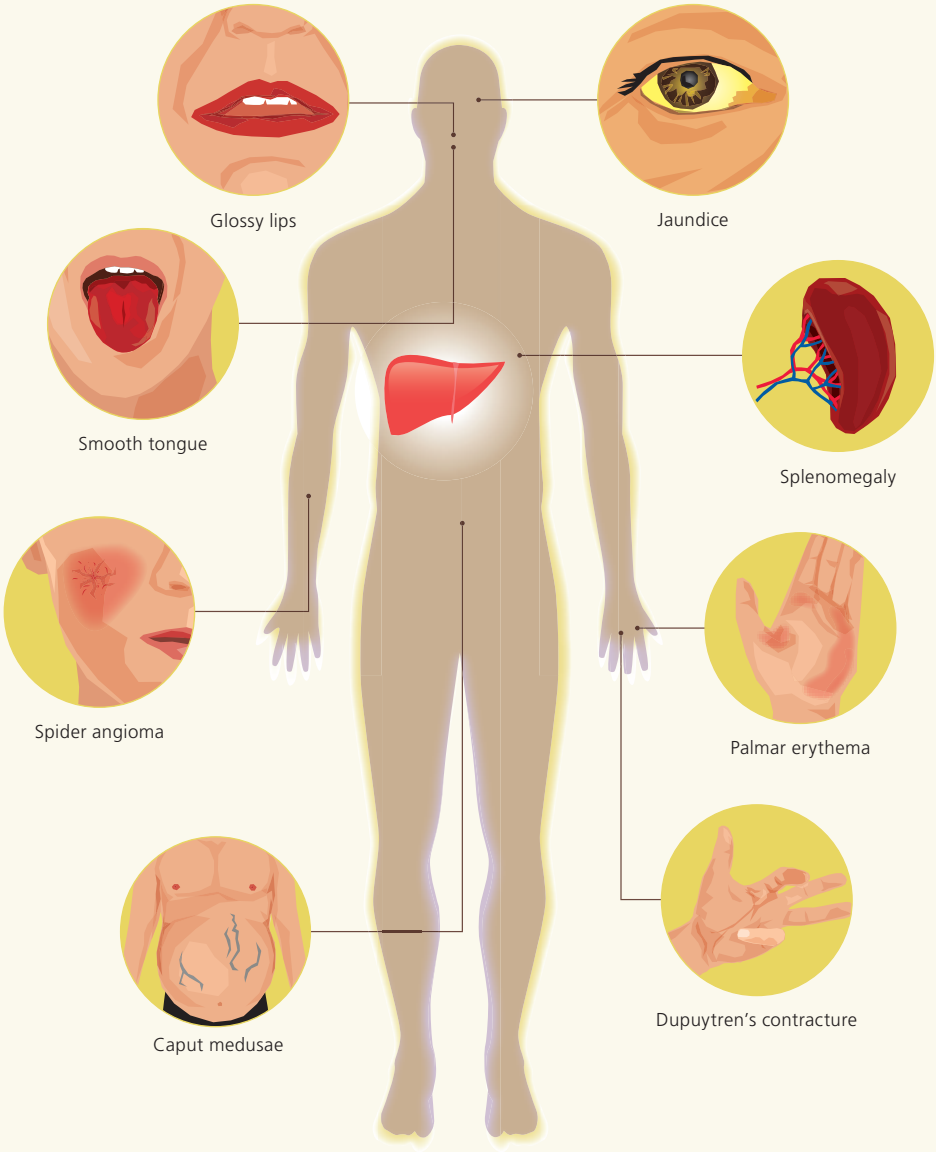


Figure 2: Typical symptoms of liver diseases

and cholinesterase. In order to avoid misinterpreting the results of panel tests comprising multiple biomarkers, it is crucial to take account of the differing half-lives of these markers. It should also be kept in mind that normal levels of transaminases do not rule out liver disease or viral hepatitis infection (tables 1–3). The generally accepted normal ranges should be viewed with some skepticism in light of recent data, as the original control populations likely included ineligible patients due to the lack of awareness or underestimation of the prevalence of non-virus-associated hepatopathies (NAFLD) and chronic hepatitis C infections.[4,5]

Biochemical markers of parenchymal liver injury	
Alanine aminotransferase **ALT** **Synonym:** **glutamic-pyruvic transaminase** **GPT**	• Half-life 47 hours • Normal range (♂ < 50 U/l; ♀ < 35 U/l) • Liver-specific at highly elevated levels • Primarily cytoplasmic localization • High levels in acute hepatitis, slightly elevated in liver tumors or drug-induced injury
Aspartate aminotransferase **AST** **Synonym:** **glutamic-oxalacetic transaminase** **GOT**	• Half-life 17 hours • Normal range (♂ < 50 U/l; ♀ < 35 U/l) • Very sensitive • Non-specific, also elevated in myocardial infarction, muscular disorders, hemolysis • Localized in cytoplasm and mitochondria • Very high in acute viral, alcoholic, and toxic hepatitis
Glutamate dehydrogenase **GLDH**	• Half-life approx. 18 hours • Normal range (♂ < 7 U/l; ♀ < 5 U/l) • Liver-specific at highly elevated levels • Only mitochondrial localization • Elevated in centrilobular injury: hypoxia, acute (toxic) hepatitis, obstructive jaundice

Table 1

Biochemical markers of bile secretion disorders or cholestasis	
Alkaline phosphatase ALP	• Half-life 1–7 days • Normal range (♂ 25–124 U/l; ♀ 25–100 U/l) • Primarily membrane-bound • Not liver-specific (isoenzymes in liver, bone, kidney, gut, placenta) • Elevated in cholestasis, hepatic infiltration, minor elevation in hepatitis and medication use
Bilirubin excretion in urine	• Elevated in hepatic and post-hepatic jaundice
γ-Glutamyltransferase GGT	• Half-life 3–7 days • Normal range (♂ < 55 U/l; ♀ < 35 U/l) • Membrane-bound • Liver-specific • Elevated in biliary cholestasis, toxic injury
Serum bilirubin Indirect/direct	• Total bilirubin: 0.2–1.1 mg/dl • Degradation product of heme • **Direct** – Normal range 0–0.2 mg/dl (conjugated) – Elevated in hepatic/post-hepatic jaundice • **Indirect** – Normal range 0.3–1.2 mg/dl – Elevated in pre-hepatic jaundice

Table 2

Parameters of synthetic function and detoxification	
Albumin	• Normal range 3.4–4.8 g/dl • Transport protein • Antioxidant/anti-inflammatory
Ammonia	• Normal range 13–55 µmol/l • Parameters of detoxification capacity • Low correlation between level and degree of encephalopathy
Cholinesterase	• Normal range 4.9–11.9 kU/l • Predictive factor for fulminant liver failure, cirrhosis, and after liver transplantation • False-high after fresh plasma infusion
Prothrombin time (PT) International normalized ratio (INR)	• PT normal range: 70–130% • INR normal range < 2 • Poor prognosis if values very high • Vitamin-K-dependent

Table 3

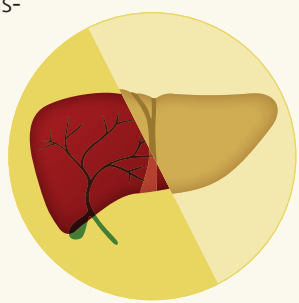
2 Differential diagnosis of parenchymal liver diseases

ALT is a liver-specific enzyme that can be detected by blood tests even with minor parenchymal injury due to its cytoplasmic localization within hepatocytes. Thanks to this high degree of sensitivity, this parameter is also very well suited for routine screening tests in the primary care setting.

AST exhibits high sensitivity yet low specificity for a hepatocellular pattern of injury, but can still be used to predict the severity of cellular necrosis due to its predominantly mitochondrial localization. The AST:ALT ratio (also known as the De Ritis ratio) simplifies differentiation between a more minor liver injury (AST:ALT < 1) and severe injury (AST:ALT > 1), as occurs with chronic hepatitis or cirrhosis.

GLDH is also localized to the mitochondria and reflects a centrilobular pattern of injury as often occurs with severe parenchymal injury, acute intoxication (e.g. with Amanita mushrooms), and perfusion disorders of the liver. GLDH is only slightly elevated in cholestatic liver diseases (fig. 3).

The level of transaminases provides insight into the etiology of a liver disease. For example, a major increase in transaminases (> 10–50-fold of normal) most likely points to fulminant viral or drug-induced hepatitis but may also reflect ischemic injury or malignant hyperthermia. Moderate elevations in transaminases (> 5-fold of normal) may be observed in mild cases of viral hepatitis, medication-induced hepatitis (table 4), alcohol-induced hepatitis, or drug-induced hepatitis (cocaine, ecstasy). Minor increases in transaminases indicate non-alcoholic fatty liver disease or liver cancer, but also occur in cholestatic liver diseases and inactive ("burned-out") cirrhosis, in which transaminase levels may even be normal. A finding of elevated transaminases requires further differentiation to acute or chronic liver disease, which is performed using the patient's medical history and clinical examination. Both thrombocytopenia and unremarkable ultrasound findings may indicate a chronic liver disease.



Transaminases should be checked again within 3 months in patients with acute liver disease, moderate elevation in liver function tests, and no signs of liver failure. If transaminase levels remain elevated or increase further, in-depth diagnosis is required. Infection with hepatitis A, B/D, C, or E viruses should always be ruled out (figs. 4 and 5). Patients with negative virus serology should be screened for metabolic disorders with liver involvement (hemochromatosis, Wilson's disease, diabetes, celiac disease, Gaucher's disease, LAL-D, etc.), and autoantibodies (ANA, AMA, SMA, SLA, pANCA), immunoglobulins and serum electrophoresis should be performed to screen for autoimmune hepatitis (AIH). In the next step, tests for less common causes such as hepatotropic viruses, bacteria, fungi, or parasites should be performed even in patients with prior negative test results. The possibility of unreported drug or alcohol consumption should also be kept in mind for patients with an otherwise unremarkable history. Urine drug testing may be useful as well as testing for CDT (carbohydrate-deficient transferrin) or ethyl glucuronide in urine or a hair sample (fig. 6). Elevated transaminases may also result from other systemic disorders, which should be incorporated into any differential diagnosis (table 5). Patients with hemolysis, intense exercise, increased protein intake, prolonged fasting, or who are postprandial may exhibit a false-positive transaminase elevation.

