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Progress in the Epidemiology and Clinical Diagnosis and Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths globally, and its epidemiological characteristics and risk factors are continuously evolving. This review systematically elaborates on the global disease burden of HCC, the main risk factors (including hepatitis B/C virus infection, non-alcoholic fatty liver disease, aflatoxin exposure, and unhealthy lifestyles), and the corresponding prevention strategies. The article provides a detailed analysis of the performance and limitations of key serological markers currently used for early diagnosis of HCC, such as alpha-fetoprotein, abnormal prothrombin, and alpha-fetoprotein variant L3. Furthermore, the review comprehensively summarizes the advancements in clinical treatment for HCC, ranging from radical approaches including surgical resection, liver transplantation, radiofrequency ablation to palliative therapies for patients with advanced disease such as transcatheter arterial chemoembolization, targeted therapy, immunotherapy, and further evaluates their efficacy, indications, and challenges. This article aims to provide a comprehensive reference for a deeper understanding of the current status of HCC prevention and control, improving early diagnostic rates, and optimizing clinical treatment strategies.

Keywords: Hepatocellular carcinoma; Epidemiology; Risk factors; Diagnostic biomarkers; Treatment

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1. Introduction

HCC is a major global public health challenge, and its epidemiological characteristics and risk factors continue to evolve. According to global cancer statistics in 2022, there are about 870,000 new cases of HCC, accounting for 80% of primary liver cancer and 760,000 deaths per year, ranking sixth in the incidence of malignant tumors and third in mortality [1]. Through in-depth analysis of its epidemiological characteristics, it is found that the disease shows significant cluster distribution characteristics among different geographical regions: East Asia, Southeast Asia and sub-Saharan Africa account for more than 75% of the global cases, of which Mongolia

has an age-standardized incidence rate (ASIRW) of 96.1/100,000, and China has become the country with the highest absolute burden of HCC with a global proportion of 42.5%. Epidemiological surveillance data show that the age-standardized incidence rate of high-income countries represented by the United States and Australia has continued to rise at an annual growth rate of 2.3–3.1% over the past decade, mainly due to the increasing burden of metabolic liver disease and changes in the epidemic trend of viral hepatitis [2]. Population characteristics analysis showed that HCC had significant gender and age preferences. The incidence rate in men is 2.6 times higher than that in women, and gender differences are particularly significant in East Asia, which may be related to male susceptibility to HBV infection, alcohol intake, and androgen receptor signaling pathway activation [3]. The age distribution has increased exponentially, with the incidence rate reaching 52.3/100,000 in people ≥ 85 years old, and patients over 40 years old accounting for 94.5% of all cases.

2. Main risk factors and prevention strategies for HCC

2.1. Prevention of hepatitis B virus infection and liver cancer

It is widely recognized that hepatitis B virus (HBV), a key causative agent in the global burden of liver disease, is closely linked to the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. But so far, the molecular mechanisms that cause cancer have not been fully and clearly explained. Epidemiological data show that about 296 million people worldwide are chronic carriers of HBV, of which about 10–25% of infected people eventually progress to HCC [4], but the carcinogenic mechanism of HBV has not been clearly studied. This persistent genomic perturbation can lead to mutations in cancer-related genes, such as the TERT promoter region, and lead to loss of function of key tumor suppressor genes such as TP53. In addition, viral proteins (such as HBx) can continuously activate oncogenesis-related signaling networks (such as the Wnt/β-catenin pathway) and promote the transformation of normal hepatocytes to malignant phenotypes in multiple dimensions by reprogramming the energy metabolism pattern of hepatocytes. On the other hand, the liver microenvironment induces chronic inflammation through HBV infection, interactions between viruses and innate immune cells, and changes in adaptive immune cells, which help the virus evade immune surveillance and promote the evolution of the disease from inflammation to tumor formation [5]. In recent years, with the increasing coverage of HBV vaccination and the widespread use of antiviral therapies, the global burden of HBV-related liver cancer has been reduced. In Taiwan region, where hepatitis B was once endemic, the incidence of liver cancer decreased by 80% after widespread hepatitis B vaccination [6]. Interferon and nucleoside analogues have also been shown to reduce the risk of liver cancer by 34% and 78%, respectively in the treatment of chronic hepatitis B [7].

