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## Next big threat for Pakistan Hepatocellular Carcinoma (HCC)

Om Parkash, Saeed Hamid

### Abstract

In our country, world hepatitis day (28th May 2013) was observed as a liver cancer day to draw global attention on the global health menace caused by Hepatocellular carcinoma (HCC). This is the right time to write a review article to apprise the nation of this growing burden of HCC caused most commonly by viruses in our country.

Pakistan is also recognized as one of the countries of the world where hepatitis C virus (HCV) is endemic. Recent large national surveys suggest an overall HCV prevalence of 4.8% and that of HBV as 2.5%. There are however communities where the sero-prevalence of HCV can be as high as 23%. No wonder that chronic liver disease is the fifth most common reason for morbidity and mortality in the country and Pakistan has been perhaps accurately called a "cirrhotic state". Hence majority of such patients are at risk of developing HCC.

**Keywords:** Hepatocellular carcinoma, Cirrhosis, Chronic liver disease, Hepatitis B, D and C.

### Introduction

Hepatocellular carcinoma (HCC) i-e Liver cancer has been one of the most important cancers in the world. As per world health organization (WHO) statistics (2000), globally there are at least 564,000 new cases of HCC per year and among them 400,000 develop in men.<sup>1</sup> Unfortunately HCC is the one of the least curable malignancies.<sup>2</sup> Hepatocellular carcinoma (HCC), accounting for 5% of cancers globally, is ranked as the 6th most common cancer and the 3rd leading cause of cancer-related death worldwide. The incidence of HCC may continue increasing over the next 20 years and to peak around 2030.<sup>3</sup> HCC is fifth most common cancer among men and second leading cause of cancer related death in world with highest case fatality rate.<sup>4</sup> Among women, HCC is the 7th most common cancer and 6th most common cancer related death.<sup>4</sup> In Pakistan prevalence of HCC varies from 3.7%-16% of malignant tumours and most common cause of HCC is viral hepatitis

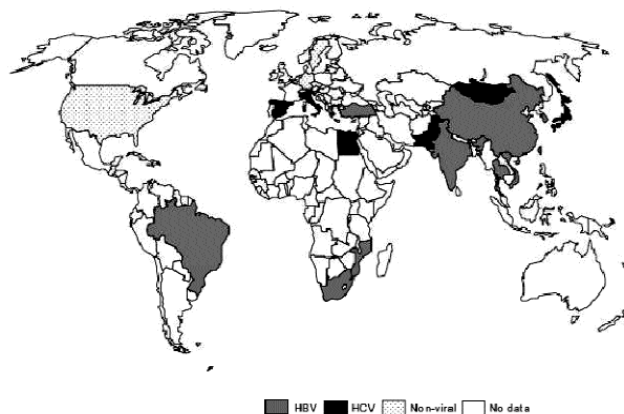


Figure-1: Global map for HCC showing etiology.<sup>14</sup>

B, C and D related cirrhosis. In Pakistan approximately 87% of HCC is caused by viral hepatitis either C (68%) or B related cirrhosis (22%) similarly another study from Hyderabad Sindh Pakistan had also shown high burden of viral associated HCC (HCV 66% and HBV 43%).<sup>5</sup> Recently a study from Karachi had shown the increasing number of admissions related to HCC and simultaneously showing highest burden of viral associated HCC. According to this report most of the cases are diagnosed at a very late stage of the disease when options are very limited for cure and less than 1% undergo resection.<sup>6</sup>

The incidence of HCC varies between diverse geographical regions between countries or geo economic zones within countries. This is a common cancer in the Asia pacific region and Africa with age standardized incidence of 14-36 per 100,000 men and this is much lower than other subcontinents such as Australia, North America and Europe.<sup>1</sup>

Most cases of HCC (approximately 85%) occur in the developing world (Sub-Saharan Africa and Eastern Asia) and among them 80% are due to chronic viral hepatitis B and C Figure-1.<sup>7</sup>

Worldwide, an estimated two billion people have been infected with the hepatitis B virus and more than 240 million have chronic (long-term) liver infections. About 600 000 people die every year due to the acute or chronic consequences of hepatitis B.<sup>8</sup>

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Every year, 3-4 million people are infected with the hepatitis C virus. About 150 million people are chronically infected and at risk of developing liver cirrhosis and/or liver cancer. More than 350 000 people die from hepatitis C-related liver diseases every year. Hepatitis C is found worldwide. Countries with high rates of chronic infection are Egypt (22%), Pakistan (4.8%) and China (3.2%). The main mode of transmission in these countries is attributed to unsafe injections or by using contaminated equipments.<sup>9</sup>

Recently a nationwide conducted survey for prevalence of HBV and HCV infection along with their risk factors in Pakistan had shown moderate to high prevalence and most common risk factor was use of unsafe injection.<sup>10</sup> Pakistan is a sovereign country in South Asia and the sixth most populous country in the world with population of over 180 million people.<sup>11</sup>

