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# Alcoholic and Metabolic Syndrome Induce Liver Injury – A Single Center Experience

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**Simple Summary**

Obesity, diabetes, and metabolic syndrome (MetS) are increasingly prevalent. Previous studies have demonstrated that these metabolic risk factors can accelerate the progression of liver disease and increase mortality rates in individuals diagnosed with alcoholic liver disease (ALD). In this study, we com-pared liver disease parameters and outcomes between patients with ALD with and without the MetS treated at our Liver Unit. We found that patients with ALD and with MetS were older, consumed less alcohol and were at increased risk for heart disease and non-liver cancers. Patients with the MetS, however, did not have higher rates of severe liver disease and its complications, liver cancer or excess mortality rates competed to those without the MetS. Recognition of this unique yet prevalent patient population at liver clinics may offer the opportunity to address these modifiable risk factors and to prevent disease progression.

**Abstract**

Clinical evidence shows toxic role of alcohol in the pathogenesis of ALD. The liver biopsy can confirm the etiology of non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH) and assess cells inflammatory activity. The histological stages of ALD are simple steatosis, ASH, and chronic hepatitis with hepatic fibrosis or cirrhosis. These stages may also be associated with several cellular and histological changes: occurrence of Mallory's hyaline, megamitochondria, or perivenular and perisinusoidal fibrosis.

Obesity and the MetS can coexist with excessive alcohol intake in a substantial proportion of this patient population. In addition, obesity and the MetS can intensify the progression of ALD and increase the incidence of hepatocellular carcinoma (HCC) and mortality rates. The aim of our study was to observe the similarity and difference between patients with ALD and MetS compared to those with only ALD and no MetS.

**Methods**

All the ALD and MetS were consulted and treated in our liver unit, either as outpatients or during hospitalization, between March 2015 and April 2019. Records of the data were reviewed, and relevant evidence was collected under anonymous information. ALD and MetS were diagnosed according to accepted international criteria. A total of 208 patients met the inclusion criteria and were included in the study.

**Results**

Seventy-five patients of the group were identified with two or more components of the MetS. After comparing the two groups, the combined ALD - MetS patient group was found to be older ($p<0.001$), consume less alcohol ($p=0.01$) and have higher rates of cardiovascular disease [19 vs. 6, ($p<0.0001$)] and extra-hepatic malignancy [8 vs. 5, $p<0.045$]. Patients with ALD - MetS did not have higher rates of cirrhosis and complications, HCC or higher mortality rates compared to ALD patients without MetS. In conclusion, ALD patients with the MetS are a unique patient population that should be counselled accordingly, addressing hepatic and non-hepatic risk factors.

**Keywords:** Alcoholic Liver Disease; Cardiovascular diseases; Cirrhosis; Diabetes Mellitus; Extra-Hepatic Malignancy; Hepatocellular Carcinoma; Metabolic Syn-drome; Metabolic Immunologic Syndromes

**Abbreviations:** ALD: Alcoholic liver disease; ASH: Alcoholic steatohepatitis; AUD: Alcohol use disorders; BMI: Body mass index; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; EASL: European Association for the Study of Liver; HCC: Hepatocellular Carcinoma; HDL: High density lipoprotein; Hb1c: Hemoglobin 1Ac; MAFLD: Metabolic Associated Liver Disease; MASLD: Metabolic Dysfunction- Associated Steatotic Liver Disease; MASH: Metabolic Dysfunction Associated Steatohepatitis; MetS: Metabolic Syndrome; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic steatohepatitis; NHANES: National Health and Nutrition Examination Survey; SAF: Steatosis Activity Fibrosis; SCAFA: Short-Chain Fatty Acids; SLD: Steatotic Liver Disease; TG: Triglyceride; WHO: World Health Organization.

## Introduction

Chronic liver disease is a major public health burden, as cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death worldwide [1]. Alcoholic liver disease (ALD) remains a major

cause of chronic liver disease. About 2 billion people consume alcohol worldwide and over 75 million are diagnosed with alcohol use disorders (AUD) and are at risk for alcohol- associated liver disease [1]. Type 2 diabetes mellitus (DM) is a chronic disease representing an indirect financial burden since patients with diabetes have about ten times greater healthcare expenses than those without diabetes. Reportedly, cardiovascular disease (CVD) is a prevalent consequence of DM, and it continues to be the major cause of mortality and disability among DM patients. Obese people are at risk for DM, metabolic syndrome (MetS), CVD, stroke, and obstructive sleep apnea. Better knowledge of DM, CVD, and obesity pathogenesis needed to create innovative techniques for lowering patient health problems and discovering new diagnostic markers for disease management. T2DM is characterized by hyperglycemia, insulin resistance (IR). Nonalcoholic fatty liv-er disease also called metabolic dysfunction–associated steatotic liver disease, MASLD, includes the umbrella term steatotic liver disease, or SLD, which covers MASLD and MetALD. This term describes people with MASLD who consume more than 140 grams of alcohol per week for women and 210 grams per week for men. Metabolic dysfunction–associated steatohepatitis, or MASH, replaces the term NASH. MAFLD was proposed as a replacement for the term nonalcoholic fatty liver disease (NAFLD), is the most prevalent type of liver disease throughout the world, of which the prevalence is one-third of the global population.

The histological features of MAFLD present as steatosis greater than 5%, in addition to a spectrum of liver injuries that include hepatocyte ballooning, lobular inflammation and fibrosis leading to cirrhosis, and liver cancer. The extrahepatic complications such as diabetes and cardiovascular disease are higher in these individuals than those patients with simple fatty liver. Subsequently, histological evaluations pro-vide key information for predicting clinical outcomes and medical management, especially for prioritizing the considerations to receive clinical interventions when detecting liver injuries. Ballooning is characterized by hepatocytes exhibiting a rounded outline and pale cytoplasm. The hepatocytes might present enlarged or normal sizes. The cytoplasmic Keratin 8/18 expression is very low. The two histologic scoring systems in MAFLD measurements, include the NAFLD Activity Score (NAS) developed by the NASH Clinical Research Network (NASH CRN) and the "steatosis, activity, fibrosis" (SAF) scoring system. Using these scores, hepatocyte ballooning is characterized with scores ranging 0-2. The number of ballooned cells none (0). There can be few and prominent, normal size hepatocytes without ballooning. Recent years have seen a dramatic increase in the worldwide prevalence of obesity and the metabolic syndrome (MetS) [2]. Approximately two billion adults worldwide are overweight or obese and over 400 million have diabetes; both of which are risk factors for non-alcoholic fatty liver disease (NAFLD) and hepato-cellular carcinoma (HCC) [1].