2.2. Hepatitis C virus infection and prevention of liver cancer

Hepatitis C virus (HCV) infection is one of the main causes of HCC in developed countries. A large number of studies have shown that the C protein encoded by the core gene of HCV can promote cancer by inhibiting p53 function and activating the Wnt/β-catenin signaling pathway. In addition, HCV viral proteins contribute to the development of steatosis and insulin resistance, exacerbating inflammation and oxidative stress, which further induce carcinogenic effects [8]. A meta-analysis showed that HCV-infected individuals had a 17-fold higher risk of developing HCC than non-infected individuals, with approximately 90% of patients developing liver cancer before cirrhosis [9]. Notably, HBV/HCV co-infection significantly increases the risk of HCC, and its synergistic effects may be related to superimposed liver injury and immunosuppression. Compared with HBV,

HCV infection is curable, especially with the advent of direct-acting antiviral drugs, which have exceeded 95% viral clearance rate [10]. Achieving a sustained virologic response is considered a cure for hepatitis C. Therefore, antiviral therapy and achieving a sustained virologic response can significantly reduce the incidence of HCC in HCV patients.

2.3. Prevention of nonalcoholic fatty liver disease and liver cancer

With the global spread of metabolic syndrome, the disease burden of nonalcoholic fatty liver disease (NAFLD) has shown a significant growth trend, with a global prevalence of about 30% [11]. It is worth noting that among the new cases of liver cancer in developed countries in Europe and the United States such as the United States, France and the United Kingdom, the incidence rate of NAFLD-related HCC has jumped to the top of the list, which has become an important feature of the current epidemiological evolution of liver cancer. In a large retrospective cohort study in the United States of 296,707 patients with NAFLD and 296,707 matched populations, the annual incidence of HCC in patients with NAFLD was 0.02/1000 person-years, 3.2 times higher than the baseline level in the general population. Of particular concern, when NAFLD progresses to the cirrhotic stage, the annual risk of cancer in patients increases sharply to 10.6/1000 person-years, confirming that the cirrhosis stage is an important turning point in triggering malignant transformation [12]. Global disease trend projections show that the disease burden of NAFLD-associated HCC may increase exponentially with the continued spread of obesity-related metabolic disorders. Patients are more likely to have metabolic diseases including, diabetes, hypertension, where the risk of HCC is increased by 2.27 times in patients with NAFLD with diabetes, suggesting that patients with NAFLD with diabetes are the key detection population for liver cancer [13]. In terms of prevention, studies have confirmed that weight loss of ≥ 10% can help improve or eliminate liver fibrosis in patients with NAFLD, and liver fibrosis, especially advanced fibrosis, is a risk factor for the development of HCC in NAFLD, so weight loss is an important measure to prevent NAFLD-related HCC [14]. In terms of drugs, aspirin, metformin, and statins have been shown to have a preventive effect on liver cancer, but it is currently believed that these drugs can only be used in patients with NAFLD with corresponding indications, not all patients with NAFLD [15,16].

2.4. Aflatoxin exposure and prevention of liver cancer

Aflatoxins are highly toxic secondary metabolites produced by the metabolism of specific toxin-producing strains of Aspergillus fungi. Epidemiological investigations have shown that AFB1 has the highest detection rate and toxicity level among fungus-contaminated foods, especially in sub-Saharan Africa and Southeast Asia, where the contamination rate of this toxin in staple crops such as corn and peanuts in hot and humid climates is as high as 30–60%. Long-term dietary intake of AFB1 has been confirmed to be a key causative factor in the occurrence of HCC, and its synergistic oncogenic effect with HBV infection can increase the risk of liver cancer by 5–30 times [17]. Epidemiological survey data showed that AFB1 exposure increased the risk of liver cancer to about 6 times, while the risk of liver cancer in HBV infected patients increased to 11 times. When the two risk factors coexist, their synergistic effect can lead to a 73-fold surge in the risk of liver cancer [18]. It is worth noting that dietary modifications, such as replacing corn with rice as a staple food, have been shown to be associated with a decrease in the incidence of liver cancer. In AFB1-contaminated areas, the implementation of a strategy combining hepatitis B vaccination schedule with standardized antiviral therapy can effectively block the synergistic carcinogenic mechanism of AFB1 and HBV, thereby significantly reducing the risk of liver cancer.