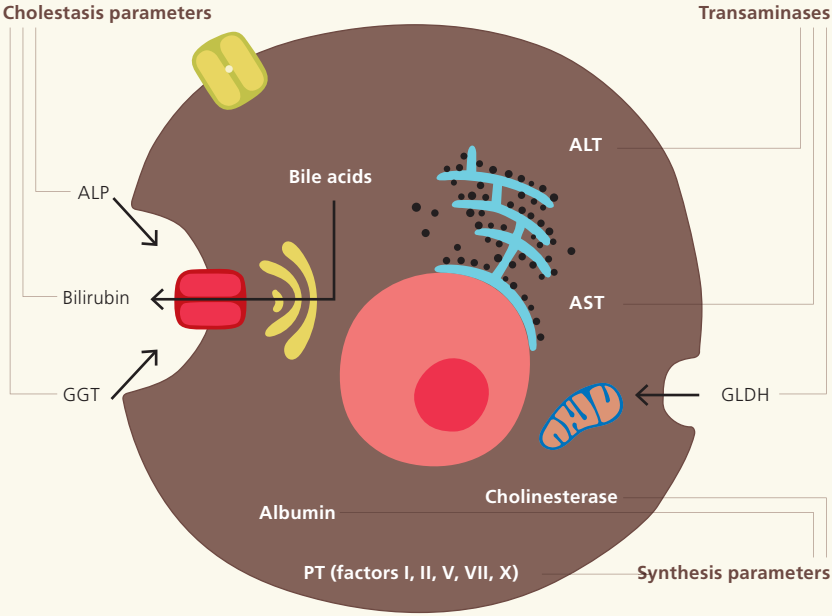


Figure 3: Enzyme localization in hepatocytes/cholangiocytes
(for abbreviations, see tables 1–3)

Drug-induced elevation of liver function tests			
	ALT	**ALP**	**ALT:ALP ratio**
Hepatocellular	≥ 2 x elevated	Normal	High (≥ 5)
Cholestatic	Normal	≥ 2 x elevated	Low (≤ 2)
Mixed type	2 x elevated	2 x elevated	

Slight elevation of GLDH > 7–200 U/l for all patterns of injury

Table 4

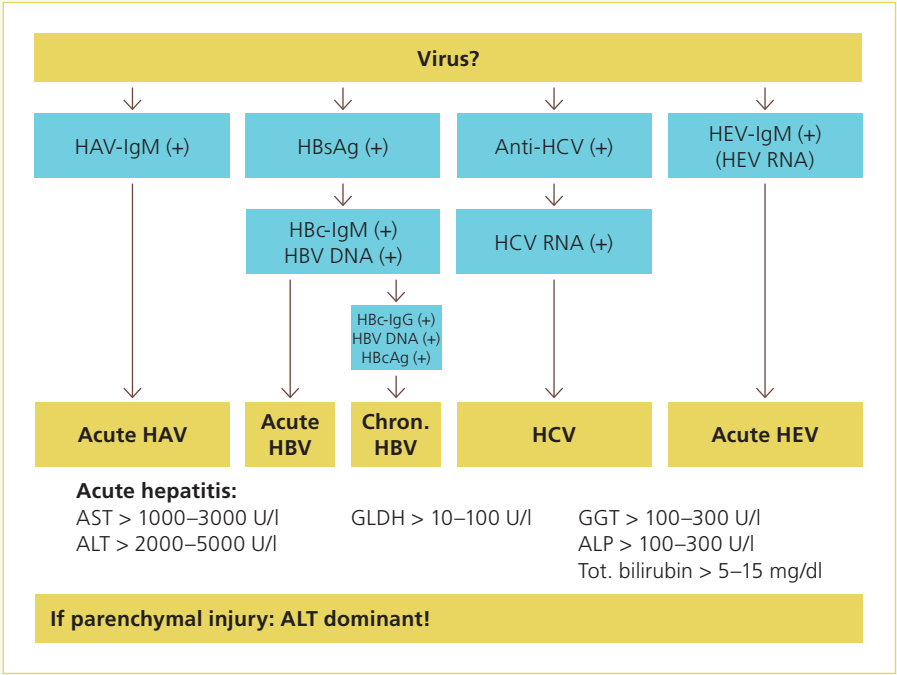


Figure 4: Diagnosis of hepatitis

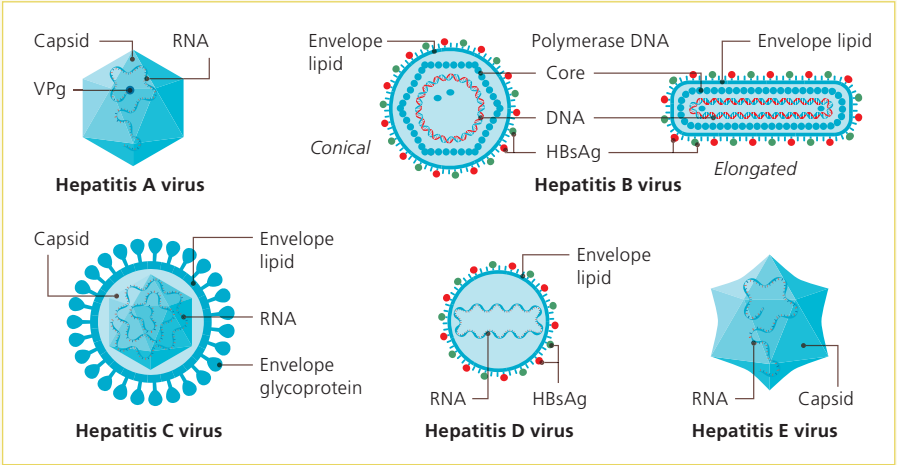


Figure 5: Hepatitis viruses

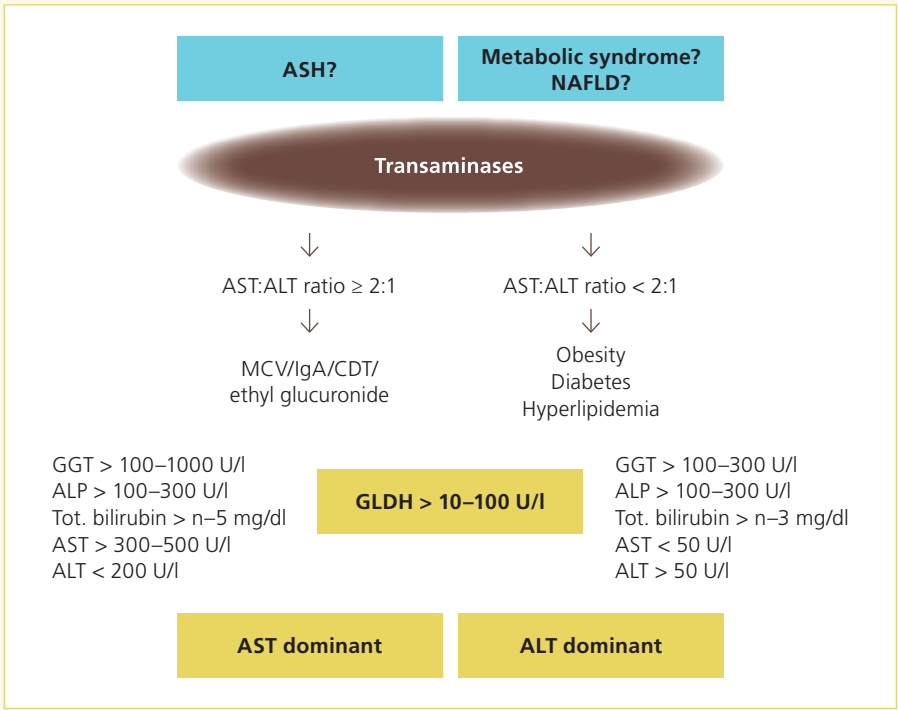


Figure 6: Differential diagnosis ASH or NAFLD/NASH

Systemic disorders with liver involvement	
Gastrointestinal disorders	Celiac disease, ulcerative colitis, Crohn's disease
Myocardial disorders	Myocardial infarction, myositis, tachycardia arrhythmia, heart surgery
Vascular disorders	Pulmonary embolism (with right heart strain)
Endocrine disorders	Addison's disease, hypo-/hyperthyroidism

Table 5

3 Differential diagnosis of cholestatic liver diseases

The parameters used to detect cholestasis are GGT and ALP, both of which are expressed in biliary epithelial cells (fig. 3). The enzyme GGT is highly specific for the liver and may be elevated both in patients with cholestatic liver diseases and those with toxicity-related injuries (resulting from diet, medication, or alcohol) or malignant infiltration (figs. 7 and 8). Elevated ALP should always be interpreted in conjunction with GGT and total bilirubin, since this enzyme is not liver-specific and very high levels may also occur in patients with osteolytic metastases, hyperparathyroidism, Paget's disease of bone, and in patients who are pregnant. Bilirubin is similarly elevated in cholestatic diseases (fig. 9) but may also potentially be elevated in late-stage cirrhosis, meaning that this parameter alone is not an indicator for cholestatic disease.

Hyperbilirubinemia is clinically correlated with jaundice of the skin above a total bilirubin level of 3 mg/dl (conjunctival jaundice above 2 mg/dl). Characterizing hyperbilirubinemia requires differentiation between elevated levels of direct and indirect bilirubin, since this allows classification as prehepatic, intrahepatic, or posthepatic jaundice (fig. 10). Indirect bilirubin accumulates when hemoglobin and other porphyrin derivatives are degraded, bind to serum albumin, and are transported to the liver. In the liver, indirect bilirubin is conjugated to glucuronic acid to form direct bilirubin which is then excreted by the hepatobiliary route. Prehepatic jaundice with a dominant elevation of indirect bilirubin thus results primarily from excessive hemolysis, but also from large hematomas or inefficient hematopoiesis. Elevation of direct bilirubin may also occur in parenchymal liver diseases such as cholestatic forms of viral hepatitis, drug-induced injury, and sepsis. Less common defects in the glucuronidation enzymes and in bilirubin transport are characterized by elevated bilirubin levels without concomitant elevation in transaminases. One exception to this rule is Gilbert's syndrome, an asymptomatic enzyme defect which is frequently detected in blood tests as isolated elevation of indirect bilirubin. Gilbert's

syndrome likely signifies a predisposition to drug-induced toxicity. Posthepatic jaundice is characterized by elevated levels of direct bilirubin and occurs in cholestatic disorders (fig. 10). In this situation, ALP and GGT are also frequently elevated. Abdominal ultrasound is a mandatory component of initial diagnosis for these patients and can often confirm a diagnosis of cholecystitis, choledocholithiasis, pancreatic cancer, or cholangiocarcinoma at this early stage.

Hyperbilirubinemia may be caused by certain medications such as salicylate drugs, methotrexate, vitamin K, anabolic steroids, azathioprine, allopurinol, steroids, anti-tuberculosis drugs, etc.

