

Effects of Endogenous Alcohol in Carcinogenesis Process of Hepatocellular Carcinoma

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ABSTRACT

Purpose: Aim of this work was to discover the patients diagnosed with alcoholic cirrhosis which in time was transformed in Hepatocellular Carcinoma, (HCT) by continue abuse alcohol and which presented, at a previous medical control, with the diagnosis of steatohepatitis after the chronic abuse of alcohol.

Materials and methods: Was take in a study consisted of 180 patients, adult men (mean age 55 years) and females, (mean age = 48), which were hospitalized and investigated for alcoholic liver diseases. Majority of patients with uncompensated liver cirrhosis, (70%), have had elevated AST in average 66 U/L value, (N= 5-38U/L). Also, they have had an AST/ALT ratio 1.36, (N = 1.33) and ratio TGP/TGO = 0.95.

Prothrombin time (PT): This blood test is not of great diagnostic value in the detection of mild hepatocellular dysfunction. A mild increase may more accurately reflect poor nutrition (vitamin K deficiency) than liver disease. However, when combined with bilirubin to generate a discriminant function, $MDF = 4.6 \times (PT - \text{reference PT}) + \text{bilirubin}$ can switch between different units, as signal of HCT.

Results: In the liver carcinogenesis process the report AST/ALT increased in 2.64 value and ratio TGP/TGO decreased in 0.67 value. Carbohydrate-deficient transferrin (CDT) which is a biomarker for chronic alcohol consumption of over 60 g ethanol / day. Was considered that the normal limit value is 31.9 U / l for women and 23.6 U / l for men. Elevated CDT levels have been reported in cases of chronic alcohol abuse, with varying degrees of liver damage. A blood alcohol level measured after drinking in the last few hours is not a good indicator of chronic alcohol abuse.

Conclusions: The constitution of large multicenter prospective cohorts of patients with alcoholic cirrhosis, involving sequential biobanking, is an unmet need in hepatology.

Keywords: Alcoholic liver disease; Cytokines; Nutrition; Steroids

Introduction

A history of habitual ethanol consumption is key in suggesting alcohol as the cause of liver disease. Hepatocellular carcinoma is the fifth most common neo-plasm and the third most frequent cause of cancer death. Early stages of hepatocarcinoma development, autophagy acts as a suppressor mechanism¹, promoting the recycling of defective organelles and unfolded proteins, prevention of oxidative stress and maintenance of genome stability². However, autophagy can also favor tumor promotion via oncogene-mediated cancer development^{3,4} and cellular adaptation to different stress, such as hypoxia or starvation^{5,6}.

Although the crosstalk between autophagy and apoptosis not well defined, a relationship has been established due to the interaction of different autophagy and apoptosis-related proteins⁷.

Materials and Methods

Following PRISMA guidelines, we searched Embase, Web of Science and PubMed (01/2020–04/2025) for studies applying H&E-based WSI computational analysis to predict prognosis or treatment response in solid tumors, with molecular pathology comparators⁸.

The synthesis aimed to provide a conceptual overview rather than a systematic or scoping analysis. A structured search strategy was developed and executed across four major electronic databases: PubMed, Scopus, Web of Science and Embase.

The literature search was restricted to publications from January 2003 to November 2025 to encompass both foundational and contemporary developments. Eligible documents included peer-reviewed original research articles, systematic reviews, meta-analyses and clinical guidelines that addressed human or animal models and were relevant to the integrative strategies discussed. Exclusion criteria comprised commentaries, editorials and conference abstracts without accessible full texts⁹.

A critical narrative analysis was conducted to synthesize key findings, evaluate methodological rigor, identify research gaps and highlight future investigative directions, in alignment with best practices for literature-based scientific assessments. Because this work is based entirely on previously published peer-reviewed research, no ethical approval was required. All included studies were examined for compliance with ethical standards and scientific rigor¹⁰.

