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Advances and Challenges in Hepatocellular Carcinoma: A Comprehensive Review

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Abstract:

Hepatocellular carcinoma (HCC) stands as a pressing global health concern. It is the predominant form of liver cancer and ranks among the leading causes of cancer-related death globally. Hepatitis B virus infection and hepatitis C infection remain the primary risk factors for the development of HCC. However, recently other factors such as cirrhosis due to chronic alcohol intake and non-alcoholic steatohepatitis have been becoming an increasingly common risk factor. The advancement and refinement of diagnostic methods play a crucial role in early diagnosis and surveillance, especially in high-risk populations. Patients diagnosed with hepatocellular carcinoma face a challenging prognosis, despite advancements in surgical techniques and other therapeutic interventions. This underscores the importance of sustained

attention to this issue. Continuous research into systemic therapies and refining diagnostic strategies is imperative to address the dynamic landscape of HCC. Efforts to reduce risk factors, coupled with improved surveillance, may contribute to a decline in HCC incidence in the future. This comprehensive review delves into current research on HCC, focusing on risk factors, symptoms, diagnosis, and treatment options.

Keywords: Hepatocellular carcinoma, cirrhosis, Non-alcoholic steatohepatitis, transarterial chemoembolization

Introduction

Liver cancer persists as a significant global health concern, with its prevalence escalating on a global scale [1,2]. Primary liver cancer is ranked as the sixth most frequently diagnosed cancer and the third leading cause of cancer-related deaths worldwide exceeded only by tumors of the lung and colorectum [3]. The projection indicates that by 2025, over 1 million individuals will be annually affected by liver cancer [4]. Hepatocellular carcinoma (HCC) is the predominant form of liver cancer, comprising 75%-85% of cases [3]. The prognosis for patients with HCC remains grim, primarily attributed to the advanced stage of cancer detected at diagnosis and high recurrence rates, reaching nearly 80% within 5 years after surgical resection [5]. This article focuses on current research into HCC risk factors, symptoms, diagnosis, and treatment options.

Risk factors

More than 90% of HCC cases manifest within the setting of chronic liver disease. Cirrhosis, stemming from various etiology, stands out as the most formidable risk factor for the development of HCC [6,7]. HCC poses a significant and frequently challenging interdisciplinary issue, with its incidence on the rise in Western countries. This increase is attributed to the growing prevalence of risk factors such as diabetes, excess body weight, chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin exposure, smoking, and heavy alcohol intake [3,8]. The primary risk factors for hepatocellular carcinoma (HCC) are undergoing a transition, marked by a decline in the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV), and a simultaneous increase in excess body weight and diabetes in various regions [9].

Chronic viral hepatitis can result in the development of cirrhosis and/or hepatocellular carcinoma (HCC). Approximately half of all HCC cases are linked to HBV infection [10]. HBV has been reported, by the World Health Organization o to be the second most significant known human carcinogen, following closely behind tobacco [11]. HBV is a double-stranded DNA-containing virus with eight genotypes (A-H). It possesses the capability to integrate its DNA into hepatic cells, functioning as a mutagenic agent. This can lead to secondary chromosomal rearrangements and an elevation in genomic instability [12]. Hepatitis B is transmitted through various means, including contaminated blood transfusions, intravenous injections, and sexual contact. Vertical transmission from mother to fetus stands out as the primary cause of HBV infection worldwide. It's noteworthy that five percent of the world's population is affected by hepatitis B [13]. In contrast to other contributors to chronic hepatitis, HBV exhibits a unique characteristic where HCC can develop without clear evidence of cirrhosis [14]. However most patients with HBV-induced HCC present with cirrhosis. Genotype C has been linked to a higher risk of HCC compared to genotypes A, B, and D [15]. Worldwide, 56% of liver cancer deaths are attributed to HBV infection [16]. The annual risk of HCC amounts to 0.5% for asymptomatic HBsAg carriers and increases to 0.8% for individuals with chronic hepatitis B. Notably, patients with HBV-related cirrhosis face a risk that is 1000 times higher for developing HCC compared to HBsAg-negative individuals [17,18,19]. As of the conclusion of 2019, 189 countries had incorporated the hepatitis B (HBV) vaccine into their national infant immunization programs. The worldwide coverage for three doses of the hepatitis B vaccine was estimated to be 85% [20]. However, the global coverage for the HBV birth-dose was relatively low at 43%, exhibiting variability across regions. Specifically, the WHO Western Pacific region reached 84% coverage, while the WHO African region, where HBV is a predominant cause of liver cancer, reported only 6% coverage [16,21]. Importantly, several cohort studies indicate that co-infection with HBV and hepatitis D virus (HDV) is linked to a heightened risk of hepatocellular carcinoma (HCC) compared to HBV infection alone. HDV necessitates the presence of HBV surface antigens for its replication and, consequently, for its infectivity. In one of the most extensive studies conducted to date, the risk of HCC was significantly elevated in individuals with acute HDV infection (relative risk [RR] 6.1, 95% confidence interval [CI] 2.8–11.7) or chronic HDV infection (RR 3.9, 95% CI 1.6–7.2) when compared to those with HBV infection alone [22].