Therefore it is assumed that incidence of HCC is expected to rise as consequence of high incidence of HBV and HCV in last quarter of last century and there is an average lag time between virus acquisition and development of cirrhosis which in turn lead to cancer in some cases. This trend is also observed in Pakistan as shown by study in Pakistan which confirmed that rising trend of HCC related admission in tertiary care hospitals.<sup>6</sup>

Globally men are more likely to develop HCC than women and a similar trend is also seen in Pakistan.<sup>2,12</sup> Globally, HCC is rarely seen in the first 4 decades of life except in South Asia where prevalence of viral hepatitis associated cirrhosis is high. Hence age adjusted incidence of HCC in Pakistan is 5.7 for men and 3.7 for women.<sup>12</sup>

**Risk factors:** Multiple risk factors have been identified for the development of hepatocellular carcinoma (HCC). These include viral hepatitis (HBV, HCV), hereditary haemochromatosis and cirrhosis of almost any cause.<sup>13</sup> The relative importance of viral hepatitis in etiology of HCC fluctuates significantly from one part of world to another region.<sup>14</sup>

**Hepatitis B:** This infection has the peculiarity of developing HCC even in the absence of cirrhosis, however 70-90% of the patients with HBV who develop HCC would have cirrhosis.<sup>15</sup> Apart from cirrhosis, there are other factors associated with HBV, which play some role in developing HCC. These factors include viral load, presence of Hepatitis Be Ag (HBeAg) and presence of hepatitis B surface Antigen (HBsAg).<sup>16</sup> Co- infection of HBV with HCV or HDV is associated with increased risk of HCC. These patients with co infection had poorer outcome as compared to mono-infection.<sup>17</sup>

**Hepatitis C:** There is a strong association between chronic hepatitis C infection and HCC but the underlying mechanism is unclear. HCV infection is the most common cause of cirrhosis<sup>18</sup> and HCC in Pakistan like in other countries such as India, Japan, European countries and also in North America.<sup>1,13,19</sup> A prospective study from Taiwan had shown 24% cumulative lifetime risk of HCC for men and 17% women of age group 30-65 years.<sup>20</sup>

**Cirrhosis:** Patients with chronic liver disease due to any cause will have an increased risk of HCC. Compensated cirrhotic patients are believed to have a 1-8% annual incidence of HCC.<sup>21</sup>

**Environmental toxins:** Environmental toxins like aflatoxin, betel nut chewing and contaminated drinking water may be contributing to the pathogenesis of HCC. However their contribution to the world wide disease burden of HCC is minimal.<sup>22,23</sup>

**Diabetes mellitus (DM) and Non Alcoholic fatty liver disease (NAFLD):** Population based studies as well as multiple systemic reviews had shown strong association of DM with HCC. A systematic review that included a total of 49 case-control and cohort studies estimated that the risk was increased by approximately 2.2-fold (risk ratio 2.2; 95% CI 1.7-3.0), although few studies adjusted for diet and obesity.<sup>24,25</sup> Another meta-analysis comprising 14 epidemiologic studies found an increased risk of HCC among diabetes patients (relative risk of 1.9).<sup>26</sup> In Pakistan around 6% of the population is suffering from diabetes hence this is also a great threat to develop HCC in this country.<sup>27</sup>

There is rising evidence that NAFLD signifies an increasingly frequent underlying liver disease in patients with HCC. It is likely that NAFLD causes HCC via cirrhosis, although the exact pathogenesis has not yet been determined. One study found that HCC in NASH was associated with obesity, diabetes, hypertension and male sex.<sup>28</sup>

Similar situation is found in Pakistan for diabetes and obesity as shown by Jafar et al in their study. According to this study about a quarter of Pakistani population is overweight or obese.<sup>29</sup> Therefore Pakistani population is at higher risk for non B non C associated cirrhosis and ultimately leading to HCC.

**Diagnosis:** Timely diagnosis of this deadly disease can be curative if the patients who are at risk of developing the HCC will be enrolled into the regular surveillance programme.<sup>30</sup> Hence early diagnosis of hepatocellular carcinoma (HCC) is feasible because of its potential of developing in the background of well known, readily identifiable and