Indirect alcohol biomarkers, which suggest heavy alcohol use by detecting the toxic effects of alcohol, include the following: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl-transferase (GGT), Mean corpuscular volume (MCV). Carbohydrate-deficient transferrin (CDT) which is a biomarker for chronic alcohol consumption of over 60 g ethanol / day. It was considered that the normal limit value is 31.9 U / l for women and 23.6 U / l for men.

Elevated CDT levels have been reported in cases of chronic alcohol abuse, with varying degrees of liver damage. A blood alcohol level measured after drinking in the last few hours is not a good indicator of chronic alcohol abuse¹¹.

Consumption of alcohol at doses up to 10 g / 1 unit / day after the onset of cirrhosis leads to the development of hepatocellular

carcinoma. Also, this amount of alcohol is a risk factor for the development of liver cancer if there are other conditions, such as diabetes or viral hepatitis B or C viruses. Obesity and diabetes also have a synergistic effect. As in other causes of advanced chronic liver disease, it is recommended that patients with alcoholic cirrhosis should be included in HCC surveillance program so that any tumor can be detected at the earliest possible stage: this strategy has been shown to enable the implementation of curative procedures that can increase survival¹².

A normal drinking is defined as one 12-oz beer, one 4- to 5-oz glass of wine or one mixed drink containing 1.5 oz of spirits (80 proof), [1 Oz = 29.57 ml]. The relative risk for the noted maladies with consumption of 4 or more drinks daily is as follows: Cirrhosis - for men, 7.5; for women, 4.8. Drinking outside of meal times increases up to 3 times the risk of alcoholic liver disease. Among older patients with alcoholism, from one third to one half develop alcoholism after age 60 years. Alcohol levels are higher in elderly patients for a given amount of alcohol consumed than in younger patients¹³. Oxidative stress induced by chronic ethanol consumption affects phospholipids and fatty acids in the cell membrane as well as α -linolenic acid with damage to cell structure¹⁴.

Biochemical tests

Blood tests are useful in the evaluation of disorders of the liver and biliary system. There are several laboratory abnormalities characteristic of alcoholic liver disease. However, these abnormalities do not necessarily correlate with disease severity.

Was take in a study consisted of 180 patients, adult men (mean age 55 years) and females, (mean age = 48), which were hospitalized and investigated for alcoholic liver diseases. Majority of patients with uncompensated liver cirrhosis, (70%), have had elevated AST in average 66 U/L value, (N= 5-38U/L). Also, they have had an AST/ALT ratio 1.36, (N = 1.33) and ratio TGP/TGO = 0.95. In the liver carcinogenesis process the report AST/ALT increased in 2.64 value and ratio TGP/TGO decreased in 0.67 value. However, not all patients with compensated alcoholic cirrhosis are at the same risk of developing HCC. The annual rates of HCC in the group with neither of these factors (age <55 years, platelet count >125,000), with 1 factor (age >55 years or platelet count <125,000) and with both factors (age >55 years and platelet count <125,000) were 0.3%, 2.6% and 4.8% (p <0.0001), respectively¹⁵.

Aminotransferases

The aminotransferases abnormalities are common in alcoholic liver disease. A disproportionate increase of serum aspartate aminotransferase, AST (GOT) compared to alanine aminotransferase, ALT (GPT) is highly suggestive of alcoholic liver injury, especially if the ratio of AST:ALT is greater than 2.0. Aminotransferase levels are generally lower than 300 IU/L and other etiologies for liver disease should be considered if the enzymes concentrations are higher than this¹⁶.

Gamma glutamyl transpeptidase

Gamma glutamyl transpeptidase (GTP) is a membrane-associated enzyme involved in the uptake of amino acids. Increased serum activity of GTP is often found in chronic alcohol users, in fact, over 70% of alcoholic individuals have elevated

GTP activity. Several other medications also increase GGTP and therefore this value must only be considered in combination with other laboratory and clinical information.

Hematologic and electrolyte abnormalities

Mean corpuscular volume (MCV), serum uric acid levels and serum electrolytes are all affected by chronic alcohol consumption. In addition, although symptoms may be nonspecific, increased serum uric acid, hypokalemia, hypomagnesemia and acidosis are indicators that alcohol may play a significant role in liver disease. Alcohol related bone marrow toxicity and/or splenic sequestration might contribute to macrocytosis (increased MCV) and thrombocytopenia. Leukocytosis is frequent in individuals with alcoholic hepatitis and may correlate with disease severity.

