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Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: Emerging Burden

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Liver is the largest solid organ in the body that performs over 100 functions. It removes the toxins and waste products from the blood stream, maintains healthy blood sugar levels, regulates blood clotting; synthesize essential body proteins and other vital functions. The liver has a big impact on lipid metabolism. Depending on the species, the liver is essentially the hub of fatty acid synthesis and lipid circulation through lipoprotein formation. The buildup of lipid droplets inside the hepatocytes ultimately results in hepatic steatosis, which can be brought on by a variety of dysfunctions, including alterations in -oxidation, very low density lipoprotein secretion, and pathways involved in the generation of fatty acids. Increased blood levels of non-esterified fatty acids could possibly be a major factor in the development of fatty liver disease. In many developed countries, non-alcoholic fatty liver disease (NAFLD) is quickly becoming the main cause of chronic liver disease and hepatocellular carcinoma (HCC) which poses significant difficulties for the detection, diagnosis, and treatment of HCC. In this review, an overview is presented of the most recent research on the epidemiology, etiology of liver cirrhosis, risk factors, and prognosis of NAFLD-HCC patients. There is a significant need to emphasize the need for NAFLD-associated HCC prevention and offer some insight into the unresolved barriers and difficulties surrounding patient surveillance strategies.

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1. INTRODUCTION

The liver is a major organ in the human body that is responsible for complex functions. Not only is the liver the largest organ in the body, but it also converts potentially harmful substances in the body, making it one of the most important organs in human metabolism [1]. “Lipid metabolism is significantly influenced by the liver. It is essentially the center of fatty acid production and lipid circulation through lipoprotein synthesis, depending on the species” [2]. “Hepatic steatosis, which may arise as a result of many dysfunctions including changes in -oxidation, very low density lipoprotein secretion, and pathways involved in the production of fatty acids, is eventually caused by the accumulation of lipid droplets inside the hepatocytes. An elevated level of non-esterified fatty acids in the blood may also play a significant role in the aetiology of fatty liver disease. Increased blood levels of non-esterified fatty acids could possibly be a major factor in the development of fatty liver disease” [3]. “Unrelated to alcohol fatty liver disease, non-alcoholic fatty liver disease (NAFLD) is characterized by hepatocyte triglyceride accumulation that exceeds 5% of the weight of the liver. Two conditions on the NAFLD spectrum are simple steatosis and nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma” [4]. NASH is characterized histological by hepatocellular ballooning, lobular inflammation, and macrovascular steatosis [5]. Nonalcoholic steatohepatitis (NASH) is characterized by excessively high levels of fat in the hepatocytes found in up to 40% of individuals with NAFLD as well as symptoms of portal and lobular inflammation and hepatocyte destruction. Some people may develop a condition called progressive fibrosis, which can result in cirrhosis. Comorbidities of NAFLD and NASH are both life-threatening that may be compounded with cardiovascular disease and hepatocellular carcinoma [6], including other medical conditions. The Fig. 1 below illustrates the complexities involved with NAFLD and NASH.

