

## Meta-Analysis Study on Alcoholic Liver Cirrhosis

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### ABSTRACT

**Background:** Heavy alcohol consumption is an inevitable cause of alcoholic liver disease with a high chance to progress to Alcoholic Liver Cirrhosis. Alcohol could damage the function of body organs and could cause cancer. Liver damage due to excessive alcohol consumption is usually presented as fatty liver (build-up of fats in the liver), steatohepatitis, fibrosis, alcoholic cirrhosis, and hepatocellular carcinoma. When liver fibrosis progresses, it will ultimately end up as alcoholic cirrhosis.

**Objective of the Study:** This article was intended to explore and investigate the possible optimal diagnosis and management of Alcoholic liver cirrhosis.

**Methods:** We searched the medical literatures to retrieve studies for the review till 30 November 2017. Electronic search in the scientific database from 1965 to 2017– (Medline, Embase. The Cochrane Library websites were searched for English Publications (both reprint requests and by searching the database). Data extracted included authors, country, year of publication, characteristics of patients, pathophysiology, risk factors, clinical manifestations, different diagnostic approaches and treatment modalities.

**Conclusion:** Absolute abstinence remains the foundation for any treatment of any acute or chronic Alcoholic Liver Disease. It's also important to understand that no treatment will cure cirrhosis or repair scarring in the liver that has already occurred and the only resort would be liver transplantation which is also debatable provided the complications it carries along. Nevertheless, timely diagnosis of alcoholic cirrhosis in people with alcoholic liver disease is the cornerstone for evaluation of prognosis or choosing treatment strategies such as nutritional and medical support and lifestyle change.

**Keywords:** Alcohol consumption, Cirrhosis, alcoholic liver diseases, fibrosis, steatosis, steatohepatitis, treatment, live transplantation, chronic liver diseases.

### INTRODUCTION

Heavy alcohol consumption causes alcoholic liver disease and is a causal factor of many types of liver injuries and concomitant diseases. It is a true systemic disease that may damage the digestive tract, the nervous system, the heart and vascular system, the bone and skeletal muscle system, and the endocrine and immune system, and could lead to cancer<sup>[1]</sup>.

Alcohol-related liver disease is linked to the pattern of alcohol consumption<sup>[2]</sup>.

- 90% -100% of heavy drinkers develop fatty liver disease.
- 10% -35% of heavy drinkers develop alcoholic hepatitis.
- 8%- 20% of heavy drinkers develop alcoholic cirrhosis

In 2004, a Danish group<sup>[3]</sup> concluded, that there was a threshold seen at a consumption level of greater than five drinks (60 g of pure alcohol) on average per day. People drinking that heavily had an increase in the rate of mortality by 27 times from alcoholic cirrhosis in men and a 35-fold increased

mortality from alcoholic cirrhosis in women compared with the Danish general population. However, there was no further dose– response relationship and no additional risk for drinking a much higher volume than 60 g day-1<sup>[3]</sup>.

Abstinence from alcohol may help people with alcoholic disease in improving their prognosis of survival at any stage of their disease; however, the more advanced the stage, the higher the risk of complications, co-morbidities, and mortality, and lesser the effect of abstinence. Being abstinent one month after diagnosis of early cirrhosis will improve the chance of a seven-year life expectancy by 1.6 times<sup>[4]</sup>.

Liver transplantation is the only radical method that may change the prognosis of a person with alcoholic liver disease; however, besides the difficulties of finding a suitable liver transplant organ, there are many other factors that may influence a person's survival<sup>[5]</sup>.

The liver is the main site of alcohol metabolism acting through two hepatic enzymes, alcohol dehydrogenase and cytochrome P-450 (CYP) 2E1.

Increased alcohol intake disrupts metabolic liver function, and, as a result, alcoholic liver disease develops <sup>[6]</sup>.

Liver cirrhosis is the most important single fatal chronic disease condition caused by alcohol consumption globally, with approximately 15% of all alcohol-attributable deaths in 2004 were as a result of liver cirrhosis. Thus, it comes as no surprise that liver cirrhosis has always been included in standard alcohol-attributable disease lists <sup>[7]</sup>.