Prothrombin time (PT)

This blood test is not of great diagnostic value in the detection of mild hepatocellular dysfunction. A mild increase may more accurately reflect poor nutrition (vitamin K deficiency) than liver disease. However, when combined with bilirubin to generate a discriminant function, Discriminant function, $MDF = 4.6 \times (PT - \text{reference PT}) + \text{bilirubin}$ where MDF - Maddrey's Discriminant Function, PT - patient's prothrombin time expressed in seconds, reference PT - reference prothrombin time, usually 11-13 seconds and bilirubin - total bilirubin level expressed in mg/dl (in Maddrey's discriminant function calculator, you can switch between different units¹⁷).

Liver biopsy

Alcoholic hepatitis may require a biopsy for definitive diagnosis. In the absence of a liver biopsy, however, a diagnosis can be made on a history of chronic, current, heavy alcohol consumption, clinical and biochemical data and the exclusion of other etiologies such as viral hepatitis. Noninvasive tests such as ultrasonography and serologies complement a thorough history and physical examination. Histology is the most sensitive measure of disease stage and is a useful prognostic indicator of disease course. It is currently the only reliable method to estimate the degree of a patient's fibrosis. Fatty liver changes alone are not as serious as perivenular sclerosis (a precursor of cirrhosis). Biopsy can also confirm the diagnosis of cirrhosis.

Ultrasound

Ultrasound is noninvasive, easy to perform and has no known accompanying risks. It is often used as a screening tool in patients with hepatic dysfunction.

Abdominal ultrasound, however, is not able to detect minimal changes in the liver or to distinguish fibrotic changes and therefore cannot predict those patients at risk to develop cirrhosis. Computed Tomography, CT scanning is useful in the diagnosis of cirrhosis, portal hypertension and liver masses¹⁸.

Discussions

A history of habitual ethanol consumption is key in suggesting alcohol as the cause of liver disease. The type of beverage most often consumed, be it beer, wine or distilled spirits does not influence the likelihood of ethanol-induced hepatotoxicity. In the gastroenterology ward, patients with compensated cirrhosis initially presented with hepatomegaly and / or splenomegaly and at the anatomopathological examination different initial degrees of progressive hepatic fibrosis. Isolated hyperbilirubinemia as

a manifestation of alcoholic liver disease without significant liver abnormalities is rarely observed, (SAFER - alcohol control initiative: <https://www.who.int/initiatives/SAFER/about>).

Bilirubin may gradually decrease when alcohol consumption is stopped¹⁹. Acetaldehyde, the result of alcohol metabolism causes liver fibrosis by the deposition of collagen fibers in liver cells. The enzyme alcohol dehydrogenase acts through two molecular mechanisms for ethanol metabolism. The first is the use of a zinc atom used to maintain and position the alcohol group on ethanol and the second is a nicotin-diamianaza cofactor (NAD) that completes the reaction (**Figure 1**).

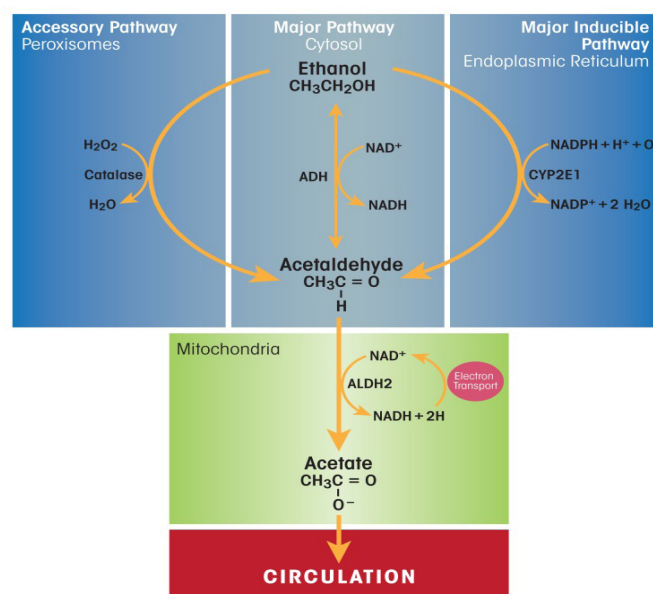


Figure 1: Major pathways of alcohol metabolism in hepatic cells. Acetaldehyde is further oxidized to acetic acid and CO₂ and water through the Krebs cycle