These factors can coexist with alcohol consumption in a substantial proportion of this population [2]. In the Third National Health and Nutrition Examination Survey (NHANES III) cohort, the prevalence of obesity and components of the MetS was 45% and 32%, respectively [3]. This high prevalence was maintained in a more recent cohorts of subjects with ALD, where more than two thirds had central obesity and more than one third had MetS [4]. Previous studies indicate a relationship between ALD and the MetS [5]. The nature of this relationship and its clinical significance is yet to be fully defined. In a large Finnish cohort study, Aberg et al demonstrated that among alcohol risk users, diabetes mellitus was the single significant predictor for a severe liver event (de-fined as first hospitalization due to liver disease or liver-related death or a diagnosis of primary liver cancer) [5]. Stepanova demonstrated in a large population based American study, that DM was an independent predictor for overall mortality in ALD subjects [3]. This same study concluded that obesity and the MetS were independent risk factors for liver related mortality in ALD patient population [3]. Boyle described the relationship between alcohol and the metabolic syndrome as bidirectional, concluding that the two exert synergistic effects, enhancing liver injury and cirrhosis [2]. Elucidating the clinical impact of these metabolic hazard factors on ALD is important for risk assessment and may eventually dictate follow-up and referral practices. The aim of our study was to investigate the clinical outcomes of ALD patients with the MetS compared to ALD patients without MetS.

## Materials and Methods

This is a retrospective case analysis of patients admitted to Kaplan Medical Center with the diagnosis of ALD as well as ALD in the presence of MetS. The patients were seen as outpatients at the Liver Unit in our center from March 2015 to April 2019. The study was approved by the institutional ethics committee prior to its initiation. Diagnosis of ALD was made according to the European Association for the Study of Liver (EASL) clinical practice guidelines [6]: documentation of regular alcohol consumption of >20 gr./day in females and >30 gr./day in males together with the presence of clinical and/or laboratory abnormalities suggestive of liver injury. Diagnosis of cirrhosis was extracted from clinic records and/or based on clinical manifestations, laboratory results, radiological characteristics, non-invasive methods of fibrosis or liver biopsy. Criteria for the diagnosis of MetS were adapted from the World Health Organization (WHO) criteria for the metabolic syndrome [7].

i. Overweight ≥27 kg/$m^2$

ii. Dyslipidemia defined as triglyceride (TG) ≥150 mg/dL or high-density lipoprotein (HDL) <40 mg/dL or use of lipid lowering medication

iii. Hypertension defined as use of antihypertensive medications

iv. Impaired fasting blood glucose of 100-126 mg/dL and/or HbA1C ≥5.7 %.


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Patients were included in the combined MetS-ALD study group if they met 2 of the above criteria or had diabetes mellitus (DM), defined as fasting glucose >126 mg/dL and/or HbA1C ≥6.5% and/or chronic use of antidiabetic medications. Patients aged <18 years or with DM secondary to chronic pancreatitis were excluded. Data was retrieved from all available records. Post-hospitalization mortality data was obtained from a national registry governed by the Israeli Ministry of the Interior. Quantitative variables were expressed as means ± SD unless otherwise specified. Continuous variables were compared using the Student t-test with frequencies being compared utilizing the two-tailed Fisher's exact test. Survival was analyzed with the Kaplan-Meir method with comparison between patient cohorts with the log-rank test. Cumulative over-all survival was adjusted for age, alcohol consumption and body mass index (BMI). p-values of <0.05 was considered significant. Statistical analysis was performed using IBM SPSS, version 27 (Inc., Armonk, NY, USA).

## Results

A total of 208 patients with ALD were identified during the study period and included in the study cohort. Two or more components of the MetS were found in 75 (36%) patients. These comprised the ALD-MetS patient group. Twenty-nine (14%) patients had a diagnosis of DM, and 10 (5%) had IFG. The combined ALD-MetS patient group was older (p<0.001), had a higher BMI (p<0.001) and consumed less alcohol (p=0.01) compared to the non-MetS ALD group. Both groups included mainly males. Patients were delineated according to country of origin, with the combined ALD-MetS group being more prevalently of North-African descent (P=0.003) compared to their non-MetS counterparts. Demographic and baseline clinical characteristics of the patient cohort are shown in Table 1. Rates of cirrhosis were 28 (37%) for the combined ALD - MetS group vs. 59 (44%) for the ALD group, with no statistically significant difference (p=0.3). Similarly, no significant differences in the rates of decompensation [11 (39%) vs. 27 (46%), p=0.6] and HCC [6 (21%) vs. 7 (12%), p=0.2] were noted between the study groups. Cardiovascular disease was significantly more prevalent in the combined ALD - MetS group [19 (25%) vs. 6 (5%), p < 0.0001], as was in the group of extra-hepatic cancer [8 (11%) vs. 5 (4%), p<0.045]. Complete results are shown in Tables 2a and 2b. A trend towards lower survival rate was observed in the combined ALD - MetS group compared to the ALD cohort. However, after adjustment for age, alcohol consumption and body mass index (BMI) no significant difference in cumulative mortality was noted (Figure 1).

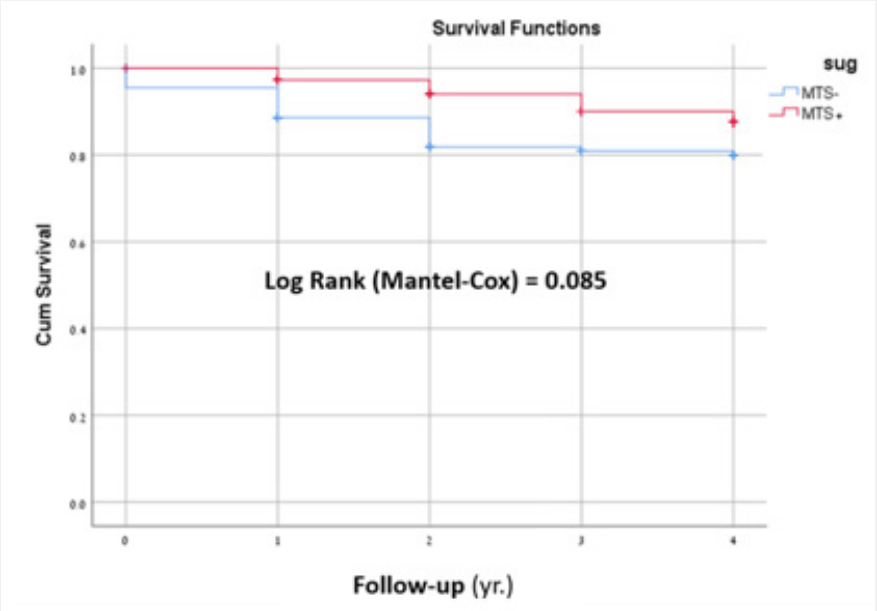


**Figure 1: Cumulative survival in ALD-MetS vs. ALD non-MetS patient group.**

**Table 1:** Baseline characteristics of the patient cohort.

| | MetS +ALD (n=75) | MetS (n=133) | p-value |
|---|---|---|---|
| Age (years) | 57±12 | 48.2±1 | <0.0001 |
| Male (%) | 67 (89) | 121 (91) | 0.7 |
| BMI (kg/m$^2$) | 27.8±5.6 | 23.7±4.2 | <0.0001 |


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| | | | | |
|---|---|---|---|---|
| Alcohol consumption (gr./day) | | 139±106 | 195±163 | 0.001 |
| Country of Origin (%) | Russia/USSR | 28 (37) | 56 (42) | 0.5 |
| | Ethiopia | 5 (7) | 14 (11) | 0.4 |
| | Israel | 12 (16) | 34 (26) | 0.1 |
| | Alger, Maroco | 20 (27) | 11 (8) | 0.0003 |