Malignant infiltration		
AST > 500–1000 U/l ALT > 500–1000 U/l	GLDH > 10–100 U/l LDH > 1000 U/l	GGT > 1000–2000 U/l ALP > 500 U/l Tot. bilirubin > n–5 mg/dl

Isolated elevated GGT and LDH, especially in lymphoma infiltration!

Figure 7: Liver function tests in malignant infiltration

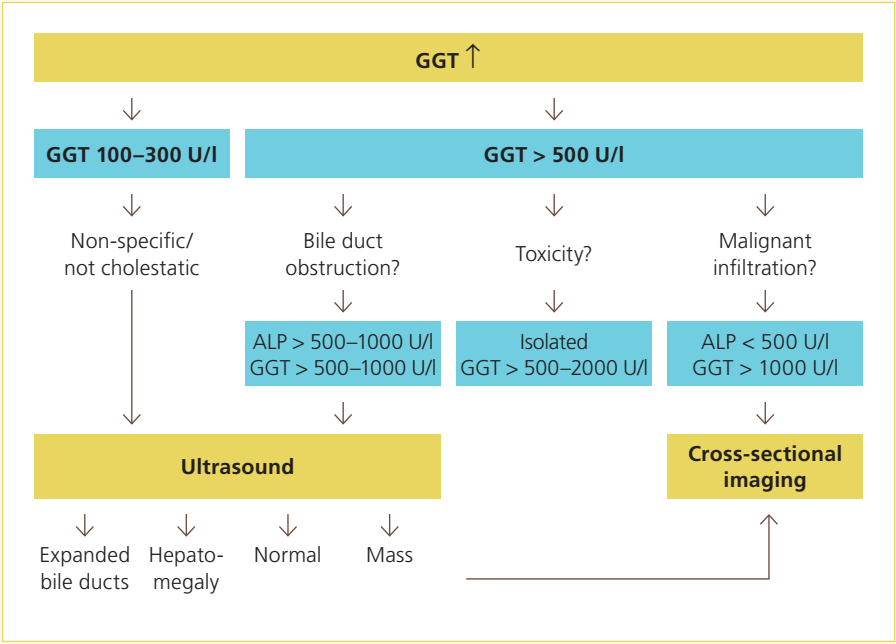


Figure 8: Algorithm for elevated GGT

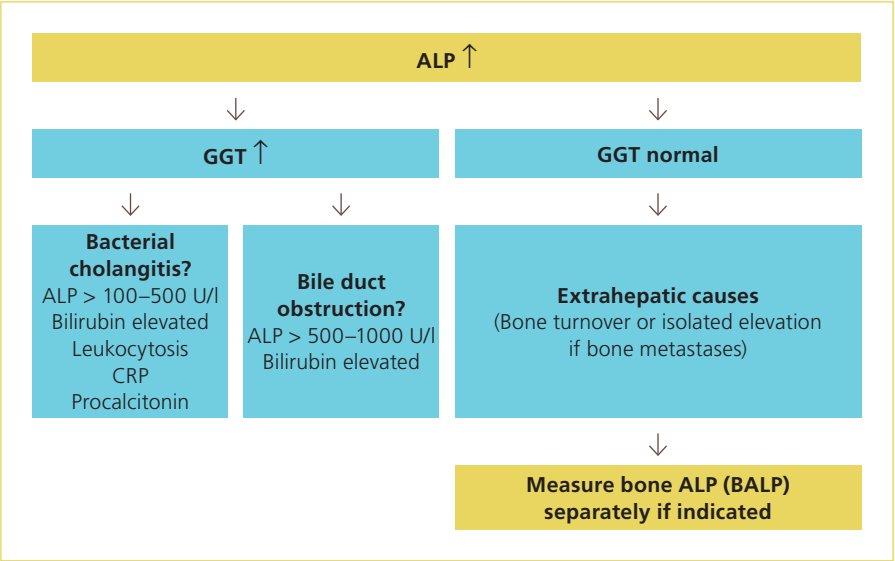


Figure 9: Algorithm for elevated ALP

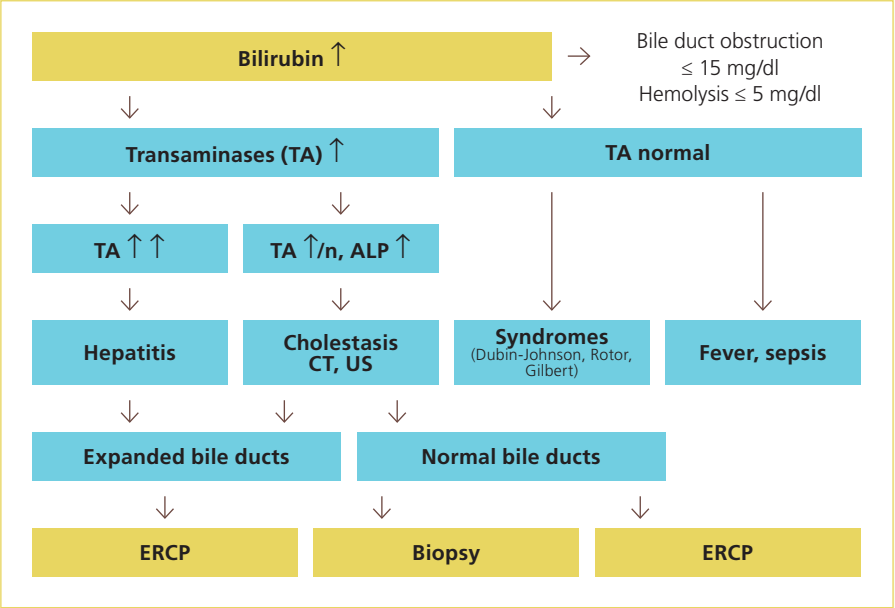


Figure 10: Algorithm for elevated bilirubin

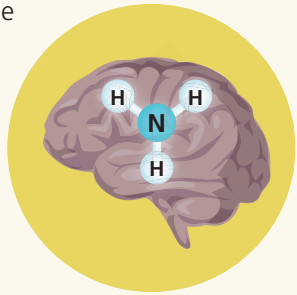
4 Parameters of synthetic function

Although cholinesterase is the most sensitive parameter for the synthetic function of the liver, its utility is limited by its half-life. Its levels are decreased at early time points in all chronic liver diseases and in cirrhosis, are lowered in metabolic disorders such as diabetes and hyperlipidemia, as well as in malnutrition and hypoalbuminemia or if certain drugs are taken (e.g. theophylline, atropine, caffeine, codeine, estrogens, morphine, corticosteroids, vitamin K). Cholinesterase is bound to albumin and tends to be a better indicator for acute liver failure due to its half-life (7–10 days).

Albumin is a protein produced by the liver that is required to transport numerous substances (hormones, drugs) in the blood and is a key regulator of intravascular oncotic pressure. Current data suggest that albumin exhibits antioxidant properties by binding to reactive oxygen species.[6] The reduced synthetic function in liver diseases leads to hypoalbuminemia. This in turn reduces the intravascular oncotic pressure, promoting extravascular diffusion of fluids which manifests clinically as edema, pleural effusion, and ascites. The function of albumin as a transport protein is also diminished, which can lead to changes in effective drug concentrations and electrolyte levels. Albumin is a key parameter in the Child-Pugh classification system for cirrhosis together with other parameters of synthetic function such as bilirubin and INR. The INR currently also plays an important role in liver transplantation priority lists as part of the MELD (Model of End-stage Liver Disease) score, which was originally developed to predict mortality for patients with a planned TIPS (transjugular intrahepatic portosystemic shunt) procedure. The INR reflects the capacity of the liver to synthesize vitamin K-dependent coagulation factors. However, current data show that patients with extremely high INR (e.g. patients with cirrhosis or acute liver failure [ALF]) are not at greater risk of bleeding, even without coagulation factor replacement or after certain interventions (central venous catheter [CVC], liver aspiration).[7] INR is also elevated in patients taking coumarin derivatives and in vitamin K deficiency. Other non-vitamin K-dependent

factors synthesized in the liver are antithrombin III, fibrinogen, and proteins S and C.

The detoxification function can be captured in laboratory tests using ammonia, which is released during protein catabolism and is eliminated by the urea cycle in the healthy liver. This capacity is diminished in advanced liver diseases or ALF, causing the blood ammonia level to increase and manifesting in the form of hepatic encephalopathy (HE). However, the magnitude of encephalopathy does not correlate with ammonia levels. Testing ammonia in blood is very sensitive to interference and should be conducted on a cooled sample within one hour of blood draw. Current developments in ammonia testing in the form of point-of-care diagnostics may reshape the role of ammonia in several different liver diseases.



5 Diagnostic tests if liver function tests are highly elevated

Acute liver failure (ALF) is defined as a rapid (within 28 days) or subacute (up to 6 months) elevation of transaminases and bilirubin with coagulopathy and emergence of hepatic encephalopathy of any grade (MHE to grade 4 HE) without known prior liver disease. From a clinical perspective, it is important to clearly distinguish liver failure with prior liver disease but without cirrhosis (acute-on-chronic) from liver failure with cirrhosis (acute-on-cirrhosis) for prognostic purposes, since the latter is associated with a much worse prognosis.[8] The King's College criteria or the Clichy criteria have become established as tools to determine whether liver transplantation is indicated, as they can help estimate the likelihood of liver failure relatively specifically, albeit with major limitations in their predictive value for spontaneous survival.[9,10] For this reason, more modern scores have been developed, including the ALFED (Acute Liver Failure Early Dynamic) model or the SOFA (Sepsis-related Organ Failure Assessment) score, which provide superi-

or predictive value yet are still hampered by several limitations, leaving clinical appraisal by experienced hepatologists and transplant specialists indispensable. Newer publications have reported that the MELD score also demonstrates a high predictive value for the likelihood of survival in ALF.[11] Other parameters such as HDL (high-density lipoprotein) cholesterol or thyroid parameters (TSH, T4, and T3) can be included as additional markers for prognostic purposes.[12-14]

Table 6 summarizes the most common causes of ALF. Rapidly determining the cause of ALF can improve outcomes. In order to immediately initiate specific treatment, both the patient's self-reported medical history and history reported by a relative or contact are crucial, while mandatory initial tests include a clinical examination and laboratory tests such as urine drug testing, serum testing of medication levels, virus serology, autoantibodies (ANA, AMA, SLA, LKM), a pregnancy test for women of childbearing age, ceruloplasmin in serum, copper in urine, iron, ferritin, and transferrin saturation.

