

Clinical Features and Treatment Strategies of Hepatocellular Carcinoma Associated with Non-alcoholic Fatty Liver Disease

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Abstract. In recent years, non-alcoholic fatty liver disease (NAFLD) has become one of the chronic liver diseases with a high incidence rate in today's world. Its fast development is caused by the wide spread of related risk factors such as metabolism, obesity, type 2 diabetes, and metabolic syndrome, which is the main reason for its fast development. It is a very important topic among the topics in public health, and it is also an important topic that medicine of the modern world must explore. This rise coincides with the growing prevalence of metabolic cause of chronic liver disease across diverse populations. Alongside the rise in underlying diseases like obesity, diabetes, and metabolic syndrome, its prevalence has been rising quickly. Compared with HCC related to traditional viral hepatitis B/C and alcoholic liver disease, NAFLD-related HCC has different epidemiological characteristics and clinical backgrounds. It has insidious early symptoms and is extremely difficult to screen, leading to most patients being diagnosed at the middle or advanced stage and missing the best treatment opportunity. Currently, the main treatment methods for hepatocellular carcinoma (HCC) are still classical methods such as resection, transplant, immunotherapy, and so on. However, it has large deficiencies in clinical efficiency and safety. This article will, based on existing literature, state the clinical features, treatment strategies, future challenges and difficulties of NAFLD-HCC, and analyze its limitations and advantages, aiming to summarize and optimize its clinical features and treatment strategies.

Keywords: Non-alcoholic fatty liver disease; Hepatocellular Carcinoma; Clinical Features; Treatment.

1. Introduction

The incidence rate and mortality of hepatocellular carcinoma (HCC) has been on the rise worldwide, viral hepatics (B, C) and alcohol related disease are the two main causes. After big changes in antiviral medicines over these years, the number of liver cancers caused by viruses is getting smaller in some places. Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by liver lipidosis. The proportion of non-alcoholic fatty liver disease is constantly increasing worldwide, and this disease is getting more popular as the increase of obesity, type 2 diabetes, etc. This disease primarily affects individuals who do not consume alcohol or consume very little alcohol, and subsequently progresses to non-alcoholic steatohepatitis. Approximately 25% of adults suffer from this liver disease, and this proportion is even higher among obese and type 2 diabetes patients, reaching 55% to 70% [1]. It is gradually replacing viral hepatitis and alcoholic liver disease as the most common kind of chronic liver disease, and has become an important cause of hepatocellular carcinoma (HCC). Compared to liver cell cancer caused by traditional causes such as viral and alcoholic factors, Non-alcoholic fatty liver disease-related hepatocellular carcinoma (NAFLD-HCC) has its own unique clinical features and pathogenesis. such as less obvious clinical symptoms, patients usually lack a background of liver cirrhosis, and a higher proportion of metabolic diseases. This directly affects the effectiveness of early monitoring and treatment. Therefore, most NAFLD-HCC patients are diagnosed at an advanced stage. At the same time, many patients have metabolic syndrome or cardiovascular diseases, resulting in poor surgical tolerance and poor treatment outcomes. Therefore, the majority of patients with non-alcoholic fatty liver cancer are diagnosed at an advanced stage, and many of them usually have metabolic syndrome or cardiovascular diseases, which results in poor surgical tolerance and poor responses to systemic treatments. Additionally, studies have found that the response of NAFLD-HCC to immune

checkpoint inhibitors (ICIs) may be lower than that of viral HCC, possibly due to differences in the immune microenvironment caused by different etiologies. Therefore, it is crucial to propose individualized treatment options for NAFLD-HCC patients based on the characteristics of patients of NAFLD. Thus, this study focuses on the clinical features and treatment strategies of NAFLD-HCC, comprehensively analyzing the latest progress in clinical cases and treatment methods. The research methods mainly include comparing the clinical manifestations of HCC related to different causes, summarizing the characteristics of NAFLD-HCC and the current status of early monitoring, and combining various treatment methods such as surgery, local ablation, radiotherapy, targeted drugs, and immunotherapy to summarize their application and limitations in NAFLD-HCC patients, with the aim of providing references for clinical practice and indicating future research directions.