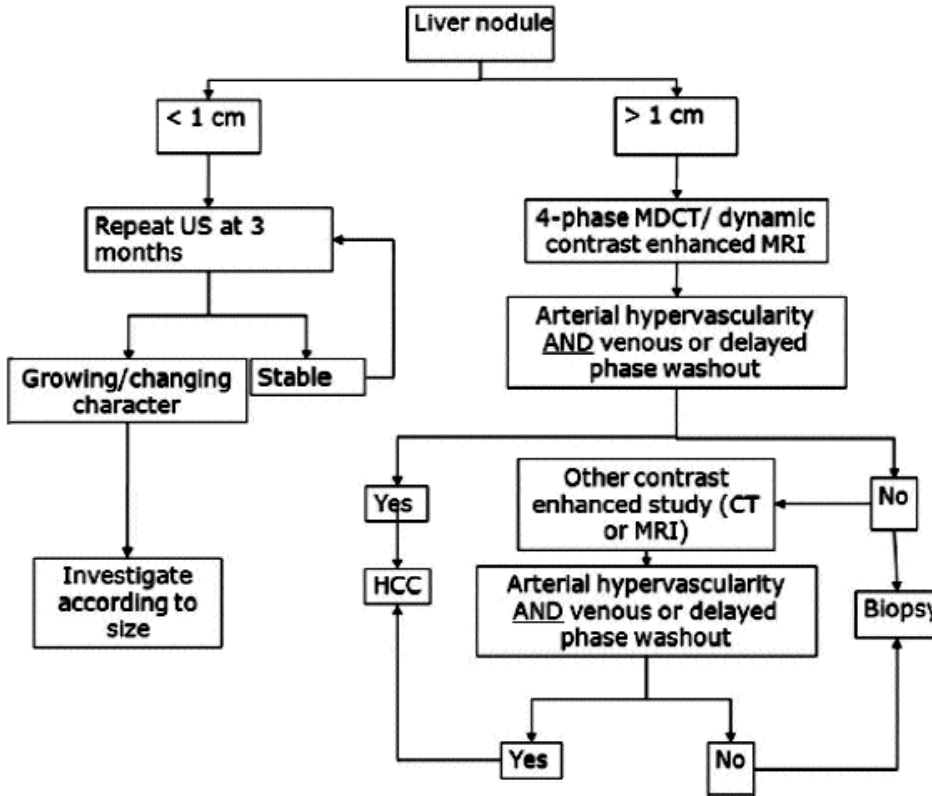


Figure-2: Diagnostic algorithm for suspected HCC. (CT: Computerized tomography, MRI: Magnetic resonance imaging, US: Ultrasound).<sup>32</sup>

potentially avoidable environmental risk factors. International societies like American association for the study of liver disease (AASLD) and European Association for the study of liver (EASL) disease recommend semiannually an Ultrasound liver and serum AFP.<sup>31</sup>

AASLD guidelines recommend that a mass found incidentally or on screening in CLD patients is likely to be HCC and Algorithm for investigation of HCC is shown in Figure-2.<sup>32</sup>

Management (Figure-3): Historically majority of the patients with HCC were diagnosed in very late stages when the patients were symptomatic and had variable degree of impairment of liver functions.<sup>32</sup> We assume that this is still the case in our country where patients are unfortunately diagnosed late when no