Abdominal imaging should be performed as rapidly as possible to rule out a vascular origin (e.g. Budd-Chiari syndrome). In patients with cardiopulmonary stability and unclear findings, many hospitals have found early minilaparoscopy to be a valuable tool for macroscopic evaluation of the liver and to collect tissue biopsies in a safe manner while also providing the option for coagulation in patients with coagulopathies.[15] This also allows detection and immediate treatment of AIH not identified using the typical autoantibodies as well as of rarer granulomatous disorders (e.g. sarcoidosis). Another low-complication alternative to biopsy for confirming an uncertain acute liver disease is a transjugular liver biopsy, although this method captures many fewer portal tracts and does not permit direct inspection.

Figure 11a–c lists examples of typical patterns of laboratory test results for acute right heart failure, acetaminophen/paracetamol intoxication, and acute AIH.

Causes of acute liver failure	
Viral hepatitis	Hepatitis A, B, C, (B+)D, E, HSV, EBV, CMV, influenza
Acute intoxication	Acetaminophen, Amanita phalloides
Idiosyncratic liver toxicity	Ecstasy, phenprocoumon, tetracycline, halothane, isoniazid, anabolic steroids, medicinal herbs
Immunological causes	AIH, GvHD
Metabolic causes	Wilson's disease, α_1-antitrypsin deficiency, non-alcoholic steatohepatitis (NASH), very rare
Pregnancy-related causes	Acute fatty liver of pregnancy, HELLP syndrome
Vascular origin	Budd-Chiari syndrome, ischemia/shock, veno-occlusive disease

Table 6

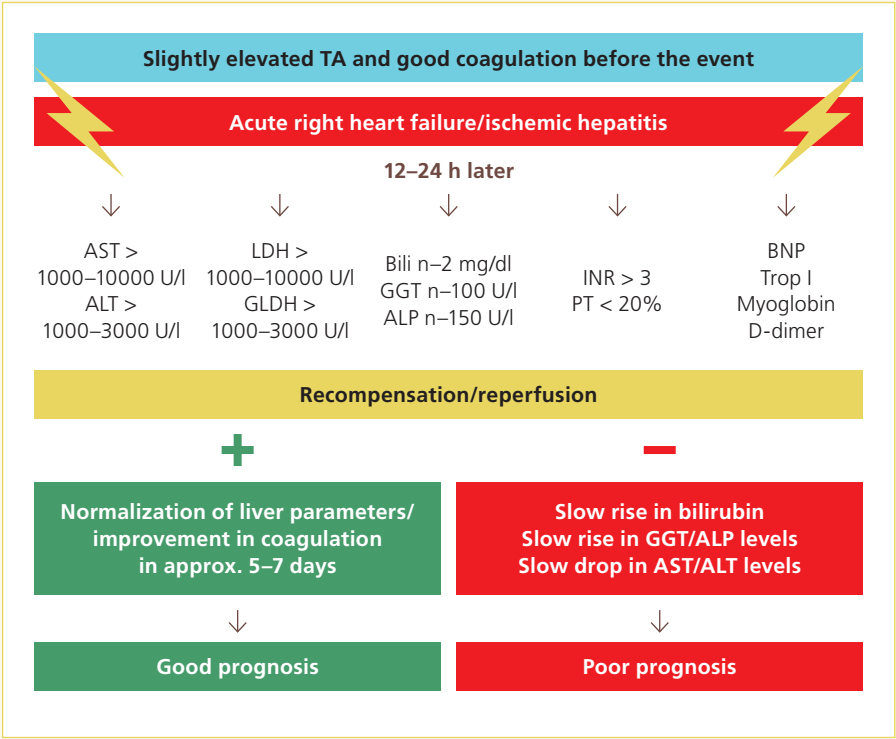


Figure 11a: Acute congestive hepatopathy

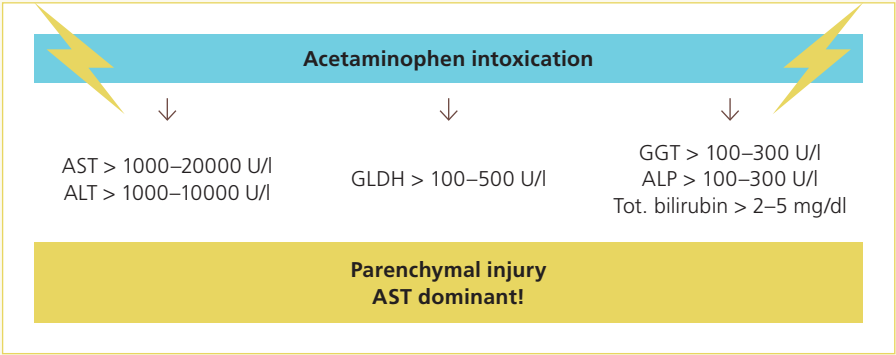


Figure 11b: Liver function tests in acetaminophen intoxication

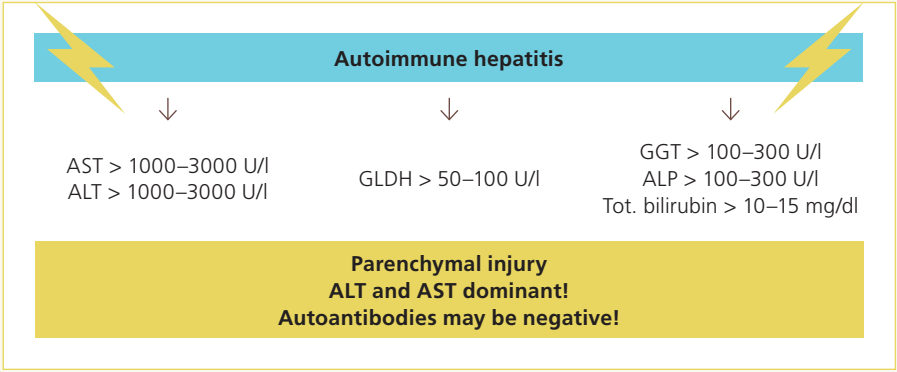


Figure 11c: Liver function tests in acute autoimmune hepatitis

6 Diagnostic tests if liver function tests are chronically elevated

Chronic liver diseases are often asymptomatic until decompensation occurs at an advanced stage of hepatopathy. When diseases are indeed detected at an early stage, then usually as an incidental finding through elevated liver function tests which should be used as an impetus for further diagnosis. Persistently elevated liver enzymes in particular should trigger investigation into the underlying cause instead of resorting to the assumption of a harmless fatty liver disease, especially since NAFLD can also have severe complications (cirrhosis, HCC).

6.1 Viral hepatitis

Due to the major implications for health policy posed by disease progression to cirrhosis and HCC, virus serology should always be performed for patients with suspected toxic injury based on their medical history (fig. 4). Although the prevalence of hepatitis B virus (HBV) infection has decreased among patients raised in Germany since the vaccination recommendation many years ago, approx. 400 million individuals worldwide are thought to be

infected. With the migration of patients from Eastern Europe, the Middle East, and Asia, this disease still remains relevant. Approx. 130–170 million people worldwide suffer from chronic hepatitis C (HCV), with 3–5 million infected persons in Europe.[16] Virus serology for patients with chronic liver disease should screen for HCV and HBV using on anti-HCV, anti-HBc, and HBsAg. Patients testing positive for HBV infection using these parameters should then undergo further testing to differentiate between anti-HBc IgM as a marker of acute infection and anti-HBc IgG as a marker of chronic infection, as well as determination of HBV DNA and HBcAg levels.[17] In the event of chronic HBV infection, HBeAg levels should be measured and hepatitis D (HDV) co-infection should be ruled out. Abdominal ultrasound should be performed every 6 months for early detection of HCC regardless of treatment regimen. Liver biopsies are increasingly less common today due to non-invasive procedures that test the extent of fibrosis, such as transient elastography (e.g. Fibroscan, fig. 12), but are still valuable in cases of uncertain liver pathology or before initiating treatment. Detection of anti-HCV should be followed by measurement of HCV RNA, genotype determination, exclusion of co-infection with HIV, and abdominal ultrasound. Liver biopsy is again only rarely required today for treatment planning, while the same non-invasive fibrosis assessment techniques established for HBV are also used here to monitor treatment outcomes. Immunocompromised patients must be tested for hepatitis E virus since this infection may also become chronic.[18]

6.2 Non-alcoholic fatty liver disease

The most common chronic liver disease in industrialized nations is non-alcoholic fatty liver disease (NAFLD). This condition afflicts approximately one-third of the European population and harbors the risk of progression to non-alcoholic steatohepatitis (NASH) and cirrhosis with the accordant consequences. NAFLD is thought to be a hepatic manifestation of metabolic syndrome and is frequently linked to insulin resistance. Other potential causes of NAFLD are gastrointestinal disorders (celiac disease, IBD), steroid therapy, chemotherapy, parenteral nutrition, and severe generalized disorders

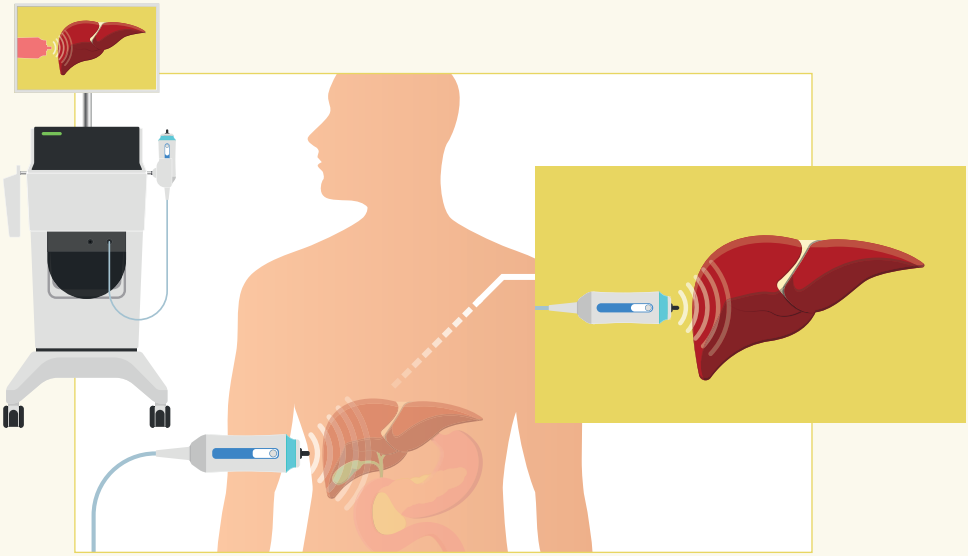


Figure 12: Non-invasive elastography of the liver for measuring liver stiffness, staging fibrosis, and determining the degree of liver injury

(fig. 13a–b). Programmed cell death (apoptosis) appears to play a crucial role in the pathogenesis of this disorder, in contrast to alcohol-related liver injury, meaning that serum markers of apoptosis (M30) will likely be of diagnostic value in the future.[19,20] In addition to dominant elevation of ALT, GGT and ferritin levels are also elevated. However, when interpreting liver function tests in patients with NAFLD (fig. 6), it must be kept in mind that the current definition of the upper limit of normal for ALT is likely too high, meaning that using ALT to screen for suspected fatty liver disease may yield false-negative results. As shown by research from our group, a decrease in liver function test levels may aid in the early detection of a chronic liver disease in patients with risk factors for NAFLD.[4,21]

To date, there is still no specific marker to confirm the diagnosis of NAFLD, with the result that a patient's medical history and the clinical examination remain key determinants together with exclusion of other parenchymal liver diseases.