2. Clinical Features

The onset characteristics of NAFLD-HCC are different from those of traditional viral and alcoholic HCC. Patients with HCC related to viral hepatitis usually have significant liver cirrhosis, while NAFLD-related HCC is very limited in terms of monitoring and screening. Since not a large proportion of the population shows typical manifestations of liver cirrhosis, studies have shown that approximately 30%–50% of NAFLD-HCC patients do not have significant liver cirrhosis at the moment of diagnosis [2,3]. Therefore, they are not within the monitoring scope of high-risk groups for HCC, resulting in a low monitoring rate for NAFLD-HCC. This means that tumors can occur without obvious fibrosis progression. Compared with alcoholic liver cell carcinoma, patients with non-alcoholic liver cancer tend to be older, the condition is not significantly severe, and they lack typical early clinical manifestations, leading to tumors often being in the middle or At the time of diagnosis, it had already reached the advanced stage, which would result in the loss of the best treatment period and the optimal opportunity for early intervention [4]. Patients with non-alcoholic fatty liver disease (NAFLD) usually have metabolic syndrome, such as obesity, type 2 diabetes, and hypertension, which not only increase the probability of developing liver cancer but also affect the treatment tolerance, efficacy, and subsequent survival rate of the patients [5]. In contrast, patients with HCC related to viral hepatitis are more likely to be detected at an early stage because they have undergone long-term follow-up and standardized monitoring.

Hepatocellular carcinoma symptoms linked to NAFLD are not readily apparent in terms of clinical manifestations. Many patients do not show typical symptoms of liver diseases in the early stage but only develop obvious clinical symptoms such as jaundice, ascites, etc. after the disease progresses. Some patients may only have non-specific symptoms, such as fatigue, loss of appetite, weight loss or pain in the right upper abdomen, which makes early identification very difficult [6]. Moreover, studies have shown that patients with non-alcoholic fatty liver disease not only have a high risk of liver cancer but also have a significantly increased incidence of extra-hepatic tumors. Studies have shown that Non-alcoholic fatty liver disease is not just a source of illness, but many other systemic diseases such as tumor, formation, and the disease process itself is because this disease affects the metabolism of the whole body [7]. In summary, the clinical characteristics of hepatocellular carcinoma related to NAFLD are extremely concealed and non-specific, which makes early diagnosis extremely difficult. Treatment Strategies

At the moment, NAFLD-HCC is still treated using the same general strategies for HCC, such as systemic treatment, liver transplantation, local ablation, radiotherapy, and surgical resection. However, the patient population with NAFLD-HCC has unique clinical characteristics, and each patient's background of onset is different. For example, patients are often older, have comorbidities such as metabolic syndrome and cardiovascular diseases, and lack early symptoms. These factors make the clinical treatment options more complex [8].

3. Treatment Strategies

3.1. Surgical and Local Treatment

Surgical resection and liver transplantation are considered the most radical treatment methods for HCC. For patients with limited lesions, normal liver function, and acceptable physical conditions, surgical resection is definitely the preferred choice and the most effective method to prolong survival. Multiple research data show that the 5-year overall survival rate for NAFLD-HCC patients after radical resection can reach 55–70%, which is comparable to the postoperative survival rate of viral HCC [2,5]. NAFLD patients usually have obesity, diabetes, hypertension, and other metabolic diseases and cardiovascular diseases. These metabolic underlying diseases increase the incidence of complications during the perioperative period. Multiple studies have pointed out that compared with viral or alcoholic HCC, the perioperative complication rate of NAFLD-HCC patients will increase by approximately 1.5–2 times. However, through preoperative control and individualized specific management, the probability of complications can be effectively reduced and the recovery quality of patients after surgery can be improved [5, 9,10].