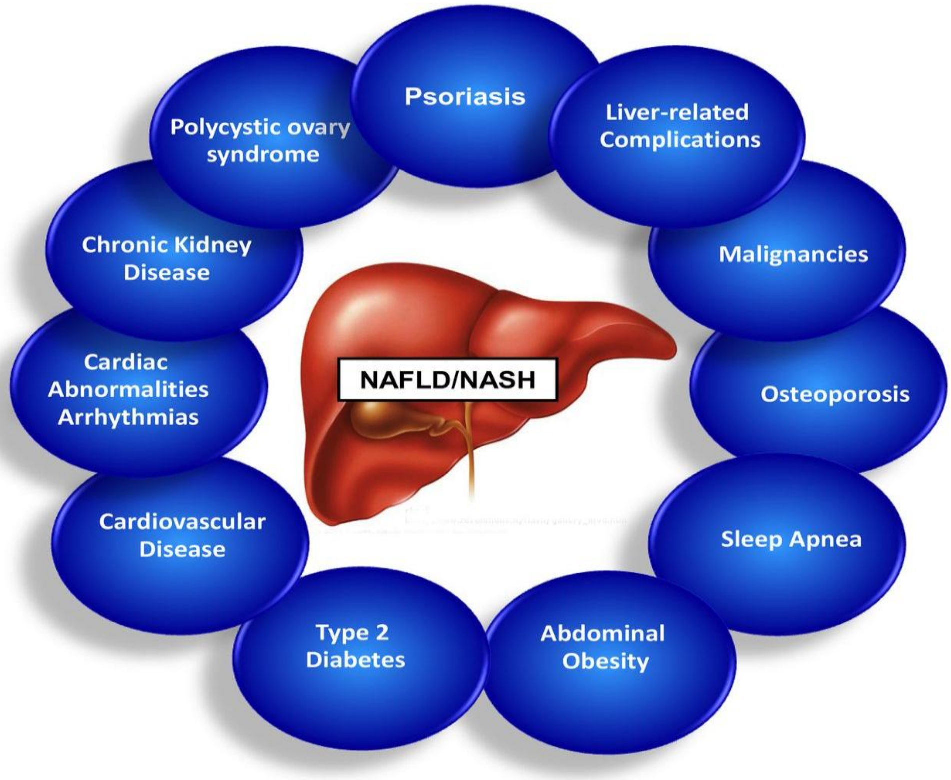

Fig. 1. Risk factors of NAFLD [7]

1.1 Epidemiology and Etiology of NAFLD

NAFLD, one of the most prevalent liver illnesses as diagnosed by imaging, affects 20 to 33% of people [8]. NASH is found in 3–16% of potential liver donors in Europe and the United States of America (USA) [9]. NASHis also a common cause of cirrhosis, and by 2020, it is projected that it will be the primary reason for liver transplantation in the USA [5,10]. Although the adolescent obesity epidemic has increased the prevalence of pediatric NAFLD, NAFLD is frequently found in persons in their fourth through sixth decades of life. The prevalence of NAFLD varies by racial group and it affects 45% of Hispanics, 33% of Whites, and 24% of African American people [11]. The prevalence of NAFLD varies by racial group and it affects 45% of Hispanics, 33% of Whites, and 24% of African American people. In White people, NAFLD affects men more often than women, however in African American and Hispanic adults, it affects both men and women equally [12].

"Non-alcoholic fatty liver disease has grown to be a serious issue because of its prevalence, difficulties in diagnosis, complex pathogenesis, and lack of approved treatments. Over the next ten years, non-alcoholic fatty liver disease may surpass hepatitis C as the leading cause of chronic liver disease in both adults and children. Non-alcoholic fatty liver disease may also eventually replace hepatitis C as the primary indication for liver transplantation" [13]. The main risk factors for NAFLD include obesity, type II diabetes, and the metabolic syndrome, which encompasses dyslipidemia and hypertension [14]. The Fig. 2 below delineates the causes of NAFLD.

1.2 Signs and Symptoms of NAFLD

There are signs and symptoms associated with NAFLD. Some of patients may complain of fatigue, right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, and lipomatosis, although the majority of NAFLD patients may not experience symptoms. End-stage liver disease can manifest in a sizable portion of cirrhosis patients. NASH can be asymptomatic in 48–100% of cases, and it is frequently found after examinations by doctors for other conditions. Even though this cohort rarely exhibits clinical stigmata of chronic liver failure, a research found that 25% of patients had splenomegaly at the time of diagnosis. A diagnosis of NASH or NAFLD is frequently made as a result of abnormal liver function tests like amino transferases (ALT and AST) or as a result of the unintentional discovery of hepatic steatosis on radiologic abdominal findings. Physical examinations may reveal hepatomegaly, which is a result of fatty infiltration in the liver [15-20].

