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Alcohol-associated liver disease — a current overview

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Abstract: Alcohol-associated liver disease (ALD) remains a major and increasingly pressing concern in hepatology. ALD includes spectrum of conditions, each with unique diagnostic and therapeutic challenges. Excessive alcohol intake is a leading preventable cause of physical harm, including ALD. The pathogenesis of ALD involves oxidative stress, inflammation, and lipid metabolism disruptions, with genetic predispositions playing a major role. ALD progresses from hepatic steatosis to steatohepatitis, and finally liver cirrhosis, which is marked by severe fibrosis and impaired liver function. Advanced ALD stages, particularly alcoholic hepatitis and liver cirrhosis, are characterized by high mortality rates. Management of ALD primarily involves strict abstinence from alcohol, which can reverse early-stage disease or halt progression. Nutritional support, vitamin supplementation, and symptomatic treatment are also essential. Liver transplantation is the only definitive treatment for alcoholic liver cirrhosis, but it is difficult for patients with a history of alcohol abuse to qualify for the procedure. Epidemiological data indicate a growing burden of ALD, especially among younger populations, exacerbated by increased alcohol consumption trends and the COVID-19 pandemic's influence on drinking behaviors. Despite ALD's significant impact, current therapies are limited, highlighting the need for innovative treatments and comprehensive patient management strategies. Individualized care, enhanced epidemiological research, and new therapeutic approaches are crucial to improving outcomes for ALD patients.

Keywords: alcohol-associated liver disease, alcohol-related liver disease, ALD, ARLD, alcoholic steatosis, alcoholic fatty liver, alcoholic hepatitis, alcoholic liver cirrhosis.

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Introduction

Alcohol-associated liver disease (ALD), also known as alcohol-related liver disease (ARLD), replaces the former term 'alcoholic liver disease' to avoid the use of the stigmatizing word 'alcoholic', according to the American Association for the Study of Liver Diseases [1]. ALD, particularly its severe forms, remains one of the most pressing concerns in the management of liver diseases overall. Excessive alcohol consumption stands as one of the foremost preventable risk factors for physical harm on a global scale. Alcohol-induced harm manifests both in the short term and long term, encompassing traffic injuries, suicide, violence, cardiovascular diseases, neoplasms, and notably, liver disease [2]. Several mechanisms are potentially linked to ethanol-induced liver diseases. For instance, acute ethanol consumption can lead to nitrification and oxidative stress, inflammation, and apoptosis. Chronic ethanol consumption results in dysregulated lipid metabolism, lipid accumulation in the liver, and alterations in the gut-liver axis by damaging the tight junctions of the intestinal epithelium [3].

The general consensus among hepatology communities classifies ALD into three main forms in terms of progression, which partially correlates with ICD-10 classification (Table 1). The treatment of ALD primarily requires complete abstinence from alcohol, which is vital for stopping disease progression and promoting liver recovery. Medical management includes nutritional support, vitamins deficiencies supplementation, effective diuretics application and corticosteroids for severe alcoholic hepatitis [4, 5]. Liver transplantation may be an option for patients with advanced liver cirrhosis who have maintained sustained abstinence from alcohol [6]. Continuous support through counseling and rehabilitation programs is crucial for achieving long-term sobriety and preventing relapse [2].

Table 1. Forms of alcohol-associated liver disease.

Name	ICD-10 code*
Alcoholic fatty liver (steatosis)	K70.0
Alcoholic hepatitis	K70.1
Alcoholic liver cirrhosis	K70.3

* other ICD-10 codes include alcoholic fibrosis and sclerosis of liver (K70.2), alcoholic hepatic failure (K70.4) and alcoholic liver disease, unspecified (K70.9).