Cirrhosis has historically been considered an irreversible outcome following severe and prolonged liver damage. However, studies involving patients with liver disease from many distinct causes have shown convincingly that fibrosis and cirrhosis might have a component of reversibility. For patients with decompensated alcoholic cirrhosis who undergo transplantation, survival is comparable to that of patients with other causes of liver disease; 5-year survival is approximately 70% <sup>[8]</sup>.

Patients can present with any or all complications of portal hypertension, including ascites, variceal bleeding, and hepatic encephalopathy. The histology of end-stage alcoholic cirrhosis, in the absence of acute alcoholic hepatitis, resembles that of advanced liver disease from many other causes, without any distinct pathologic findings <sup>[9]</sup>.

**DIAGNOSIS OF CIRRHOSIS**

**Table 1:** Semi-quantitative histopathological scoring systems for progression of fibrosis to cirrhosis. Conversion grid for the stages of hepatic fibrosis\*

Test Method	Publication Year	Stage of fibrosis						
Desmet <sup>[11]</sup>	1994	F0	F1	F1	F2	F3	F4	F4
Ishak <sup>[12]</sup>	1995	F0	F1	F2	F3	F4	F5	F6
Brunt <sup>[13]</sup>	1999	F0	F1	F1	F2	F3	F4	F4
METAVIR <sup>[14]</sup>	2003	F0	F1	F1	F2	F3	F4**	F4**
Kleiner <sup>[15]</sup>	2005	F0	F1	F1	F2	F2	F3	F4
Batts-Ludvig <sup>[16]</sup>	2010	F0	F1	F1	F2	F3	F4	F4

The reproducibility of the METAVIR score was validated using a slightly modified METAVIR score, that is, the portal tract/septal fibrosis score, in order to investigate the amount of fibrosis and to study the influence of centrilobular fibrosis and portal tract/septal fibrosis in alcoholic chronic liver disease. The amount of portal tract/septal fibrosis in people with alcoholic chronic disease was greater than the amount of centrilobular fibrosis in the control group of people with viral chronic hepatitis disease, which suggested that portal tract/septal fibrosis was more frequent in alcoholic chronic liver disease than in viral chronic hepatitis. However, centrilobular fibrosis forms with the advance of fibrosis in cirrhosis. The prognostic value of the METAVIR fibrosis score in alcoholic liver disease still needs to be established <sup>[14]</sup>.

Usually, Fatty liver is diagnosed in the asymptomatic patient who is undergoing evaluation for abnormal liver function tests.

The diagnosis of alcoholic cirrhosis rests on finding the classic signs and symptoms of end-stage liver disease in a patient with a history of significant alcohol intake. Patients tend to underreport their alcohol consumption, and discussions with family members and close friends can provide a more accurate estimation of alcohol intake.

In order to determine the proper diagnostic method, we must be informed and notified firstly about the different stages the liver passes through before reaching Cirrhosis.

**STAGES OF FIBROSIS BEFORE TURNING INTO CIRRHOSIS**

There are five stages of liver fibrosis by METAVIR <sup>[10]</sup>

- F0 = no fibrosis;
- F1 = mild fibrosis;
- F2 = significant fibrosis;
- F3 = severe fibrosis;
- F4 = cirrhosis.