MetS=Metabolic syndrome; BMI = Body mass index

## Discussion

In this single center cohort study, we found that approximately one third of ALD patients are also afflicted with components of the metabolic syndrome and about 15% were diabetic. This finding is consistent with the 25% worldwide prevalence of the MetS, with higher prevalence in Western countries [5] reaching 47.3% among American adults [8]. Our study found that patients with ALD, combined with the MetS are older, have a higher BMI and consume less alcohol compared to ALD patients without MetS. Previous studies support this conclusion, demonstrating that obesity confers predisposition to the development of more advanced liver disease amongst alcohol consumers [9,10] and that the metabolic syndrome and/or type 2 DM may promote the development of ALD in this patient population [11]. The cause of this so-called accelerated progression of ALD is yet to be elucidated. Further studies must determine whether baseline metabolic derangement enhances the ethanol induced liver injury or is an expression of the additive injury of Metabolic Associated Liver Disease (MAFLD) [11]. We found no significant differences between the two study groups regarding the prespecified main hepatic outcomes. These findings do differ from previous epidemiologic studies addressing this issue, with most concluding that a supra additive effect of MetS and its components on ALD does exist. Among investigated outcomes higher rates of cirrhosis [12] decompensated liver disease [13] and HCC [14] were reported. It is important to note that study methodologies are heterogeneous. Specifically, our patient population differed from most studies. Our study is performed in a hepatology referral center. As a result, our cohort is more selective vs. large-scale general population cohorts, such as the NHANES III.

In our study, cardiovascular disease and extra-hepatic cancers were more prevalent in the combined ALD-MetS group. This observation reflects the well-accepted finding that the metabolic syndrome is associated with a range of extrahepatic disease manifestations, particularly cardiovascular disease [11,15]. An increased risk of several common cancers in non-alcoholic steatohepatitis NASH [16] is also well documented. It is important to note that excessive alcohol consumption, per-se, is also considered a risk factor for several extra-hepatic cancers [17] and cardiovascular disease [18], also contributing to these outcomes. Several other factors such as age, degree of fitness, nutrition, presence of obesity and related cardiometabolic risk factors, BMI, autoimmune diseases, sex, and genetics influence the severity of the disease [19-27]. Daily, appreciatively half of the body cholesterol elimination from the body occurs via its degradation to the bile acids [28]. Bile acids are metabolic signalling factors, lipid solubilizers and regulators of bile-acid homeostasis. Bile-acid-activated signalling pathways have become therapeutic targets for metabolic disorders. Thomas and his team [29] reviewed how the signalling functions of bile acids can be exploited in the development of for obesity, type 2 diabetes, hypertriglyceridemia and atherosclerosis, as well as other associated chronic diseases such as non-alcoholic steatohepatitis. Metabolic dysfunction – associated steatohepatitis, or MASH, replaces the term NASH [30] as concluded by the consensus group.

The metabolic dysfunctions in the presence of alcohol misuse or in comorbidity increases the impact on the liver [31-35]. Chronic alcohol consumption is a risk factor for tumours of the oral cavity, gastro-intestinal tract, liver, pancreas and the female breast. Numerous mechanisms contribute to alcohol-induced carcinogenesis including the action of cytochrome P-450 (CYP). CYP2E1 is one of the P450 enzymes which are responsible for over 90% of the oxidation and reduction of chemicals including drugs, vitamins, steroids, chemical carcinogens, and industrial solvents. CYP2E1 driven oxidative stress leads to mitochondrial damage. In our previous article we explained that ALD and NAFLD lead to abnormal accumulations of fat in the liver followed by an evolution from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Morphological changes in the liver mitochondria, perivenular and perisinusoidal fibrosis, cellular ballooning, and accumulation of fibrosis lead to the development of cirrhosis [36]. Specific biomarkers may help to monitor the inflammation and repair in MAFLD and in estimating the contribution of alcohol intake and the metabolic syndrome to liver steatosis [37,38]. Alcohol effects on hepatic lipid metabolism through various mechanisms, leading synergistically to an accumulation of fatty acids (FA) and triglycerides. Obesity, as well as, the dietary fat [saturated fatty acids (FA) versus poly-unsaturated fatty acids (PUFA)] may modulate the hepatic fat.

Gut flora maintains the individual health and constitutes an important factor in the pathogenesis of various diseases. The microbiota can be influenced by age, genetics, host environment and diet [39]. Diet has an impact upon both the composition and the function of the micro-biota through influencing the development of both immune and metabolic factors. A future prospective study may demonstrate the potential of dietary manipulation of the gut


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microbiota and its metabolome as a modality to both maintain health and treat diseases [40,41]. The microbiome encompasses bacteria, fungi, and viruses [42]. Microbiome preserves epithelial barrier function [43-46]. The components of the microbiome metabolize unabsorbed carbohydrates from nutrients and transform them to short-chain fatty acids (SCFA). SCAFA represents an energy supply for the body [47]. The malfunction of the intestinal microbiome affects the small intestinal barrier function [48] and influences the physiology of the GI system leading to dysbiosis [49,50]. Dysbiosis influences the host's immune response via interactions between the microbiota and the ingested food. Bacterial overgrowth may develop because of intestinal tract secretions, gastric acid and bile acid secretion, pancreatic enzymes and mucin production play an important role in microbial population and its activity into intestine. The metabolites produced by bacteria are signaling to epithelial cells of intestine to enhance or diminish their metabolism and to produce and/or eliminate toxic substances. The changed microbial signaling in dysbiosis results in shifts in both GI motility and metabolism. The gut microbiota, which is changed by chronic alcohol consumption, may also play an important role in hepatic steatosis and alcoholic liver disease [46,47].

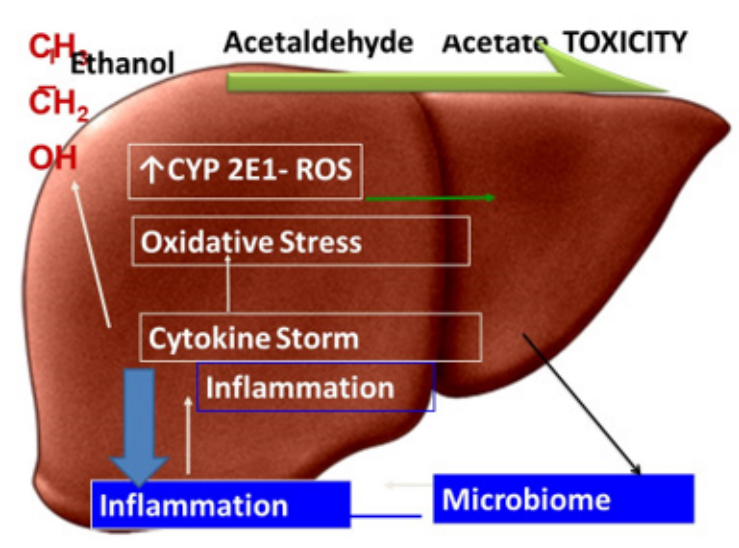


**Figure 2:** Metabolome and alcohol- induced damage to the liver.

**Table 2:** Outcome of patient cohorts.

**Table 2a:** Hepatic outcomes.

| | | MetS + ALD (n=75) | MetS (n=133) | p-value |
|---|---|---|---|---|
| Cirrhosis (%) | | 28 (37) | 59 (44) | 0.3 |
| Decompensated Cirrhosis (%) | | 11 (39) | 27 (46) | 0.6 |
| | Bleeding Varices (%) | 1 (4) | 8 (14) | 0.2 |
| | Ascites (%) | 11 (39) | 25 (42) | 0.8 |
| | Encephalopathy (%) | 0 (0) | 1 (2) | 0.5 |
| HCC (%) | | 6 (21) | 7 (12) | 0.2 |