The prognosis of ALD largely depends on the disease stage and the patient's ability to abstain from alcohol. Early-stage ALD, such as alcoholic fatty liver (AFL), is reversible with alcohol cessation. However, progression to alcoholic hepatitis, fibrosis, or liver cirrhosis significantly worsens the outlook. Patients with severe alcoholic hepatitis or advanced liver cirrhosis face higher risks of mortality and complications. Sustained abstinence from alcohol is crucial for improving outcomes and can stabilize or partially reverse liver damage in the early stages. Regular medical follow-ups and supportive care are essential for managing the disease and enhancing the quality of life [2, 7].

Epidemiology

Excessive alcohol consumption is one of the leading preventable risk factors for physical and social harm globally. It accounts for 5.3% of global deaths and 5.1% of the global burden of disease

and injury, and it remains the primary cause of liver cirrhosis. The majority of alcohol-related disease burden affects individuals aged 15–44, impacting mostly young people in their most productive years. ALD is one of the most deadly consequences of alcohol use. Additionally, alcohol can exacerbate insulin resistance, type 2 diabetes mellitus, overweight, and obesity, among other metabolic risk factors, thereby accelerating the development and progression of chronic liver disease in susceptible individuals [7, 8].

Only individuals abusing alcohol develop ALD [9]. Most of these individuals experience mild hepatomegaly due to steatosis, a benign and reversible condition after 6–8 weeks of alcohol abstinence. However, steatohepatitis develops in 25–35% of these individuals, and liver fibrosis or cirrhosis develop in 8–20%, for reasons still unknown [10], with the genetic factors being strongly taken into consideration. Genetic variants in HSD17B13, MBOAT7, PNPLA3 and TM6SF2 affect ALD progression and the risk of hepatocellular carcinoma (HCC) [11]. Liver cirrhosis is confirmed in 18% of patients with heavy alcohol consumption through necropsy, and in 17–31% through biopsy. The relative risk of developing liver cirrhosis increases with the amount and duration of alcohol consumption. Consuming 40–60 g of alcohol per day increases the risk sixfold compared to 20 g per day over 10–12 years, and 60–80 g per day increases the risk 14 times. 50% of individuals consuming 210 g of alcohol daily for 22 years and 80% for 33 years develop liver cirrhosis. Generally, cirrhosis is considered inevitable with daily consumption of 180–200 g over 25 years. In women, the amounts are typically halved. According to European standards, one standard measure of alcohol is constituted by 10 grams of pure alcohol. For women, the recommended safe dose is up to two standard drinks, whereas for men up to three standard drinks. It's also advised to have alcohol-free days each week to prevent tolerance and dependence. Abstinence can improve the course of existing cirrhosis [1, 10, 12].

Epidemiological studies should consider factors like regularity of drinking (binge drinking) and whether alcohol is consumed on an empty stomach or after meals. From a liver damage perspective, episodic drinking is less harmful than daily consumption of smaller amounts, as the liver can regenerate. It's recommended to abstain from alcohol at least two days per week and to drink with meals rather than between them. Liver damage is related to the amount of alcohol consumed, not the type of drink [8].

Although there is some precise data on alcohol liver cirrhosis prevalence and morbidity, there is less information on alcoholic steatosis or hepatitis. It is estimated that about 50% of liver cirrhosis cases are alcohol-related, with geographical differences (e.g., 10% in Islamic countries, 90% in France) [10]. There is no current data from Poland concerning alcoholic cirrhosis.

In Poland, the percentage of alcohol-attributable conditions (AAC) mortality in all-cause mortality increased for both men and women across all age groups from 2002 to 2019. Over 17 years, there were 130,000 AAC deaths, with 63% occurring in middle-aged individuals (45–64 years) [13]. Little is known about what part of this mortality is caused by or connected with ALD. There may be a need to conduct extensive epidemiological studies on this issue. Around 2000s Poland's alcohol consumption was lower than average, but many European countries have since reduced alcohol intake, while in Poland consumption had been increasing. By 2019 ACC mortality rate, including alcoholic liver cirrhosis, doubled, most probably as a result of the increase in alcohol consumption. In Europe by 2019 alcoholic liver cirrhosis had become the dominant cause of fatal liver cirrhosis cases, accounting for 50% of such deaths in men and nearly 70% in women. According to Eurostat data, present alcohol consumption in Poland does not differ significantly from the European average; however, since the COVID-19 pandemic, there has been a noticeable upward trend [13, 14].