Fatty liver disease can be easily identified on ultrasound, typically by comparison to the renal parenchyma and using attenuation with high skin-capsular distance. However, despite the existence

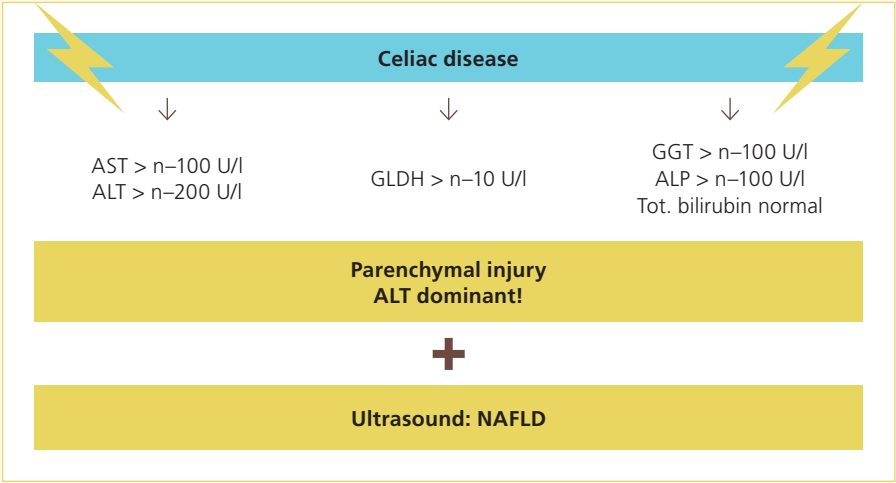


Figure 13a: Liver function tests in celiac disease

of ultrasound-specific criteria, assessment of severity suffers from high inter-observer variance. Liver biopsy remains the gold standard for grading and staging fatty liver as well as evaluating fibrosis in NAFLD. A new method that is especially useful for capturing the early stages of fatty liver disease is the CAP (controlled attenuation parameter) method which can be measured using modern transient elastography equipment.[22,23]

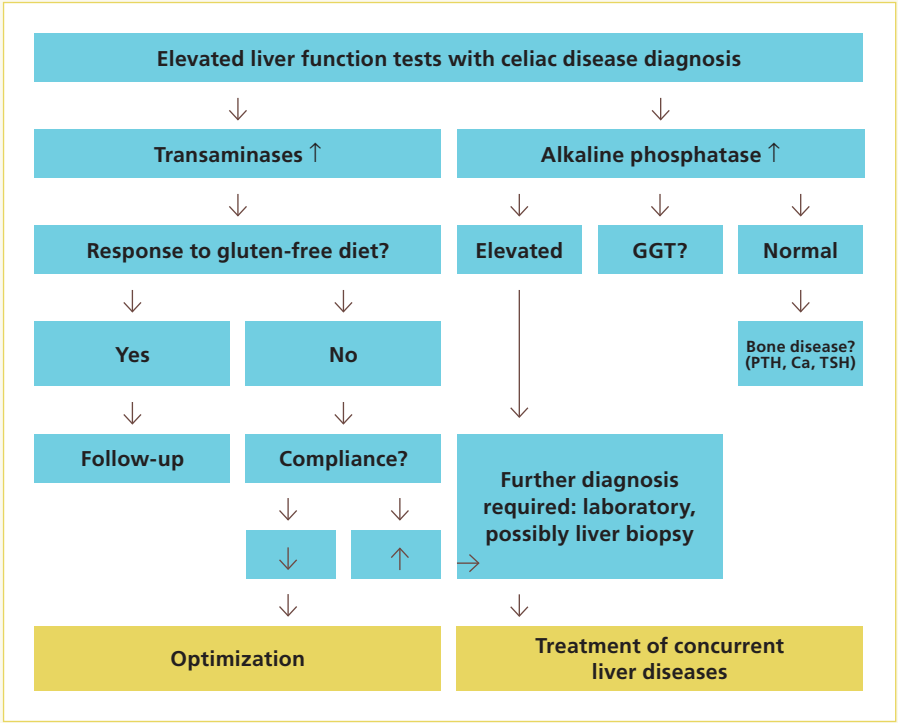


Figure 13b: Diagnostic algorithm for liver disease in patients with celiac disease (modified from: Rubio-Tapia & Murray, Hepatology 2007)

6.3 Alcohol-related liver disease

Alcohol-related liver disease is the second-most common chronic liver disease in Germany, and typically presents with AST higher than ALT (AST:ALT > 1),[24] elevated GGT, elevated MCV (mean corpuscular volume), and elevated IgA levels. The serum level of CDT (carbohydrate-deficient transferrin) is a useful parameter when alcohol consumption is suspected yet denied by the patient; however, it may also be false-positive in cases of cirrhosis or during pregnancy. At our hospital, we use detection of ethyl glucuronide in urine or a hair sample, which can retrospectively identify alcohol consumption up to 3 months later (fig. 6).

6.4 Autoimmune liver diseases

Immune disorders of the liver are rare but are of crucial diagnostic importance, since early initiation of effective treatment may prevent progression to cirrhosis. Hence, patients with chronic liver disease of unknown origin should be screened for these disorders.

AIH is a disease that primarily afflicts women (80%) with a specific genetic predisposition (HLA-B8, -DR3, and -DR4). It is associated with elevated transaminase levels that jump up during inflammatory flares and is characterized by an early reduction in the synthetic function of the liver. The disorder is diagnosed after exclusion of a viral etiology by detection of hypergammaglobulinemia, positive autoantibodies (ANA, SMA, LKM, or SLA), and typical histological findings (table 7). Other immune-mediated disorders of the liver that may present as variants of AIH are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), which are classified as cholestatic liver diseases. For PBC, over 90% of patients are middle-aged women who frequently experience excruciating itching. In addition to elevated parameters of cholestasis, elevated IgM levels are also typically observed. This disorder is also diagnosed by the detection of autoantibodies (AMA subtype M2) and the appropriate histology. PSC is a stenosing disease of the bile ducts with recurring cholangitis (fig. 14) that is often associated with inflammatory bowel disease. The autoantibodies in this case are elevated pANCA titers. However, the diagnosis can be bolstered by imaging of the bile ducts, with the preferred method being the non-invasive magnetic resonance cholangiopancreatography (MRCP), and ERCP only being recommended in case of uncertain

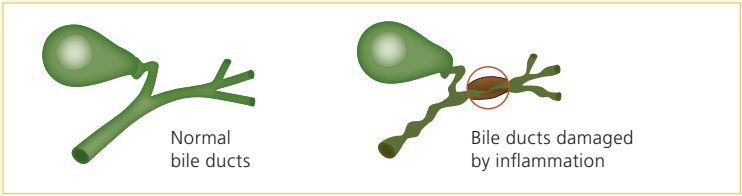


Figure 14: Healthy extrahepatic bile ducts (left) and inflamed bile ducts (right) resulting from autoimmune reactions in PSC patients.

findings or therapeutic intention. There is a high risk of colorectal and biliary cancer with this disease, requiring regular early detection screening examinations (fig. 15).

AIH criteria ≥ 6: AIH likely, AIH criteria ≥ 7: AIH confirmed		
Variable	**Cut-off**	**Points**
ANA or SMA	≥ 1:40	1*
ANA or SMA	≥ 1:80	2*
LKM	≥ 1:40	2*
SLA	Positive	2*
IgG	> Upper limit of normal (ULN) > 1.1-fold above ULN	1 2
Liver histology	Consistent with AIH Typical of AIH	1 2
Exclude viral hepatitis	Yes	2
*Maximum score for all antibodies: 2		

Table 7

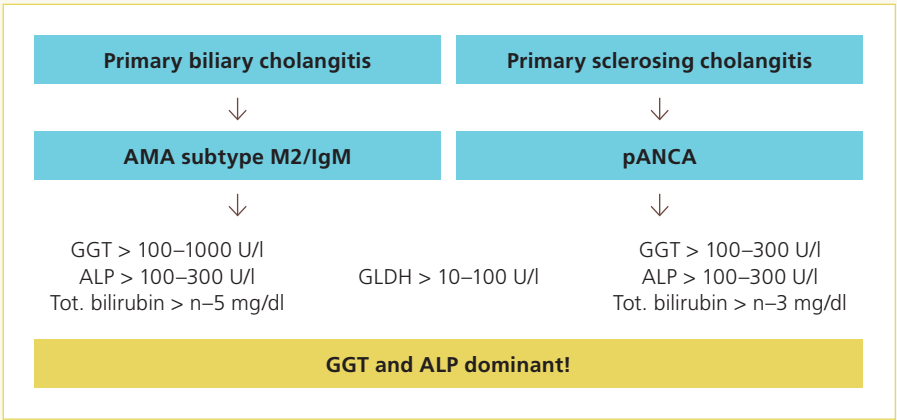


Figure 15: PBC and PSC

6.5 Metabolic liver diseases

Rare metabolic disorders with hepatic manifestations must be taken into consideration as differential diagnoses in cases of chronic liver disease of unknown origin, especially in patients with a relevant family history. These disorders include Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency. Wilson's disease is a disorder of copper accumulation that is inherited in an autosomal recessive pattern and whose early stages are characterized by neurological symptoms and progression of the liver disease. It is important to measure copper levels in 24 h urine in patients suspected of having this disease. Measuring serum levels of ceruloplasmin can be helpful, but may also yield false-low results in some situations including acute infections or cirrhotic liver diseases.

Hemochromatosis is the most common liver disease caused by a congenital metabolic deficiency (1:1000 in Europe, M:F = 10:1). This disorder is characterized by iron overload in the parenchyma of numerous organs, which can lead to hepatopathy, arthropathy, diabetes, and other endocrinopathies as well as to heart failure and neurological symptoms. Indications of this disease include elevated globulins, serum iron, ferritin, and transferrin saturation. In classical hemochromatosis, over 90% of patients are homozygous for the C282Y mutation in the HFE gene; however, only 25% of these individuals develop clinically apparent hemochromatosis.