This pyruvic acid, as a result of transamination amino acids, is converted to glucose by gluconeogenesis. People who consume large amounts of alcohol can become overweight through excess NADH which can be used to synthesize glycerol and to synthesize fatty acids with increasing lipid synthesis. NADH in the electron transport chain can also be used for the synthesis of adenosine triphosphate, (ATP), as a source of cellular energy²⁰.

Ethanol can inhibit the activity of genes for the synthesis of inducible nitric oxide, in response to the stimulation of bacteria by inhibiting the activity of macrophages, contributing to the contribution to the impairment of antimicrobial defense after alcohol consumption.

The increase in proinflammatory cytokines, IL-6, IL-17, tumoral necrosis factor, TNF-alpha), plays a central role in the pathophysiology of alcoholism (**Figure 2**).

Epigenetic changes in cycle cells include histones by acetylation, phosphorylation, hypomethylation of DNA. Dysregulation of miRNA biogenesis has been found in non-viral HCC subtypes and oxidation of ethanol influences the expression of miR-217, miR-155 and miR-212. In recent years, microRNAs, miR-155, have been found to help increase TNF-alpha production and sensitize liver cells to produce more TNF-alpha in response to liposaccharide activation (LPS). LPS endotoxin is recognized by the Toll-like receptor complex (TLR)-4 on macrophages or Kupffer cells in the liver and contributes

to the production of proinflammatory cytokines leading to liver damage. precursors to carcinogenesis²¹.

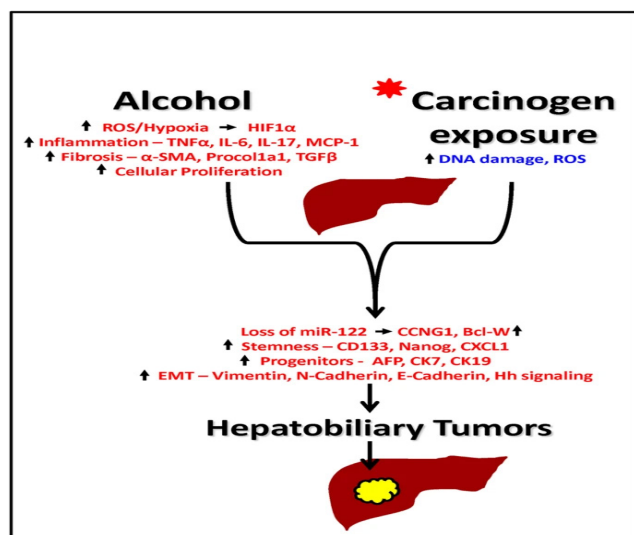


Figure 2: Increased proinflammatory cytokines, IL-6, IL-17, particularly TNF alpha, play a central role in the pathogenesis of Alcoholic Liver Disease.

Polymorphisms exist in the enzymes ADH, CYP2E1 and ALDH. Differences in ADH and ALDH certainly contribute to the negative association with ethanol dependence in some Asian populations. HLA phenotypes, a genetic predisposition toward alcoholism and female gender may also contribute to overall risk. Chronic alcohol abuse increases gut permeability resulting in high circulating endotoxin that reaches the liver via portal circulation.

Endotoxin (lipopolysaccharide or LPS) is recognized by the Toll-like receptor (TLR)-4 complex on resident macrophages or Kupffer cells in the liver, leading to production of proinflammatory cytokines, tumor necrosis factor (TNF)-α and resulting in injury to liver cells (hepatocytes)²², (Figure 3).

