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# Pathogenesis and risk factors of liver cirrhosis, A systematic review

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ABSTRACT

The typical final stage of many chronic liver diseases, cirrhosis is also a major source of morbidity and death. Nonalcoholic fatty liver disease, also known as (NAFLD) is now the most widespread cause of chronic liver disease globally and may soon rank among the top causes of cirrhosis as a result of the rising obesity and metabolic syndrome epidemics. It is crucial to raise awareness and comprehension of NAFLD liver. NAFLD cirrhosis has not yet been the subject of a published systematic review. Thus, this paper discusses contemporary research on the epidemiological studies, risk factors, clinical manifestation, diagnosis, therapy, and prediction of NAFLD cirrhosis.

## INTRODUCTION

In general, and in the case of cirrhosis of the liver in particular, alcohol is a significant risk factor for both conditions.[1] In fact, in a society without alcohol, the incidence of morbidity and death associated with liver cirrhosis would decrease by nearly half.[2] In the US, liver cirrhosis-related deaths have increased.[3] also Europe[4] in women more so than in males. Although alcohol use is somewhat to blame, liver disease is now understood to be a complex disease process.[5] Different classifications of liver disorders, which are thought to be largely caused by alcohol, have been created as a result of how important alcohol is to the aetiology of liver disease. The World Classification of Disorders [WCD[6] recognises a number of alcoholic liver diseases (ICD-10, K70), which are occasionally seen as phases[7] that progress from relatively minor and reversible stages like alcoholic liver damage (K70.3) and an alcoholic hepatic dysfunction (K70.4) to more severe or irreversible stages like alcoholic hepatic fibrosis and disease of the liver (K70.2). It has been determined that drinking alcohol—especially excessive drinking over time—plays a significant role in the development and aetiology of many illnesses.[8] Alcohol usage, however, may contribute to the development of all forms of cirrhosis since liver disorders are complex.[9] Because daily alcohol consumption, even one drink, may influence the prevalence of liver cirrhosis,[10] Therefore, while assessing the consequences of alcohol consumption, it is essential to consider both alcoholic or not alcoholic liver cirrhosis. The majority of epidemiological studies to date has focused on the relationship between alcohol use and the occurrence or death of liver cirrhosis.[11] It adhered to the early research of Lelbach along with others in terms of epidemiology.[12] who proposed a strong correlation between the amount of alcohol consumed and liver cirrhosis on the basis of research in individuals with alcohol use disorders.[13] The most prevalent clinical endpoint for liver damage caused by a range of chronic liver disorders is liver cirrhosis.[14] Geographically, the causes of cirrhosis vary; in western nations, the most frequent causes are drinking, chronic hepatitis C illness, and nonalcoholic fatty liver disease (NAFLD).[15] while in the Asia-Pacific area chronic hepatitis B virus infection is the main

factor contributing to liver cirrhosis[16] Besides genetic conditions like hemochromatosis and Wilson's disease, there are several other factors that contribute to liver cirrhosis.[17] main sclerosing cholangitis and primary cirrhosis of the biliary tract[18] and autoimmune liver disease[19] Some instances are cryptogenic or idiopathic. NAFLD has recently emerged as one of the main causes of chronic liver illness in Western nations like the United States, where it has a prevalence of up to 30% in people of all ages.[20] NAFLD has thus received a lot of attention as a significant contributor to chronic liver disorders.[21] Despite the fact that liver cirrhosis has a variety of underlying causes, certain pathological traits are present in all cases, including the degeneration and death of hepatocytes, the replacement of the liver parenchyma through fibrotic cells and regenerating nodules, and the loss of liver function.[22] In the progression in all chronic liver illnesses to cirrhosis, fibrosis serves as a crucial pathological mechanism.[23]

KEY,WORDS – Pathogenesis,risk factors, liver cirrhosis, nonalcoholic fatty liver disease

## SIGN AND SYMPTOMS

- Weakness
- Loss of appetite
- Weight loss
- Pain around the liver area
- Fatigue, nausea