HCC - Hepatocellular carcinoma

MetS - Metabolic syndrome

**Table 2b:** Non-hepatic outcomes.

| | MetS+ ALD (n=75) | MetS- (n=133) | p-value |
|---|---|---|---|
| Cardiovascular Disease (%) | 19 (25) | 6 (5) | < 0.0001 |
| Extra-hepatic malignancy (%) | 8 (11) | 5 (4) | 0.045 |

MetS -Metabolic syndrome


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## Alcohol and Endotoxin

ALD is associated with elevated plasma endotoxin levels in alcoholic patient [48-50]. The patient has high levels of endotoxin. The endotoxemia results in an increase level of lipopolysaccharides (LPS) [51]. The intestinal permeability is let-ting microbiota and LPS out of the GI tract [52]. LPS enter via the portal tract in the liver injuring the parenchyma, Ethanol effects glycosylation of epithelial mucins, which alters the protective mucus layer and may cause a change in adherent bacterial species [53]. The effect of alcohol on intestinal permeability is in part due to the bacterial metabolism of ethanol to acetaldehyde [53]. Patients with alcoholic liver disease have an overgrowth of Candida sp. compared to non-alcoholic controls [54-58]. Moreover, 2 weeks of abstinence from alcohol reduces the proportion of Candida albicans in patients with alcohol-use disease. In addition, mice fed a chronic diet supplemented with alcohol have an increase in Meyerozyma guillermondii [59]. Alcohol misuse leads to functional and morphological changes in liver [60- 69]. Continuing alcohol misuse leads to persistent parenchymal damage [70-79]. The combination of metabolic distress and alcohol misuse leads to inflammation and cellular distress [80-87]. The critical role of toll-like receptor (TLR) 4 in alcoholic liver disease is independent of the other TLRs and represents together with other biomarkers a diagnostic test to evaluate the degree of liver injury [88-93]. Alcohol mixed with drugs with high lipophilicity and extensive metabolism in the liver (> 50%) are associated with an increased hepatotoxic potential, especially in combination with a high daily dose (> 100 mg daily). In addition, drugs that form reactive metabolites, exert mitochondrial toxicity, and inhibit bile acid transporters in in vitro test systems, like lymphocyte toxicity assay (LTA) or/and human hepatic cells in culture are associated with increased DILI risk in humans [27]. Concomitant administration of multiple hepatotoxic drugs has also been associated with an increased risk of drug-induced liver injury (DILI) in individuals with alcohol misuse [27].

The impact of host age, sex, and race and ethnicity on ALD-Met susceptibility is not well established because of the lack of large exposure-based epidemiological studies to compare DILI incidence with drug-treated controls with the same dis-ease. Although standardized ALD incidence increases with patient age, this may be explained by the fibrosis accumulation in the liver in older individuals [27]. Abstinence is the most effective therapy in ALD [36,37]. The highest effective treatment for MAFLD is based on lifestyle changes, diet, and physical activity. The most urgent need is for the widespread adaptation of the necessary lifestyle changes that can decrease the prevalence of the disease, and adding up, its morbidity and rate of progression. In addition, it is possible to reverse the severity of hepatic fibrosis. Much work is necessary to understand the role of the bacteria, their interactions within the complex milieu of the intestinal micro-biome, and the possible effects of fungi and viruses within the intestine. In addition, there is a role of genetics and downstream effects on inflammation, metabolites, and intestinal permeability [94-103]. An observational study describes the mortality due to cirrhosis and liver cancer in the United States, 1999-2016, including ALD and MAFLD individuals [104]. Recent advances in the therapeutic landscape for alcohol and metabolic dysfunction -induced liver injury offer new opportunities to personalize treatment and improve outcomes for patients with moderately to severely active disease [105-108].

Leading experts examine the latest clinical evidence and guidelines for the newest targeted therapies for ALD and MAFLD and should share practical strategies for integrating these therapies into practice [105-113]. We hope that by sharing our study we will contribute to show the importance of collaborative work between patients; clinician; laboratory strategies to achieve individualized treatment plans that align the latest evidence with the unique needs; goals; and preferences of each patient. There is also a need to evaluate and synthesize pre-clinical and clinical research focused on associations between the oral microbiome and neuropsychological disorders with a specific focus on MetS according to pre-defined clinical and microbiome methodology. Various host genetic factors related to drug-metabolizing enzymes and transporters have been reported as increasing DILI susceptible individual reactions. A missense variant (rs2476601) in PTPN22, which has been associated with other autoimmune disorders, appears to be a risk factor for all-cause DILI across multiple racial and ethnic groups for specific or herbal dietary products and the common drugs chronic hepatitis are inflammation, necrosis and fibrosis in liver tissues. The macrophages (Kupffer cells, hepatic stellate cells (Ito cells) and sinusoidal endothelial cells foster the formation and emitting of pro-inflammatory signals of cytokines, chemokines, lipid and reactive oxygen species (ROS) and activate the inflammatory response that leads to hepatic cells necrosis and apoptosis. Apoptotic bodies derived from the damaged hepatic cells activate Kupffer cells to secrete transforming growth factor beta 1, endothelial growth factor and platelet-derived growth factor, which can promote the trans-formation of activated hepatic stellate cells into myofibroblasts [114-119].

Acute cholestatic hepatitis is the presence of cholestasis accompanied by more prominent lobular inflammation. In chronic cholestasis, the cholestasis persists and may have severe bile duct injury or progress to bile duct loss. Less common histological manifestations of drug-induced liver injury (DILI) include fatty liver disease, drug-induced steatosis, and drug-induced steatohepatitis. Steatosis may be purely micro vesicular, which is primarily related to mitochondrial injury, mixed micro vesicular and macro vesicular, or purely macrovascular steatosis [120-150]. The link between alcohol consumption, its toxicity and the gut microbiome is presented in Figure 2. Our study has several limitations. It is a retrospective analysis, therefore, subject to data-collection biases. Data was collected from digital medical records that may be incomplete or lacking. The study was performed in a single medical center. Therefore, the results reflect our patient


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population. Finally, alcohol intake is self-reported by patients and subject to recall bias. Future work will include identifying the patients for further studies including biomarkers of inflammation and repair, and possible virology.

