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Hepatocellular carcinoma – a complicated matter

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Abstract

Hepatocellular carcinoma and socioeconomic status of a population have a complicated relationship. While the determinants that are associated with increasing the risks of getting the disease are attributing the incidence and prevalence in certain regions, the availability of essential healthcare plays the main role in favourable prognosis and lower mortality rates.

Running title: Hepatocellular carcinoma

Keywords: hepatocellular carcinoma (HCC), Hepatitis B Virus infection (HBV), Hepatitis C Virus infection (HCV), socioeconomic status, liver diseases

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Introduction

Liver cancer appearance has been increasing rapidly and it is one of the top major causes of death in many countries [1]. Hepatocellular carcinoma (HCC) is the most significant form [2] and risk factors of HCC are hepatitis B (HBV) and hepatitis C (HCV) infection through medical procedure, sexual activity and other insanitary conditions, obesity and alcohol intake [3]. Management of HCC essentially involves prevention measures like vaccination and precautions, well established guidelines and procedures [3], and easy access to screening processes. Socioeconomic status, which includes marital status, insurance status, education, household income of the population, has influences on the risks of getting HCC and the disease status.

Hepatocellular carcinoma

The factors leading to HCC are influenced by both environmentally and genetically. Infection of HBV and HCV takes the main role by 55.7% of HCC development. Liver cirrhosis, excessive alcohol consumption, non-alcoholic steatohepatitis (NASH), ingestion of aflatoxin B1 (which is the fungi that contaminate stored cereals like peanuts and wheat), nonalcoholic fatty liver diseases (NAFLD), diabetes mellitus, tobacco and genetic diseases are also the causes of HCC. The symptoms as results of impaired liver function can be listed as pain in the upper-right quadrant of the abdomen, palpable masses appearance, weight loss, jaundice, ascites and fever, producing negative impacts on quality of life, physical and mental health, social life of the individuals [4].

Early detection and accessibility of therapy are important for the survival rate and quality of life of the patient. Depending on the stage of the disease, surgical resection, local ablation, liver transplant and palliative care, which is basically the last of the treatment plan, are the options for the patient and the medical team [4].

Socioeconomic status

The socioeconomic status of a population is not simply determined only by their income. Education, employment status, migration background and a complex combination of environmental and social conditions drive this phenomenon [5]. Geographic accessibility, availability of appropriate type of care, financial accessibility and cultural-social acceptability also matter here [6].

Connection between socioeconomic status and risk factors

HBV, believed to be the leading factor of HCC, transmits through blood, semen and other body fluid from infected persons via sexual contact, syringes, pregnancy, delivery and sharing needles, syringes and other drug injection equipment. This is vaccine-preventable liver infection [7]. However, due to unavailability of vaccine and its high costs, and little knowledge about the vaccine, only 16.4% of healthcare workers, who are most likely to be infected because of occupational contact with the patients, are vaccinated in Basaso, 2020 according to the studies [8]. Another example is the amount of pre-clinical students of a medical college in Nepal 2020. Only half of them have good knowledge of the vaccine and 39.2% were never vaccinated with the main reason for lack of vaccination programs [9].

Another risk factor, alcohol consumption is also influenced by socioeconomic status of the public. Excessive alcohol intake can lead to huge negative effects on the heart and liver. Alcoholics usually face stroke, high blood pressure, cardiomyopathy, liver steatosis, fibrosis, cirrhosis and most significantly hepatocellular carcinoma in this case. According to studies on countries with highest and lowest alcohol consumption in 2019, regions where people with religions that do not favour alcohol show significantly low consumption rate [10]. It also shows that individuals with lower income, educational and work status drink less than those with managerial and professional positions [11]. Heavy tobacco smoking can also cause HCC, specifically when an individual is exposed to both ethanol and tobacco [12].

Fungal infection is one of the factors leading to HCC, especially in low-income countries like those in Asia-Pacific region and Africa where inspection control on crops, maize and groundnuts that can be contaminated with aflatoxin is neither existent nor forced like in developed countries with strict rules implemented by their government. Nearly 45 million of the world's population has exposure to aflatoxin and this is a terrifying leading cause to many of HCC patients [13].

Biomarkers of HCC

Biomarkers are compounds in our system that work as indicators for physiologic or pathologic processes or how our body responds to therapeutic or diagnostic procedures. It is unlikely to diagnose based only on one type of biomarker because of its specificity and sensitivity. Alpha fetoprotein (AFP) and diagnostic imaging using ultrasounds are mainly recommended for early HCC detection. However, serum AFP level is not clear in approximately 80% of small HCCs and HBV or HCV infection can also give AFP elevation without HCC development. Molecular biomarkers can also give details about biological behaviour of the tumour. Therefore, they can be used to determine prognosis after liver resection, transplantation and survival and recurrence rate.LCA-bound fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP) are known to be superior to AFP in predicting waitlist dropout among patients with HCC [14,15].