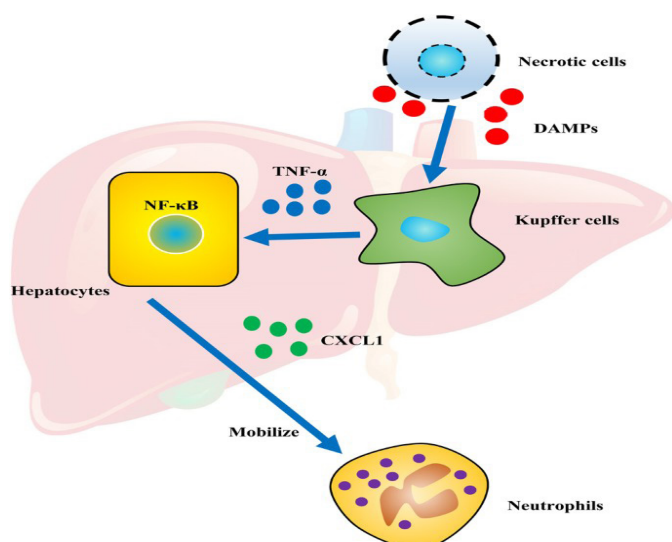


Figure 3: The typical inflammatory cytokines, such as TNF-α, IL-1 and IL-6, are primarily produced by inflammatory monocytes, macrophages.

Chronic alcoholics have elevated levels of immunoglobulins, especially in IgG and IgA classes with B cell dysfunction. produce inflammatory cytokines. Recent studies have also shown that decreased T cell proliferation after chronic alcohol abuse

could be caused by impaired monocyte function by producing inflammatory cytokines²³, (Figure 4).

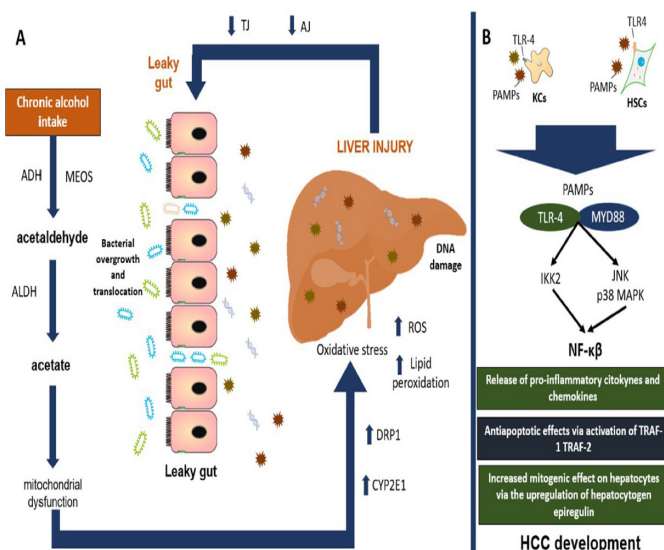


Figure 4: Alcohol-induced steatohepatitis is tightly associated with LPS-TLR4 signaling. Among BM-derived cells, Kupffer cells/macrophages highly express TLR4 and produce inflammatory cytokines.

The enzyme ALDH is mainly involved in liver cancer. Overexpression of ALDH enzymes, such as ALDH-1, ALDH-3A1 and ALDH-18A1, gives cancer cells a survival advantage because oxidative stress from high metabolic activity leads to free radical generation (ROS), lipid peroxidation and aldehyde accumulation. toxic, which can inhibit the proliferation and survival of cancer cells. As an antioxidant, the enzyme ALDH can decrease apoptosis of immunogenic cells and limit tumor progression by reducing the stress of the endoplasmic reticulum and the production of ROS²⁴.

Immediate and total abstinence from alcohol is critical for patients with alcoholic liver disease. Continued drinking is associated with disease progression, while abstinence benefits patients at any stage of disease, Global Burden of Disease (GBD) 2023 database; <http://ghdx.healthdata.org/gbd-results-tool>.