A multi-society cooperation, including the Latin American Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver, has proposed a new definition of steatotic liver disease. This includes specific diagnostic criteria for ALD, metabolic dysfunction-associated steatotic liver disease (MASLD), and the intersection of both conditions (MetALD). The COVID-19 pandemic has also negatively impacted alcohol consumption patterns worldwide, which is expected to increase the ALD burden in the near future. Considering the significant trend of a rapid increase in MASLD incidence, earlier and more frequent occurrences of liver disease, including overlapping forms (MetALD), can be expected [14, 15].

Pathogenesis

Alcohol metabolism predominantly occurs in the liver, where it is initiated by the enzyme alcohol dehydrogenase (ADH). In the presence of oxygen and the coenzyme NADPH, ADH converts alcohol into acetaldehyde, a highly reactive and toxic metabolite. This conversion takes place in the cytosol of hepatocytes. Subsequently, acetaldehyde is metabolized to acetate by acetaldehyde dehydrogenase (ALDH) within the mitochondria. Another critical enzyme involved in alcohol metabolism is cytochrome CYP2E1, which is found in the endoplasmic reticulum and mitochondria. Chronic alcohol consumption activates CYP2E1, leading to the production of reactive oxygen species (ROS), which contribute to liver inflammation and damage. Additionally, the microsomal ethanol-oxidizing system plays a role in alcohol metabolism, particularly under conditions of chronic alcohol use. This system accelerates the breakdown of alcohol, resulting in the rapid formation of toxic metabolites and subsequent tissue damage. The toxic effects of acetaldehyde, along with the generation of ROS, contribute significantly to the pathogenesis of alcohol-related liver diseases [9, 16].

In alcoholic hepatitis, hepatic macrophages (Kupffer-Browicz cells and circulating monocytes) increase in number and produce cytokines, initiating an inflammatory response. These macrophages, known as M1 macrophages, produce abundant cytokines such as TNF, Il-1β, Il-12, Il-18, and Il-23. Neutrophils, stimulated by those cytokines, infiltrate the liver, enhancing inflammation and hepatocyte damage. Interestingly, some studies suggest neutrophils may also promote tissue repair. T lymphocytes play roles in antigen presentation and hepatocyte damage through cytotoxic effects and macrophage activation [12, 16].

During inflammation, hepatocytes release cytokines, promoting neutrophil and macrophage infiltration and as a result ALD progression. Chemokines like CXCL1 and Il-8, elevated in alcoholic hepatitis, correlate with disease severity. Hepatic stellate cells, responsible for fibrosis, are activated by chronic inflammation and produce extracellular matrix components. Kupffer-Browicz cells and toxic metabolites from alcohol also activate stellate cells. NK cells can induce apoptosis in stellate cells, but alcohol directly blocks this effect, promoting fibrosis. Inflammasomes, multiprotein complexes, activate caspase-1, releasing active cytokines like formerly mentioned Il-1β, which further promotes liver fibrosis and inflammation [16, 17].

Chronic alcohol use increases intestinal permeability, allowing microbial products to reach the liver and activate inflammatory responses [3]. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) trigger inflammation. PAMPs, such as lipopolysaccharide (LPS) from Gram-negative bacteria, activate Kupffer-Browicz cells via Toll-like receptors, leading to cytokine and chemokine production. DAMPs, released during cell death, further exacerbate inflammation [16].

Intestinal microbiota, affected by alcohol, plays a significant role in liver inflammation. Dysbiosis, characterized by reduced beneficial bacteria and increased harmful ones, promotes ALD. Increased intestinal permeability allows microbial products to translocate to the liver, triggering inflammatory responses. Short-chain fatty acids, produced by beneficial bacteria, maintain intestinal barrier integrity and have immunological roles. However, chronic alcohol use disrupts this balance, contributing to ALD progression [18, 19].