## Conclusion

The combined ALD-MetS patient is now increasingly prevalent, therefore, inevitably encountered by practicing clinicians. Our study highlights the im-portance of recognizing and addressing these modifiable risk factors in ALD patients for minimizing disease progression, preventing additional morbidity and mortality and for risk stratification. It is metabolized to acetate via acetaldehyde dehydrogenase. Acetate is excreted from the liver. The enzyme - Cytochrome P450 2E1 (CYP 2E1) is involved in metabolizing alcohol and producing reactive oxygen species (ROS) that are toxic to the liver. Genetic polymorphisms of ethanol metabolizing enzyme, CYP 2E1 activation may change the se-verity of ASH and NASH. Immune response to alcohol in ASH, as well as the role of other risk factors such as its comorbidities with chronic viral hepatitis in the presence or absence of human deficiency virus are taken into consideration. Gastro-intestinal flora (microbiome) produces toxin (endotoxin that enters the liver via the portal vein and contributes to toxicity. The toxic metabolites and dysfunctional microbiome inflame the liver cells that will produce a storm of the proinflammatory cytokines such as tumor necrosis alpha, interleukins (IL) beta, IL 6, chemokines IL8 and RANTES contributing to the liver damage and to recruitment of profibrogenic cytokine Transforming Growth Factor (TGF) beta.

## References


1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS (2019) Burden of liver diseases in the world. J Hepatol 70(1): 151-171.
2. Boyle M, Masson S, Anstee QM (2018) The bidirectional impacts of alcohol consumption and the metabolic syndrome: Cofactors for progressive fatty liver disease. J Hepatol 68(2): 251-267.
3. Stepanova M, Rafiq N, Younossi ZM (2010) Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: A population-based study 59(10):1410-1415.
4. Singh A, Vigni A, Tabbaa A, Scott A, Mansouri M (2018) Increased Prevalence of Obesity and Metabolic Syndrome in Patients with Alcoholic Fatty Liver Disease. Am J Gastroenterol 113(Oct): S465.
5. Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A (2018) Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. Hepatology 67(6): 2141-2149.
6. Thursz M, Gual A, Lackner C, Mathurin P, Moreno C (2018) EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol 69(1): 154-181.
7. Huang PL (2009) A comprehensive definition for metabolic syndrome. DMM Dis Model Mech 2(5-6): 231-237.
8. Åberg F, Byrne CD, Pirola CJ, Männistö V, Sookoian S. Alcohol consumption and metabolic syndrome: Clinical and epidemiological impact on liver disease. J Hepatol.
9. Iturriaga H, Bunout D, Hirsch S, Ugarte G (1988) Overweight as a risk factor or a predictive sign of histological liver damage in alcoholics. Am J Clin Nutr 47(2): 235-238.
10. Naveau S, Giraud V, Borotto E, Aubert A, Capron F (1997) Excess weight risk factor for alcoholic liver disease. Hepatology 25(1): 108-111.
11. Chiang DJ, McCullough AJ (2014) The impact of obesity and metabolic syndrome on alcoholic liver disease. Clin Liver Dis 18(1): 157-163.
12. Raynard B, Balian A, Fallik D, Capron F, Bedossa P (2002) Risk factors of fibrosis in alcohol-induced liver disease. Hepatology 35(3): 635-638.
13. Åberg F, Helenius-Hietala J, Puukka P, Jula A (2017) Binge drinking and the risk of liver events: A population-based cohort study. Liver Int 37(9): 1373-1381.
14. Åberg F, Färkkilä M, Männistö V (2020) Interaction Between Alcohol Use and Metabolic Risk Factors for Liver Disease: A Critical Review of Epidemiological Studies. Alcohol Clin Exp Res 44(2): 384-403.
15. Adams LA, Anstee QM, Tilg H, Targher G (2017) Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 66(6): 1138-1153.
16. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D (2012) Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 35(11): 2402-2411.
17. Rumgay H, Murphy N, Ferrari P, Soerjomataram I (2021) Alcohol and cancer: Epidemiology and biological mechanisms. Nutrients 13(9): 1-13.
18. O'Keefe JH, Bhatti SK, Bajwa A, DiNicolantonio JJ, Lavie CJ (2014) Alcohol and cardiovascular health: the dose makes the poison…or the remedy. Mayo Clin Proc 89(3): 382-393.
19. De Abreu VG, Martins C, De Oliveira PAC, Francischeatti EA (2017) High-molecular weight adiponectin/HOMA-IR ratio as a biomarker of metabolic syndrome in urban multiethnic Brazilian subjects. PLoS One 12(7): e0180947.
20. Keska A, Lutoslawska G, Czajkowska A, Tkaczyk J, Mazurek K (2013) Variability in HOMA-IR, lipoprotein profile and selected hormones in young active men. Sci World J 2013: 1-6.
21. Guarino D, Nannipieri M, Iervasi G, Taddei S, Bruno RM (2017) The role of the autonomic nervous system in the pathophysiology of obesity. Front Physiol 8: 665.
22. Russo B, Menduni M, Borboni P, Picconi F, Frontoni S (2021) Autonomic nervous system in obesity and insulin-resistance. The complex interplay between leptin and central nervous system. Int J Mol Sci 22(10): 5187.
23. Konstantinidou SK, Argyrakopoulou G, Tentolouris N, Karalis V, Kokkinos A (2022) Interplay between baro-reflex sensitivity, obesity and related cardiometabolic risk factors. Exp Ther Med 23(1):1-13.
24. Karayannis G, Giamouzis G, Tziolas N (2013) Association between epicardial fat thickness and weight homeostasis hormones in patients with noncachectic heart failure. Angiology 64(3): 173-180.
25. Koleva DI, Orbetzova MM, Nikolova JG, Deneva TI (2016) Pathophysiological role of adiponectin, leptin and asymmetric dimethylarginine in the process of atherosclerosis. Folia Med (Plovdiv) 58(4): 234.
26. Pérez-Pérez A, Vilariño-García T, Fernández-Riejos P, Martín-González J, Segura-Egea JJ (2017) Role of leptin as a link between metabolism and the immune system. Cytokine Growth Factor Rev 35: 71-84.
27. Neuman MG, Cameron RG, Shear NH, Bellentani S, Tiribelli C (1995) Effect of tauroursodeoxycholic and ursodeoxycholic acid on ethanol-induced cell injuries in the human Hep G2 cell line. Gastroenterology 109(2): 555-563.



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28. Thomas C, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K (2008) Targeting bile-acid signalling for metabolic diseases. Nat Rev Drug Discov 7(8): 678-693.

29. McGlone ER, Bloom SR (2019) Bile acids and the metabolic syndrome. Ann Clin Biochem 56(3): 326-337.

30. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S (2023) AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):1797-1835.

31. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K (2018) The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 67: 328-357.

32. Cusi K, Isaacs S, Barb D, Basu R, Caprio S (2022) American Association of Clinical Endocrinology Clinical Practice Guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract 28: 528-562.

33. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M (2021) Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol 116: 723-732.

34. Mózes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M (2022) Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut 71: 1006-1019.

35. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ (2018) Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 67: 123-133.