2.5. Lifestyle and prevention of liver cancer

The latest epidemiological survey confirmed that lifestyle-related risk factors have become a key regulatory variable for the risk of HCC. The continuous accumulation of research data shows that behavioral characteristics such as smoking, alcohol consumption and high-fat diet patterns have a multi-dimensional impact on the oncogenic process of liver cancer through epigenetic regulation and metabolic homeostasis imbalance. A 2017 meta-analysis that included 22 cohort studies and 31 case-control studies involving 9,722 HCC cases and 1,718,302 participants found a 55% increased risk of smoking-related HCC [19]. In contrast, a 2023 meta-analysis that included 13 cohort studies and 8 case-control studies with a total of 5,980 HCC cases and 2,494,279 participants found that coffee consumption reduced the risk of HCC by 47% [20]. In addition, a 2024 meta-analysis evaluated 7 cohort studies and 6 case-control cases, revealing different effects of diet on HCC risk: high scores on the Healthy Eating Index were associated with a significant reduction in HCC risk (HR = 0.67, 95% CI: 0.54–0.85), adherence to the Stop Hypertension Dietary Approach (DASH) diet (HR = 0.77, 95% CI: 0.66–0.91) and Mediterranean diet (HR = 0.65, 95%) CI: 0.56–0.75) was associated with a reduced risk of HCC [21]. Therefore, adjusting the above lifestyle factors and establishing a multidisciplinary health management model may reduce the burden of HCC from the source.

3. Diagnostic markers of HCC

3.1. Alpha-fetoprotein

Early screening for liver cancer plays a decisive role in improving clinical outcomes for patients. Clinical data show that early cases with a tumor diameter of ≤ 2 cm can have a five-year survival rate of 70–90% after radical treatment. In contrast, the five-year survival rate for advanced patients is less than 20%. Early identification enables clinicians to implement radical interventions such as hepatectomy, transplantation, and radiofrequency ablation, significantly improving patients' survival benefits and quality of life. However, the reality is not optimistic, and the early detection rate of liver cancer in our country is less than 20%, which has become the main bottleneck restricting the overall prognosis of liver cancer. As the gold standard serological marker for the diagnosis of liver cancer, alpha-fetoprotein (AFP) has been widely verified for its clinical value. This glycoprotein is specifically secreted by fetal hepatocytes and yolk sacs during embryonic development, and is usually expressed at a low level in the serum of healthy adults, but is abnormally expressed in pathological processes such as hepatocellular carcinoma, hepatitis and cirrhosis. Based on its unique expression pattern, AFP has been established as a core indicator for HCC screening and diagnosis. Research data show that AFP has a screening sensitivity of 41–65% and a specificity of 80–94% for hepatocellular carcinoma in the cirrhotic population, confirming its high clinical differentiation efficacy [22]. In the early stages of hepatocellular carcinoma progression, the detection rate is as low as 1/3 [23]. The reason for AFP's limitation in practice is that 80% of small liver cancer cases do not show elevated serum AFP. On the other hand, false positives affecting specificity between hepatocellular carcinoma and other liver-related diseases, including cirrhosis and acute hepatitis, have been a challenge. Therefore, there is an urgent need to develop new liver cancer screening markers to improve the accuracy and effectiveness of early diagnosis.