Primary	Obesity, glucose intolerance, type 2 diabetes, hypertriglyceridemia, low HDL (high-density lipoprotein) cholesterol, hypertension
Nutritional	Protein-calorie malnutrition, rapid weight loss, gastrointestinal bypass surgery, total parenteral nutrition
Drugs	Glucocorticoids, estrogens, tamoxifen, amiodarone, methotrexate, diltiazem, zidovudine, valproate, aspirin, tetracycline, cocaine
Metabolic	Lipodystrophy, hypopituitarism, dysbetalipoproteinemia, Weber–Christian disease
Toxins	*Amanita phalloides* mushroom, phosphorus poisoning, petrochemicals, *Bacillus cereus* toxin
Infections	Human immunodeficiency virus, hepatitis C, small bowel diverticulosis with bacterial overgrowth

Fig. 2. Causes of NAFLD

1.3 Pathophysiology of NAFLD

The onset and progression of non-alcoholic fatty liver disease (NAFLD) are influenced by both environmental and genetic variables. Patients with NAFLD who have first-degree relatives are more at risk than the general public. cAMP-responsive element-binding protein H (CREBH) or the silent information regulatory sirtuin 1 (SIRT1) regulates gene expression by maintaining the chromatin structure and amino-terminal ends of histones. According to genetic research, SIRT1 activation may contribute to the emergence of NAFLD. Through aberrant DNA methylation, NAFLD is set off, which leads to cancer [21-23].

In 1998, a two-hit pathogenesis model was discovered by Day and James [24]. The initial blow is brought on by insulin resistance, which causes triglyceride droplets to build up in the cytoplasm of hepatocytes, resulting in steatosis. Due to decreased elimination and increased transport of free fatty acids and triglycerides to the liver, insulin resistance results in buildup. Additionally, an abundance of carbs stimulates the liver's production of de novo fatty acids. Hepatocellular damage caused by the second strike and the emergence of NASH are complex. The liver is more susceptible to damage when there are too many fatty acids present. The injury is thought to be caused by peroxisomal fatty acid oxidation, reactive oxygen species (ROS) production from the mitochondrial respiratory chain, cytochrome P450 fatty acid metabolism, and hepatic metabolism of gut-derived alcohol. As adipose tissue releases inflammatory mediators including leptin, tumornecrosis factor (TNF)-alpha, and interleukin (IL)-6, damaging hepatocytes andobesity also contribute to the second hit. Hepatocytes experience cytoskeletal aggregation, ballooning, apoptosis, and necrosis [25-28]. In the second hit, insulin resistance is also included. NASH develops and progresses as a result of sinusoidal collagen deposition brought on by the activation of hepatic stellate cells and portal fibrosis caused by ductular proliferation. These alterations have been associated with insulin resistance, which is now thought to be the driving factor behind the development of progressive fibrosis and NASH from steatosis [29-34].

