

Would Screening the Above 50's for Hepatocellular Carcinoma (HCC) in an Endemic Hepatitis B Virus (HBV) Belt Be Cost-effective?

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ABSTRACT

Although primary prevention is most important, the future of hepatocellular carcinoma (HCC) still relies on secondary prevention via the effective treatment of the causative hepatitis B virus (HBV) or hepatitis C (HCV) infections and, surveillance of high-risk individuals for early diagnosis and management. In low resourced regions such as in Sub-Saharan Africa, a combination of a high- resolution contrast enhanced ultrasonography (CEUS) and tumour marker (alpha- fetoprotein) testing can increase sensitivity for detecting HCC. They are convenient, non-invasive and easily accessible and assessable screening methods. The author proposes that there may be a survival benefit and cost-effectiveness in screening all people above 50 in an endemic HBV belt. The cost per tumour detected may be inversely proportional to the tumour incidence in an endemic HBV region.

Keywords: Hepatocellular Carcinoma, Screening, Over 50's, Endemic Hepatitis B Belt

INTRODUCTION

Hepatocellular carcinoma (HCC) is a global health problem as it is a major cancer burden with a very poor prognosis. With 905,700 new cases in 2020 (just under 5% of all cancers) and 830,200 deaths, liver cancer is the third leading cause of cancer deaths worldwide after lung and colorectal cancer [1]. HCC represents over 90% of primary liver cancers with a 5-year survival rate of approximately 18% [2]. More than 80% of cases are found in Africa or East Asia (100 cases per 100,000 populations in S. Africa and S.E Asia). This is related to the early exposure to hepatitis B virus (HBV) or hepatitis C virus (HCV) with men having a three to eight-fold greater risk of developing HCC than women [3]. The rising incidence in the West is due to HCV epidemic, nonalcoholic fatty liver disease (NAFLD) in the setting of obesity with/without associated diabetes mellitus type 2, and heavy alcohol consumption [4]. In the United States the incidence has tripled since the 1980's with > 40,000 new cases in 2020. The incidence is expected to increase globally by 55% between 2020 and 2040 [1]. HCC is suspected in patients with cirrhosis when there is deteriorating liver function, acute complications or decompensation of

Vol No: 11, Issue: 02

Received Date: May 23, 2026

Published Date: October 15, 2026

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Citation: Weledji EP. (2026). Would Screening the Above 50's for Hepatocellular Carcinoma (Hcc) in an Endemic Hepatitis B Virus (Hbv) Belt Be Cost-effective? Mathews J Gastroenterol Hepatol. 11(2):43.

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chronic liver disease (ascites, encephalopathy, variceal bleed, jaundice) and the development of upper abdominal pain and fever. The locally advanced HCC may present with weight loss, anorexia, abdominal pain and hepatomegaly. Outcomes depend heavily on stage; early-stage median survival is > 60 months, but advanced stage survival is often less than 1 year [3]. The HBV can be directly oncogenic by incorporating into host genetic material and HCC occurring without cirrhosis especially in the younger age group [5]. Otherwise, it takes 10 years to develop chronic hepatitis, 20 years to develop cirrhosis and 30 years to develop HCC from the dysplastic changes in the cirrhotic process [3,6]. Therefore, patients at risk are patients in the 50-70-year age group with the risk of being chronic carriers of HBV in the endemic HBV belt. It is often diagnosed late because early stages are asymptomatic.

Screening/ Surveillance

The American Association for the Study of Liver Diseases (AASLD) prefers the use of the term surveillance over screening for early detection of HCC as it involves the repeated use of screening tests at repeated intervals. Surveillance for HCC is indicated in all cirrhotic patients, other specific groups such as hepatitis B carriers with positive family history of HCC and those with high HBV DNA levels. Both radiological and serological tests in the above patients are recommended by the AASLD [7]. Many tissues regain the ability to produce alpha-fetoprotein (AFP), a plasma glycoprotein normally produced during gestation by the fetal liver and yolk sac especially while undergoing malignant degeneration. Ultrasound (US) and AFP are the more widely used methods for surveillance. US is operator-dependent, has a sensitivity of 65%-80% and specificity of 48%-94% which depends on the size of the HCC nodule. Thus, focal lesions on US should be verified using a four-phase multidetector CT (MDCT) or a dynamic contrast-enhanced MRI as these modalities have higher sensitivity (89%) and specificity (94%) for lesions greater than 1 cm. A contrast-enhanced study is required to demonstrate the typical 'wash out' of the contrast seen in HCC. HCC has arterial blood supply exclusively, whereas the rest of the liver has both portal venous and arterial supply. In the arterial phase HCC enhances more than the liver, whereas arterial contrast in non-tumor liver is diluted by the portal venous blood. In the venous phase, HCC enhances less than liver as it has no venous blood supply, and the arterial blood flowing through HCC no longer contains contrast whereas the non-tumor liver is entered by contrast in the venous blood.

