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Risk stratification of primary liver cancer

Risk stratification of PLA

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Abstract

The risk stratification of primary liver cancer (PLA) discussed in a review of viral hepatitis and PLA could lead to misunderstandings by readers. For example, a single study or a small number of studies cannot comprehensively summarize the risk factors of PLA, is not included in the family history of liver cancer, and chronic hepatitis D is listed as a medium risk factor for the development of PLC. Currently, PLA prediction models with good clinical validation values have been applied clinically, such as the Toronto hepatocellular carcinoma (HCC) risk index (THRI), REACH-B model, and PAGE-B model. Therefore, the Chinese, together with several research societies, have formulated the "Guideline for stratified screening and surveillance of primary liver cancer (2020 edition)." This guideline outlines PLC screening in at-risk populations, both in hospitals and communities. It is recommended to stratify the at-risk population into four risk levels: low-, intermediate-, high-, and extremely high-risk. This is highly recommended and applied in clinical practice.

Core Tip: PLA prediction models with good clinical validation values have been applied clinically, such as the Toronto hepatocellular carcinoma (HCC) risk index (THRI), REACH-B model, and PAGE-B model. Therefore, the Chinese, together with several research societies, have formulated the "Guideline for stratified screening and surveillance of primary liver cancer (2020 edition)." This guideline outlines PLC screening in at-risk populations, both in hospitals and communities. It is recommended to stratify the at-risk population into four risk levels: low-, intermediate-, high-, and extremely high-risk. This is highly recommended and applied in clinical practice.

TO THE EDITOR

I have read an article with title: "**Viral hepatitis and hepatocellular carcinoma: From molecular pathways to the role of clinical surveillance and antiviral treatment**"[1] with great interest. This is a very good systematic review which fully discusses the etiology, risk factors, and pathogenesis of primary liver cancer (PLA). High-, medium-, and low-risk factors of PLA were analyzed. However, the term "risk factors for the development of PLA" in this article could lead to misunderstandings by readers.

First, a single study or a small number of studies cannot comprehensively summarize the risk factors of PLA. Perhaps a meta-analysis is more reasonable. A meta-analysis of chronic hepatitis B hepatocellular carcinoma (HCC) from China[2] included 3,165 cases and 10,896 controls from 27 studies. The results showed that, from the currently available evidence, Chinese people with a high viral load, not treated with antiviral treatment, with a family history of liver cancer, of male sex, and with chronic HBV infection are at risk of developing HCC. In another meta-analysis of risk factors for nonalcoholic fatty liver disease (NAFLD) and HCC, 18 studies involving 470,404 patients were included. In NAFLD patients before cirrhosis, the incidence of HCC was 0.03/100 person years. In patients with liver cirrhosis, the incidence rate was 3.78/100 person years[3]. However, it still needs to be noted that the risk factors of PLA that can be seen at present are for a specific disease, and there is still a lack of meta-analysis on the risk factors of all PLA. Many studies have analyzed PLA risk factors. Among them, the studies that have been highly recognized mentioned the Toronto hepatocellular carcinoma (HCC) risk index (THRI) which takes into consideration five variables, including age, gender, platelet count, and the cause of liver cirrhosis (0, 0, 36, 54, and 97 for autoimmune liver disease, hepatitis C with sustained virological response [SVR], other liver diseases, fatty hepatitis, untreated chronic hepatitis C or chronic hepatitis B, respectively). A total of 366 points of the THRI model[4] were constructed. The 5-year cumulative incidence rates of HCC in the low- (<120 points), medium- (120–240 points), and high- (>240 points) risk groups were 1.2% and 4.5%, 4%, respectively, and 15, and the 10-year cumulative incidence rates of HCC were 3%, 10%, and 32%, respectively.

The THRI model was also validated in China. For patients with cirrhosis classified into low-, medium-, and high-risk groups, the 5-year cumulative incidence rates of HCC were 0%, 13%, and 34%, respectively, and the area under the receiver operating characteristic curve (AUC) of the prediction model is 0,707[5]. The significance of the THRI model is that even in patients with liver cirrhosis who are at high risk of HCC, it is still necessary to conduct further risk stratification to distinguish the extremely high-risk population of HCC.

HBV infection is the main cause of HCC. Even without cirrhosis, there is only 6.5% chance of 2%–9.5% of hepatitis B virus (HBV) infected individuals to progress to HCC in their lifetime. Some scholars in Taiwan and China have built the REACH-B model with a total of 17 points, including sex, age, alanine aminotransferase (ALT) HBeAg status, and HBV DNA level, aiming at the risk stratification of HBV-infected individuals who have not received antiviral treatment[6]; scores of 0–5, 6–11, and 12–17 are low, medium, and high risk, respectively . The incidence of HCC in the lowest (0) and highest (17) scores within 3, 5, and 10 years is 0.0% and 23.6%, 0.0% and 47.4% and 0.0% and 81.6%, respectively.

HBV remains a risk factor for HCC after antiviral treatment. Based on the 5-year results of oral antiviral treatment with entecavir or tenofovir in 1,815 CHB patients in Europe, the PAGE-B model with three parameters, including age, sex, and platelet count, and a total score of 25 points was constructed to evaluate the risk of HCC in patients with HBV infection after antiviral treatment[7]. According to the score, the patients were divided into three groups: low-risk (0–9 points), medium-risk (10–17 points), and high-risk (18–25 points). The 5-year cumulative incidence of HCC in the low-, moderate-, and high-risk groups was 0%, 0%–4%, and 16%–17%, respectively. The Korean cohort verified that the PAGE-B model was equally effective in Asian populations, and the AUC for 5-year HCC predictive power was 0.77[8].