3.2. Abnormal prothrombin

In order to improve the accuracy of liver cancer diagnosis, in recent years, some new serological markers have

been discovered and studied, among which abnormal prothrombin, the Protein Induced by Vitamin K Absence or Antagonist-II, PIVKA-II has attracted much attention. As a key molecular marker of abnormal vitamin K metabolism, PIVKA-II is produced by hypocarboxylation of the prothrombin precursor caused by hepatocyte carboxylase dysfunction. Clinical studies have confirmed that PIVKA-II is significantly elevated in the serum of patients with liver cancer, and its effectiveness as a tumor marker for HCC is outstanding, with excellent diagnostic specificity and sensitivity. The internationally recognized threshold for PIVKA-II to detect liver cancer is 40.0 mAU/mL, and when serum PIVKA-II ≥ 40.0 mAU/mL, it suggests that patients are at higher risk of developing primary liver cancer, chronic liver disease, and benign liver space-occupying lesions [24]. Compared with the traditional marker AFP, PIVKA-II shows unique clinical detection advantages: it still maintains stable expression characteristics in patients with liver decompensation, and the sensitivity to AFP-negative HCC cases is increased to 40–60%. This complementary diagnostic efficacy effectively compensates for the detection limitations of AFP and has been included in the HCC surveillance guidelines of the Japanese Society of Hepatology [25]. The serum metabolism cycle of this marker is about 40–72 hours, which allows it to dynamically reflect the response of tumor treatment and becomes an important auxiliary index for efficacy evaluation. The comparative study found that the specificity and sensitivity of AFP alone were 84.67% and 63.10%. The specificity and sensitivity of PIVKA-II alone were 86.00% and 81.55%, indicating that PIVKA-II had superior diagnostic efficacy. When the combined detection strategy of the two is adopted, the sensitivity can be increased to 81.95% while maintaining a high specificity of 89.33%, which significantly optimizes the early differential diagnosis of liver cancer compared to single marker detection [26].

3.3. Alpha-fetoprotein heteromer L3

Alpha-fetoprotein L3 isoform (AFP-L3), as an important glycosylation modification isoform of alpha-fetoprotein, is specifically expressed in hepatocellular carcinoma cells, and its high affinity binding to lentil lectin (LCA) makes it a specific diagnostic marker [27]. When the threshold was set ≥ 10%, it could identify microscopic liver cancer with a diameter of < 2 cm on average 4.0 ± 4.9 months before imaging development, with a sensitivity of 48% and a specificity of 81%. Notably, the sensitivity of AFP-L3% detection is significantly positively correlated with tumor burden, and its sensitivity can be increased to 90% in HCC patients with tumor diameter ≥ 5 cm [28]. In addition, the GALAD multiparameter model integrating age, gender, AFP, AFP-L3%, and DCP significantly improved the recognition ability of early-stage liver cancer, with a sensitivity of 84% and a specificity of 90.9%, which has significant advantages over single diagnostic marker detection [29].

4. Treatment-related progression of HCC

4.1. Surgical resection

As the preferred intervention for early HCC, radical resection is indicated to strictly meet the following criteria: single lesion diameter < 5 cm or multiple lesions (3 ≤) and maximum diameter ≤ 3cm; Liver function reserve needs to be maintained within the range of Child-Pugh grade A/B; The ECOG PS score of performance status was 0, and there was no evidence of large vessel invasion or distant metastasis. Evidence-based medical data show that patients with early HCC who meet the above criteria can achieve an overall survival rate of 50–70% at 5 years after surgery [30,31]. However, despite the significant efficacy of radical resection for early HCC, there are multiple limitations in practical application: First, surgery has very high requirements for the regenerative

reserve function of the patient's liver. Patients with significant portal hypertension or incomplete liver function in Child-Pugh class C have a 15.6% risk of perioperative liver decompensation; Secondly, the incidence of acute liver failure caused by postoperative portal hypertension exacerbation and insufficient residual liver volume was about 8.9–12.4%, which has become the main bottleneck limiting surgical safety. More noteworthy, the high recurrence rate after liver cancer surgery is still a major clinical problem, even in very early cases with a tumor diameter of ≤ 2 cm, the risk of tumor recurrence at 5 years after surgery is still as high as 70% [32].