36. Malnick SDH, Alin P, Somin M, Neuman MG (2022) Fatty Liver Disease-Alcoholic and Non-Alcoholic: Similar but Different. Int J Mol Sci 23(24): 16226.

37. Neuman MG, French SW, French BA, Seitz HK, Cohen LB, et al. (2014) Alcoholic and non-alcoholic steatohepatitis. Exp Mol Pathol 97(3): 492-510.

38. Abdul-Hai A, Abdallah A, Malnick SD (2015) Influence of gut bacteria on development and progression of non-alcoholic fatty liver disease. World J Hepatol 7(12): 1679-1684.

39. Denny JE, Powell WL, Schmidt NW (2016) Local and Long-Distance Calling: Conversations between the Gut Microbiota and Intra- and Extra-Gastrointestinal Tract Infections. Front Cell Infect Microbiol 6: 41.

40. Wu GD (2016) The Gut Microbiome, Its Metabolome, and Their Relationship to Health and Disease. Nestle Nutr Inst Workshop Ser 84: 103-110.

41. Malnick SDH, Fisher D, Somin M, Neuman MG (2021) Treating the Metabolic Syndrome by Fecal Transplan-tation-Current Status. Biology (Basel) 10(5): 447.

42. Heshmati H (2021) Gut Microbiome Modulation in the Management of Nonalcoholic Fatty Liver Dis-ease.

43. Carlsson LM, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA (2020) Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study N Engl J Med 383(16): 1535-1543.

44. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ (2008) The Metabolic Syndrome. Endocr. Rev 29(7): 777-822.

45. Luissint AC, Parkos CA, Nusrat A (2016) Inflammation and the Intestinal Barrier: Leukocyte-Epithelial Cell Interactions, Cell Junction Remodeling, and Mucosal Repair. Gastroenterology 151(4): 616-632.

46. Odenwald MA, Turner JR (2017) The Intestinal Epithelial Barrier: A Therapeutic Target? Nat Rev Gastroenterol Hepatol 14 (1): 9-21.

47. Vancamelbeke M, Vermeire S (2017) The Intestinal Barrier: A Fundamental Role in Health and Disease. Expert Rev Gastroenterol Hepatol 11(9): 821-834.

48. Köhler H, McCormick BA, Walker WA (2003) Bacterial-Enterocyte Crosstalk: Cellular Mechanisms in Health and Disease. J Pediatr Gastroenterol Nutr 36(2): 175-185.

49. Shindo K, Machida M, Koide K, Fukumura M, Yamazaki R (1998) Deconjugation Ability of Bacteria Isolated from the Jejunal Fluid of Patients with Progressive Systemic Sclerosis and Its Gastric PH. Hepatogastroenterology 45(23): 1643-1650.

50. Ghoshal UC, Srivastava D (2014) Irritable Bowel Syndrome and Small Intestinal Bacterial Overgrowth: Meaningful Association or Unnecessary Hype. World J Gastroenterol 20(10): 2482-2491.

51. Cani PD (2016) Gut Microbiota: Changes in Gut Microbes and Host Metabolism: Squaring the Circle? Nat Rev Gastroenterol Hepatol 13(10): 563-564.

52. Lynch SV, Pedersen O (2016) The Human Intestinal Microbiome in Health and Disease. N Engl J Med 375(24): 2369-2379.

53. Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, et al. (2017) Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. Cell Metab 26(4): 611-619.

54. Barbara G, Feinle-Bisset C, Ghoshal UC, Santos J, Vanner SJ (2016) The Intestinal Microenvironment and Functional Gastrointestinal Disorders. Gastroenterology 150(6): 1305-1318.

55. Bouter KE, Van Raalte DH, Groen AK, Nieuwdorp M (2017) Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. Gastroenterology 152(7): 1671-1678.

56. Cox TO, Lundgren P, Nath K, Thaiss CA (2022) Metabolic Control by the Microbiome. Genome Med 14(1): 1-13.

57. Perler BK, Friedman ES, Wu GD (2023) The Role of the Gut Microbiota in the Relationship Between Diet and Human Health. Annu Rev Physiol 85: 449-468.

58. Llopis M, Cassard AM, Wrzosek L, Boschat L, Bruneau A, et al. (2016) Intestinal Microbiota Contributes to Individual Susceptibility to Alcoholic Liver Disease Gut 65(5): 830-839.

59. Gangarapu V, Ince AT, Baysal B, Kayar Y, Kılıç U (2015) Efficacy of Rifaximin on Circulating Endotoxins and Cytokines in Patients with Nonalcoholic Fatty Liver Disease. Eur J Gastroenterol Hepatol 27(7): 840-845.

60. Yu Y, Tong Y, Wu L, Yu X (2022) Helicobacter Pylori Infection Eradication for Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial. Sci Rep 12(1): 1-10.

61. Del Barrio M, Lavín L, Santos-Laso Á, Arias-Loste MT, Odriozola A, et al. (2023) Faecal Microbiota Transplantation, Paving the Way to Treat Non-Alcoholic Fatty Liver Disease. Int J Mol Sci 24(7): 6123.

62. Neuman MG, Seitz HK, Teschke R, Malnick S, Johnson-Davis KL, et al. (2022) Molecular, Viral and Clinical Features of Alcohol- and Non-Alcohol-Induced Liver Injury. Curr Issues Mol Biol 44: 1294-1315.

63. Tang H, Becky MS, Axhemi A, Chen X, Hillian AD (2012) Ethanol-induced oxidative stress via CYP2E1 pathway disrupts adiponectin secretion from adipocytes. Alcohol Clin Exp Res 36: 214-222.



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64. You M, Rogers CQ (2009) Adinopectin: A key adipokine in alcoholic fatty liver. Exp Biol Med 234: 850-859.

65. Rogers CQ, Ajmo JM, You M (2008) Adiponectin and alcoholic fatty liver disease. 60: 790-797.

66. Natarajan SK, Rasineni K, Ganesan M, Feng D, McVicker BL, et al. (2017) Structure, function and metabolism of hepatic and adipose tissue lipid droplets: Implications in alcoholic liver disease. Curr Mol Pharmacol 10: 237-248.

67. Dolganiuc A, Thomes PG, Ding WX, Lemasters JJ, Donohue TM (2012) Autophagy in alcohol-induced liver diseases. Alcohol Clin Exp Res 36: 1301-1308.

68. Rasineni K, Donohue TM, Thomes PG, Yang L, Tuma DJ (2017) Ethanol-induced steatosis involves impairment of lipophagy, associated with reduced Dynamin 2 activity Hepatol Commun 1: 501-512.

69. Forsyth CB, Voigt RM, Kesharvarzian A (2014) Intestinal CYP2E1: A mediator of alcohol-induced gut leakiness. Redox Biol 3: 40-46.

70. Sharma SP, Suk KT, Kim DJ (2021) Significance of gut microbiota in alcoholic and non-alcoholic fatty liver diseases. World J Gastroenterol 27: 6161-6179.

71. Compare D, Coccoli P, Rocco A, Nardone OM, De Maria S (2012) Gut-liver axis: The impact of gut microbiota on nonalcoholic fatty liver disease. Nutr Metab Car-diovasc Dis 22: 471-476.

