

The Latest Research Progress of Non-alcoholic Fatty Liver Disease-related Hepatocellular Carcinoma

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Abstract: *In modern society, with the improvement of people's living standards and the change of diet structure, non-alcoholic fatty liver disease (NAFLD) has become one of the most common chronic liver diseases worldwide. This disease seriously affects the quality of life of patients, and may also lead to serious complications such as cirrhosis and liver cancer, which brings heavy life burden to patients and their families. The incidence of hepatocellular carcinoma (HCC) in patients with NAFLD is significantly higher than that in patients without NAFLD. The risk of HCC in patients with NAFLD is closely related to the severity of fatty liver and the degree of liver fibrosis. The occurrence of HCC in patients with NAFLD is also related to metabolic diseases such as insulin resistance, obesity, and type 2 diabetes. This article focuses on the epidemiology, pathogenesis, early diagnosis and treatment of HCC.*

Keywords: Non-alcoholic fatty liver disease, Hepatocellular carcinoma, Means of treatment, Research progress.

1. Introduction

1.1 Research Background

NAFLD is a global health problem that affects about 25% of the global population [1]. With the increasing prevalence of NAFLD, the incidence of hepatocellular carcinoma (HCC) associated with NAFLD is also increasing. According to statistics, NAFLD has become one of the main causes of HCC. NAFLD is a kind of chronic liver disease, which mainly includes two types: simple fatty liver and steatohepatitis. In the simple fatty liver stage, the fat content in the liver is slightly increased, but the liver function is normal. However, as the disease progresses, hepatocyte damage and inflammation occur in the steatohepatitis stage. If the condition deteriorates further, it may develop into cirrhosis, which eventually leads to HCC. At present, the pathogenesis of NAFLD-associated hepatocellular carcinoma is not fully understood. However, studies have suggested that disorders of fat metabolism, oxidative stress and inflammatory response in fatty liver may be related to the occurrence and development of HCC. In addition, the presence of metabolic syndrome such as insulin resistance and diabetes mellitus in NAFLD patients may also increase the risk of HCC. In recent years, the research on NAFLD-associated hepatocellular carcinoma has been deepened. A growing number of studies have confirmed that effective interventions can reduce the risk of HCC in patients with NAFLD. For example, by controlling body weight, improving dietary habits, increasing exercise and other lifestyle changes, fat deposition and inflammation in the liver can be effectively reduced. In addition, for patients who already present with cirrhosis, medical treatment can be used to reduce the risk of HCC. NAFLD-associated hepatocellular carcinoma has become one of the main causes of hepatocellular carcinoma worldwide, and enough attention should be paid to the prevention and treatment of this disease. Future studies are needed to further elucidate the pathogenesis of NAFLD-associated hepatocellular carcinoma and provide more effective prevention and management strategies for

clinical practice.

1.2 Research Purpose

The aim of this thesis is to explore the latest research progress of NAFLD-associated hepatocellular carcinoma. First, we will review the molecular mechanisms underlying the transformation of NAFLD into HCC, including the role of lipid metabolism disorders, oxidative stress, chronic inflammation, and cell proliferation. Secondly, we will discuss the current non-invasive biomarkers and imaging methods for the diagnosis and evaluation of NAFLD-associated HCC, as well as the advantages and disadvantages of these methods. Next, we will introduce the current treatment strategies for NAFLD-associated HCC, including medical therapy, interventional therapy, and surgical treatment, and discuss the indications, efficacy, and safety of these treatment methods. To help doctors better formulate treatment plans and evaluate the prognosis of patients. Through these discussions and studies, we hope to provide more accurate and effective strategies for the diagnosis, treatment and prognosis evaluation of NAFLD-associated hepatocellular carcinoma, thereby improving the prognosis and quality of life of patients.