## PATHOGENESIS OF LIVER CIRRHOSIS

## DIFFERENT TYPE OF CELL INVOLVE IN THE PATHOGENESIS OF LIVER CIRRHOSIS

### HSCs

HSCs, sometimes referred to as fat-storing tissues, Ito tissues, lipocytes, perisinusoidal tissues, or vitamin A-rich cells, are cells that are primarily used for storing vitamin A along with other retinoids. The Disse region of a healthy liver is where they are located.[24] After multiple traumatic events and/or contact with inflammatory cytokines including tumour necrosis factor, interleukin (IL)-1, platelet-derived growth factors, and growth factor transforming, HSCs move from being in a dormant to active state. The process of liver fibrosis development and the formation of collagen both depend on the activation of HSC.[25] HSC activation results in proliferation, migration, contraction after transforming into myofibroblasts, and significant collagen and extracellular matrix production, all of which contribute to fibrosis in the liver.[26]

### LSECs

LSECs make up the endothelium, also known as the endothelial lining, which is the term used to describe the sinusoidal wall. The distinguishing structural element of LSECs is the fenestrae present on the surface of the endothelium.[27] The endothelial fenestrae, with a diameter of 150-175 nm, act as a dynamic filter to enable the exchange of fluids, substances, and particles between sinus liquid or the parenchymal tissues.[28] LSECs with strong endocytosis potential.The quantity of fenestrae may be reduced or defenestrated as a result of persistent alcohol abuse.[29] Cirrhosis liver is often found to have a subendothelial barrier and defenestration of capillary the epithelial[30] It is widely known that retinol deficiency has the capacity to activate HSCs, transform them into skeletal muscle cells with enhanced ECM production, and ultimately cause perisinusoidal fibrosis and liver.[31] Hepatic endothelium defenestration and capillarization are hypothesised to be important factors in the onset of perisinusoidal fibrosis because they alter retinol metabolism. According to studies on humans as well as pets, LSECs have the capacity to produce cytokines such as IL-33, which can stimulate HSCs and promote fibrosis.[32] Defenestration and capillarization of the LSEC, two major factors to the hepatic dysfunction associated with liver cirrhosis, result in defective substrate transport..[33] Contrarily, differentiated LSECs can hasten regression and halt the progression of fibrosis by promoting the conversion of activated HSCs to quiescence through VEGF-induced NO production.[34]

### KCs

KCs are specialist macrophages located in the lining membranes of the liver's sinusoids and are a part of the reticuloendothelial system. They are also known as Browicz-Kupffer cells and stellate phagocytes.[35] The pathogenesis of several liver illnesses has been shown through research using animal models to show that KCs play a part.[36] KCs may be stimulated by a variety of hazardous conditions, such as viral infection, alcohol usage, a diet high in fat, or iron buildup. Activated KCs kill hepatocytes during viral infection because they function as cells that present antigens and secrete toxic soluble mediators. According to several studies, KC-mediated hepatic inflammation exacerbates liver damage and fibrosis.[37] KCs act as a mediator in the activation of HSCs and fibrosis formation. Studies carried out in vitro have shown that KC-conditioned medium can enhance PDGF receptor expression in cultured rat HSCs, encouraging activation with higher matrix formation or cell growth.[38] TGF-1 produced from KC stimulates the proliferation and collagen production of rat HSCs fed a diet high in

lipids and alcohol.[39] Alcohol can increase the quantity of the blood's powerful KCs activator lipopolysaccharide, which is generated by gram-negative bacteria.[40] Hereditary hemochromatosis, which promotes HSC activation and the synthesis of collagen in the the liver tissues, may be brought on by iron overload in KCs, which causes ICAM-1 expression on hepatocytes.[41] Gelatinase produced by active KCs breaks down collagen type IV, changing the phenotype of HSCs.[42] By consuming apoptotic bodies and creating death ligands that include TNF- and Fas ligand, KCs promote inflammation and fibrogenesis.[43] KCs induced by -glucans also cause the release of thromboxane A2, which increases stress at the portal in both natural and fibrotic livers.[44]