72. Parlesak A, Schäfer C, Schütz T, Bode JC, Bode C (2000) Increased intestinal permeability to mac-romolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alco-hol-induced liver disease. J Hepatol 32: 742-747.

73. Mathurin P, Deng QG, Keshavarzian A, Choudhary S, Holmes EW (2000) Exacerbation of alcoholic liver injury by enteral endotoxin in rats. Hepatology 32: 1008-1017.

74. Bode C, Kugler V, Bode JC (1987) Endotoxemia in patients with alcoholic and non-alcoholic cirrhosis and in subjects with no evidence of chronic liver disease following acute alcohol excess. J Hepa-tol 4: 8-14.

75. Rao R (2009) Endotoxemia and gut barrier dysfunction in alcoholic liver disease. Hepatology 50: 638-644.

76. Ferrier L, Bérard F, Debrauwer L, Chabo C, Langella P (2006) Impairment of the intestinal barrier by ethanol involves enteric microflora and mast cell activation in rodents. Am J Pathol 168: 1148-1154.

77. Mutlu EA, Gillevet PM, Rangwala H, Sikaroodi M, Naqvi A (2012) Colonic microbiome is altered in alcoholism. Am J Physiol Gastrointest Liver Phys-iol 302: G966-G978.

78. Yang AM, Inamine T, Hochrath K, Chen P, Wang L, et al. (2017) Intestinal fungi contribute to development of alcoholic liver disease. J Clin Invest 127: 2829-2841.

79. Lang S, Duan Y, Liu J, Torralba MG, Kuelbs C (2020) Intestinal Fungal Dysbiosis and Systemic Immune Response to Fungi in Patients With Alcoholic Hepatitis. Hepatology 71: 522-538.

80. Akkız H (2021) The Gut Microbiome and Hepatocellular Carcinoma. J Gastrointest Cancer 52: 1314-1319.

81. Hartmann P, Lang S, Zeng S, Duan Y, Zhang X, et al. (2021) Dynamic Changes of the Fungal Microbiome in Alcohol Use Disorder. Front Physiol 12: 699253.

82. Sun S, Wang K, Sun L, Cheng B, Qiao S (2020) Therapeutic manipulation of gut microbiota by polysaccharides of Wolfiporia cocos reveals the contribution of the gut fungi - induced PGE2 to alcoholic hepatic steatosis. Gut Microbes 12: 1830693.

83. Couch RD, Dailey A, Zaidi F, Navarro K, Forsyth CB (2019) Alcohol induced alterations to the human fecal VOC metabolome.

84. Fischer P, Grigoras C, Bugariu A, Nicoara-Farcau O, Stefanescu H, et al. (2019) Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig. Liver Dis 51: 1685-1691.

85. Mohammad S, Thiemermann C (2021) Role of metabolic endotoxemia in systemic inflammation and potential interventions. Front Immunol 11: 594150.

86. McDaniel K, Huang L, Sato K, Wu N, Annable T, et al. (2017) The let-7/Lin28 axis regulates activation of hepatic stellate cells in al-coholic liver injury. J Biol Chem 292: 11336-11347.

87. Nanji AA, Khettry U, Sadrzadeh SM, Yamanaka T (1993) Severity of liver injury in experimental alcoholic liver disease. Correlation with plasma endotoxin, prostaglandin E2, leukotriene B4, and thromboxane B2. Am J Pathol 142: 367-373.

88. Hritz I, Mandrekar P, Velayudham A, Catalano D, Dolganiuc A (2008) The critical role of toll-like receptor (TLR) 4 in alcoholic liver disease is independent of the common TLR adapter MyD88. Hepatology 48: 1224-1231.

89. Francis H, McDaniel K, Han Y, Liu X, Kennedy L, et al. (2014) Regulation of the extrinsic apoptotic pathway by microRNA-21 in alcoholic liver in-jury. J Biol Chem 289: 27526-27539.

90. Keshavarzian A, Fields JZ, Vaeth J, Holmes EW (1994) The differing effects of acute and chronic alcohol on gastric and intestinal permeability. Am J Gastroenterol 89: 2205-2211.

91. Wu N, McDaniel K, Zhou T, Ramos-Lorenzo S, Wu C, et al. (2018) Knockout of microRNA-21 attenuates alcoholic hepatitis through the VHL/NF-κB signaling pathway in hepatic stellate cells. Am J Physiol. Gastrointest Liver Physiol 315: G385-G398.

92. Ponziani FR, Bhoori S, Castelli C, Putignani L, Rivoltini L, et al. (2019) Hepatocellular Carcinoma Is Associated with Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease. Hepatology 69: 107-120.

93. Elamin EE, Masclee AA, Dekker J, Jonkers DM (2013) Ethanol metabolism and its effects on the intestinal epithelial barrier. Nutr Rev 71: 483-499.

94. Grewal RK, Mahmood A (2010) The effects of ethanol administration on brush border membrane glycolipids in rat intestine. Alcohol 44: 515-522.

95. Yan AW, Fouts DE, Brandl J, Stärkel P, Torralba M (2011) Enteric dysbiosis associated with a mouse model of alcoholic liver dis-ease. Hepatology 53: 96-105.

96. Bull-Otterson L, Feng W, Kirpich I, Wang Y, Qin X (2013) Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the Effect of Lactobacillus rhamnoses GG treatment. PLoS ONE 8: 4-13.

97. Engen PA, Green SJ, Voigt RM, Forsyth CB, Keshavarzian A (2015) The Gastrointestinal micro-biome: Alcohol effects on the composition of intestinal microbiota. Alcohol Res 37: 223-236.

98. Chu H, Duan Y, Lang S, Jiang L, Wang Y, et al. (2020) The Candida albicans exotoxin candidalysin promotes alcohol-associated liver disease. J Hepatol 72: 391-400.

99. Llopis M, Cassard AM, Wrzosek L, Boschat L, Bruneau A (2016) Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. Gut 65: 830-839.



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100. Chen P, Torralba M, Tan J, Embree M, Zengler K, et al. (2015) Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. Gastroenterology 148: 203-214.

101. Kirpich IA, Petrosino J, Ajami N, Feng W, Wang Y, et al. (2016) Saturated and Unsaturated Dietary Fats Differentially Modulate Ethanol-Induced Changes in Gut Microbiome and Metabolome in a Mouse Model of Alcoholic Liver Disease. Am J Pathol 18: 765-776.

102. Hylemon PB, Zhou H, Pandak WM, Ren S, Gil G (2009) Bile acids as regulatory molecules. J Lipid Res 50: 1509-1520.

103. Boursier J, Diehl AM (2016) Nonalcoholic Fatty Liver Disease and the Gut Microbiome. Clin Liver Dis 20: 263-275.

104. Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F (2014) Intestinal permeability, gut bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Nat Acad Sci 111: E4485-E4493.

105. Kirpich IA, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, et al. (2008) Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: A pilot study. Alcohol 42: 675-682.

106. Stadlbauer V, Mookerjee RP, Hodges S, Wright GAK, Davies NA (2008) Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. J Hepatol 48: 945-951.