The PAGE-B team recently added two parameters, age and liver stiffness measurement; thus, the maximum total score is now 15 points and divided into low-risk (<5 points), medium-risk (6–10 points), and high-risk (>11 points) levels. The cumulative incidence

of HCC in 12 years was 0.0%, 4.0%, 0.0%, and 13.8%. In conclusion, the 5-year cumulative incidence rate of HCC was still 5.5% in patients with chronic HBV infection treated with antiviral therapy, especially those classified in the high-risk group (7%–8.4%). However, the negative predictive rate of HCC in 5[8] and 12[6] years in the low-risk group is as high as 97.5%–100%. In untreated individuals infected with HCV, serum HCV RNA, ALT, and HCV genotype 1b were independent predictors of HCC[10]. Risk prediction models have a long history in predicting HCC incidence rate in CHB patients. Currently, approved models are as follows: CU-HCC, GAG-HCC, Page-B, mPAGE-B, REACH-B and mREACH-B[11, 12]. A meta-analysis used six models to perform AUC validation on 22 studies published between 2011 and 2020[13]. The AUC values of the six models ranged from 0.715 to 0.778. In the antiviral treatment subgroup, the AUC values of mREACH-B, GAG-HCC and mPAGE-B were 0.785, 0.760 and 0.778, respectively. In the subgroup of liver cirrhosis, the recognition performance of all models is very poor (AUC < 0.7). The clinical application of these models can improve patients' prognosis and aid them in making informed decisions about treatment. However, these models were derived from different cohorts with or without antiviral treatment and affected by many factors. There are no guidelines for publishing the same standardized guide to predict the risk of HCC among CHB patients[14-16] .

Second, among the risk factors, there was no family history of PLA. In the HBV- or HCV-infected population, first-degree relatives with a family history of PLA significantly increased the risk of HCC[17-19]. Scholars in Taiwan and China have followed up 22,472 residents and a total of 362,268 people / year, and 374 cases of HCC have been detected. HBV patients with a family history of HCC were 2.5 times more likely to develop HCC than those without a family history [19]. A similar cohort of 7933 non-PLA patients and 201 patients with PLA from China also showed that the risk of HCC was 2.76 higher (95% CI, 1.88–4.05) in individuals without HBV infection but with a family history of PLA, but in the population with HBV positive and family history of primary HCC, the risk of HCC was 41.34 (95%CI 23.69 –72.12)[17]. Therefore, first-degree

relatives infected with HBV and HCV with a family history of liver cancer had a significantly increased risk of HCC in [18] at all stages, which requires special attention. Third, untreated chronic hepatitis D virus infection was classified as a moderate risk factor in the analysis of HCC risk factors, with an OR of 3.9. HDV is a defective virus dependent on HBV infection. Chronic hepatitis D inevitably overlaps with chronic hepatitis B. As described in the article, chronic hepatitis D is considered the most serious form of chronic viral hepatitis, leading to rapid progression of liver cirrhosis and higher mortality. More than 10% of patients infected with chronic hepatitis D virus develop cirrhosis within 5 years of infection, and more than 80% of patients suffer from liver cirrhosis decompensation within 30 years[20]. Recent cohort studies have found that compared to patients with a single HBV infection, the risk of patients with HDV infection is nine times higher, although it is generally believed that HDV does not represent a major risk factor for the development of HCC[21, 22]. In addition, persistent hepatitis D virus replication has been a risk factor for liver disease progression to cirrhosis and HCC[23]. A European study on the collaborative action of viral hepatitis showed that the incidence of HCC in patients with anti-hepatitis D virus-positive cirrhosis increased by 3.2 times compared with those with negative hepatitis [21]. Other recent studies have shown that patients with HDV/HBV co-infection have an increased risk of HCC compared to patients with HBV infection alone (adjusted HR = 9.30)[24]. A large study estimated that the risk of HCC in patients with chronic hepatitis D virus infection (RR = 3.9) was significantly higher than that in patients with a single HBV infection[25].

Therefore, the Chinese, together with several research societies have formulated the **"Guideline for stratified screening and surveillance of primary liver cancer (2020 edition)"[26]**. China has a high incidence of PLC, and chronic HBV infection is still the greatest risk factor for HCC. According to the high-risk factors, the guidelines for screening at-risk populations were divided into low-, intermediate-, high-, and extremely high-risk groups (Table 1) and propose monitoring and timing based on

ultrasound findings and alpha fetoprotein level. Abdominal ultrasonography combined with serum alpha-fetoprotein examination (routine surveillance) is recommended every 6 mo for patients at high risk of PLC. Routine surveillance every 3 mo and enhanced computer tomography/ magnetic resonance imaging examination every 6–12 mo are recommended for patients at an extremely high risk of PLC. The surveillance interval can be extended every 1 year or longer for those with low-risk or intermediate-risk PLC because their annual incidence of PLC is very low. However, the cost-effectiveness of these recommendations remains to be evaluated. We believe that the stratified analysis of risk factors and screening recommendations for PLA in China can be successfully implemented by doctors to aid the early diagnosis and treatment of PLA. Of course, large sample verification and observation are required.

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