AFP alone is not an independent screening test for HCC. The upper limit of normal serum AFP concentration is less than 10-15 ng/ml. Although AFP is the most commonly used serological diagnostic test, the sensitivity and specificity vary with the size of the nodule and the cut-off values utilized. It has 55%-60% sensitivity and 88%-90% specificity for a cut-off value of 20 ng/ml compared to a 17% sensitivity and 99.4% specificity for a cut-off value of 400 ng/ml. In addition, AFP may be elevated in patients with adenoma, testicular or germ cell tumors, intrahepatic cholangiocarcinoma, gastric and colon carcinomas [7]. Therefore, the diagnosis of HCC should rest on radiological and histopathological evidence and, AFP alone is limited [6,7].

Staging and Treatment

Both HCC and the underlying cirrhosis along with the patient's condition may affect the mortality of the patient. Similarly, the biology of the disease and the risk factors are different in the East and West. An ideal staging system should take into account the tumor burden, functional state of the liver, and performance status of the patient. The Barcelona Clinic Liver Cancer (BCLC) staging system is currently the most widely utilized staging system worldwide as it includes tumor stage, liver functional status, and physical status of the patients and links the various stages to treatment modalities and estimated life expectancies [8]. Although HCC is the one of the few tumors that can be treated by both resection and transplantation, there are several treatment options available to patients diagnosed with HCC [7-11]. Treatments share a high incidence of tumor recurrence due to the persistence of the underlying cirrhosis that represents a preneoplastic condition. The treatment algorithms are guided by the extent of tumor burden (extrahepatic spread, vascular invasion, number of tumors, tumor diameter), severity of underlying liver dysfunction, size of future liver remnant (FLR), functional status, and comorbidities of the patient. Transplantation and resection continue to be the major curative intent therapeutic options available to patients with HCC. Patients with early-stage disease (i.e., HCC falling within the Milan criteria- solitary lesion $\leq$ 5 cm or $\leq$ 3 lesions with the largest diameter $\leq$ 3 cm and absence of macroscopic vascular invasion or extrahepatic disease) and advanced cirrhosis including Child-Pugh class B/C and portal hypertension are thought to be candidates for transplantation. Thus, it is the small HCC (<5cm in diameter) in the setting of cirrhosis which is better treated by liver

transplantation as it clears both the HCC and the underlying liver disease. There is excellent long-term disease-free survival exceeding 70% at 5 years [8]. Resection remains the treatment of choice for patients without any significant underlying liver disease. Resection can offer cure in less than 20% of patients with no underlying liver disease or Child A cirrhosis because of local spread (high recurrence rate) and severity of pre-existing cirrhosis. An overall 5-year survival of 60% is expected and disease-free survival is better after anatomical (5-year 63%) than non-anatomical resection (35%) [9]. Tumor differentiation and vascular invasion are important predictors of survival after surgical resection or liver transplantation [3-9]. Minimally invasive surgery has the benefit of less physiological insult than open surgery in liver cirrhosis. Ablative treatment, chemoembolization, and systemic therapies play an important role as well. Due to cadaveric organ shortage liver resection or tumor ablation (radiofrequency or microwave ablation (RFA/MWA), transarterial chemo-embolization (TACE) or more recently transarterial radio-embolization (TARE) may be effective bridge to transplantation if they fulfill the Milan criteria [7-11]. The problem of systemic chemotherapy in HCC stems from the coexistence of the two diseases (HCC and cirrhosis) and the poor chemosensitivity of HCC. Once cirrhosis or chronic liver disease is established, the benefits of antiviral therapy in preventing HCC development are not robustly demonstrated. The inhibition of viral replication by the anti HBV nucleoside analogue, *lamivudine* resulted in significant improvement in liver function in patients with decompensated HBV induced cirrhosis and not candidates for liver transplantation [9,11]. These have been markedly improved by the advent of new antiviral therapy including nucleoside analogues, a combination of immunotherapy for advanced HCC, and targeted molecular therapy such as *sorafenib* in advance disease. There is also the need for provision of therapy that is most appropriate for the stage of the disease [8].