Approximately 25% of all HCC cases are associated with HCV infection [10]. In Europe, Japan, Latin America, and the United States, cirrhosis induced by HCV infection stands as one of the primary causes of HCC [10,12]. HCV is a small, single-stranded RNA virus characterized by substantial genetic variability. There are six distinct genotypes of HCV identified. Genotypes I, II, and III are prevalent in Western countries and the Far East, whereas genotype IV predominates in the Middle East [23,24]. Patients infected with HCV were found to have a 17 times higher risk of developing HCC than those uninfected [25,26,27]. The risk of HCC in patients with HCV is primarily linked with the development of cirrhosis or chronic liver damage with bridging fibrosis since HCV does not integrate into the host genome [28]. A crucial component of HCV control involves improving infection control through safety measures. This includes practices such as screening blood transfusions, preventing mother-to-child transmission, supplying clean needles, and ensuring infection control in healthcare facilities [29]. As of now, there is no vaccine accessible for preventing HCV infection. However, an 8-week to 12-week regimen of orally administered direct-acting antiviral agents seems to effectively cure HCV infection in the majority of cases [30]. A successful treatment with the achievement of sustained virologic response (SVR) has been reported to decrease the risk of HCC development by 50%-80% [31]. Due to the usually asymptomatic nature of chronic infections, an estimated 290 million infected persons remain undiagnosed [32].

Presently, there is a growing number of individuals developing cirrhosis due to chronic alcohol intake. Excessive, chronic alcohol consumption of 40-60 grams on a daily basis is a known contributor to alcoholic liver disease, cirrhosis, and HCC [33]. Alcohol-related cirrhosis accounts for 15-30% of HCC cases, depending on the geographical region [34]. Non-alcoholic steatohepatitis (NASH) is considered a precursor step in the development of HCC. This issue concerns mainly patients with diabetes mellitus or obesity.

Due to the rising prevalence of obesity, NASH has emerged as the predominant cause of cirrhosis in numerous regions worldwide [35]. While the annual incidence of HCC is lower in cirrhosis related to NASH at 1–2% per year compared to viral-related cirrhosis at 3–5% per year, the incidence remains above 1.1 per 100 person-years. This suggests that surveillance is cost-effective and should be implemented in cases of NASH-related cirrhosis [36]. Individuals with obesity and diabetes have a twice higher likelihood of developing HCC compared to those who are not obese and do not have diabetes [33].

Aflatoxin B1 (AFB1) is a mycotoxin produced by the fungus Aspergillus flavus, which contaminates stored foods like rice, corn, soybeans, and peanuts. Particularly in regions such as Asia and Africa, aflatoxin serves as a major risk factor for the development of HCC. It has been proposed that a high intake of AFB1 in patients infected with HBV represents an additional risk factor for the development of HCC [37,38,39,40]. There has been a decrease in incidence and mortality rates of HCC in many high-risk countries in Eastern and Southeast Asia, which was likely connected to the increase in sanitary standards and the reduction in aflatoxin exposure [3].