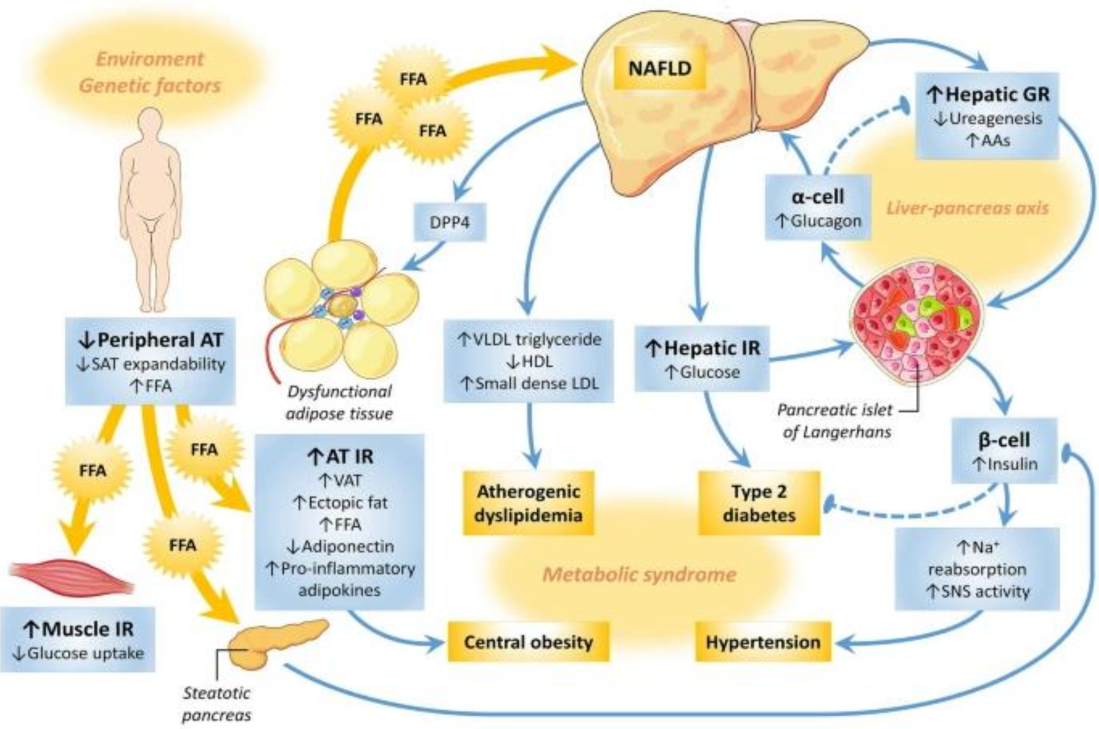

Fig. 3. Pathophysiology of NAFLD [35]

2. ASSOCIATION OF NAFLD WITH HCC

The most typical primary liver cancer, hepatocellular carcinoma (HCC), typically develops in the setting of liver cirrhosis. The third highest rate of cancer-related mortality occurs with liver cancer, which is the fifth most prevalent cancer overall [36]. While overall cancer mortality is typically declining, liver cancer is killing people the fastest. Between 2000 and 2016, the death rate from liver cancer increased by 43% (10.5 to 15.0 per 100,000) for males and 40% (4.5 to 6.3 per 100,000) for women in the United States of America [37]. Although surveillance and treatments have improved, the total 5-year survival rate is only about 15% [38]. HCC has become a substantial public health concern as a result of the increasing burden of disease incidence and mortality [39-44].

Nonalcoholic fatty liver disease, often known as NAFLD, is an acute disorder that can progress to hepatic cirrhosis and, ultimately, liver cancer. NAFLD must show signs of hepatic steatosis and not have any additional explanations for the liver's fat accumulation (e.g., alcohol consumption). The majority of the time, metabolic comorbidities like obesity, diabetes, and dyslipidemia are linked to NAFLD. Simple steatosis or steatohepatitis (NASH), in which steatosis is accompanied by liver inflammation and either or both liver fibrosis and steatosis, are both parts of NAFLD. Due to the metabolic growth of etiological variables (such as diabetes and obesity), the incidence of NAFLD is increasing globally in both Western and Asian nations [45-47].

2.1 Epidemiology of HCC-NAFLD

According to a number of meta-analyses and cohort studies with sizable sample sizes, 25–30% of the world's population has NAFLD, with the Middle East and South America having the highest frequency and Africa having the lowest [48]. NAFLD prevalence has been rising yearly, which has increased the frequency of adverse NAFLD-related outcomes like HCC and mortality. In fact, it is predicted that by 2030, the prevalence of NASH, an advanced type of NAFLD, will have doubled globally [46,49-51].