An α_1-antitrypsin deficiency presents clinically with cholestatic liver disease before the age of 60. Measurement of serum α_1-antitrypsin is sufficient for diagnosis and genetic testing is not required for screening. However, a newly developed dried blood spot test can be used to verify suspected cases.

6.6 Lysosomal storage diseases

6.6.1 Gaucher's disease

Gaucher's disease is a lysosomal storage disease caused by a hereditary defect in the metabolism of the lipid compound glucocerebroside. Cells called "Gaucher cells" can usually be detected in the spleen, liver, bone marrow, and occasionally in the lungs. These organs thus represent the clinical targets of Gaucher's disease.

Gaucher's disease is chronic and characterized by hepatosplenomegaly, hematologic pathologies (anemia, thrombocytopenia), bone disease, and by neurological symptoms in some patients. Disease onset and severity of clinical symptoms vary greatly. Splenomegaly may develop in early childhood and lead to hypersplenism with anemia, leukopenia, and thrombocytopenia. Gaucher's disease should be ruled out in particular for patients from Arabic countries and Turkey with liver disease of uncertain origin.

6.6.2 Lysosomal acid lipase deficiency

The hereditary lysosomal acid lipase deficiency (LAL-D) is a lysosomal storage disease.

It is also called Wolman disease when it presents in the first months of life and cholesteryl ester storage disease (CESD) in children and adults. These different variants of LAL-D are currently classified as a standalone disorder that can manifest in all age classes.[25]

Due to the great variations in clinical presentation depending on the age of onset, special training is required for awareness of LAL-D and especially for its clinical symptoms and diagnosis. Using modern methods, adult patients in particular can be diagnosed at an early time point of the disease when it is still asymptomatic. This is relevant with regard to the comorbidities and mortality of LAL-D which can now be reduced using novel treatments and supportive therapies.

LAL-D is a hereditary disease inherited in an autosomal-recessive pattern which results from a homozygous or compound heterozygous mutation in the LIPA (lipase A, lysosomal acid, cholesterol esterase) gene. This mutation reduces or completely eliminates the activity of the LAL enzyme. The severity of symptoms and the age of onset can vary depending on the form of the disease. As a result of this mutation, these lipids accumulate in hepatocytes and macrophages, in the spleen, in the gastrointestinal tract, or in the blood vessels. Over time, this pathological accumulation leads to organ damage.[26] The spectrum of clinical manifestations ranges from dyslipidemia (pathological LDL:HDL quotient), hepatic dysfunction, hepatomegaly and/or splenomegaly, persistently elevated transaminases, and microvesicular steatosis to fibrosis and cirrhosis.

Rare diseases such as LAL-D should be taken into consideration as differential diagnoses and ruled out during the diagnosis process, especially if a patient's symptoms do not clearly correspond with the disease profile of NAFLD/NASH.

6.6.3 Niemann-Pick disease

Niemann-Pick disease is another lysosomal storage disease which is inherited in an autosomal-recessive pattern. Similar to the other disorders in this group, Niemann-Pick disease is subdivided into three different types which are classified based on their pathophysiology and clinical presentation. Niemann-Pick disease types A and B (NPA and NPB) arise from the same pathophysiology, which is reduced activity of acid sphingomyelinase (ASMase). ASMase catalyzes the cleavage of ceramides from sphingomyelin and is localized to both lysosomes and the plasma membrane. In contrast, Niemann-Pick type C (NPC) is defined by a genetic mutation shared by the lysosomal proteins NPC1 and NPC2 and results in defective cholesterol transport from the lysosomes. The common final pathway of all types is disordered lipid metabolism with the accumulation of sphingomyelin and cholesterol in the liver and spleen.[27] Regardless of the classification, nearly all patients have hepatosplenomegaly, typically as the first symptom of the disease. They may also consecutively develop hepatic complications such as hepatitis, which is characterized by elevated transaminases, fibrosis, and cirrhosis. NPB and NPC are characterized not only by visceral symptoms but also primarily by neurological manifestations that predominate in adolescence and adulthood.[23,27] For NPB, pulmonary involvement is also an issue: Deposits of sphingomyelin in lung tissue often contribute heavily to patients' morbidity and mortality by triggering restrictive or interstitial lung disease.[27] An α_1-antitrypsin deficiency should also be kept in mind as a differential diagnosis.

This condition is diagnosed using both the patient's clinical presentation as well as laboratory tests which frequently reveal cytopenia, mainly thrombocytopenia, as well as dyslipidemia with low HDL, elevated LDL, and elevated triglycerides. ASMase activity in lymphocytes or cultured fibroblasts should also be determined. Genetic tests can also be used to detect mutations at the molecular level.

6.7 Infectious diseases

Finally, several different infectious diseases can lead to elevated transaminase levels, which are usually transient. Although some of these diseases are rare in Germany, they should be taken into consideration with foreign patients or patients returning from travel. Table 8 provides an overview of the relevant bacterial, viral, parasitic, and other infectious diseases.

The following infections typically cause hepatosplenomegaly			
Infectious diseases with hepatic involvement		**Pattern of liver injury**	**Liver function tests**
Bacteria	Gram-positive and gram-negative (esp. E. coli)	Cholestatic pattern	Bili. elevated up to 15 mg/dl and higher, ALP + TA moderate elevation
	Staphylococcus aureus and group A streptococci	Hepatitis	Elevated TA and sometimes bilirubin
	Listeria	Liver abscesses, granulomatous pattern	Elevated TA and sometimes bilirubin
	Staphylococci	Abscesses and cholestatic pattern	ALP disproportionately elevated
	Streptococci	Abscesses and cholestatic pattern	ALP disproportionately elevated
	Shigella	Cholestatic pattern	ALP disproportionately elevated
	Salmonella	Abscesses, hepatitis	ALP elevated, AST > ALT
	Brucella	Granuloma, abscess Rarely acute hepatitis	Moderate ALT elevation
	Legionella	Steatosis and hepatitis	Non-specific elevation of TA in 50%, bili. elevation in up to 20%
	Bartonella	Hepatitis, peliosis hepatis	Non-spec. elevation of TA
	Neisseria	Hepatitis with disseminated infection, perihepatitis (FHC syndrome)	ALP elevation in 50%
	Chlamydia trachomatis	Perihepatitis (FHC syndrome)	Non-spec. elevation of TA
	Tuberculosis	Miliary tuberculosis, granuloma. Localized with and without bile duct involvement	Disproportionate isolated elevation of ALP in granulomatous form
	Syphilis (Treponema pallidum)	Hepatitis, granulomatous pattern	Disproportionate isolated elevation of ALP in granulomatous form
	Borrelia	Steatosis and hepatitis	Non-spec. TA elevation up to 47%
	Leptospirosis	Cholestatic pattern	Bili. up to 30 mg/dl, TA < 5 x ULN

Infectious diseases with hepatic involvement		Pattern of liver injury	Liver function tests
Bacteria	Rickettsia	Hepatitis and cholestasis	AST and bili. elevation
	Coxiella burnetii	Acute hepatitis, pyrexia	Disproportionate isolated elevation of ALP
	Clostridia	Cholestasis, hepatitis, abscesses	Bili., ALP elevated and moderate TA elevation
	E. coli	Hepatitis, cholestasis, granuloma	Slight elevation of TA
Fungi	Histoplasmosis, actinomycosis		
Parasites	Amoeba	Abscesses, cholestasis	ALP and GGT elevation
	Malaria	Hepatitis	TA elevation
	Trypanosomes	Eosinophilia and hepatitis	TA elevation
	Toxoplasma	Hepatitis	TA elevation
Helminths	Fasciola hepatica	Cholestasis	Eosinophilia, bili., ALP and GGT elevation
	Echinococcus granulosus, Echinococcus multilocularis	Cholestasis	ALP and GGT elevation
	Helminths, Enterobius vermicularis (nematode)	Hepatitis	Slight TA elevation
	Schistosomiasis	Hepatitis	TA elevation (ALT > AST) GGT > ALP elevation Bili. normal
	Ascariasis	Cholangitis, cholecystitis, abscesses	Bili., ALP, GGT elevation
Viruses	CMV, EBV, HSV, HIV, rubella, chickenpox, yellow fever, coxsackie, adenoviruses, paramyxoviruses, Lassa, Marburg, Ebola, Dengue fever, SARS-CoV-2	Hepatitis up to acute liver failure	Massive elevation of TA ALP, GGT and bili. elevation less prominent

Table 8

7 Liver scores

A liver biopsy is the gold standard for diagnosing and staging liver fibrosis prior to treatment. Liver complications lead to severe complications in 0.3% of cases and fatal complications in 0.03% of cases.[28] Histology of these biopsies captures the parameters of hepatocellular injury (e.g. ballooning of hepatocytes), inflammation, biliary patterns of injury, and fibrosis or defects in hepatic architecture. A key problem in histological evaluation is how to translate a continuous process such as liver fibrosis into a score system using an ordinal scale. This may result in discrepancies in the histological evaluation of the stage of fibrosis (sampling error). For this reason, non-invasive, blood test-based quantification of fibrosis is increasingly gaining in importance. Nonetheless, the two most relevant invasive scores will also be described below:

The **NAFLD Activity Score (NAS)** uses the sum of scores for steatosis (0–3 points), hepatocyte ballooning (0–2 points), and inflammation (0–3 points) based on histology in order to quantify the severity of steatohepatitis. Scores from 0–2 points are not considered diagnostic for steatohepatitis, while scores of 3–4 points denote possible NASH and 5–8 points denotes definite NASH.

Another invasive, semi-quantitative tool to differentiate between NAFLD and NASH and to determine the activity of NASH is the **Steatosis, Activity, and Fibrosis (SAF) score**. NAFLD is defined in this score as the presence of steatosis in at least 5% of hepatocytes. This criteria plus hepatocyte ballooning and lobular inflammation are defined as the presence of NASH.

Non-invasive scores

Numerous laboratory parameters can be used to describe the extent of liver injury and fibrosis, either in isolation or in combination. The following section will discuss a selection of the many scores which have been published. The cut-offs have been taken directly from the original publications. Strictly speaking, these cut-offs are only valid within the population in which they were determined. Hence, they should be considered an aid to interpretation. Some of the different scoring systems can also be generated using simple routine laboratory parameters (table 9) as well as from special metrics (table 10).

APRI score

The APRI score (Aspartate Aminotransferase to Platelet Ratio Index) determines the likelihood of fibrosis/cirrhosis in patients with chronic HCV infection and is calculated using the AST level and the platelet count.

Interpretation:

Index > 1.5 → Cut-off for significant fibrosis

Index < 0.5 → Exclusion of significant fibrosis

Index > 2 → Cut-off for cirrhosis

Index < 1 → Exclusion of cirrhosis

BARD score

The BARD score (BMI, AST:ALT, diabetes) can be used to predict the risk of progression to advanced fibrosis in patients with NAFLD.