Bile acids also influence liver disease pathogenesis. Dysbiosis affects bile acid metabolism, leading to the production of toxic secondary bile acids. These acids, elevated in alcoholics, damage intestinal and hepatic cells. The interaction between the liver and intestine is crucial, with bile acids affecting microbiota composition and gut health impacting liver inflammation. The farnesoid X receptor (FXR) in intestinal and liver cells regulates bile acid synthesis. Dysbiosis reduces FXR activity, increasing toxic bile acid production and contributing to liver damage. PAMPs and LPS from Gram-negative bacteria further stimulate liver inflammation, with endotoxin levels elevated in ALD. Peptidoglycans and lipoteichoic acid from Gram-positive bacteria also initiate inflammatory responses, exacerbating liver damage [3, 12, 19].

Alcoholic fatty liver

Alcoholic hepatic steatosis, AFL, involves the accumulation of intrahepatic triacylglycerols in at least 5% of the liver. This condition is often benign and reversible, resolving once alcohol consumption ceases if it is solely of alcoholic etiology. Histologically, it begins with lipid droplets in perivenular hepatocytes, spreading to mid-lobular and eventually periportal hepatocytes [17]. Ethanol inhibits kinase AMPK, reducing fatty acid oxidation and increasing lipogenesis. This process also downregulates receptor PPARα, further decreasing fatty acid oxidation. Ethanol induces the activation of protein SREBP-1, which promotes the transcription of lipogenic genes, increasing fatty acid synthesis [16, 18].

AFL develops in more than 90% of individuals who are heavy drinkers and is characterized by fat accumulation in hepatocytes [20]. Guidelines regarding appropriate alcohol consumption were sometimes inconsistent. The National Institute of Alcohol Abuse and Alcoholism defined heavy drinking as more than three drinks for women and four drinks for men on a given day. One drink is considered as a 10 g portion of ethanol. The use of questionnaires such as CAGE or AUDIT can be helpful in confirming alcohol misuse [2, 21].

Most patients with AFL are asymptomatic and unaware of their condition. When present, symptoms may include fatigue, malaise, and right upper quadrant discomfort. Physical examination can reveal an enlarged liver, but this is not a common finding and the enlargement may be not pronounced. If enlarged, liver size assessment can be achieved using imaging techniques, including ultrasound, which can reveal features of steatosis, such as increased echogenicity of the liver parenchyma, poor visibility of hepatic vessels, or heterogeneity of the parenchyma tissue [20, 22].

Diagnosis is based on medical interview and constellation of other clinical findings. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may be elevated but are not specific, even though in AFL there is a AST > ALT correlation observed but this phenomenon known as increased De Ritis ratio (with value more than 1) is more important when it comes to alcoholic hepatitis diagnosis. Common findings include macrocytosis (increased MCV in complete blood count), low platelet count (PLT) or elevated gamma-glutamyltransferase (GGT), but these

laboratory results are non-specific. Authors highlight the limited utility of GGT, as its activity can be elevated in other conditions and remains elevated for a relatively long time [17, 23].

Elevated triglycerides and cholesterol levels can be indicative of excessive alcohol consumption due to disrupted lipid metabolism and contribute to the worsening liver condition or even cause overlapping syndrome as previously mentioned MetALD [18, 22]. Other more advanced imaging methods such as CT or MRI are rarely used solely in diagnosis of AFL disease even though they can visualize liver parenchymal abnormalities and provide more precise quantification of liver fat content and. Liver biopsy is a confirmatory test showing macrovesicular steatosis, especially around the central vein, but it is not commonly used in clinical practice due to the unfavorable risk-to-benefit ratio for this particular benign condition [1, 15, 24].