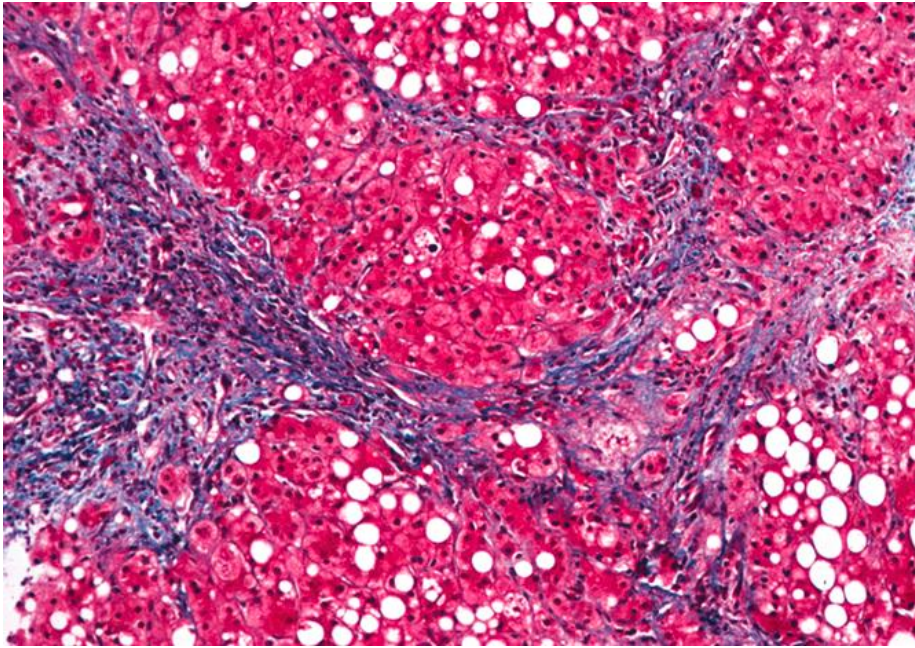
Table 1 is presenting other widely used systems for classification of fibrosis in people with alcoholic liver disease <sup>[11-16]</sup>. Yet we have concentrated in our research review on alcoholic cirrhosis alone, Hence, METAVIR score is the method of choice.

**Table 2:** Diagnostic algorithm for chronic liver disease <sup>[17]</sup>

Screening measures	Step 1: General laboratory testing	Step 2: Specific laboratory testing	Step 3: Molecular and invasive studies
History (identification of risk constellations)	ALT, AST, GGT, AP, bilirubin	Hepatitis serology (HBsAg, anti-HCV)	Ceruloplasmin, copper in 24-hour urine sample, genetic testing for Wilson disease
Physical examination	Complete blood count, platelet count, routine coagulation studies	Autoantibody testing(ANA, SMA, LKM, SLA, p-ANCA, AMA)	HFE mutation
Serum ALT and GGT	Total protein, albumin, serum electrophoresis	Quantitative immunoglobulins(IgA, IgG, IgM)	A1-antitrypsin genotype (PIZZ)
Ultrasonography	Cholesterol, triglycerides, glucose	Ferritin, transferrin saturation, iron	Liver biopsy, MRCP, ERC (for suspected PSC)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; AP, alkaline phosphatase; HBsAg, hepatitis B surface antigen; anti-HCV, anti-hepatitis-C antibodies; ANA, antinuclear antibodies; SMA, smooth-muscle antibodies; LKM, liver/kidney microsome antibodies; SLA, antibodies against soluble liver antigen; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; AMA, anti-mitochondrial antibodies; HFE, the “high-iron” gene responsible for hereditary hemochromatosis; MRCP, magnetic resonance cholangiopancreatography; ERC, endoscopic retrograde cholangiography; PSC, primary sclerosing cholangitis.

The overall clinical diagnosis of alcoholic liver disease, using a combination of physical findings, laboratory values, and clinical acumen, is relatively accurate. Liver biopsy is required if the etiology of liver disease is unclear, or if its stage cannot be determined from the findings of the tests mentioned above. In cases of suspected cirrhosis, transcutaneous liver biopsy is essential if the clinical findings leave the diagnosis in doubt or if the biopsy is expected to yield information about the cause of cirrhosis that will affect the choice of treatment <sup>[18]</sup>. To enable the reliable staging of hepatic fibrosis, the punch cylinders used for liver biopsy should be at least 15 mm long, and at least 10 portal fields should be examined per sectional level <sup>[19]</sup>.