Fibrosis, portal pressures and ascites also often improve with the cessation of drinking. Patients hospitalized with alcoholic hepatitis are usually very ill with a short-term mortality between 20-50%. Several factors are associated with poor prognosis, especially signs of poor hepatic function (jaundice, encephalopathy and coagulopathy). In patients who are not infected, leukocytosis and hepatic inflammation also parallel poorer outcomes²⁵.

Individuals differ in their ability to metabolize alcohol through genetic differences in alcohol dehydrogenase (ADH), the enzyme that catalyzes the oxidation of ~80% of ethanol to acetaldehyde, a known carcinogen. Individuals differ in their ADH genotype and one locus in particular (ADH3) is polymorphic in Caucasian populations²⁶.

Using data from the Long Island Breast Cancer Study Project, we examined whether fast metabolizers of alcohol, as measured by the ADH1-13 genotype, have a higher risk of breast cancer from alcohol intake compared with those individuals who are slow metabolizers, but consume similar amounts of alcohol²⁷.

Among individuals homozygous for the metabolizing allele, (ADH1-13), a lifetime alcohol consumption of 15–30 g/day (~1–2 drinks per day) increased breast cancer risk by 2-fold (OR = 2.0, 95% CI = 1.1–3.5). In contrast, the increase in risk from a lifetime alcohol consumption of 15–30 g/day was less pronounced in the intermediate and slow metabolizing groups, respectively: ADH1-23 (OR = 1.5, 95% CI 0.9–2.4) and ADH2-23 (OR = 1.3, 95% CI 0.5–3.5). Fast metabolizers who drank 15–30 g/day of alcohol had 2.3 times (95% CI 1.3–4.0) greater risk of breast cancer than non-drinkers who were intermediate or slow metabolizers²⁸.

World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project expert report 2018: alcoholic drinks and the risk of cancer. Accessed May 30, 2022. <http://www.dietandcancerreport.org>. Additionally, a meta-analysis published Dec. 5, 2024, in Breast Cancer Research that Terry co-authored found reducing alcohol use was associated with a lower risk of developing hormone receptor-positive breast cancer. Chronic alcohol consumption leads to disruption of the intestinal barrier, including a thicker mucus layer and widened paracellular spaces (spaces between epithelial cells), which enable translocation of MAMPs and eventually bacteria.

However, bacteria are larger than the disrupted paracellular spaces, indicating an alternative route for bacteria to cross the gut barrier. Increased thickness of the mucus layer reduces bacterial mobility, which results in an increased contact time between bacteria and epithelial cells, facilitating translocation. At the same time, various molecules present in the mucus layer that can provide an antimicrobial response in a healthy state such as AMPs that directly kill bacteria as well as soluble immunoglobulin A (sIgA) molecules that can bind to bacteria - are decreased in patients with ALD and in mice fed a chronic ethanol diet²⁹.

Besides the difference of administering antibiotics that are absorbable vs. nonabsorbable, possible reasons for these different outcomes could include the presence of antibiotic-resistant bacteria, secondary effects of antibiotics and effects of antibiotics on the immune system.

Alcohol compromises the enterocyte barrier by nitro-oxidative stress and altered tight junctions. Moreover, increased apoptosis of enterocytes has been linked to ethanol-induced intestinal barrier dysfunction. Both of these effects impact the intestinal immune system. To understand the importance of the intestinal immune system in ALD, factors and components such as epithelial cells and their interactions must be highlighted³⁰.

In the other study from 2022, found, among people who drank more than two drinks per day, people who reduced their drinking to about one drink per day had an 8% lower cancer risk than those who continued to drink heavily, (International Agency for Research on Cancer: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf. (Last update: 18 May 2026). Additionally, a meta-analysis published Dec. 5, 2024, in Breast Cancer Research that Terry co-authored found reducing alcohol use was associated with a lower risk of developing hormone receptor-positive breast cancer³¹.

Many people remain unaware that alcohol can increase cancer risk (- Institute of Health Metrics and Evaluation; <https://vizhub.healthdata.org/gbd-results-tool> (people consumed harmful amounts of alcohol in 2023).