2. Epidemiology of NAFLD-associated Hepatocellular Carcinoma

There are differences in the prevalence and regional distribution of NAFLD. The prevalence of NAFLD is high in developed countries such as Europe and the United States, especially in people with obesity and diabetes. In China, with the development of economy and the improvement of living standards, the prevalence of NAFLD is also showing an upward trend. According to relevant studies, the prevalence of NAFLD is about 25% globally and 27% in Asia [1]. Although only 0.04% of NAFLD patients will convert to HCC, the incidence of HCC will significantly increase after the progression to non-alcoholic steatohepatitis (NASH). HCC

incidence is rising in recent years [2], NAFLD has become an important factors lead to the pathogenesis of HCC [3], a retrospective study found that 244 of 1562 patients with HCC patients for NAFLD correlation between HCC, visible with the high incidence of HCC incidence will further increase of NAFLD.

3. Pathogenesis of NAFLD-associated Hepatocellular Carcinoma

Insulin resistance and metabolic disorders play a crucial role in the pathogenesis of NAFLD-associated hepatocellular carcinoma. Insulin resistance can lead to hyperinsulinemia and hyperglycemia, which promote liver fat deposition and lipid peroxidation. Lipid peroxidation products such as free radicals and lipid peroxides can damage the membrane and mitochondria of liver cells, leading to hepatocyte injury and inflammation. Insulin resistance can also lead to metabolic disorders, including impaired glucose tolerance, impaired insulin secretion, dyslipidemia, and lipid peroxidation. These metabolic disorders can further aggravate liver fat deposition and lipid peroxidation, and promote liver inflammation and fibrosis. Liver inflammation and fibrosis can promote the proliferation and transformation of liver cells, thereby increasing the risk of NAFLD-related hepatocellular carcinoma [4].

Oxidative stress refers to the situation in which the amount of reactive oxygen species produced by the body exceeds the detoxification ability of antioxidants. It usually occurs when the body's oxidation and antioxidant systems are out of balance, and it is a pathological state that tends to oxidation. As the center of oxidative metabolism, the liver is the main target of oxidative stress-induced body damage, mainly through the stress pathway of hepatocytes, leading to liver inflammation and fibrosis [5]. Oxidative stress is one of the important pathological process, development of NAFLD in NAFLD and NASH play an important role in the process of progress, antioxidants may become important targets [6] for the treatment of NAFLD.

The role of gut microbiota in the pathogenesis of NAFLD-associated hepatocellular carcinoma cannot be ignored. Dysbiosis of gut microbiota can affect liver lipid metabolism and inflammatory response, thereby increasing the risk of NAFLD-associated hepatocellular carcinoma. The intestinal microecology is composed of intestinal bacteria themselves and their common metabolites with the body, which can participate in the regulation of the body's metabolic homeostasis and the composition of the immune defense system, such as food digestion, host immunity, the formation of intestinal barrier and the prevention of pathogen invasion [7]. The gut-liver axis refers to the bidirectional relationship between the gut and its microbiota and the liver, which is formed by the integration of signals generated by dietary, genetic, and environmental factors. This interplay is established by the portal vein, which transports gut-derived products directly to the liver, as well as by hepatic feedback pathways for bile and antibody secretion into the gut. The disorder of intestinal bacteria can lead to the disorder of bile acid metabolism, which affects the absorption and utilization of fat and glucose and accelerates the progression of NAFLD [8]. Secondly, intestinal flora disorder can affect the ability of

the liver to clear very low density lipoprotein, and very low density lipoprotein mediated triglyceride secretion is an important factor in the development of NAFLD [9].

4. Early Diagnosis of NAFLD-associated Hepatocellular Carcinoma

NAFLD correlation in the early diagnosis of hepatocellular carcinoma (HCC) is the key to improve the patients survival rate and quality of life. Early diagnosis can not only provide timely intervention and treatment, but also reduce the difficulty and cost of treatment. Therefore, early diagnosis has important clinical significance in the treatment of NAFLD-associated hepatocellular carcinoma. Chinese guidelines for the diagnosis and treatment of primary liver cancer [10] suggest that serum alpha-fetoprotein screening for high-risk groups of liver cancer is helpful for early diagnosis and treatment of liver cancer, and high-risk groups should be screened at least once every six months. Ultrasonography is the most commonly used liver imaging method in clinical practice, which can dynamically observe tumor blood perfusion in real time and evaluate the therapeutic effect after operation. CT and MRI are still the primary imaging methods for the diagnosis of liver cancer. However, these examination methods have certain limitations. For example, imaging examination for liver cancer early detection has the certain difficulty, vulnerable to the influence of hepatic steatosis and inflammation. However, laboratory tests require a large number of samples and complex detection processes, and some tumor markers are not highly sensitive and specific. Therefore, we need to explore more sensitive, specific and accurate methods for early diagnosis. For example, molecular biology techniques can be used to detect gene mutations and expression differences in liver tumors to detect lesions at an earlier stage. In addition, the combination of biomarkers and imaging techniques can be used to improve the accuracy of early diagnosis.