In several developed nations, NAFLD is already the HCC cause that is spreading the fastest. In 2016, there were 1.8 cases of HCC per 1,000 person-years among NAFLD patients, and there were 5.3 cases of overall mortality per 1,000 person-years [52]. Depending on whether they also have NASH or cirrhosis, NAFLD patients have varying rates of NAFLD-related HCC. The risk of developing HCC is greater in those with extensive fibrosis or cirrhosis. For instance, the incidence rate of HCC in patients with NAFLD at a stage before cirrhosis was 0.03 per 100 person-years and 3.78 per 100 person-years in patients with cirrhosis [46,50,53]. Twenty to fifty percent of HCC instances come from the latter group of patients. Additionally, there are regional differences in the prevalence of NAFLD-related HCC in individuals with non-cirrhotic NAFLD. In patients from the USA and Europe, the incidence of HCC varies from 0.1 to 1.3 per 1,000 person-years. However, research from Asia revealed that the annual incidence of HCC ranged from 0.04% to 0.6%. Interesting to note, research conducted in Asia, the USA, and Europe discovered a greater risk of HCC among patients with non-cirrhotic NAFLD who had NASH and fibrosis [54]. The annual incidence of HCC varies among patients with cirrhotic NAFLD from 0.7% to 2.6% [55]. Additionally, these Asian findings are consistent with those from the United States of America and Europe [50].

2.2 Pathophysiology of NAFLD to HCC

The pathophysiology of NAFLD to HCC causes significant medical complexities. 20-50% of HCC instances come from many groups of patients. Although obesity and type 2 diabetes mellitus (T2DM) are known to be pre-carcinogenic diseases, they frequently combine with NAFLD, and therefore the severity of the disease neoplastic potential may be underestimated. Among all malignancies associated with obesity, HCC (in men) is thought to carry the highest cancer risk (fourfold) [24]. HCC, which is most frequently linked to severe fibrosis or cirrhosis but can also occur in earlier pre-cirrhotic stages of the disease, can manifest in NAFLD patients. The precise mechanism in these situations is not fully understood, but it is likely connected to the pathophysiology of the underlying illness rather than the fibrotic process alone. Direct signaling effects of lipids or lipid intermediates (in particular FAS ligands) may contribute to these pathogenetic features by activating pro inflammatory pathways such as nuclear factors kappa B (NF-κB), activator protein 1 (AP-1), JNK and STAT3, and down regulating PTEN. Overall, cirrhosis caused by NASH appears to have a lower relative HCC risk and death rate than cirrhosis caused by viruses or alcohol. However, the most frequent reason for HCC-related liver transplantation is in individuals with NASH [57-59].