This association for fast metabolizers who drank 15–30 g/day was particularly pronounced among premenopausal women (premenopausal women OR = 2.9, 95% CI = 1.2–7.1; postmenopausal women OR = 1.8, 95% CI = 0.9–3.8). These population-based data support the hypothesis that fast metabolizers of alcohol have a higher risk of breast cancer risk, from alcohol intake than slow metabolizers. ADH, alcohol dehydrogenase, BMI, body mass index, CI, confidence interval, LIBCSP, Long Island Breast Cancer Study Project or, odds ratio³².

The reduced activity of ALDH-, B1, was found to be protective in patients with hepatocellular carcinoma (HCC), by influencing the oxidation of short-chain aldehydes, including acetaldehyde and propionaldehyde, against hepatocellular proliferation induced liver neoplasm (Figure 5).

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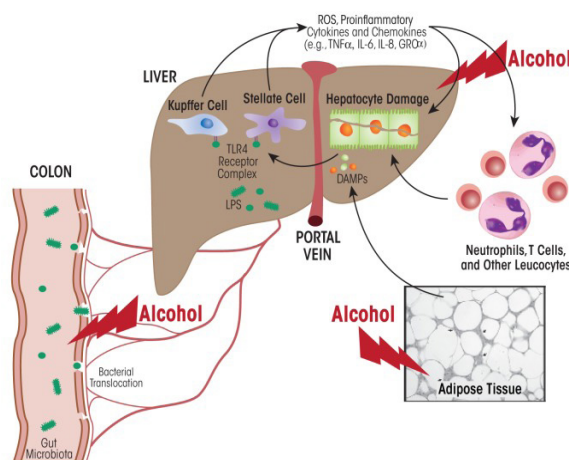


Figure 5: Decreased T cell proliferation after alcohol use might be due to impaired accessory cell/monocyte function.

In people with alcoholic hepatitis, promoters of liver cancer, the ratio of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) is greater than 2: 1. AST and ALT levels are almost always lower than 500. The increased AST / ALT ratio is due to pyridoxal deficiency. phosphate, which is required for the synthesis of the enzyme ALT.

Other observations include macrocytosis of red blood cells, mean corpuscular volume (VEM), > 100) and increases in serum levels of gamma-glutamyl transferase (GGT), alkaline phosphatase and bilirubin. Folate levels are low in alcoholic patients due to decreased intestinal absorption, increased need for folate in the bone marrow in the presence of alcohol and increased urinary loss³³.

Leukocyte depletion reflects the severity of liver damage. Histological features may include Mallory bodies, giant mitochondria, hepatocyte necrosis and neutrophil infiltration into the area around the blood vessels (Figure 6).

Recent studies have confirmed that moderate consumption of red wine is associated with high plasma levels of omega-3 polyunsaturated fatty acids, decreased blood viscosity, increased insulin sensitivity, decreased platelet count and aggregation and altered plasma coagulation protein levels. HDL-cholesterol, cardio-protector. As for the types of alcoholic beverages, especially wine with a variety of polyphenols, including phenolic

acids, tannins, resveratrol, flavonoids, have an anti-carcinogenic antioxidant and anti-inflammatory effects, in contrast to the carcinogenic ethanol³⁴.

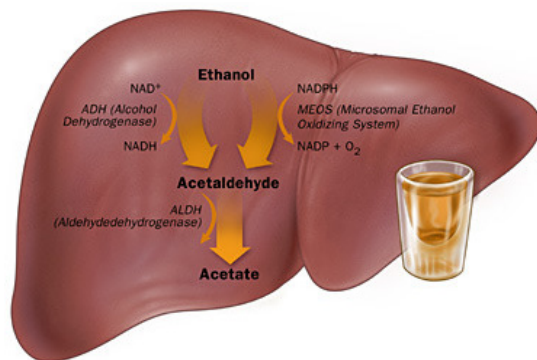


Figure 6: Products of ethanol metabolism in the liver.