Patients with NAFLD-HCC can also benefit from liver transplantation. According to the data, the 5-year survival rate after liver transplantation surgery is 65% to 75%, which is similar to the survival rate of patients with viral hepatocellular carcinoma [4]. Although metabolic diseases may increase postoperative cardiovascular complications and the risk of rejection (20% and 22%), the effect of liver transplantation remains good through immunosuppressive regimens and metabolic management [2,4,11]. Summing it all up, it would rather be best to improve the long-term survival of the patient NAFLD- HCC that through Surgery or Local.

3.2. Local Ablation and Radiotherapy

As for the patients with early cancer and who cannot undergo surgery because of the physical condition, the application prospect of local ablation therapy is more obvious. In terms of the main techniques currently used in clinical applications, there are two primary methods: RFA and MWA. RFA generates heat through high-frequency current, causing the tumor tissue to undergo coagulative necrosis; while MWA utilizes higher temperatures and greater thermal effects to ablate larger lesion areas in a shorter period of time. This treatment method can directly destroy the tumor tissue through the thermal effect. Multiple studies have indicated that for single tumors with a diameter of ≤ 3 centimeters, RFA and surgical resection have similar 5-year local control rates in overall survival, approximately 68%, but for larger tumors, the risk of local recurrence is still relatively high [2,4]. Because many patients with NAFLD present with obesity and features of metabolic syndrome, achieving full ablation coverage of the tumor can be technically challenging, which may consequently raise the likelihood of local recurrence and post-procedural complications [9, 12].

Stereotactic body radiotherapy (SBRT) is a treatment option for patients who cannot undergo surgery or ablation therapy. SBRT can more precisely target the tumor lesion and reduce damage to the surrounding normal liver tissue. Studies have shown that SBRT has comparable local control rate and short-term survival rate to ablation therapy [3, 13]. However, due to the potential for occult liver dysfunction in patients with non-alcoholic fatty liver disease (NAFLD), radiation therapy requires close monitoring to reduce the risk of liver damage [14, 15]. The combined treatment of SBRT with radiofrequency ablation/microwave ablation can improve local control rate and survival rate, but the specific therapeutic effect of SBRT in NAFLD patients still needs further verification.

3.3. Systemic Therapy

Systemic therapy is currently the most commonly used treatment method for non-alcoholic fatty liver disease and hepatocellular carcinoma (NAFLD-HCC). For example, it has been demonstrated that multi-target tyrosine kinase inhibitors (TKIs), similar to the effects of lenvatinib and sorafenib, it markedly improves overall survival in advanced HCC patients.

Sorafenib is the earliest targeted drug to be approved. According to the research, in the SHARP study, the median survival period was 10.7 months [9]. Lenvatinib showed a median survival period of 13.6 months in the REFLECT study, which was slightly longer than that of sorafenib [16].

Immune checkpoint inhibitors (ICIs) are currently the main therapeutic strategy for hepatocellular carcinoma (HCC). Immune checkpoints such as nivolumab and atezolizumab have good safety and effect in clinical trials for PD - 1 / PD - L1 immune checkpoint inhibitors [16]. Regarding the overall survival rate in the IMbraves150 research, the survival rate of bevacizumab and atezolizumab combination therapy was 67.2%, which was much higher than the single drug (sorafenib) of 67.2% and 54.6%, respectively [17]. Nonetheless, patients with HCC associated with NAFLD have a distinct intrahepatic immune milieu, including decreased T-cell activity. This may have a negative impact on the efficacy of immunotherapy.

The combined systemic treatment strategy is gradually becoming the main trend in the future. For example, the combination of targeted therapy and immunotherapy (Lenvatinib + anti-PD-1 antibody) or immunotherapy combined with immunotherapy (such as anti-PD-1 + anti-CTLA-4) have shown better efficacy than individual treatments, improving tolerance and therapeutic effects while prolonging progression-free and overall survival. This means that future systemic treatment plans will not be limited to single-drug treatment, providing more options for the treatment of NAFLD- HCC patients and improving survival rates.