Diagnosis and screening

HCC can be diagnosed through a combination of patient history, physical examination, and noninvasive imaging methods like ultrasound, MRI, and CT scans. In numerous cases, HCC is asymptomatic, and when symptoms do manifest, they typically align with those of chronic liver disease. These symptoms may include jaundice, discomfort in the right upper abdominal area, abdominal swelling, weakness, weight loss, and fever [37,41]. Nevertheless, a significant proportion of HCC cases occur within a specified patient population, such as those with chronic hepatitis B, C, or cirrhosis, and many individuals are diagnosed through surveillance efforts [42,43]. Asymptomatic HCC often might be identified incidentally on cross-sectional imaging performed for unrelated reasons. Screening for HCC in patients with high risk, especially in those diagnosed with cirrhosis is recommended every six months. A 6-month screening interval has been shown to enhance survival compared to annual surveillance and demonstrates outcomes that are non-inferior to a 3-month interval. [40,44,45,46,47]. The most commonly used screening methods are serum levels of alpha-fetoprotein and ultrasound (US) imaging [41]. Currently, histological diagnosis of HCC is seldom necessary, as non-invasive methods are preferred. In cirrhotic patients, HCC can be diagnosed non-invasively by relying on radiologic findings if specific imaging characteristics are present [48].

US has been reported to have a sensitivity of 58–89% and a specificity higher than 90% [49,50]. The specificity and sensitivity of US depend on the size of the tumor. The ability to detect tumors with a diameter of 3-5 cm is typically around 80-95%, while for tumors smaller than 1 cm, the sensitivity is in the range of 60-80% [51,52]. The majority of lesions with a diameter of less than 1 cm detected on ultrasonography, are not HCC or are very challenging

to diagnose accurately. Therefore, cross-sectional imaging is not deemed necessary, and short-term follow-up involving repeat ultrasonography after 3 months is considered sufficient. For lesions with a diameter of 1 cm or larger, the recommended imaging modalities are either quadruple-phase CT or dynamic contrast-enhanced MRI. These methods provide more detailed and enhanced visualization to aid in the accurate diagnosis and characterization of the lesions [7,53]. In both CT scans and MRIs, hepatocellular carcinoma (HCC) lesions appear brighter than the surrounding liver during the arterial phase and less bright than the surrounding parenchyma in the venous and delayed phases. This contrast is due to the differential blood supply of the tumor compared to the background liver [54]. Referred to as 'arterial enhancement and delayed washout,' this phenomenon has a sensitivity of 89% and a specificity of 96% for HCC, establishing it as the radiological hallmark of HCC. This characteristic is often sufficient for a diagnosis without the need for histological confirmation [55]. However, it's important to note that the specificity of MRI using hepatobiliary contrast agents appears to be lower than that using extracellular agents, leading to uncertainty regarding its role in the non-invasive diagnosis of HCC [56].

The prognosis for hepatocellular carcinoma (HCC) is strongly influenced by the tumor stage. Curative treatment options offer a 5-year survival rate exceeding 70% for early-stage HCC, in contrast to a median survival of approximately 1–1.5 years for symptomatic advanced-stage cases treated with systemic therapies [2]. Therefore the surveillance of high-risk patients. especially in those with cirrhosis and HBV infection is highly recommended. Abdominal ultrasonography is the most frequently recommended surveillance modality. However, growing evidence indicates that it is dependent on the operator and exhibits poor performance in specific patient subgroups, such as those with obesity and NASH [57]. Certain researchers have suggested the utilization of CT and MRI for hepatocellular carcinoma (HCC) screening as an alternative to ultrasound, particularly in cases involving obese individuals and those with advanced cirrhosis. Nevertheless, these modalities are not considered cost-effective, and there is a potential risk of cumulative radiation exposure from multiple CT scans [58.59]. Tumor markers can be employed alongside the US, however, the sensitivity of serum alpha-fetoprotein (AFP) is limited. It contributes to the additional detection of only 6–8% of cases, often accompanied by high false-positive results, consequently elevating the cost of surveillance [50,60,61]. Moreover, the serum level of alpha-fetoprotein (AFP) does not consistently correlate with tumor growth, and recent evidence indicates that its utility is less reliable than previously thought [62]. Consequently, the guidelines from the American

Association for the Study of Liver Diseases (AASLD) do not recommend measuring serum AFP levels for the purpose of surveillance and diagnosis [47].