Interpretation:

Score 0–1 → Low risk of advanced fibrosis

Score 2–4 → High risk of advanced fibrosis

NAFLD Fibrosis Score (NFS)

The NFS predicts the degree of liver fibrosis in patients with an initial NAFLD diagnosis based on the variables of age, BMI, insulin resistance/diabetes, AST:ALT ratio, platelet count, and albumin.

Interpretation:

Score < -1.455	→ F0–F2 fibrosis
Score -1.455–0.675	→ Indeterminant fibrosis
Score > 0.675	→ F3–F4 fibrosis

ELF Score

The Enhanced Liver Fibrosis (ELF) test determines the degree of fibrosis using a combined measurement of hyaluronic acid (HA), tissue inhibitor of matrix metalloproteinase-1 (TIMP1), and amino-terminal propeptide of procollagen type III (P3NP).

Interpretation:

Score < 7.7	→ No to mild fibrosis
7.7 to < 9.8	→ Moderate fibrosis
9.8 to < 11.3	→ Severe fibrosis
> 11.3	→ Cirrhosis

Forns Index

The Forns index, which has been validated by independent studies, uses indirect serum markers to predict significant fibrosis in patients with chronic HCV infection with a high degree of certainty. The variables are platelets, GGT, age, and total cholesterol.

Interpretation:

Index < 4.2	→ 71.4% probability of F0–F1 fibrosis
Index > 6.9	→ 78.6% probability of F2–F4 fibrosis

FibroTest

The FibroTest predicts the degree of fibrosis regardless of the underlying cause and is based on the variables of α_2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, and age.

Interpretation:

Score 0.00–0.21 → F0 fibrosis (METAVIR score)

Score 0.28–0.31 → F1 fibrosis (METAVIR score)

Score 0.49–0.58 → F2 fibrosis (METAVIR score)

Score 0.59–0.72 → F3 fibrosis (METAVIR score)

Score 0.75–1.00 → F4 fibrosis (METAVIR score)

FIB-4 Index

The FIB-4 score is a very good tool to identify advanced fibrosis in a non-invasive manner. The FIB-4 score is calculated using age, platelet count, and transaminases. The FIB-4 score must be interpreted with caution for patients ages ≤ 35 years old.

Interpretation:

Index ≤ 1.3 → Low risk of advanced fibrosis

Index > 3.25 → High risk of advanced fibrosis

CHeK Score

The CHeK score can be used as a screening or monitoring tool for progression or improvement under therapy in patients who are overweight or obese or have other metabolic risk factors, since liver transaminases often remain unremarkable in these situations. The score comprises the five parameters of age, adiponectin (surrogate marker for fatty tissue function), GGT, HbA1c, and M30 (apoptosis marker). The score allows non-invasive prediction of the risk of NASH and monitoring of lifestyle modifications.

Interpretation:

To detect NASH with high sensitivity, an appropriate cut-off must be selected for the CHeK score, e.g. a limit of 0. Patients with NASH can then be detected with 91.7% sensitivity using the CHeK score.

FAST Score

The FAST score (Fibroscan-AST) is intended to identify patients with progressive NASH. This algorithm incorporates the AST:ALT ratio measured by laboratory test together with liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), and evaluation of steatosis by controlled attenuation parameter (CAP) using the Fibroscan system.

The FAST score is a relatively new model whose reliability cannot yet be evaluated.

GALAD Score

In addition to AFP (alpha-fetoprotein), two other HCC markers are available in Germany as CE-certified laboratory tests: AFP-L3 (HCC-specific subfraction of total AFP) and DCP (des-gamma-carboxy prothrombin). The GALAD score comprises the parameters of gender, age, AFP-L3, AFP, and DCP. Using this internationally validated model, early stages of HCC can be detected at a sensitivity of at least 75% and a specificity of 89%.[29] The GALAD score has been shown to be an especially effective method for early detection of HCC in NASH patients.[30]

Interpretation:

A GALAD score of -0.63 serves as a cut-off for optimal sensitivity and specificity regardless of HCC stage. If this cut-off is exceeded, additional imaging procedures should be performed.

ALBI Score

The ALBI score was developed to reflect liver function objectively with the highest degree of reproducibility possible, and to allow reliable prediction of the prognosis of patients with either HCC or cirrhosis.[31] Its parameters comprise albumin and bilirubin, stratified into three risk groups. It is thus used to predict overall survival (OS).

Interpretation:

Score ≤ -2.60	→ Grade 1 Median OS 18.5–85.6 months
Score > -2.60 to ≤ -1.39	→ Grade 2 Median OS 5.3–46.5 months
Score > -1.39	→ Grade 3 Median OS 2.3–15.5 months

MELD Score

The MELD score (Model for End-stage Liver Disease) predicts the severity of a liver disease and is used to facilitate the allocation of a donor organ for patients with severe liver disease. The calculation is performed using serum creatinine, bilirubin, and INR. If dialysis was performed within the previous week, the creatinine value is set to 4.0. The predictive value has been further improved by the integration of sodium (MELD-Na).

Interpretation:

The score ranges from 6 to 40 points. The higher the score, the higher the 3-month mortality.

Score	Formula (analyte [unit] upper/lower limit of normal)	Etiology
APRI[32]	AST [U/l] ÷ ULN ÷ PLT [10^9/l] × 100	HCV
Forns Index[33]	7.811 – 3.131 × ln (PLT [10^9/l]) + 0.781 × ln (GGT [U/l]) + 3.467 × ln (age [years]) – 0.014 × TC [mg/dl]	HCV
FIB-4[34]	Age [years] × AST [U/l]) ÷ (PLT [10^9/l] × √(ALT [U/l]))	HCV/HIV, NAFLD
Fibroindex[35]	1.738 – 0.0064 × PLT [10^9/l] + 0.005 × AST [U/l] + 0.463 × γ-globulin [g/dl]	HCV
GUCI[36]	AST [U/l] ÷ ULN × INR × 100 ÷ PLT [10^9/l]	HCV
LOK Score[37]	y = exp [(1.26 × AST [U/l] ÷ ALT [U/l]) + (5.27 × INR) – (0.0089 × PLT [10^9/l]) – 5.56] score = y ÷ (1 + y)	HCV
HUI Score[38]	y = exp [3.148 + 0.167 × BMI + 0.088 × TBIL [µmol/l] – 0.157 ÷ ALB [g/l] – 0.019 × PLT [10^9/l]]; score = y ÷ (1 + y)	HBV
DELTA Fibrosis Score (DFS)[39]	(ALB [g/l] < 1.19 × LLN) ⇒ 1 + (GGT [U/l] > 0.5 × ULN) ⇒ 1 + (CHE [U/l] < 1.46 × LLN) ⇒ 1 + (age [years] > 42) ⇒ 1	HDV
BARD[40]	(BMI ≥ 28) ⇒ 1 + (AST [U/l]/ALT [U/l] ≥ 0.8) ⇒ 2 + (diagnosis = type 2 DM) ⇒ 1	NAFLD
NAFLD Fibrosis Score (NFS)[41]	– 1.675 + 0.037 × age [years] + 0.094 × BMI + 1.13 × (diagnosis = type 2 DM or IFG) ⇒ 1 + 0.99 × AST [U/l]/ALT [U/l] – 0.013 × PLT [10^9/l] – 0.66 × ALB [g/dl]	NAFLD
ALBI[31]	$\log_{10}$ (TBIL [µmol/l]) × 0.66) + (ALB [g/l] × – 0.085)	Cirrhosis of all causes, esp. HCC
MELD[42]	3.78 × ln (TBIL [mg/dl]) + 11.2 × ln (INR) + 9.57 × ln (*CREA [mg/dl]) + 6.43 *(CREA [mg/dl] > 4) ⇒ CREA = 4; *(dialysis or CVVHD within previous 2 weeks) ⇒ CREA = 4	Severity of liver disease regardless of cause

Table 9

Score	Formula (analyte [unit] upper/lower limit of normal)	Etiology
ELF Test[43]	2.494 + 0.846 × ln (HA [µg/l]) + 0.735 × ln (P3NP [µg/l]) + 0.391 × ln (TIMP1 [µg/l])	Various
Fibrometer[44]	0.4184 × GLU [mmol/l] + 0.0701 × AST [U/l] + 0.0008 × FER [µg/l] – 0.0102 × PLT [10^9/l] – 0.0260 × ALT [U/l] + 0.0459 × weight [kg] + 0.0842 × age [years] + 11.6226	Various (viral hepatitis, NAFLD, ALD)
FibroTest[45]	y = 4.467 × $\log_{10}$ (A2M [g/l]) – 1.357 × $\log_{10}$ (HPG [g/l]) + 1.017 × $\log_{10}$ (GGT [U/l]) + 0.0281 × age [years] + 1.737 × $\log_{10}$ (TBIL [µmol/l]) – 1.184 × APOA1 [g/l] + (gender = m) ⇒ 0.301 – 5.540; score = y ÷ (1 + y)	Various
Hepascore[46]	y = exp [– 4.185818 – (0.0249 × age [years]) + (gender = m) ⇒ 0.7464 + (1.0039 × A2M [g/l]) + (0.0302 × HA [µg/l]) + (0.0691 × TBIL [µmol/l]) – (0.0012 × GGT [U/l])]; score = y ÷ (1 + y)	HCV
Shasta[47]	– 3.84 + (41 ≤ HA [ng/ml] ≥ 85) ⇒ 1.7 + (HA [ng/ml] > 85) ⇒ 3.28 + (ALB [g/dl] < 3.5) ⇒ 1.58 + (AST [U/l] > 60) ⇒ 1.78	HIV, HCV
GALAD[48]	– 10.08 + 0.09 × age [years] + 1.67 × (gender = m) ⇒ 1 + 2.34 × $\log_{10}$ (AFP [ng/ml]) + 0.04 × AFP-L3 [%] + 1.33 × $\log_{10}$ (DCP [ng/ml])	HCC
CHeK[49]	(0.037373 × age [years]) – (0.35163 × ADIP [µg/ml]) + (0.064638 × GGT [U/l]) + (1.397096 × HbA1c [%]) + (0.01375 × M30 [U/l]) – 8.503788	NASH
FAST Score[50]	y = exp (– 1.65 + 1.07 × ln (LSM [kPa]) + 2.66 × 10^{-8} × CAP^3 [dB/m] – 63.3 × AST^{-1} [U/l]); score = y ÷ (1 + y)	NAFLD