5. Treatment Strategies for NAFLD-associated Hepatocellular Carcinoma

Still lack special treatment for NAFLD related HCC [11], compared with other causes of HCC patients, patients with NASH and is set to undergo surgery treatment of HCC patients often for the elderly, there are complications or complications, the progress of hepatic insufficiency is lighter, cancer is usually bigger. Due to the relatively low rate of liver cirrhosis in NAFLD, and the difficulty in detecting small focal changes in fatty liver by screening methods such as ultrasound scanning, some NAFLD-related HCC are missed and delayed in diagnosis. The time to diagnosis of cancer is prolonged, which subsequently delays the opportunity for patients to receive treatment [12].

For the treatment of hepatocellular carcinoma (HCC), NAFLD correlation important surgical radical surgery treatment [13]. There is no unified conclusion on whether NAFLD-related HCC can obtain better long-term benefits from hepatectomy. Some studies have shown that NAFLD-related HCC can obtain longer survival time after hepatectomy, and surgical treatment is a good choice for NAFLD-related HCC [14]. Related studies have shown that

NAFLD HCC after radical surgery, postoperative tumor recurrence rate is lower than hepatitis caused by HCC [15]. Liu L et al. reviewed 1325 patients with HCC who underwent hepatectomy from January 2014 to December 2018, and pointed out that patients with NAFLD-related HCC who underwent hepatectomy had better recurrence-free survival and overall survival compared with patients with HCC of other causes [16]. Because most of the patients with NAFLD-related HCC are elderly and have many comorbidities and complications, preoperative evaluation should be emphasized to achieve a better prognosis.

Liver transplantation is an important radical treatment for NAFLD-related HCC, especially for patients with small hepatocellular carcinoma who are not suitable for surgical resection and radiofrequency ablation [10]. Castello B et al., in a study in 2019, showed that the 3-year and 5-year survival rates of NAFLD patients after liver transplantation were not significantly different from the results of liver transplantation for other reasons [17]. Related HCC after liver transplantation in patients with NAFLD, in fact, the leading cause of death are cardiovascular diseases, sepsis and severe obesity, these risk factors suggest need to meet the conditions for the surgical treatment in patients with NAFLD thorough preoperative examination, Considering that 70% of perioperative cardiac complications are the cause of death in nearly half of NAFLD-related HCC patients after liver transplantation, preoperative coronary angiography is recommended [11]. Due to the numerous risk factors, whether patients with NAFLD-related HCC are suitable for surgical treatment has become a real challenge for medical teams, which inevitably requires interdisciplinary collaborative research.

As an important means to stay in HCC, radiofrequency ablation (RFA) is recommended for a single tumor with a diameter ≤ 5 cm, or 2-3 tumors with a maximum diameter ≤ 3 cm [10]. Local radiofrequency ablation has the advantage of lower liver function requirements compared with hepatectomy. A retrospective study [18] showed that radiofrequency ablation in the treatment of NAFLD-related HCC could achieve similar overall survival and disease-free survival compared with HCC caused by other causes.

According to the Chinese Guidelines for the diagnosis and treatment of primary liver Cancer [10], transcatheter arterial chemoembolization (TACE) is a common non-surgical treatment for HCC, which is mainly suitable for patients with poor liver function who cannot tolerate surgery, and some patients with advanced liver cancer [19]. A study showed that treatment with conventional NAFLD related HCC and non NAFLD HCC in complications and no difference between the total survival rate and survival is convenient, the related research is less, still can't prove the efficacy and safety of in the treatment of NAFLD associated with conventional HCC, still need more clinical research to confirm.