Abstinence from alcohol is the most effective treatment. Ceasing alcohol intake can reverse steatosis and prevent progression to more severe liver disease. Ensuring adequate nutrition is important to support liver health [4]. Pharmacotherapy is not typically required for alcoholic steatosis alone but may be considered for associated conditions or complications [5]. AFL is considered the initial stage of alcohol-related liver disease, marked by fat accumulation in the liver secondary to chronic alcohol intake. Early detection and alcohol abstinence are crucial to prevent progression to more severe liver damage as alcoholic steatosis is reversible [8].

Alcoholic hepatitis

Uncontrolled AFL leads to inflammation, initially associated with the steatosis itself. This condition is known as alcoholic steatohepatitis (ASH). ASH is a histologic diagnosis characterized by significant steatosis, inflammatory cell infiltration, chicken wire-like fibrosis, and hepatocyte ballooning, often accompanied by the formation of Mallory bodies. Patients with ASH progress to liver cirrhosis in 8%–20% of cases, and those with alcoholic liver cirrhosis progress to hepatocellular carcinoma (HCC) in 3%–10% of cases [25]. The diagnosis of alcoholic hepatitis (AH) is based on clinical presentation, including jaundice (especially abrupt onset of it), right upper quadrant abdominal pain, fever, elevated serum bilirubin (>3 mg/dl), mildly elevated AST levels (>50 but <400 IU/l), and an De Ritis ratio of >1.5 [5, 20].

In patients with AH, several laboratory abnormalities can be typically observed, some of them also found in AFL. Increased MCV, GGT and low PLT are common, both often associated with chronic alcohol consumption. Anemia may also be present due to nutritional deficiencies, especially B_{12} vitamin, and eventually direct toxic effects of alcohol on the bone marrow. An elevated white blood cell count, specifically neutrophilia, frequently larger than 20,000/μl, is seen in AH. This increase in neutrophils reflects the body's response to inflammation and potential infection, indicating an acute inflammatory process in the liver. CRP as well as erythrocyte sedimentation rate levels are typically elevated in AH, serving as a nonspecific marker of systemic inflammation. Higher CRP levels correlate with the severity of liver inflammation and can help in assessing the extent of the disease. Due to the liver's reduced synthetic ability, serum albumin levels decrease, leading to edema and symptoms characteristic of liver cirrhosis. The liver's secretory function can be assessed more accurately by measuring plasma cholinesterase levels, which also decline with impaired hepatic protein synthesis [17, 20, 23].

In clinical practice, severe AH has high short-term mortality. Clinical management involves the use of oral corticosteroids, where the MELD or Maddrey Discriminant Function (MDF) score can be useful tool. Generally, the MELD score outperforms the MDF score in predicting

short-term mortality in AH. Glucocorticosteroid therapy should be considered when the MELD score exceeds 20. It is recommended to administer oral prednisolone at a dose of 40 mg/day, as hepatic conversion of prednisone in AH is believed to be impaired [5, 26].

Alcoholic hepatitis can coexist with liver cirrhosis, even though liver cirrhosis is considered as the more serious form of ALD. In such cases, all factors requiring management in decompensated alcoholic liver cirrhosis should be regarded. Severe AH is associated with high mortality, a 3-month estimate obtainable from the MELD score. To evaluate the response to steroid therapy on the 7th day of treatment, the Lille score should be calculated, and if it exceeds 0.45, discontinuation of steroids is recommended. Some authors suggest the inclusion of N-acetylcysteine, but there is no conclusion in current clinical studies [26, 27].

Severe alcoholic hepatitis (AH), when unresponsive to glucocorticosteroids, as determined by the Lille score, may indicate the need for liver transplantation. In cases of worsening liver function, increasing bilirubinemia, and deterioration of the patient's overall condition, liver replacement seems to be the only viable therapy. However, the requirement to maintain an abstinence period for liver transplantation qualification complicates potential surgical interventions. In such cases, liver dialysis methods, such as Molecular Adsorbent Recirculating System (MARS), may come to be useful, but those are costly procedures, and in fact — it is a series of procedures that need to be regularly repeated. Due to high compliance level required from liver transplantation candidates, in clinical practice liver transplantations are performed seldom when it comes to AH or ALD in general [6, 28, 29].