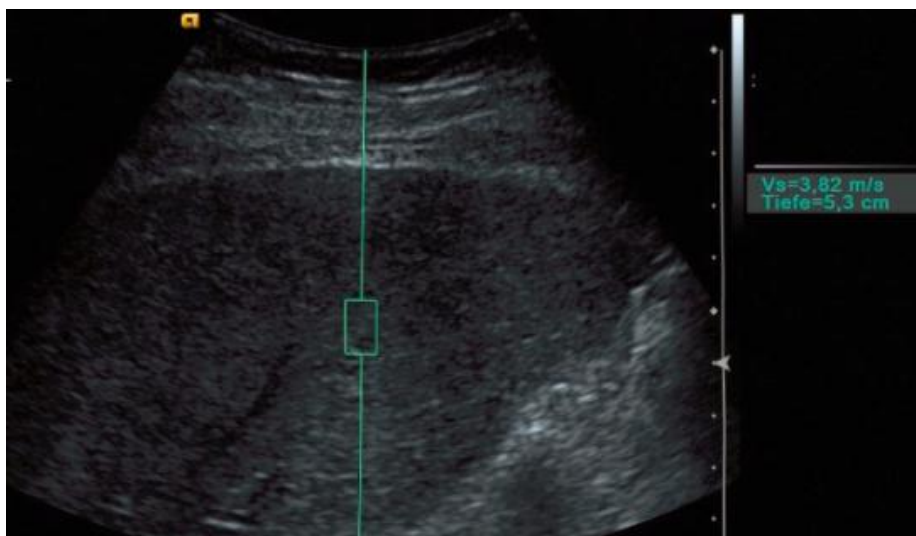


**Figure 1:** Alcoholic cirrhosis. Fibrous septa act as a bridge between centrilobular regions and portal tracts with the development of cirrhosis (trichrome stain,  $\times 200$ )<sup>[20]</sup>

A number of laboratory and ultrasound-based methods have been developed recently for the noninvasive diagnostic evaluation of cirrhosis. These noninvasive methods often obviate the need for liver biopsy when the only question to be answered is the stage of fibrosis; nonetheless, the information they provide must always be considered in the light of the accompanying clinical findings<sup>[21]</sup>. Ultrasound is an inexpensive

method that has been used for years in clinical practice to diagnose alcoholic cirrhosis<sup>[22]</sup>.

Ultrasound parameters for assessing cirrhosis in people with alcoholic liver disease encompass among others liver size, bluntness of the liver edge, coarseness of the liver parenchyma, nodularity of the liver surface, size of the lymph nodes around the hepatic artery, irregularity and narrowness of the inferior vena cava, portal vein velocity, and spleen size<sup>[23]</sup>



**Figure 2:** ARFI ultrasonography in cirrhosis: the measured value of 3.82 m/s implies cirrhosis<sup>[21]</sup>.



## TREATMENT OF CIRRHOSIS

### 1. Nutritional Support

The main purpose of nutritional therapy is to improve PCM and correct nutrient deficiencies. This can be accomplished via oral, enteral, or parenteral methods, or a combination of these modalities.

Guidelines for Meeting Nutritional Goals. In 1997, the European Society for Clinical Nutrition and Metabolism created guidelines for meeting nutritional goals in patients with end-stage liver disease<sup>[24]</sup>. They recommend initiation of enteral feeding when oral intake is inadequate. In patients with compensated cirrhosis, the guidelines recommend that patients consume 25-35 kcal/kg body weight per day of nonprotein energy and 1-1.2 g/kg body weight per day of protein or amino acids. In patients with complicated cirrhosis associated with malnutrition, nonprotein energy should be increased to 35-40 kcal/kg body weight per day and protein intake should be increased to 1.5 g/kg body weight per day. According to the guidelines, protein intake should be decreased to 0.5-1.5 g/kg body weight/day if stage I or II encephalopathy is present, and to 0.5 g/kg body weight/day if stage III or IV encephalopathy is present. More recent evidence suggests that protein restriction should not be recommended, even in the setting of episodic hepatic encephalopathy<sup>[25]</sup>.

