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Review

Stratified screening of hepatocellular carcinoma in high-risk populations

Peng Li, Huiguo Ding*

Department of Gastroenterology and Hepatology, Beijing You'an Hospital Affiliated with Capital Medical University, Major Infectious Diseases Innovation Center, Fengtai District, Beijing 100069, China

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Abstract

The worldwide prevalence of hepatocellular carcinoma (HCC) is substantially increasing. Approximately 50% of all cases occur in China. However, more than 85% of cases are diagnosed at an advanced disease stage, thus missing the effective treatment window. Currently, the 5-year survival rate for HCC patients is less than 15%. Despite the use of new therapeutic strategies for HCC in clinical practice. The metabolic syndromes and human immunodeficiency virus (HIV) infections are to be considered as new HCC high-risk-population. Furthermore, liver cirrhosis patients with HBV mutations or with cirrhotic nodules are regarded as HCC extremely high-risk populations. This mini-review provides an overview of HCC new high-risk populations and of stratified screening strategies that are based on the latest clinical studies.

Keywords: Hepatocellular carcinoma; High-risk populations; Screening; Early diagnosis

1. Introduction

With the development of antiviral drugs, hepatitis C may become a curable disease [1], and the outcome of hepatitis B patients may improve [2]. The liver cirrhosis and hepatocellular carcinoma (HCC) induced by hepatitis B and C were decreased [3]. Planned immunization against HBV and mother-infant HBV infection have been advocated in China in the last 10 years, causing a significant reduction in the HBV-related HCC incidence rate [4]. However, why is the worldwide prevalence of HCC substantially increasing [5,6]? Epidemiological studies have confirmed that diabetes, non-alcoholic fatty liver disease (NAFLD) may be an independent risk factor for HCC [7,8]. Recently, human immunodeficiency virus (HIV) infection, a new risk factor for HCC, has been reported [9]. This mini-review provides an overview of HCC new high-risk populations and of stratified screening strategies that are based on the latest clinical studies.

2. HCC high-risk populations

2.1. Chronic viral hepatitis with FH (+)

HBV and HCV infections play an important role in the occurrence and development of HCC. It is estimated that 70% of primary hepatocellular carcinomas are caused by HBV or HCV infection [10]. A case–control study in the USA found that the risk of HCC in individuals whose first-degree relatives (parents, children, siblings) had a family history of HCC [FH (+)] was 3.9 times that of individuals without HCC family history [19]. The cumulative incidences of HCC over 17 years in the FH (+)/HBsAg (+), FH (−)/HBsAg (+), FH (+)/HBsAg (−), and FH (−)/HBsAg (−) populations were 15.8%, 7.5%, 0.65%, and 0.62%, respectively [11]. Therefore, HBV infected individuals with FH (+) are regarded as high risk for HCC.

2.2. Liver cirrhosis

Various causes of cirrhosis are currently recognized as high-risk factors for HCC. Approximately 80–90% of HCC occurred in liver cirrhosis patients. It has been estimated that

* Corresponding author. Tel.: +86 10 83997155; fax: +86 10 63295525.
E-mail address: dinghuiguo@medmail.com.cn (H. Ding).
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Table 1
Comparison of recommendations for HCC surveillance in different guidelines.

Characteristics	AASLD guideline [16]	EASL guideline [26]	APASL guideline [27]
HCC risk population	(1) Cirrhotic patients with different etiology. (2) HBV carriers of Asian origin (male>40 yr, female > 50 yr). (3) African/North American Blacks with hepatitis B. (4) HBV carriers with family history of HCC.	(1) Cirrhotic patients with Child-Pugh stage A, B and stage C awaiting liver transplantation. (2) HBV carriers with active hepatitis or family history of HCC. (3) Chronic hepatitis C with advanced fibrosis F3.	Cirrhotic HBV and HCV patients.
Surveillance benefit uncertain patients	(1) HBV carriers younger than 40 (males) or 50 (females). (2) Hepatitis C patients with fibrosis F3. (3) Non-cirrhotic NAFLD	No explanation	No explanation
Surveillance modality	US	US	US and AFP
Interval (mo)	6	6	6

AASLD: American Association for Study of Liver Disease; EASL: European Association for the Study of the Liver; APASL: Asian Pacific Association for the Study of the Liver; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: non-alcoholic fatty liver disease; US: ultrasound; AFP: α-fetoprotein; HCC: hepatocellular carcinoma.

70% of cirrhosis cases are caused by chronic HBV or HCV infection in China [5]. The annual incidence rate of HCC in patients with decompensated hepatitis B-induced cirrhosis was 2–5% [12]. Currently, the international consensus is that effective antiviral therapy can reduce the incidence of HCC in patients with hepatitis B-related cirrhosis [13]. However, some studies have showed that failure of the antiviral treatment or viral resistance mutations increase the incidence of HCC [14]. An investigation in 38 European countries in 2006 showed that drinking alcohol accounted for 9.4% of the risk among all risk factors for HCC [15]. The incidence of HCC in patients with stage-IV PBC is similar to that in patients with HCV-related cirrhosis [16]. HCC was detected in 73.4% of patients with micronodular cirrhosis, suggesting that HCC is closely associated with cirrhotic liver nodules [17]. Therefore, liver cirrhosis is considered to be a high-risk factor for HCC, and patients with HBV mutations or antiviral failure or with cirrhotic nodules (≥1 cm) are regarded as HCC extremely high-risk population.