4.2. Liver transplantation

As an important radical means of early-stage hepatocellular carcinoma, the application of liver transplantation treatment needs to strictly follow the Milan standard: if it is a single tumor, its diameter must be less than or equal to 5 cm; If there are multiple lesions, the number of lesions shall not exceed 3, and the diameter of the largest lesion shall not exceed 3 cm, and at the same time, there will be no invasion of large blood vessels and extrahepatic metastasis. According to the 2022 guideline data of the International Liver Transplantation Association (ILTS), the 5-year survival rate of HCC patients who strictly meet the Milan criteria after liver transplantation is 73.5%, the 10-year survival rate is maintained at 52.4%, and the 5-year tumor-free survival rate of patients after surgery reaches 85.2%, which reduces the risk of recurrence by 2.6 times compared with traditional liver resection, fully reflecting the unique advantages of liver transplantation in tumor biological control. A multicenter retrospective study of 2645 patients with HCC liver transplantation who met the Milan criteria showed that the survival rates at 1, 5, and 10 years after surgery were 89.3%, 71.3%, and 59.0%, respectively [33]. Although liver transplantation provides significant survival benefits for patients with early-stage HCC, its clinical application still faces multiple challenges. The primary limiting factor is the global shortage of donor livers, which severely constrains the accessibility of this therapy. Another key challenge is the need for lifelong immunosuppressive therapy to prevent graft rejection, which not only increases the financial burden on patients, but also leads to long-term immunosuppression, significantly increasing the risk of opportunistic infections including cytomegalovirus pneumonia and invasive fungal infections; and also the risk of metabolic syndrome. What is even more alarming is that immunosuppression may weaken the body's immune surveillance function, thereby increasing the risk of tumor recurrence.

4.3. Radiofrequency ablation

Radiofrequency ablation (RFA) is the most commonly used local ablation technique for HCC, and the indications for tumor ablation are mainly for patients with early-stage HCC with small, small tumors, and well-located tumors. As a minimally invasive interventional treatment technology for HCC, its clinical indication scope focuses on: the maximum diameter of a single lesion < 3 cm; A group of patients with multiple lesions (≤ 3) and a maximum diameter of ≤ 3 cm per lesion. In addition, tumor ablation can be used as an alternative treatment for patients with early-stage HCC who cannot tolerate surgical resection due to poor liver function or who refuse surgery. This is because tumor ablation is minimally invasive, has less impact on liver function, and can preserve liver tissue and function to the greatest extent while controlling the tumor locally. As an important local treatment for early-stage hepatocellular carcinoma, the efficacy of radiofrequency ablation has been clinically verified. A retrospective cohort study of 301 patients who met the Milan criteria confirmed that for single lesions with a maximum diameter of < 2 cm, the complete clearance rate of the lesion after RFA was more than 95%, and the 5-year overall survival rate of patients was 79.0%. For patients with tumors between 2 and 3 cm in diameter, the

complete ablation rate is approximately 85% and the 5-year survival rate is 70.9% [34]. Because the ablation area is difficult to completely cover the tumor tissue, it is easy to residue, resulting in an increased recurrence rate. When the tumor is located close to important structures such as large blood vessels, bile ducts, and gallbladder, it may damage these structures during the ablation process, causing serious complications.

4.4. Hepatic artery chemoembolization

Transcatheter Arterial Chemoembolization (TACE) is the standard interventional treatment for BCLC stage B HCC, and its molecular basis is based on the unique angiogenesis characteristics of liver cancer lesions: about 85% of the tumor's blood supply comes from the hepatic artery branch. A systematic retrospective analysis of 101 studies and a total of 10,108 TACE treatment cases revealed that the objective response rate of this therapy reached 52.5%, and the overall survival rates at 1 year, 2 years, 3 years, and 5 years after surgery were 70.3%, 51.8%, 40.4%, and 32.4%, respectively, with a median overall survival of 19.4 months [35]. The specific efficacy varies depending on individual patient differences, tumor characteristics, and other factors. However, TACE treatment also has some limitations. After receiving TACE treatment, the risk of tumor recurrence and metastasis is relatively high, and the mechanism of this phenomenon can be mainly attributed to two aspects: on the one hand, it is difficult to completely remove all malignant cells, and residual lesions may continue to proliferate; On the other hand, hypoxia in the tumor microenvironment after embolization triggers the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), which provides a pathological basis for tumor invasion and metastasis. In addition, TACE may cause abnormal liver function, inflammatory reactions in the biliary system such as cholecystitis, and post-embolization syndrome that manifested as systemic reactions such as fever and abdominal pain, with a complication rate of about 15–30%.