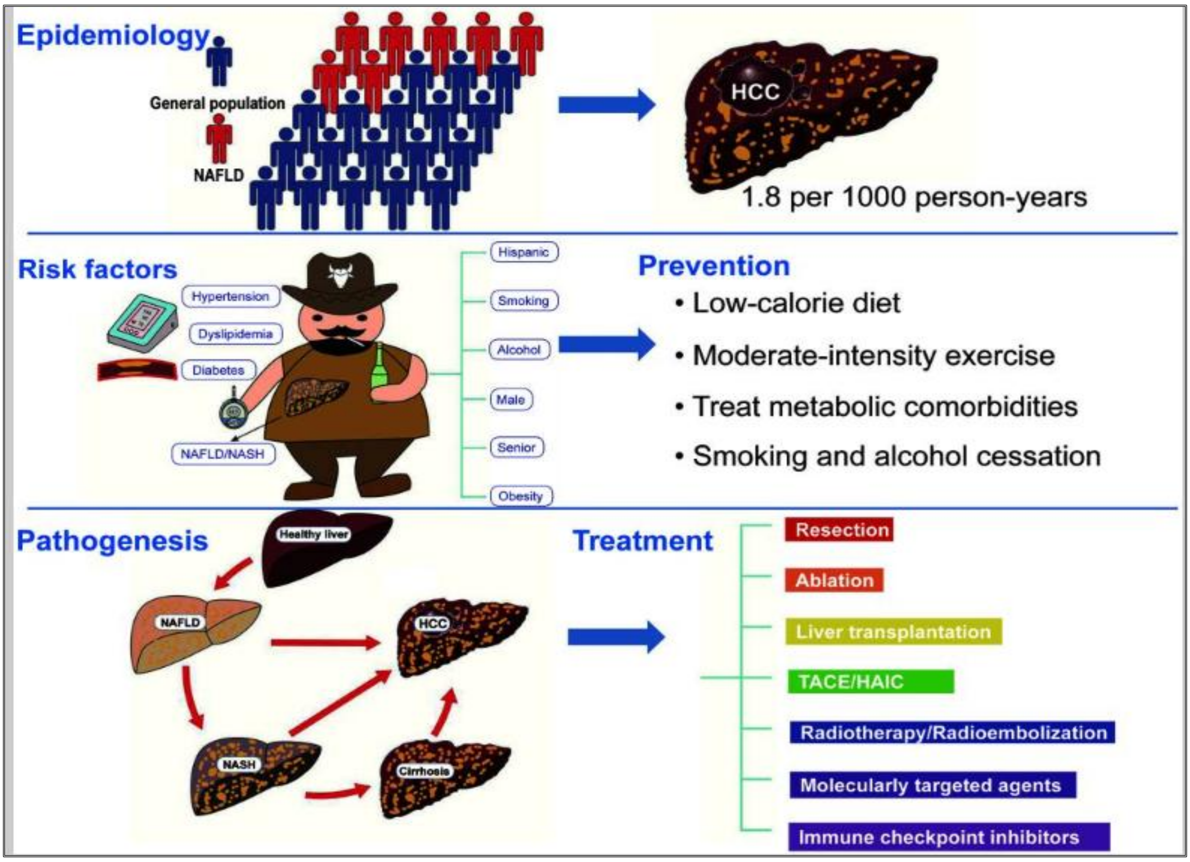

Fig. 4. Epidemiology, risk factors and pathogenesis of HCC-NAFLD [56]

Thoroughly documented information has been presented about how HCC develops in a cirrhotic liver. These include cyclic compensatory regeneration and proliferation, which primarily promote tumor formation, together with chronic damage with hepatocellular degradation. NAFLD patients frequently also have insulin resistance (IR), which along with hepatic steatosis and low-grade chronic inflammation fosters an environment that is favorable for tumor formation. A hormonal imbalance caused by IR and hyper insulinemia can result in inflammation, oxidative stress, lipotoxicity, and overstimulation of the IGF-1 axis. As a result of leptin activating PI-3K/Akt signaling and pro-inflammatory cytokines including TNF and IL-6 enhancing JNK/NF-B and JAK/STAT3 pathways, genes involved in cell proliferation, migration, and survival are expressed. On the other hand, several tumor suppressor factors, like PTEN and SOCS3, are down regulated and ineffective in regulating pro-tumorigenic signaling. In aggressive HCC samples, lipid metabolites of Stearoyl CoA desaturase activity are linked to abnormal palmitate signaling. Additionally, cholesterol-related mitochondrial abnormalities increase membrane organization, which boosts chemotherapy resistance [31,60-65].

“A higher risk of HCC is also attributed to dietary variables and genetic factors such the PNPLA3 rs738409 variation. Diets high in fat and fructose can boost the liver's de novo lipogenesis and lipoperoxidation as well as the release of cytokines that promote inflammation. Changes in Gut microbiota brought on by obesity encourage the translocation of bacterial products (like endotoxins, Lipopolysaccharides (LPS), and deoxycholic acid), which reach the liver and favor the secretory phenotype associated with senescence in HSCs, which in turn secrete various inflammatory and tumor-promoting substances in the liver” [66-69].

3. AVAILABLE TREATMENTS

“Different treatment modalities are currently advised based on tumor stage but not aetiology in various nations and regions' recommendations for the diagnosis and treatment of HCC. When compared to HCC caused by Hepatitis B virus (HBV), Hepatitis Cvirus (HCV), or alcohol, NAFLD-related HCC is different in terms of pathogenic causes, epidemiology, histological traits, stages of tumor development, and consequences. Patients with NAFLD-related HCC, for instance, commonly exhibit traits associated with the metabolic syndrome such as advanced age, obesity, type 2 diabetes, or cardiovascular issues. These elements could influence a patient's prognosis and therapy selection. Numerous studies have investigated how patients with other kinds of HCC exacerbates after various treatments in light of the rising incidence of NAFLD-related HCC. These studies, which are summarized below, explored outcomes following liver transplantation, transarterial chemoembolization (TACE), radiation, targeted medications, immunotherapy, and/or postoperative adjuvant therapy" [71-74].