2.3. Metabolic syndromes

Metabolic syndromes include insulin resistance, obesity, hypertension, and hyperlipidemia. Recently, a large-scale epidemiological survey of 2897 Chinese individuals showed that the incidence rate of diabetes in patients with HCC was significantly higher than in healthy 40–60 year old individuals (15.6% vs. 11.5%, respectively) [18].Therefore, metabolic syndromes, especially in non-alcoholic steatohepatitis are regarded as high risk for HCC and should be recommended for HCC screening [19].

2.4. HIV infection

As a result of significant improvements in the efficacy of highly active anti-retroviral therapy (t-HAART), HIV/AIDS patient survival time has been prolonged. As a consequence, concomitant malignancies have become an important cause of death in HIV patients [20,21]. A prospective cohort study recently demonstrated that the HCC incidence was 6.72/1000 person-years in 371 cases of HIV infection with liver cirrhosis (95% HCV and 9% HBV) [9]. Therefore, HIV-infected patients, especially those with HCV or HBV infections, are also considered as HCC high risk population.

2.5. Shortcomings of the current guidelines recommendation for HCC screening

For populations of HCC high risk, in European, United States and Asia–Pacific Region guidelines, HCC were screened using B-ultrasound or combination with serum alpha-fetoprotein (AFP) every 6 months, as shown in Table 1 [22]. However, this current screening program has some shortcomings. First, although AFP is widely accepted as a biological marker for HCC diagnosis, the low sensitivity was recently reported as a screen for HCC [23]. In addition, 30–40% of HCC patients were AFP-negative. Second, although B-ultrasound has a sensitivity of 65.0–80.0% and a specificity of 90.0% for HCC screening, this screening procedure depends on operator experience. Some new serological diagnostic markers have been studied in recent years; they include the lens culinaris agglutinin-reactive fraction of AFP(AFP-L3), glypican-3(GPC3), des-γ-carboxyprothrombin (DCP), and golgi protein 73(GP73), all of which have been employed for the screening and early diagnosis of HCC [24]. Its have limitations for the early diagnosis and screening of HCC. Therefore, a reasonable stratification of the HCC high risk population was performed.

2.6. Stratified screening of HCC high risk populations

In the last decade, there has been a marked increase in the therapeutic options for HCC. Nevertheless, curative options are only useful in the case of early detection. Currently, the 5-year survival rate for HCC patients is less than 50%, despite the use of new therapeutic strategies for HCC in clinical practice [25]. One cohort study included 255 patients with decompensated HBV-induced cirrhosis who were followed for 4 years. Some of these patients were screened for HCC at 3-month intervals using serum AFP and GPC3, in combination

Table 2
The stratified screening strategies of HCC high risk populations.

Stratified HCC risk populations	Low risk populations	High risk populations	Extremely high risk populations
Clinical characteristics	(1) HBV carriers with normal ALT. (2) Metabolic syndrome with normal ALT and age < 50 yrs. (3) Hepatitis C patients with fibrosis < F3.	(1) HBV infection with FH (+) (2) CHB and age > 40yrs (males) or 50 (females). (3) Compensated cirrhotic patients. (4) CHB patients with HBV mutations (A1762T/G1764A). (5) Alcoholic, metabolic syndrome, autoimmune patients and sustained abnormal ALT. (6) HIV and HBV/HCV co-infection and abnormal ALT.	(1) Cirrhotic nodules >1 cm with different etiology (2) Cirrhotic patients with family history of HCC. (3) Compensated cirrhotic patients with FH(+). (4) Decompensated HBV cirrhotic patients failure to antiviral therapy. (5) Cirrhotic patients and HBV A1762T/G1764A mutations or antiviral resistance-related gene mutations (rtA181T).
Screening modality	US and AFP	US and AFP	US ,AFP and AFP-L3, GPC3,DCP,GP73
Interval (mo)	24	6	3

ALT: alanine transaminase; CHB: chronic active hepatitis B; FH(+): family history of HCC of the first-degree relatives.

with liver B-ultrasonography. A total of 68.8% of HCC patients was BCLC-A stage HCC, but only 5.9% of HCC in patients performed the routine screening (6-month intervals using AFP and/or B-ultrasonography) [28]. If serum AFP levels increase, it is necessary to test other serum biomarkers and to shorten the screening interval to 1−2 months. If B-ultrasound examination reveals an atypical hyperplastic nodule with a diameter of >1 cm, a CT scan and/or an MRI are strongly recommended for screening. Therefore, different screening strategies were studied by stratifying the population at high risk for HCC into 3 categories, low risk, high risk and extremely high risk shown in Table 2. However, there is little evidence for its effectiveness in clinical practice. The optimization of screening programs should be studied in the future. B-ultrasonography is the most promising tool for screening, but the debate about serum biomarkers such as AFP and screening interval length is not yet over.

Author contributions

Li P contributed to data collection and prepared the manuscript. Ding HG was responsible for the project and the final manuscript.

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