System is also known as systemic therapy, including molecular targeted therapy, immunosuppressive therapy, chemical therapy, Chinese medicine treatment, including basic diseases of liver cancer of antiviral treatment and symptomatic treatment and protecting liver support therapy, etc., due to the onset of the HCC secrecy, only thirty percent of patients have the opportunity to receive radical surgical

treatment, Systemic therapy plays an indispensable role in advanced HCC [10]. At present, there is no consensus on the therapeutic effect and application of systemic therapy for NAFLD-related HCC. A recent retrospective study [20] found that sorafenib could achieve similar survival outcomes in patients with NAFLD-related HCC as those with HCC caused by other causes. A multicenter retrospective study [21] suggested that the median survival time and overall survival rate of patients with NAFLD-related HCC treated with lenvatinib were higher than those of patients with HCC caused by viral and other causes. A randomized controlled study [22] showed that immunotherapy was effective in viral-associated HCC, but not in HCC caused by non-viral hepatitis. The retrospective study of lenvatinib monotherapy versus lenvatinib combined with immunotherapy in patients with advanced HCC also found that the overall survival and progression-free survival of the two groups were similar. But for NAFLD correlation between HCC, combined treatment group patients' overall survival and progression-free survival were significantly better than monotherapy [23], so patients with NAFLD may not be able to benefit immune therapy, but the related research is still less, still need to be more clinical research is needed.

6. Prevention of NAFLD-associated Hepatocellular Carcinoma

NAFLD is the result of the interaction of many factors. Therefore, the prevention of NAFLD requires intervention from many aspects. First of all, lifestyle should be improved, including reasonable diet, moderate exercise and weight control to avoid obesity. Secondly, excessive alcohol consumption should be avoided, as alcohol is one of the important factors leading to the development of NAFLD. In addition, blood glucose and lipid levels should be controlled, as insulin resistance and metabolic disorders are key factors in the pathogenesis of NAFLD. Finally, long-term use of medications that damage the liver should be avoided, as well as exposure to toxic chemicals.

Early detection and intervention is the key to the prevention of NAFLD correlation hepatocellular carcinoma (HCC), and it has been proved that proper physical exercise and weight loss can reduce the risk of HCC in patients with NAFLD [24], Kim G research [25] found that metformin treatment diabetes the HCC incidence can be reduced by about 7%. Similarly, the use of statins may have a suppressive effect on HCC development, especially in patients with diabetes or cirrhosis who are at high risk for HCC. Diet control and bariatric surgery can reduce the incidence of diabetes and reduce the degree of liver fibrosis, thereby reducing the incidence of HCC [26]. A retrospective study involving 2,272,642 patients found that drinking two cups of coffee per day was associated with a 35% reduction in the incidence of HCC, independent of the presence of alcohol, high body mass index, smoking, viral hepatitis [27].

7. Research Prospects of NAFLD-associated Hepatocellular Carcinoma

At present, the pathogenesis of NAFLD-associated hepatocellular carcinoma is not fully understood, and further

in-depth research is needed to reveal its exact occurrence and development process. For example, the relationship between intestinal microbiota and NAFLD-associated hepatocellular carcinoma should be further studied to understand how it promotes the occurrence and development of liver cancer by affecting liver metabolism and immune response. At present, the diagnosis of NAFLD-associated hepatocellular carcinoma mainly relies on imaging examination and liver biopsy, but these methods have certain limitations. Therefore, more accurate diagnostic methods, such as non-invasive detection of specific markers through blood or urine, need to be developed to improve the accuracy of diagnosis. Current treatment strategies for NAFLD-associated hepatocellular carcinoma include lifestyle intervention, drug therapy, liver transplantation, and surgical treatment. However, these methods have limited therapeutic effects and some side effects. Therefore, more effective treatment strategies, such as gene therapy and immunotherapy, need to be further studied to improve the therapeutic effect. Anyhow, NAFLD correlation research advances in the hepatocellular carcinoma is mainly focused on the mechanism of the new exploration, more accurate diagnosis method of research and development, the more effective treatment strategies of exploration and public health education and policy support, and so on. The development of these research directions will help to improve our understanding of NAFLD-associated hepatocellular carcinoma, provide more possibilities for prevention and treatment, and thus reduce the threat of NAFLD-associated hepatocellular carcinoma to human health.

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