Medical therapy

Standard supportive therapy for patients hospitalized with acute alcoholic hepatitis should include treatment of alcohol withdrawal, nutritional support including vitamins, (thiamine, folate and pyridoxine) minerals (phosphate, magnesium and zinc) and an aggressive search for potential infections. Protein should not be restricted, even in patients with encephalopathy. Specific therapy for severe alcoholic hepatitis should be initiated if the discriminant function is greater than 32 or the patient has hepatic encephalopathy³⁵.

Currently, the American College of Gastroenterology recommends corticosteroid therapy (prednisolone 40 mg/day or methylprednisolone 32 mg/day for 4 weeks) if there is no evidence of active infection, gastrointestinal bleeding or pancreatitis and the creatinine level is less than 2.5 mg/dL. Recent studies suggest that pentoxifylline, a tumor necrosis factor inhibitor, may also decrease mortality by preventing deterioration of renal function. Long-term treatment of alcoholic liver disease is not straightforward.

Several studies have evaluated the benefits of treatments including nutrition, propylthiouracil, colchicine, polyunsaturated lecithin, s-adenosylmethionine, pyridoxine and pyrrolidone. To date, the American Gastroenterological Association and the American Association for the Study of Liver Diseases endorse only nutritional supplementation for routine use. Drug treatment is aimed at reducing portal inflow or collateral or intrahepatic resistance (hepatic venous pressure gradients below 12 mm Hg reduce the danger of variceal bleeding)., (IARC: Alcoholic beverages, (IARC, 2012b).

Use of beta-blockers has been shown to decrease portal pressures, but side effects of the drugs are sometimes prohibitive. Propranolol is a non-selective beta-blocker that has been studied extensively and is effective in decreasing portal pressures. It decreases the risk of variceal bleeding both as primary prophylaxis and after an initial episode of bleeding. The dose needs to be titrated to decrease resting heart rate by 25%. There are no other medical therapies that can be recommended to prevent variceal bleeding³⁶.

Use of vasopressin in acutely bleeding patients is effective and works by decreasing splanchnic blood flow. It should be administered in an intensive care unit through a central venous access line. Side effects include vasoconstriction in other

vascular beds, including cardiac vessels. Vasopressin should be administered with sublingual nitroglycerin. Octreotide or somatostatin is now the preferred drug for acute variceal bleeding. It also acts as a vasoconstrictor, but works only on the splanchnic bed and consequently has fewer side effects. It is given as an IV bolus at 50 micrograms, followed by a constant infusion of 50 micrograms per hour³⁷.

Limited overview

This review may have led to the omission of recent or less-visible studies despite systematic screening. Secondly, the inclusion of single and pan-tumor models, as well as diverse biomarker types, broadens scope but introduces heterogeneity, limiting comparability across studies. Furthermore, this review focuses primarily on predictive performance, with clinical integration largely unaddressed. Lastly, the review is restricted to academic literature and excludes commercial tools used by vendors to showcase their model and its performance. Future work should prioritize external validation of developed models across independent cohorts to assess robustness and generalizability, alongside efforts to evaluate clinical utility and integration into diagnostic workflows³⁸.

Conclusion

If successfully integrated into clinical pathways, these models could reduce costs, expand access to molecular testing and ultimately reshape precision oncology by turning routine histology into a platform for molecular insight³⁹.

Several genetic variants have been reported to be associated with a higher risk of HCC inpatients with alcoholic cirrhosis and might offer an opportunity for the individual management of patients as a function of their genetic backgrounds. The constitution of large multicenter prospective cohorts of patients with alcoholic cirrhosis, involving sequential biobanking, is an unmet need in hepatology⁴⁰.

These advances will enable the adaptation of screening, preventive measures and the criteria for early diagnosis, which should optimize the allocation of limited resources in this large but difficult-to-manage patient population.

Abbreviations

ALDH2- acetaldehyde dehydrogenase 2;

ALD-alcoholic liver disease;

AMPK-AMP-activated protein kinase;

AGS-acetaldehyde-generating system;

ALC-alcoholic liver cirrhosis;

CYP2E1-cytochrome p450;

ECM- extracellular matrix;

HCC-hepatocellular carcinoma;

HBV: hepatitis B virus;

HCV: hepatitis C virus;

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