Implication of Surveillance/Screening on Treatment Outcome

Surveillance for high-risk patients (Hepatitis B/C, alcoholic liver disease, and increasingly NAFLD can lead to earlier detection and better potentially curative treatment [12]. Earlier studies fail to show improvement in patient management and survival by screening. Unfortunately, it is ethically and practically unjustifiable to prove conclusively that screening programs are effective in improving patient

management through prospective randomized trials. However, more recent studies demonstrate that screening can increase the chance of curative treatment and more importantly improve survival even after the adjustment of lead-time bias. This is enhanced by the improvement in medical treatment and technology. It is important to note that lead time bias is where early detection of HCC through screening, makes survival appear longer even if the patient's actual life-span remains unchanged. Length bias occurs where screening detects slower-progressing indolent diseases that have better prognoses. They are more likely to be found than fast-growing, aggressive tumors leading to an overestimation of survival time [12,13]. The effectiveness of screening is thus best for the moderately- growing tumors. In countries with a low prevalence of HCC, screening for HCC is not cost-effective.

According to the World Health Organization (WHO), there are 10 criteria for a cost-effective screening program [14]: (i) the condition should be an important health problem; (ii) accepted treatments are available; (iii) facilities for diagnosis and treatment are available; (iv) the condition can be recognizable in the latent/ early stage; (v) suitable tests for screening are available; (vi) the screening tests are acceptable to the population; (vii) the natural history of the condition is well understood; (ix) the cost of diagnosis and treatment should be economically balanced with the whole medical expenditure; and (x) case-finding should be continued. The screening for HCC basically fulfills nearly all the WHO criteria with the exception of cost-effectiveness. In the developing sub-Saharan African countries, the cost of diagnosis and the treatment may not be economically balanced with the whole medical expenditure. In countries with a high prevalence of HBV such as in sub-Saharan Africa and, with knowledge of the natural history of the disease, the screening program may be more cost-effective when screening older patients. The author proposes that there may be a survival benefit and cost-effectiveness in screening all people above 50 in an endemic HBV belt. US and AFP levels are the most widely used method for surveillance. In resourced centers, computed tomography (CT) scan or magnetic resonance imaging (MRI) is preferred over contrast enhanced ultrasound (CEUS) as a first-line examination for the non-invasive diagnosis of HCC because of their higher sensitivity and their utility for analysis of the whole liver. A surveillance interval of 6 months is utilized based on the

tumor doubling times of approximately 6 months. Although serum alpha fetoprotein is elevated in only 50-60% of cases of HCC the presence of a discrete mass within a cirrhotic liver, together with an alpha fetoprotein > 500ng/ml is diagnostic [12,13,15]. In low resourced HBV endemic regions such as in Sub-Saharan Africa, a combination of a high- resolution contrast enhanced ultrasonography (CEUS) and tumor marker (alpha- fetoprotein) testing can increase sensitivity for detecting HCC. They are convenient, non-invasive and accessible and assessable screening methods. The cost per tumor detected may be inversely proportional to the tumor incidence in an endemic HBV region. Although primary prevention is more important, the future of HCC still relies on secondary prevention by the effective treatment of the causative hepatitis B and C infections and surveillance of high-risk individuals for early diagnosis and management. Primary prevention by vaccination against HBV to all newborns and high-risk adults who failed to receive vaccination at birth [16], testing blood donors, needle exchange programs and, encouraging safe life styles may see marked decline of the disease in future generations. Antivirals should be given to all patients that meet the criteria for treatment for HBV and HCV infection. Suppression of HBV and eradication of HCV infection decreases the risk of HCC development [7].

CONCLUSION

There may be a survival benefit and cost-effectiveness in screening people above 50 in an endemic HBV belt using contrast-enhanced ultrasound (CEUS) and alpha-fetoprotein (AFP) levels. Public health policies and interventions should be implemented to address the significant mortality of hepatocellular carcinoma (HCC).

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