Alcoholic liver cirrhosis

Cirrhosis of the liver is considered the final and irreversible stage in the progression of ALD, although it is at times co-diagnosed with alcoholic hepatitis. This distinction is emphasized in the new ICD-11 classification, which provides two separate subcodes (Table 2). Alcoholic liver cirrhosis does not necessarily need to be preceded by AH; it often develops subtly and insidiously, with symptoms gradually increasing over time. It is sometimes diagnosed incidentally or at the point when endogenous factors lead to the decompensation of liver cirrhosis and acute clinical symptoms emerge [22, 30].

Table 2. Alcohol-associated liver disease in ICD-11.

Code	Name
DB94.0	**Alcoholic fatty liver**
DB94.1	**Alcoholic hepatitis**
DB94.10	AH with liver cirrhosis
DB94.1Y	Other specified AH
DB94.1Z	Unspecified AH
DB94.2	**Alcoholic liver fibrosis**
DB94.3	**Alcoholic cirrhosis of liver without hepatitis**
DB94.Y	Other specified ALD
DB94.Z	Unspecified ALD

Alcoholic liver cirrhosis does not significantly differ from liver cirrhosis of other etiologies. Hypogonadism generally and feminization in men are more pronounced. It is often diagnosed in moment of exacerbation due to AH. Stable liver cirrhosis of the liver is associated with chronic fatigue, a characteristic appearance (large abdomen, prominent torso, thin and emaciated limbs), mild coagulation disorders, and telangiectasias, with the 'caput medusae' being a specific form, where collateral circulation vessels are visible on the abdominal wall. Hepatomegaly and splenomegaly may be present; however, in advanced liver cirrhosis, the liver becomes atrophic (hepatomegaly is more characteristic of active AH). Liver cirrhosis is a progressive disease that eventually leads to laboratory and clinical signs of decompensation [22, 26, 30].

Laboratory tests reveal findings similar to those seen in earlier stages of alcoholic liver disease. A slight increase in alpha-fetoprotein may accompany liver cirrhosis and does not necessarily mean HCC [11]. Additional abnormalities emerge during exacerbation of alcoholic liver cirrhosis. During these times, in addition to blood count abnormalities resulting from chronic alcohol abuse, hypoalbuminemia intensifies, ammonia levels may rise, and electrolyte disturbances such as hypokalemia and hyponatremia occur. Coagulation disorders, particularly prolonged prothrombin time, are of the greatest significance, as this is the only laboratory parameter with confirmed prognostic value for liver cirrhosis prognosis [5, 30, 31].

Nevertheless, it is the clinical picture of the patient what raises suspicion of liver cirrhosis decompensation. Rapidly increasing ascites, peripheral edema, pleural effusion, reduced physical activity, and ultimately, consciousness disturbances due to hepatic encephalopathy (HE) strongly suggest that the cause of the patient's deteriorating health is previously diagnosed ALD [22]. It is always helpful to determine whether strict alcohol abstinence has been maintained as liver cirrhosis decompensation cause can be multifactorial, not necessarily connected with alcohol intake [4].

The diagnosis of previously unrecognized alcoholic liver cirrhosis rarely requires a liver biopsy, due to characteristic clinical presentation and patient's alcohol abuse history. It is also often contraindicated due to active haemorrhagic diathesis, especially when core needle biopsy would be performed. A liver biopsy may be considered for the differential diagnosis of rare causes of cirrhosis, when there is a suspicion of two conditions overlapping, or for the definitive assessment of a lesion suspected of HCC [24, 25]. With use of non-invasive techniques for assessing fibrosis of liver parenchyma, such as elastography (FibroScan®) [32], esophagogastroduodenoscopy (EGD) appears to be the only invasive method with significant clinical value in alcoholic liver cirrhosis. This is particularly relevant as EGD can simultaneously serve as a diagnostic and a therapeutic tool (e.g., managing bleeding from esophageal varices and visualizing portal hypertensive gastropathy) [33].