4. NOVAL THERAPIES; A NEW HOPE

"For the treatment of HCC, a number of cutting-edge medicines are being researched, with an emphasis on immunotherapy methods. Immune checkpoint inhibitors' early trials showed promising safety and tolerance as well as modest signs of efficacy. Although all HCC etiologies have reported responses, which may be encouraging for patients with NAFLD-HCC, early indications from Phase III studies point to failure as single agent therapies in "all comer" trials and stratification biomarkers as well as combination approaches are likely to be required. Additional conventional therapy, such as locoregional therapies, pharmacological therapies (sorafenib, lenvatinib), or possibly other immune therapies, may be used in combination methods" [75-77].

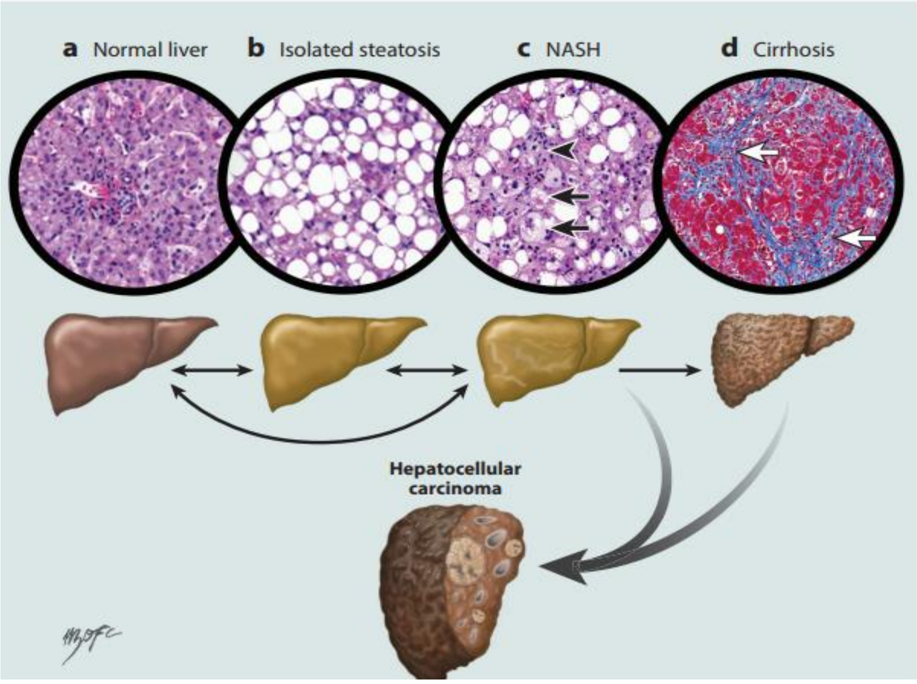

Fig. 5. From NAFLD to HCC [70]

Table 1. Currentt treatments For HCC-NAFLD

Available treatments	Treatment outcomes
Liver resection	Better disease-free survival
Radiofrequency ablation	Similar overall survival
Transplantation of Liver	Similar overall survival
Transarterial chemoembolization	Similar overall survival
Radiotherapy	Similar overall survival
Radioembolization with yttrium-90	Similar overall survival
Tyrosine kinase inhibitors	SOS
Sorafenib	Similar overall survival (SOS)
Lenvatinib	Better progression-free survival
Adjuvant therapy	SOS

Tumor vaccines, adoptive cell transfer using chimeric antigen T cells, natural killer cells, tumor infiltrating lymphocytes, and cytokine-induced killer cells are additional immunological strategies that are now undergoing pre-clinical studies [76]. In light of these changes, there is hope that within the next five to ten years, patients with NAFLD-HCC will have access to medicinal therapies that are more successful or easier to tolerate.