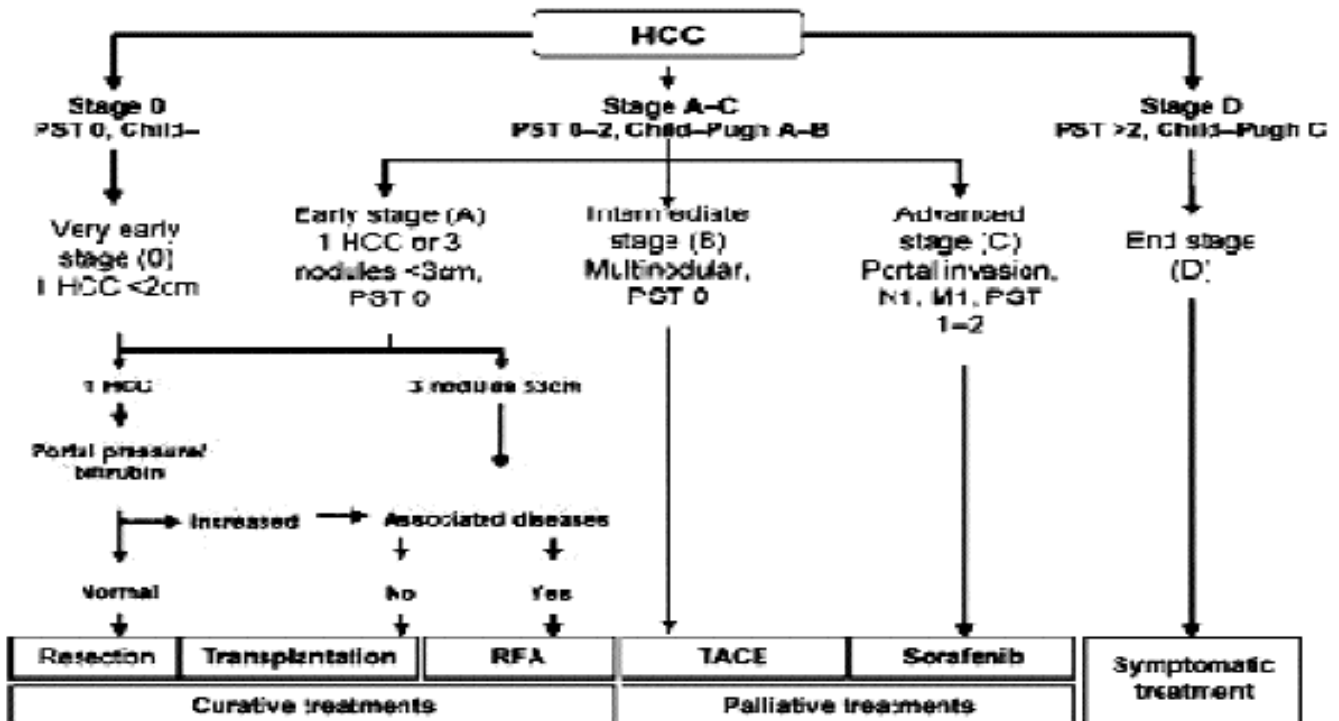


Figure-3: BCLC staging system and treatment allocation.<sup>32</sup>

effective treatment can be offered to improve survival. Based on better surveillance programme, these patients can be picked early and definitive or curative therapy (surgical resection or radiofrequency ablation) can be given or they can be offered a liver transplant or palliative therapy like Trans-arterial chemoembolization (TACE).

### Prevention

HCC prevention due to HBV infection: Vaccine for hepatitis B (produced by recombinant DNA technology) was first licensed in United States in 1981. The vaccine is administered in a three doses series with good efficacy and safety.<sup>14,33</sup> HBV vaccine within 12-24 hours after birth, followed by a 3 dose regimen, had shown significant effect in prevention of vertical transmission of HBV common in Asia.<sup>33</sup>

Recently decline in incidence of HCC and its associated mortality has been confirmed in Taiwan population where first HBV immunization programme was established in 1984.<sup>34</sup>

In 1992, world health organization (WHO) recommended the addition of HBV vaccine into national immunization programme. Among the 192, 158 member nations had implemented the infant HBV vaccine programme by year 2005 and 62% of these countries claimed  $\geq 80\%$  coverage.<sup>14</sup> In Pakistan HBV vaccine was incorporated in July 2001. One of the studies from Karachi had shown 86% of health care worker to be vaccinated.<sup>35</sup> In Pakistan, vaccination should be targeted to the high risk persons like intravenous drug abusers, sex workers, patient on regular dialysis and family members of index cases of HBV infection.

Other strategies include the avoidance of reuse of used injections or unnecessary injections, use of new blade or razor for each person at barber shop, avoiding homo or heterosexual malpractices. Physicians should hold health awareness session on preventing strategies for blood borne infection.

HCC prevention due to HCV infection: there is no such vaccine for HCV infection however research is going on to develops the new prophylactic and therapeutic vaccine. In the absence of vaccine for HCV, its prevention is more difficult than the prevention of HBV hence requiring the integrated strategies including the safe injection practices and avoidance of unnecessary injection, routine screening for blood before donation, avoiding going to non-qualified dental doctors for dental procedures, ear piercing or circumcision to be done by a certified doctor with clean instruments and proper disposal of used needles.

Regarding HCV infection, if it is cured successfully in time before the development of cirrhosis, both cirrhosis and HCC can be prevented.<sup>36</sup>

Other causes of cirrhosis: All the other conditions (alcoholic liver disease, non alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis etc), which can potentially lead to cirrhosis and ultimately HCC, should be timely managed, to substantially reduce the risk of HCC.

Avoidance of environmental risk factors like aflatoxins which is produced by strains of *Aspergillus*, can also decrease the incidence of HCC.<sup>37</sup>

Good glycaemic control in diabetic patients with antidiabetic medications like thiazolidinedione or metformin has been associated with a decreased risk for HCC.<sup>24</sup>

### Conclusion

It is established that Pakistan is a poor country with scarcity of resources and with high burden of all the risk factors for HCC, therefore a big challenge of high burden of HCC is confronted. Unfortunately majority of these patients with HCC are diagnosed late with high mortality and morbidity hence they are left with palliative treatment only. Even the treatment modalities are not available in major cities of Pakistan except in few selected centers where only high affluent people can reach. We therefore assume that HCC will be the next big threat to Pakistan. Our physicians should be made aware of this menace and should be taught about the surveillance for HCC because regular surveillance for HCC will detect HCC at an early stage where some curative options can be availed. This is the time that we can raise a voice against this menace which is causing untimely mortality and morbidity. This is a potentially preventable tumour by vaccinating the masses for HBV and adopting prevention strategies for HCV infection.

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