Treatment and Management

Regrettably, the diagnosis of HCC is frequently established in the advanced stages of the disease when patients exhibit symptoms and already have some level of liver impairment. Approximately 80–90% of cases of HCC arise in individuals with cirrhosis. Consequently, the utilization of various therapeutic options may be constrained due to the patient's overall health status. Tumor staging plays a crucial role in guiding treatment decisions for HCC. While several staging systems exist for HCC patients, the Barcelona Clinic Liver Cancer classification is currently considered the most effective and widely used [6,63,64]. The best treatment is determined based on tumor stages and the anticipated benefits of major interventions and consists of various therapeutic choices: surgical resection, transplantation, ablation, transarterial chemoembolization (TACE), and systematic therapy. In general, individuals with early-stage HCC tumors and an optimal profile according to BCLC are the preferred candidates for surgical treatment or local ablation [47,65,66]. BCLC has been presented in Figure 1. Curative therapy options like resection, liver transplantation, and local ablation methods are viable only during the initial stages of the disease [41,67,68]. Regrettably, 60% to 70% of HCC patients receive a diagnosis when the disease has already progressed to an advanced stage, leading to palliative care as the predominant approach [69]. In such situations, transarterial chemoembolization (TACE) emerges as the most suitable therapeutic option.

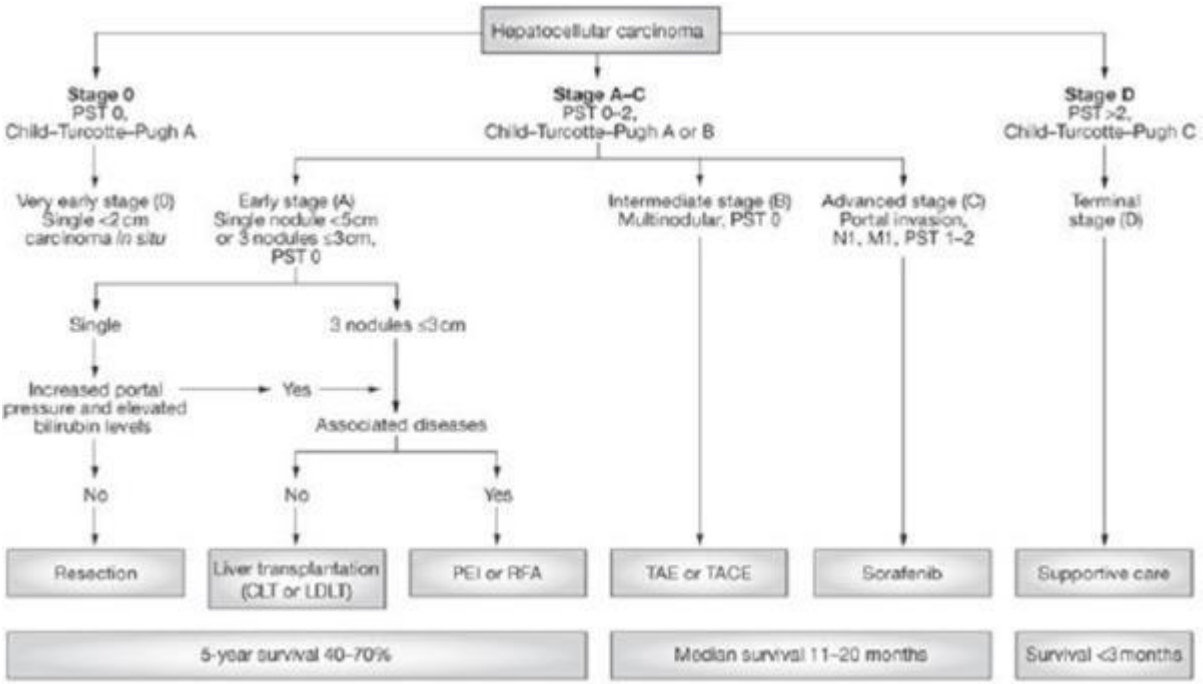

Figure 1.