## RISK FACTORS

## HISTOLOGICAL SUBTYPES

The main risk factor for NAFLD turning into cirrhosis is the histological subtype. The two primary histological types of NAFLD are nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL).[45] In NASH as opposed to NAFL, cirrhosis development occurs more frequently. Only 1% of individuals with NAFL develop cirrhosis, compared to 11% of those with NASH, according to a longitudinal research with a typical duration on 15.6 years of follow-up.[46] Furthermore, cirrhosis developed more quickly from NASH. Patients with NASH had a yearly fibrosis progression rate of 0.14 stages vs 0.07 stages for those with NAFL.[47]

## METABOLIC FACTORS

Numerous studies have revealed that the biggest metabolic factor influencing the development of NAFLD into cirrhosis is diabetes.[48] A based on populations matched prospective cohort analysis was carried out by Porepa et al. using administrative health records from Ontario (Canada) (1994–2006). Matches were made between 2,059,708 people without diabetes and 438,069 people who had just received a diabetes diagnosis. After a median monitoring of 6.4 a while, 1,119 (3.71%) diabetic patients and 1,896 (1.34%) those without diabetes both developed cirrhosis.[49] According to Nderitu et al.'s analysis of 509,436 members of the Swedish Apolipoprotein Death Risk (AMORIS) cohort among 1985 and 1996, 2,775 individuals experienced the development of cirrhosis. Diabetes and high blood sugar levels were also independently linked to cirrhosis. The development of NAFLD cirrhosis was also influenced by other metabolic variables, such as hyperlipidemia, obesity, and antihypertensive.

## GENETIC POLYMORPHISMS

For high-prevalence disorders including obesity, T2DM, heart disease, and cirrhosis, genetic variables are thought to account for 30% to 50% of the risk.[50] Our knowledge of the genetic factors that contribute to the development of NAFLD has considerably benefited from GWAS (genome-wide association studies) and candidate gene research. A number of the genetic variations linked to the development of NAFLD have been found through GWAS investigations. The not synonymous single-nucleotide in PNPLA3 (rs738409 c.444 C4G, p.Ile148Met), which contains the patatin-like phospholipase domain, has been verified across several patient cohorts and is one of the loci that was discovered. Notably, this SNP's presence shows a strong correlation with the onset of NAFLD cirrhosis.[51]

## AGE

In a UK retrospective cohort research, 351 people living with biopsy-proven Liver were separated into three age groups: older (60), middle-aged (50–60), and younger (50). people with cirrhosis were noticeably older than people without cirrhosis. Risk factors such as high blood pressure, obesity, diabetes, and high cholesterol levels were substantially more prevalent in older adults.[52] 796 individuals who had biopsy-proven NAFLD were divided into two groups in a cross-sectional multinational research from the United States: old patients (65) and nonelderly patients (18–65). In comparison to non-elderly NAFLD patients, elderly individuals showed considerably greater rates of advanced fibrosis. Additionally, risk factors including diabetes and insulin resistance were not more prevalent in the senior individuals.[53] However, the length of the illness versus the age directly may be responsible for the connection between age or cirrhosis in NAFLD.[54]

## OTHER FACTORS

Gender, race, and a family history on metabolic disease are additional risk factors for cirrhosis advancement in NAFLD patients. There are conflicting findings about the role of gender in the progression of cirrhosis in NAFLD patients.[55] Gender was not a standalone risk factor for fibrosis advancement, according to an ongoing investigation of NAFLD patients. Men's gender may be an independent risk variable for fibrosis, according to a few studies. According to certain research, women are more likely than men to have advanced fibrosis. Despite the fact that Black people had a reduced chance of developing NASH than White people did, there was no discernible difference in the number of individuals in the United States who had severe fibrosis.[56] According to a recent study, 68.8% (779/1133) of people having NASH cirrhosis had a family history of metabolism characteristics, and those individuals are more likely to be diagnosed with the disease at a

young age of under 45. According to those findings, cirrhosis risk factors such as a family record with metabolic disorders and an early age at NAFLD cirrhosis diagnosis include metabolic features.

## CONCLUSION

The chance of developing liver cirrhosis increases tenfold in the presence of alcohol. Even with moderate alcohol use, women may still be more at risk than males. More advanced study is required to clarify the function of additional risk variables, including as genetic susceptibility, weight status, risk factors for metabolic disease, and drinking habits throughout the course of a person's lifetime. High amounts of drinking should be prevented, and those who do should get measures to lower their intake.

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