5. CONCLUSION

NAFLD is now the main contributor to HCC and the most common cause of chronic liver disease globally. Compared to HCC from other etiologies, patients with NAFLD-HCC are typically older and have more comorbidities. The fact that NAFLD-HCC tends to appear at a late stage and that HCC can develop in the absence of cirrhosis as well as the subpar HCC surveillance program in NAFLD contribute to an overall poor prognosis. The utilization of curative procedures including liver resection, Orthotopic liver transplantation (OLT), and ablation is reduced due to the late stage of presentation, patient age, and comorbidities. Long-term survival following therapy is equivalent to that of patients without NAFLD, despite the fact that NAFLD patients undergoing these therapies are more likely to experience surgical problems and hence require careful preoperative screening and optimization. TACE and systemic treatments for NAFLD-HCC have not been thoroughly researched, however obesity may decrease their efficacy, and long-term metformin use may be linked to tumor sorafenib resistance. Additional research is required to fully assess this effect and determine whether this link holds true for other systemic treatments. Clinical guidelines now have a uniform approach for all causes of HCC, and NAFLD has historically only contributed a modest amount of supporting data to this algorithm. The requirement to revise clinical guidelines for this particular group will become clear as NAFLD-HCC prevalence rises globally. NAFLD-HCC prevention is a top priority which will entail taking public health efforts to lower metabolic risk factors, develop NAFLD screening tools, and evaluate people with established NAFLD for HCC even in the absence of cirrhosis.

6. FUTURE PERSPECTIVES

The global prevalence of metabolic syndrome has made NAFLD the primary cause of chronic liver disease and may soon make it the primary cause of HCC. NAFLD can directly progress to HCC without fibrosis or cirrhosis, and since patients are not routinely screened for NAFLD, HCC is frequently diagnosed at an advanced stage, leading to worse long-term survival. Clinical characteristics typical of metabolic syndrome, such as old age, obesity, type 2 diabetes, or cardiovascular complications may increase the risk of NAFLD-related HCC. Third, the presence of metabolic syndrome alongside HCC may restrict treatment options, such as by preventing liver transplantation or raising the risk of cardiovascular problems following surgery. Last but not least, despite the fact that numerous research have explored the metabolomics and lipidomics of NAFLD and NASH, precise molecular traits and diagnostic markers continue to be elusive [78].

The principles used in the diagnosis and treatment of HCC caused by NAFLD are also used for HCC derived from other etiologies. The key is primary prevention may beneficial for patients. Aspirin, statins, and medications like metformin have been recommended as major preventive measures. As medications to treat NAFLD become more accessible, secondary prevention will become more efficient. Tertiary prevention, such as NAFLD prevention, early detection, and prompt, customized treatment of NAFLD-related HCC, should also receive attention [79,80]. More patients will have the chance to get curative treatment, which improves long-term results, if NAFLD-related HCC can be identified early. The most crucial step in enhancing secondary prevention is screening for HCC, but only if patients at high risk are identified. Currently, individuals with cirrhosis serve as the focus group for monitoring in HCC guidelines. Only those with severe liver fibrosis or cirrhosis who have NAFLD or NASH are recommended for routine screening, according to NAFLD guidelines [72,81].

Individualized care is significant and a hallmark in patients’ treatment outcomes. The comorbidities of NAFLD patients should be taken into consideration because not all treatments are appropriate for all individuals with NAFLD-related HCC. For individuals with NAFLD-related HCC, specific biological indicators may help in determining the best course of treatment. Ineffective treatment expenditures and unneeded risk of problems could be decreased by using markers to identify which patients would benefit the most from Immune checkpoint inhibitor (ICI) therapy and molecularly tailored medications. For instance, a multicenter retrospective study discovered that in patients with advanced HCC, tumor response to ICI therapy and levels of C-reactive protein and alpha-fetoprotein accurately predicted overall survival [82]. The aforementioned issues and difficulties with NAFLD/NASH prevention, screening, diagnosis, and treatment offer a route for basic and clinical study. Future improvements in NAFLD-related HCC diagnosis, therapy, and management may result from ongoing clinical and scientific initiatives.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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