4. Prevention

The remodeling of lifestyle is an economically effective preventive measure. A large amount of evidence-based medical research indicates that through balanced diets such as the Mediterranean diet pattern and physical exercise, the long-term risk of HCC can be reduced at the source. At the same time, complete abstinence from alcohol is necessary, especially for those with liver fibrosis or metabolic abnormalities.

NAFLD often serves as the metabolic liver disease, and its management must go beyond the liver itself and adopt a multidisciplinary integrated co-morbidity management model. Effective control of type 2 diabetes, optimization of lipid abnormalities, and management of cardiovascular risks can not only improve the overall metabolic health of patients but also have a synergistic effect on preventing HCC. For instance, statin therapy in patients with NAFLD and hyperlipidemia has been shown to be safe and may additionally lower the risk of HCC through its pleiotropic effects [18].

5. Challenges and Difficulties

NAFLD-HCC currently faces multiple challenges. Firstly, most patients with NAFLD do not exhibit typical manifestations of liver cirrhosis, and early symptom screening and monitoring are often overlooked. Therefore, most patients are diagnosed only in the middle or late stages of the disease, missing the best opportunity for surgery or local treatment, which has a negative impact on the survival rate and treatment outcome of the patients [14].

Second, most patients with hepatocellular carcinoma and non-alcoholic fatty liver disease also have other metabolic conditions (e.g., obesity, type 2 diabetes, hypertension, and cardiovascular diseases), which makes treatment more complicated and risky. Moreover, the postoperative infection rate, delayed wound healing, and the incidence of cardiovascular events have significantly increased, resulting in a 20% to 30% increase in postoperative mortality [2]. Additionally, these underlying diseases also affect drug tolerance, thereby significantly reducing the efficacy of targeted therapy and immunotherapy.

Drug tolerance and toxic reactions are issues that need to be overcome in immunotherapy. Studies have found that in patients with NAFLD using sorafenib and lenvatinib, the incidence of adverse reactions such as fatigue, rash, and liver toxicity is approximately 10%–15% higher than that in viral HCC [9,19]. Moreover, some patients show low responsiveness to ICIs, which is related to the unique

immune microenvironment of NAFLD, such as activation of liver macrophages and inhibition of T cell function [9,12].

Finally, most current treatment strategies for NAFLD-HCC are still designed based on the treatment methods for viral or alcoholic HCC [20,21]. However, NAFLD-HCC presents unique molecular and immunological characteristics that distinguish it from other etiologies of HCC, which may account for the suboptimal response to conventional therapies. The suitability of efficacy and risks for NAFLD-HCC patients is questionable. Future research should actively conduct prospective clinical studies to clarify the real efficacy and drug resistance mechanisms of individualized treatment in NAFLD-HCC patients.

6. Conclusion

The primary cause of HCC has progressively shifted from viral hepatitis to NAFLD. Its unique clinical characteristics - including occurrence in the absence of liver cirrhosis, late diagnosis, and heavy burden of metabolic comorbidities - pose a comprehensive challenge to the current HCC prevention and treatment system.

Although existing HCC treatment methods (surgery, local ablation, systemic therapy, etc.) can be applied to NAFLD-related HCC, due to the presence of multiple underlying diseases, the treatment effect is limited; moreover, the response of NAFLD-related HCC to immune checkpoint inhibitors (ICIs) may be lower than that of viral HCC, suggesting that different etiologies may have unique immune microenvironment differences. These particularities all lead to challenges in diagnosis and treatment. Therefore, a multivariate model integrating genetic, clinical, biochemical, and imaging indicators should be developed to precisely identify those NAFLD patients without liver cirrhosis but with high HCC risk, so as to achieve early intervention and targeted screening. And gradually adopt individualized treatment to improve their treatment methods, providing a new direction for liver cancer treatment strategies. The development of NAFLD-HCC poses new challenges for liver cancer. Therefore, NAFLD-HCC remains a problem that needs research and solution in the medical field, from prevention, screening, diagnosis to treatment, to build a comprehensive, individualized, and precise prevention and treatment system.

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