### 2. Pharmacological Treatment

**Table 3:** investigated treatments for alcoholic liver disease<sup>[9]</sup>

Treatment	Routine Use Recommended?	Potential Benefit
Abstinence	Yes	Survival
Nutritional support	Yes	Survival, laboratory
Corticosteroids	Yes	Survival
Pentoxifylline	Consider if DF $\geq$ 32	Survival, less renal failure
Propylthiouracil	Consider (preliminary data)	No
Infliximab	No	No
Colchicine	No	No
Insulin, glucagon	No	No
Calcium channel blocker	No	No
Vitamin E	No	No
SAMe	No	No
Silymarin (milk thistle)	No	No
Liver transplantation	Consider(for decompensated cirrhosis)	Survival 70% at 5 yr

Recent studies advocated the use of nocturnal branched-chain amino acid (BCAA) administration<sup>[26]</sup>. It is believed that BCAAs that are consumed during the day are primarily used as a source of energy for physical exercise, whereas when administered at night, BCAAs might be preferentially used for protein synthesis<sup>[26]</sup>.

Researchers are investigating the efficacy of several antifibrotic agents which can block the fibrosis of liver, a condition before the scarring of liver tissue. Fibrosis is associated with excessive deposition of extracellular matrix (ECM) and fibroblasts have been the excessive source of ECM.

Counteracting the synthesis and secretion of ECM molecules is the focus of antifibrotic agent. Transforming growth factor  $\beta$  (TGF $\beta$ ) is implicated in fibrosis and blocking TGF $\beta$  ameliorates the experimental fibrosis. However, TGF $\beta$  independent fibrosis mediated by cytokines can also occur in liver.

Two humanized antibodies against TGF $\beta$ , one by Genzyme (GC1008) and Lilly (LY2382770) are under clinical trials at phase I and Phase II respectively for non-liver fibrosis (Clinical Trials.gov). Antibodies against other important molecules are targeted for many other organ fibrosis<sup>[27]</sup>. Another approach of the treatment could be degradation of ECM molecules. Collagen, a component deposited during fibrosis can be degraded by matrix metalloproteinases and experimentally increasing the expression of such metalloproteinases like MMP-8 has been shown to ameliorate the symptoms of fibrosis in experimental models<sup>[28]</sup>.

Another approach could be application of microRNAs (miRNA) or miRNA mimetics but delivery of such agents is a challenging task for the current scientists.

Patients with liver cirrhosis are recommended for screening of liver cancer and one of the markers of liver cancer;  $\alpha$ -fetoprotein in blood<sup>[29]</sup> in addition to imaging test which includes ultrasound, magnetic resonance imaging (MRI), or computerized tomography (CT) scan can be employed.

Despite development, there are not that many options for the treatment of liver cirrhosis; transplant of the liver is the only solution.

There is an immediate need for the development of drugs which can block the progression of liver from fibrosis to cirrhosis and reverse the process for the growth of hepatocytes which can replace the scarred tissue thus restoring the liver function.

### 3. Liver transplantation

Alcoholic cirrhosis was responsible for 21% of all orthotopic liver transplants in 2015 in the United States, according to the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) report [30]. Liver transplantation appears to be cost-effective for alcoholic liver disease, albeit possibly less so than for transplantation for some indications such as primary biliary cholangitis and primary sclerosing cholangitis [31]. Patients with advanced cirrhosis can be considered for liver transplantation, provided they are total abstainers. In such cases, a five year post-transplantation survival can reach anything up to 85% [32].

### CONCLUSION

Absolute abstinence is a basic condition for any treatment of acute or chronic Alcoholic liver diseases. Patients with advanced liver cirrhosis who demonstrably abstain can be considered for liver transplantation, which leads to a significant prolonged life expectancy. The crucial step in ALD prevention is in the prevention of alcohol abuse, whereas the prevention of liver injury in active alcohol abusers is not clinically applicable. Nevertheless, timely diagnosis of alcoholic cirrhosis in people with alcoholic liver disease is the cornerstone for evaluation of prognosis or choosing treatment strategies such as nutritional and medical support and lifestyle change.

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