The radiological image of liver cirrhosis is quite characteristic but it does not indicate alcoholic aetiology [31]. On ultrasound, notable features include an irregular, polycyclic liver edge, a reduction in the size of the right lobe of the liver, fluid accumulation in peritoneal recesses, splenomegaly, and possibly the dilation of the portal vein (>15 mm), indicating portal hypertension. In other imaging techniques such as CT or MRI similar findings are apparent. Cirrhotic liver is characterized by heterogeneous liver parenchyma with areas of varying attenuation due to fibrosis (hypodense area) and regenerative nodules or steatotic hyperdense areas. Density in MRI may be reverse depending on particular sequence (T1 or T2) [30, 34].

Treatment of compensated liver cirrhosis relies on strict alcohol abstinence, a low-fat, high-protein diet (1.5 g/kg body weight), strict fluid intake (1.5 l/day), and the supplementation of any potential vitamin deficiencies (thiamine, vitamins C, D3, E and B12), which is particularly important following periods of heavy alcohol use when nutrient absorption was impaired [4]. Natrium chloride

intake restriction is advised in prevention of ascites. The use of hepatoprotective drugs does not seem to have significant importance [22, 35]. Increasingly, the role of smoking is emphasized as a factor that not only promotes fibrosis and increases the risk of decompensation in alcoholic liver cirrhosis but also contributes to the development of HCC which is mainly caused by liver cirrhosis [25].

When alcoholic liver cirrhosis is decompensated, treatment includes basic therapy, such as nutritional management and symptomatic treatment, which primarily involves skillful management of the patient's water-electrolyte balance. Due to the tendency for fluid accumulation in body cavities, diuretics remain the cornerstone of treatment. Spironolactone is recommended at an initial dose of 100 mg/day, to which furosemide can be added at an initial dose of 40 mg/day, or alternatively torsemide. Dehydration therapy should be monitored by fluid balance avoiding a daily loss of more than 1000 ml fluids to prevent the concentration of toxic liver metabolites [22]. The treatment of edema can be supplemented with human albumin infusions in cases of severe hypoalbuminemia. Tense ascites, which reshapes the navel (grade III ascites) should be punctured and fluid drained under blood pressure monitoring. After draining more than 3 liters of fluid at once, the risk of reflex hypotension emerges and increases proportionally to the drained volume. Refractory ascites can be an indication to paracentesis but it rarely is a solution in the long term [1, 20, 35].

A patient with liver cirrhosis is generally immunocompromised due to impaired production of many proteins, including those involved in pathogen defense. Ascitic fluid in the peritoneal cavity is particularly susceptible to infections, likely due to the proximity of pathogenic gut microbiota and the compromised intestinal mucosa caused by ongoing subclinical inflammation [16, 17]. Infection of the ascitic fluid is referred to as spontaneous bacterial peritonitis. Furthermore, each patient with alcoholic liver cirrhosis is suspected of having profound nutritional deficiencies, which increases susceptibility to literally all infections. Fever or elevated inflammatory markers, particularly procalcitonin, necessitate the implementation of broad-spectrum empirical antibiotic therapy. Prophylactic antibiotic therapy may also be considered, especially in cases of AH with accompanying liver cirrhosis, where infection symptoms overlap with those of AH, complicating the diagnostic process [1, 5, 26].

A significant complication of liver cirrhosis is hepatorenal syndrome (HRS), which in the case of alcoholic liver cirrhosis typically presents as acute kidney injury (type 1 HRS). It is diagnosed based on a sudden increase in serum creatinine levels, after excluding other potential causes of renal function deterioration. Treatment requires the initiation of fluid therapy, often accompanied by human albumin infusions. Additionally, vasopressin analogs or somatostatin analogs are used in a similar regimen to that employed in the pharmacotherapy of esophageal varices [35, 36]. Another clinically described syndrome is hepatopulmonary syndrome (HPS), which is characterized by platypnea (dyspnea that worsens in an upright position) and hypoxemia (PaO_2 <60 mmHg in arterial blood) [22].