107. Slevin E, Baiocchi L, Wu N, Ekser B, Sato K (2020) Kupffer Cells: Inflammation pathways and cell- cell interactions in Alcohol-associated liver disease. Am J Pathol 190: 2185-2193.

108. Tsochatzis EA, Bosch J (2014) Liver cirrhosis. Lancet 383: 1749-1761.

109. Tapper EB, Parikh ND (2018) Mortality due to cirrhosis and liver cancer in the United States. Observational study. BMJ 362: k2817.

110. OShea RS, Dasarathy S, McCullough AJ (2010) Alcoholic liver disease. Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Hepatology 51: 307-328.

111. Menon KV, Gores GJ, Shah VH (2001) Pathogenesis, diagnosis, and treatment of alcoholic liver disease. Mayo Clin Proc 76: 1021-1029.

112. (2012) EASL clinical practical guidelines: Management of alcoholic liver disease. J Hepatol 57: 399-420.

113. Schwarzinger M, Baillot S, Yazdanpanah Y (2017) Alcohol use disorders and the burden of chronic hepatitis C in France. A nationwide retrospective cohort study. J Hepatol 67: 454-461.

114. Roerecke M, Nanau R, Rehm J, Neuman M (2016) Ethnicity matters: A systematic review and me-ta-analysis of the non-linear relationship between alcohol consumption and prevalence and incidence of hepatic steatosis. EBioMedicine 8: 317-330.

115. Neuman MG, Maor Y, Nanau RM, Melzer E, Mell H (2015) Alcoholic liver disease: Role of cytokines. Biomolecules 5: 2023-2034.

116. Neuman MG (2019) Biomarkers of drug-induced liver toxicity. Ther Drug Monit 41(2): 227-234

117. Teschke R, Eickhoff A, Brown AC, Neuman MG, Schulze J (2020) Diagnostic Biomarkers in Liver Injury by Drugs, Herbs, and Alcohol: Tricky Dilemma after EMA Correctly and Officially Retracted Letter of Support. Int J Mol Sci 21: 212.

118. Zimmerman HJ (1968) The spectrum of hepatotoxicity. Perspect Biol Med 12: 135-161.

119. Zimmerman HJ (1999) Hepatotoxicity: The adverse effects of drug and other chemicals on the liver 8: 320-346.

120. Navarro VJ, Senior JR (2006) Drug-related hepatotoxicity. N Engl J Med 354: 731-739.

121. Neuman MG (2008) Veno-occlusive disease of the liver induced by traditional herbal medicine. Roum. J Rev Hepatol 4: 7-9.

122. Lee WM, Senior JR (2005) Recognizing drug-induced liver injury: current problems, possible solutions. Toxicol Pathol 33: 155-164.

123. Malnick S, Maor Y, Melzer E, Ziv-Sokolowskaia NN, Neuman MG (2017) Severe hepatocytotoxicity linked to denosumab. Eur Rev Med Pharmacol Sci.

124. Neuman MG, Ishay JS, Waron M, Zimmerman HJ, Eshchar J (1991) Hepatotoxicity induced by the Oriental hornet (Vespa orientalis) venom sac extract. Pharmacol Toxicol 69: 1-36.

125. Neuman MG, Cohen L, Opris M, Nanau RM, Hyunjin J (2015) Hepatotoxicity of Pyrrolizidine Alkaloids. J Pharm Pharm Sci a Publ Can Soc Pharm Sci Soc Can des Sci Pharm 18: 825-843.

126. Neuman MG, Cohen LB, Steenkamp V (2017) Pyrrolizidine alkaloids enhance alcohol-induced hepatocytotoxicity in vitro in normal human hepatocytes. Eur Rev Med Pharmacol Sci 21: 53-68.

127. Pessayre D, FeldmanG, Haouzi D, Fau A, Moreau A (1999) Hepatocyte Apoptosis triggered bynatural substances (cytokines, other endogenous molecules and foreign toxins). in Handbook of experimental pharmacology: Apoptosis modulation by drugs.

128. Neuman MG (1999) Inducers of cytochrome P450 2E1 enhance methotrexate-induced hepatocytoxicity. Clin Biochem 32: 519-536.

129. Aithal GP, Rawlins MD, Day CP (2000) Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. J Hepatol 33: 949-952.

130. Andrade RJ, Robles M, Lucena MI (2009) Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf 8: 709-714.

131. Daly AK (2010) Drug-induced liver injury: past, present and future. Pharmacogenomics 11: 607-611.

132. Hollenberg PF (2002) Characteristics and common properties of inhibitors, inducers, and activators of CYP enzymes. Drug Metab Rev 34: 17-35.

133. Assis DN, Navarro VJ (2009) Human drug hepatotoxicity: a contemporary clinical perspective. Expert Opin Drug Metab Toxicol 5: 463-473.

134. Danan G, Benichou C (1993) Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 46: 1323-1330.

135. De Bus L (2010) Severe drug-induced liver injury associated with prolonged use of linezolid. J Med Toxicol Off J Am Coll Med Toxicol 6: 322-326.

136. Fontana RJ (2010) Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 52: 730-742.

137. Zimmerman HJ, Chomet B, Kulesh MH, McWhorther CA (1961) Hepatic hemosiderin deposits. Incidence in 558 biopsies from patients with and without intrinsic hepatic disease. Arch Intern Med 107: 494-503.



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138. Malnick S, Maor Y, Neuman MG (2022) Green Tea Consumption Is Increasing but There Are Significant Hepatic Side Effects. GastroHep.

139. Bonkovsky HL (2006) Hepatotoxicity associated with supplements containing Chinese green tea (Camellia sinensis). Annals of internal medicine 144: 68-71.

140. Javaid A, Bonkovsky HL (2006) Hepatotoxicity due to extracts of Chinese green tea (Camellia sinensis): a growing concern. Journal of hepatology 45: 334-336.

141. Jimenez-Saenz M, Martinez-Sanchez MD (2006) Acute hepatitis associated with the use of green tea infusions. Journal of hepatology 44: 616-617.

142. Molinari M (2006) Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transplant. Off. Publ. Am. Assoc. Study Liver Dis Int Liver Transplant Soc 12: 1892-1895.

143. Stevens T, Qadri A, Zein NN (2005) Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. Annals of internal medicine 142: 477-478.

144. Elinav E (2007) Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity. J Hepatol 47: 514-520.

145. Schoepfer AM (2007) Herbal does not mean innocuous: Ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife?? products. J Hepatol 47: 521-526.

146. Stickel F, Shouval D (2015) Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol 89: 851-865.

147. Neuman MG (2001) Apoptosis in diseases of the liver. Crit Rev Clin Lab Sci 38: 109-166.

148. Bedossa P (2010) Harmony in liver fibrosis.. Journal of hepatology 52: 313-314.

149. Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A (2013) Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. World J Hepatol 5: 353-363.

150. Nunes V, Mendez-Sanchez N (2020) Impact of Herbal and Dietary Supplements Causing Drug-Induced Liver Injury in Latin America. Clin. liver Dis 16: 83-86.


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