Barcelona Clinic Liver Cancer (BCLC) classification. *PST – Performance Status Test.

(Source: Janevska D, Chaloska-Ivanova V, Janevski V. Hepatocellular Carcinoma: Risk Factors, Diagnosis and Treatment. Open Access Maced J Med Sci. 2015 Dec 15;3(4):732-6. doi: 10.3889/oamjms.2015.111. Epub 2015 Oct 29. PMID: 27275318; PMCID: PMC4877918. [85])

The surgical approach to HCC treatment yields optimal outcomes, with a 5-year survival rate ranging from approximately 70% to 80% [6,7]. This encompasses both hepatic resection and liver transplantation and has traditionally served as the cornerstone of curative therapies for HCC. For patients without underlying cirrhosis, a single tumour, and good liver function, where the risk of post-operative hepatic decompensation is not a significant concern, hepatic resection is regarded as the preferred treatment option [6,7,65,70]. The recurrence of HCC following hepatic resection remains a significant challenge, with recurrence rates reaching as high as 70% at 5 years, even in patients with a single tumor measuring 2 cm or smaller [71]. Long-term outcomes of surgical resection are suboptimal, with a 70% recurrence rate and a 10-year survival of 7–15% [72]. Liver transplantation is considered in patients with cirrhosis and small, unresectable tumors [73]. The major problem in this approach is the long waiting time stemming from small organ availability. However, the outcomes of liver transplantation in HCC have been very promising with a 5-year survival rate of 70%, a 10-year survival rate of 50%, and recurrence rates of 10–15% after 5 years [74]. The choice between resection and

transplantation involves evaluating the patient's liver function, the presence and extent of portal hypertension, performance status, availability of the organs, and tumor characteristics, including size, number, and involvement of the hepatic and portal veins.

Local ablation encompasses various techniques, such as radiofrequency ablations (RFA), and microwave ablation (MWA). This technique is optimal as a useful, first-line approach in small, unresectable, early-stage HCC tumors [75]. RFA is the most commonly used technique in ablative therapy due to its high efficacy, with a reported 5-year survival rate in the range of 40% to 70% [76,77]. MWA holds the advantage of creating a larger ablation zone compared to RFA because multiple needles can be used simultaneously [78]. Multiple trials comparing RFA and MWA have indicated no differences in the efficacy and primary endpoint or in local tumor progression at the 2-year mark [79,80,81].

Recently TACE has been globally accepted as a standard treatment in patients with intermediate-stage HCC [6]. Inclusion criteria for consideration for TACE are patients with well-compensated liver function, with a large single nodule (< 5 cm) or multifocal HCC, without indications of vascular invasion or extrahepatic spread [65]. Furthermore, TACE plays a pivotal role in palliative treatment [82,83].

The review of the literature indicates a steady increase in researchers' interest in the topic of HCC, its risk factors, screening, and treatment options. Various systemic therapies are in development and carry the possibility of significantly improving the outcome of patients with HCC, however, the critical element in HCC management remains diagnosing the disease in its very early stages and consistently surveilling patients with a high risk of developing HCC [84]. Despite the significant reduction in HCC incidence achieved through vaccinations and antiviral therapies, there is a steady increase in its occurrence due to other contributing factors like alcohol abuse and NASH [36]. It appears that efforts targeted at reducing the risk factors associated with NASH may also contribute to a decline in HCC incidence in the future. Implementing improved surveillance methods for individuals at risk could enhance the detection of more patients with HCC at a curative stage of the disease.

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