4.5. Targeted therapy

Molecular targeted therapy has become a core strategy for the systemic treatment of advanced HCC, which exerts anti-tumor effects by precisely blocking key biological processes such as tumor cell proliferation and neovascularization. Sorafenib is a representative drug among multi-target tyrosine kinase inhibitors, and the key principle of its function is to specifically inhibit important signaling pathways such as VEGFR and PDGFR. By hindering the regeneration of tumor blood vessels and delaying the proliferation of tumor cells, sorafenib produces a dual antitumor effect [36]. Based on this molecular targeting characteristic, the drug has become the first-line standard treatment for unresectable advanced HCC since its approval in 2007, and is strictly suitable for advanced cases with Child-Pugh grade A/B liver function, with portal vein cancer thrombus or extrahepatic metastasis. Notably, novel oral multi-target inhibitors such as lenvatinib, regorafenib, and cabozantinib that have been validated in phase III clinical trials to significantly prolong median survival in patients with advanced HCC [37].

4.6. Immunotherapy

Immune Checkpoint Inhibitors (ICI) therapy has brought a new model to the systemic treatment of advanced hepatocellular carcinoma. From a mechanistic point of view, PD-1/PD-L1 inhibitors can block the core pathway of tumor immune escape, restore the anti-tumor activity of cytotoxic T lymphocytes, and then trigger a durable immune response. ICIs have shown superior clinical benefits in prolonging overall survival compared to sorafenib. In particular, after the approval of the dual immunoblockade regimen, the 3-year survival rate of patients successfully exceeded 22%, and the survival benefit increased by 36% compared with monotherapy.

In addition, immune combined anti-angiogenic therapy has a synergistic effect by modulating the tumor microenvironment, and its progression-free survival is longer than that of atezolizumab alone [38,39]. However, immunotherapy still faces significant challenges. Although ICI therapy has improved survival in some patients, the overall response rate is still limited to 15–20%, which is closely related to biomarkers such as tumor mutational burden, PD-L1 expression level, and T cell infiltration. In addition, the incidence of immune-related adverse reactions such as thyroid dysfunction and colitis can reach 30–40%, which require close monitoring and management.

5. Treatment-related progression of HCC

HCC remains a significant global health challenge with a heavy disease burden, particularly in East Asia and Africa. Its epidemiology is undergoing a dynamic shift, characterized by the rising contribution of metabolic factors like NAFLD in Western countries, even as viral hepatitis remains a predominant cause in endemic regions. Primary prevention through vaccination (HBV), antiviral therapy (HBV/HCV), lifestyle modifications, and dietary interventions against aflatoxin is the cornerstone for reducing the long-term risk of HCC.

For early detection, moving beyond the traditional reliance on AFP alone is crucial. The incorporation of novel biomarkers like PIVKA-II and AFP-L3, especially within multivariate models such as GALAD, significantly enhances the sensitivity for detecting early-stage, curable tumors.

The therapeutic landscape for HCC has become highly complex and stratified. Curative options like resection, ablation, and transplantation offer excellent outcomes for early-stage disease but are limited by strict criteria, organ availability, and high recurrence rates. For advanced stages, the paradigm has evolved from a single-agent sorafenib to a multitude of options, including other TKIs and, most notably, combination immunotherapy (atezolizumab + bevacizumab), which has set a new benchmark for survival. Despite these advances, challenges such as treatment resistance, patient selection, and managing unique toxicity profiles of novel agents remain.

The future of HCC management lies in continued refinement of risk stratification, validation of novel biomarkers for early detection, and the development of more effective and personalized combination therapies that integrate local and systemic modalities to further improve patient outcomes.

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