Transjugular intrahepatic portosystemic shunt (TIPS) is a surgical procedure that creates a channel between the portal and hepatic veins to reduce portal hypertension and manage refractory ascites or the risk of severe variceal bleeding. Highly invasive procedures are less frequently used in cases of patients with alcoholic liver cirrhosis due to low compliance. The situation is similar for techniques such as the MARS, which theoretically could serve as a bridge to liver transplantation qualification for patients with end-stage alcoholic cirrhosis, but in practice, this strategy is not utilized due to economic reasons and difficulties in qualification for liver transplantation, which is currently — as ought to be stated — the only causal treatment for alcoholic liver cirrhosis [2, 5, 6, 29].

Conclusions

Recommendations to avoid using the stigmatizing term 'alcoholic' have been to a substantial extent adopted for the term of ALD. However, even though this anti-discriminatory inclination in modern nomenclature involves all forms of ALD, referenced papers hardly show a trace of it apart from ALD case. Only Mackowiak *et al.* [21] consequently changed 'alcoholic' to 'alcohol-associated' in whole terminology, e.g. alcohol-associated steatosis. A naming consensus has yet to be reached, which is accurately reflected in the 'old' nomenclature still present in the official ICD-11 classification. Therefore, in this overview, adherence to the commonly known terms for ALD subtypes was opted.

The ICD-11 classification emphasizes the possibility of the coexistence of AH and alcoholic liver cirrhosis, partially disrupting the generally accepted consensus of dividing ALD into three subtypes. Similarly to ICD-10, it maintains the diagnosis of alcoholic liver fibrosis, which serves as a prelude to fully-developed cirrhosis. Histologically, cirrhosis of the liver is characterized by severe fibrosis; therefore, the diagnosis of alcoholic fibrosis is rarely established, and if so, it is typically based on non-invasive liver fibrosis assessment techniques. Liver cirrhosis is a clinical diagnosis, whereas fibrosis is identified through imaging studies or, if necessary, histopathological examination. The absence of alcoholic liver failure in the ICD-11 classification indicates the relatively low utility of this code, as there are no specific features distinguishing hepatic failure caused by alcohol, and it can be caused by either alcoholic liver cirrhosis or AH [17, 31].

All these nuances indicate that dividing ALD into three categories is overly simplistic and does not fully capture the pathogenesis and the diagnostic-therapeutic process of ALD phenomenon. A patient with confirmed alcohol abuse should be treated individually, rather than attempting to classify their clinical condition into one of the three previously mentioned subgroups [1, 15].

Moreover, majority of evidence suggests that ALD is not only a currently significant issue but one that is increasingly gaining importance. The rising consumption of alcohol and the prevalence of risk factors contributing to the development of ALD indicate that it will remain a persistent problem for hepatological treatment [7, 9, 31]. At the same time, breakthrough therapies are still lacking, and the only effective alternative for treating liver cirrhosis remains liver transplantation,

Table 3. Minimal conditions which indicate liver transplantation by Child-Pugh classification.

Two of the following:	Any disturbances of consciousness and hyperammonemia
	Any ascites
	INR >1.7
	Albumin <35 g/l
	Total bilirubin >35 μmol/l
Only one of the following:	Drowsiness and disorientation (HE)
	Tense ascites
	INR >2.3
	Albumin <28 g/l
	Total bilirubin >50 μmol/l

which is particularly difficult to obtain for patients with a history of alcohol abuse. Symptomatic treatment does not provide a significant increase in survival for individuals with ALD [6, 27].

According to the widely recognized three-tier Child-Pugh classification, indications for transplantation are present at grade B and C, where moderate deviations in two of the five assessed criteria or one considerable deviation (Table 3) are sufficient to achieve grade B [37]. This illustrates the fact that liver transplantation is in most cases the recommended treatment approach, although it is indeed challenging to implement when it comes to ALD. Here comes the question: is it possible to do more for ALD patients?

Conflict of interest

None declared.

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