Cellular origin of HCC

80% of total liver volume is occupied by hepatocytes. The component of liver mass also includes parenchyma cells which are biliary epithelial cells (BECs) and non-parenchymal cells: sinusoidal endothelial cells, stellate cells, portal fibroblasts, immune cells and Kupffer cells. Hepatic progenitor cells (HPCs) can differentiate into either hepatocytes or BECs. Under normal conditions, hepatocytes are rarely divided in the adult liver but they have the ability to regenerate tremendously upon liver injury resulting from chronic liver inflammation. Pro-inflammatory cytokines (such as IL-6, TNF-α) and anti-inflammatory cytokines - Transforming Growth Factors α and β (TGF-α and β), different transcription factors (Nuclear factor kappa-light--chain-enhancer of activated B cells (NF-κβ), signal transducer and activator of transcription 3 (STAT-3)), their signalling pathway are significantly leading to HCC development. Studies have found that all existing hepatocytes and distinct populations of BECs and HHPCs can step up and be involved in injury repairs. However, for HCC, there has been debates on whether HCC originates from hepatocytes or HPCs, despite the epithelial origin of HCC [14,16].

Molecular mechanism of HCC

Development and prognosis of HCC has a large set of mechanisms. One of the different factors is loss of cell cycle control where proliferation clusters can be found. Either higher expression of proliferation-associated genes or lesser expression of CIP/KIP family members of proteins p21/27 can lead to over-expression of the molecules which can cause HCC. One of the examples dedicated to this will be tremendous expression of PKM2, a principal metabolic enzymes in glycolysis as well as a transcriptional co-activator regulating gene expression of HIF-1 α, β-care in/TCF, signal transducer, sterol regulatory element-binding protein 1a (SREBP-1a) and nuclear factor erythroid 2-like 2 (NRF2), which are associated with HCC development. Moreover, these enzymes attach to the outer membrane of mitochondria and show non-metabolic enzyme function either by directly regulating the expression of tumour related genes or by indirectly promoting glycolysis for carcinogenic cells with the help of HIF-1 action. Another pathway is the loss of senescence control, the irreversible growth inhibition of the cells at DNA checkpoint. The genetically altered cells will proliferate [17,18].

Genetic causes

Apart from environmental factors influenced by socioeconomic status, genetic problems can also lead to HCC. Some single gene defects of which carrier can rarely be found in general population, like alpha-1 antitrypsin deficiency, glycogen storage disease type 1, hemochromatosis, acute intermittent, cutaneous tardy porphyria, hereditary tyrosinemia type 1, have high risk of HCC. Polygenic syndromes such as autoimmune hepatitis, type 2 diabetes, family history of HCC, hypothyroidism, non-alcoholic steatohepatitis, which are partly modified by socio--environmental factors can increase incidence of HCC. However, we have to keep in mind that a few of the genetic syndromes may cause HCC themselves even in the conditions of lacking environmental factors [12]. Diabetes together with obesity can lead NAFLD to cirrhosis and HCC. Obesity in adults is found to be higher in developed countries than in Southeast Asia countries [19].

Management of HCC

Surveillance of blood-based markers, most commonly AFP, can improve the survival rate with 70% of 5-yr survival in patients with early stage and less than 5% at advanced stage but patients in low income countries are mostly diagnosed based on clinical features because of lack of sophisticated imaging equipment. By that time, the tumour is recognized only when it has reached an advanced stage and becomes inoperable [13,20]. The best example can be found in Japan where a nationwide surveillance system for HCC has been established since after the high incidences in the 1980s. The Japan Society of Hepatology focused on improving the early diagnosis of high risk patients and managed to bring up the changing trend in a positive way [21].

Despites of well-established treatment options for different stages of HCC, there is difficulty in access to advanced procedures in developing countries due to insufficiency of expertise and resources. Furthermore, in countries with no public funding or subsidy for diagnosis and treatment, payment for the medical care is generally out-of-pocket for the individuals. This is not affordable for the majority of the population [22].

Stages that patients have to go through to get a liver transplant is also a series of struggles. The medical care facilities have their priorities based on MELD scores (Model for End Stage Liver Disease), which describes that a patient has to be in the state of needing the liver transplant within three months. In addition, a living donor who resembles the patient physically is required. If not, non-ideal donors with past drug history, old donors or individuals with HBV, HCV infection become the only option for the patients [23]. In addition, high cost medications, procedures and resources used for long-waiting for transplantation has a huge financial impact even on the NHS, the second world largest single payer healthcare system [24].

Conclusions

HCC is one of the most common cancers all over the world, significantly influenced by the socioeconomic status of the population. Depending on the

accessibility of medical care, life-style and surrounding conditions, incidence rates and prognosis differences are found to be extreme. These facts are pointing that each and every individual needs to be more aware of the disease status on their own and the nations and their health organisations are still in need to expertise on better policy and plan to bring more accessibility to the people.

Ethical approval
The study was a descriptive one. No human or animals were a subject of examinations.

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Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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