Table 10

8 Conclusions for clinical practice

- All patients with acute elevations of liver function tests with increased transaminase levels or signs of liver failure and chronically (> 6 months) elevated liver function tests should undergo core diagnostic tests for elevated liver enzymes
- Acute liver failure requires rapid diagnosis and treatment in an intensive care setting with timely contact to a transplantation center
- Cryptogenic liver diseases are primarily of autoimmune etiology and require further elucidation using special biochemical markers and liver biopsy
- The most common chronic liver disease is non-alcoholic fatty liver disease, which is usually associated with metabolic syndrome
- The use of liver scores can help predict liver status, activity, and progression
- Early diagnosis and treatment of a chronic liver disease are crucial for preventing the development of cirrhosis and hepatocellular carcinoma

Abbreviations

A2M Alpha-2-macroglobulin

ADIP Adiponectin

AFP Alpha-1-fetoprotein

AFP-L3 Lectin-reactive α-fetoprotein

AIH Autoimmune hepatitis

ALB Albumin

ALF Acute liver failure

ALP Alkaline phosphatase

ALT Alanine aminotransferase

AMA Antimitochondrial antibodies

ANA Antinuclear antibodies

APOA1 Apolipoprotein A1

ASH Alcoholic steatohepatitis

AST Aspartate aminotransferase

BMI Body mass index

BNP B-type natriuretic peptide

Ca Calcium

CAP Controlled attenuation parameter

CHE (Butyryl)-cholinesterase

CREA Creatinine

CT Computed tomography

CVVHD Continuous veno-venous hemodialysis

DCP Des-gamma-carboxy prothrombin

DM Diabetes mellitus

ERCP Endoscopic retrograde cholangiopancreatography

FER Ferritin

GGT γ-Glutamyltransferase

GLDH Glutamate dehydrogenase

GLU Glucose

GOT Glutamic-oxaloacetic transaminase (synonym for AST/ASAT aspartate aminotransferase)

GPT Glutamic-pyruvic transaminase (synonym for ALT/ALAT alanine aminotransferase)

HA Hyaluronic acid

HbA1c (Glycated) hemoglobin A1c

HCC Hepatocellular carcinoma

HL Half-life

HPG Haptoglobin

IFG Impaired fasting glucose

INR International normalized ratio

LAL-D Lysosomal acid lipase deficiency

LDH Lactate dehydrogenase

LKM Anti-liver-kidney microsomal antibodies

LLN Lower limit of normal

LSM Liver stiffness measurement

M30 Cytokeratin 18 neoepitope M30 (CK-18 M30)

Na	Sodium
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
pANCA	Perinuclear antineutrophil cytoplasmic antibodies
P3NP	Procollagen type III N-terminal peptide
PBC	Primary biliary cholangitis
PLT	Platelets
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PTH	Parathyroid hormone
SLA	Anti-soluble liver antigen antibodies
TA	Transaminases
TBIL	Total bilirubin
TC	Total cholesterol
TIMP1	Tissue inhibitor of metalloproteinases-1
TPN	Total parenteral nutrition
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	Ultrasound

References

1. Lademann J, Kolip P. Schwerpunktbericht: Gesundheit von Frauen und Männern im mittleren Lebensalter. Gesundheitsberichterstattung des Bundes, Robert Koch-Institut in Zusammenarbeit mit dem Statistischen Bundesamt. 2005 (ISBN 3-89606-160-7).
2. Baumeister SE, Völzke H, Marschall P, John U, Schmidt CO, Flessa S, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. Gastroenterology. 2008;134(1):85–94.
3. Dollinger MM, Fechner L, Fleig WE. [Early diagnosis of liver diseases]. Internist (Berl). 2005;46(4):411–20.
4. Kälsch J, Bechmann LP, Heider D, Best J, Manka P, Kälsch H, et al. Normal liver enzymes are correlated with severity of metabolic syndrome in a large population based cohort. Sci Rep. 2015;5:13058.
5. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137(1):1–10.
6. Oettl K, Birner-Gruenberger R, Spindelboeck W, Stueger HP, Dorn L, Stadlbauer V, et al. Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival. J Hepatol. 2013;59(5):978–83.
7. Bedreli S, Sowa JP, Gerken G, Saner FH, Canbay A. Management of acute-on-chronic liver failure: rotational thromboelastometry may reduce substitution of coagulation factors in liver cirrhosis. Gut. 2016;65(2):357–8.
8. Canbay A, Tacke F, Hadem J, Trautwein C, Gerken G, Manns MP. Acute liver failure: a life-threatening disease. Dtsch Arztebl Int. 2011;108(42):714–20.
9. Renner EL. How to decide when to list a patient with acute liver failure for liver transplantation? Clichy or King's College criteria, or something else? J Hepatol. 2007;46(4):554–7.
10. Schmidt LE, Larsen FS. MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. Hepatology. 2007;45(3):789–96.
11. Yantorno SE, Kremers WK, Ruf AE, Trentadue JJ, Podestá LG, Villamil FG. MELD is superior to King's college and Clichy's criteria to assess prognosis in fulminant hepatic failure. Liver Transpl. 2007;13(6):822–8.
12. Anastasiou O, Sydor S, Sowa JP, Manka P, Katsounas A, Syn WK, et al. Higher Thyroid-Stimulating Hormone, Triiodothyronine and Thyroxine Values Are Associated with Better Outcome in Acute Liver Failure. PLoS One. 2015;10(7):e0132189.
13. Bechmann LP, Jochum C, Kocabayoglu P, Sowa JP, Kassalik M, Gieseler RK, et al. Cytokeratin 18-based modification of the MELD score improves prediction of spontaneous survival after acute liver injury. J Hepatol. 2010;53(4):639–47.
14. Manka P, Olliges V, Bechmann LP, Schlattjan M, Jochum C, Treckmann JW, et al. Low levels of blood lipids are associated with etiology and lethal outcome in acute liver failure. PLoS One. 2014;9(7):e102351.

15. Denzer U, Arnoldy A, Kanzler S, Galle PR, Dienes HP, Lohse AW. Prospective randomized comparison of minilaparoscopy and percutaneous liver biopsy: diagnosis of cirrhosis and complications. J Clin Gastroenterol. 2007;41(1):103–10.

16. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10(9):553–62.

17. Cornberg M, Protzer U, Petersen J, Wedemeyer H, Berg T, Jilg W, et al. [Prophylaxis, diagnosis and therapy of hepatitis B virus infection – the German guideline]. Z Gastroenterol. 2011;49(7):871–930.

18. Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis E virus infection. Gastroenterology. 2012;142(6):1388–97.e1.

19. Canbay A, Friedman S, Gores GJ. Apoptosis: the nexus of liver injury and fibrosis. Hepatology. 2004;39(2):273–8.

20. Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology. 2003;125(2):437–43.

21. Kaelsch J, Kaelsch H, Heider D, Sowa JP, Bechmann LP, Kahraman A, et al. Are current normal ranges settled to high? Prevalence of abnormal liver transaminases in a population-based cohort – the Heinz Nixdorf Recall Study. Internist (Berl). 2013;54:33.

22. Arslanow A, Stokes CS, Weber SN, Grünhage F, Lammert F, Krawczyk M. The common PNPLA3 variant p.I148M is associated with liver fat contents as quantified by controlled attenuation parameter (CAP). Liver Int. 2016;36(3):418–26.

23. Myers RP, Pollett A, Kirsch R, Pomier-Layrargues G, Beaton M, Levstik M, et al. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. Liver Int. 2012;32(6):902–10.

24. Cohen JA, Kaplan MM. The SGOT/SGPT ratio – an indicator of alcoholic liver disease. Dig Dis Sci. 1979;24(11):835–8.

25. Pullinger CR, Stock EO, Movsesyan I, Malloy MJ, Frost PH, Tripuraneni R, et al. Identification and metabolic profiling of patients with lysosomal acid lipase deficiency. J Clin Lipidol. 2015;9(5):716–26.e1.

26. Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013;58(6):1230–43.

27. Sun A. Lysosomal storage disease overview. Ann Transl Med. 2018;6(24):476.

28. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology. 1990;99(5):1396–400.

29. Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144–53.

30. Best J, Bechmann LP, Sowa JP, Sydor S, Dechene A, Pflanz K, et al. GALAD Score Detects Early Hepatocellular Carcinoma in an International Cohort of Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol. 2020;18(3):728–35.e4.

31. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach – the ALBI grade. J Clin Oncol. 2015;33(6):550–8.

32. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518–26.

33. Forns X, Ampurdanès S, Llovet JM, Aponte J, Quintó L, Martínez-Bauer E, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology. 2002;36(4):986–92.

34. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.

35. Koda M, Matunaga, Y Kawakami, M Kishimoto Y, Suou T, Murawaki Y. Fibroindex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. Hepatology. 2007;45:297–306.

36. Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol. 2005;40(7):867–72.

37. Lok AS, Ghany MG, Goodman ZD, Wright EC, Everson GT, Sterling RK, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology. 2005;42(2):282–92.

38. Hui AY, Chan HL, Wong VW, Liew CT, Chim AM, Chan FK, et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple noninvasive predictive model. Am J Gastroenterol. 2005;100(3):616–23.

39. Da BL, Surana P, Kleiner DE, Heller T, Koh C. The Delta-4 fibrosis score (D4FS): A novel fibrosis score in chronic hepatitis D. Antiviral Res. 2020;174:104691.

40. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut. 2008;57(10):1441–7.

41. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.

42. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.

43. Parkes J, Bialek SR, Bell BP, et al. ELF serum markers accurately distinguish fibrosis severity in chronic hepatitis C: an external validation study. Hepatology. 2006;44(Suppl 1):321.

44. Calès P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konaté A, et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology. 2005;42(6):1373–81.

45. Contreras RH, Callewaert NLM. Serum marker for measuring liver fibrosis. U.S. patent 7244619;2007.

46. Adams LA, Bulsara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem. 2005;51(10):1867–73.

47. Kelleher TB, Mehta SH, Bhaskar R, Sulkowski M, Astemborski J, Thomas DL, et al. Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: the SHASTA index. J Hepatol. 2005;43(1):78–84.

48. Amoros R, King R, Toyoda H, Kumada T, Johnson PJ, Bird TG. A continuous-time hidden Markov model for cancer surveillance using serum biomarkers with application to hepatocellular carcinoma. Metron. 2019;77(2):67–86.

49. Canbay A, Kälsch J, Neumann U, Rau M, Hohenester S, Baba HA, et al. Non-invasive assessment of NAFLD as systemic disease – A machine learning perspective. PLoS One. 2019;14(3):e0214436.

50. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;5(4):362–73.

FALK FOUNDATION e.V.

Leinenweberstr. 5
79108 Freiburg
Germany

U46E 5-6/2021 HOF