World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Demographics, risk factors, clinical manifestations, staging and liver function tests of hepatocellular Carcinoma: A literature review

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World Journal of Advanced Research and Reviews, 2024, 24(03), 2087-2093

Publication history: Received on 08 November 2024; revised on 21 December 2024; accepted on 23 December 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.24.3.3853

Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, with an increasing prevalence worldwide. Hepatocellular carcinoma is the sixth most prevalent cancer and the third most frequent cause of cancer-related death. The incidence of HCC is higher in men than in women. HCC often occurs in individuals with chronic liver disease, especially those caused by hepatitis B and C virus infection, excessive alcohol consumption, and non-alcoholic liver disease (NAFLD). The pathogenesis of HCC involves multiple factors, including genetic mutations, epigenetic changes, and disruption of cellular pathways that lead to uncontrolled cell growth. Clinical symptoms of HCC are often nonspecific and appear at an advanced stage, leading to delayed diagnosis. BCLC (Barcelona Clinic Liver Cancer) staging is used to determine the stage of hepatocellular carcinoma (HCC) development and assist in treatment planning. Liver function tests, including measurements of SGOT, SGPT, bilirubin, Albumin, PT and AFP, help in the diagnosis and monitoring of the disease. Therefore, early detection and more innovative therapeutic approaches are essential to improve the survival of HCC patients.

Keywords: Hepatocellular Carcinoma; Liver cancer; Hepatitis; Cancer; BCLC

1. Introduction

Liver cancer is one of the most common and frequently found types of cancer in society, with the incidence continuing to increase. According to the WHO Global Cancer Observatory (GCO) report, there are an estimated 866,136 new cases of liver cancer worldwide in 2022. Hepatocellular carcinoma is the most common type of liver cancer, accounting for about 75-85% of all liver cancer cases [1].

Hepatocellular carcinoma (HCC) is consistently more common in men than in women, with a global incidence ratio of approximately 2:1. This difference is largely due to higher risk factors in men, such as alcohol consumption, chronic hepatitis infection, smoking cigarettes, and having increased iron stores. [2].

Common symptoms of hepatocellular carcinoma include abdominal pain, fatigue, and weight loss. Loss of synthetic liver function often results in hepatic encephalopathy, jaundice, and ascites. High portal pressure results in new or difficult-to-control ascites and variceal bleeding. Hepatomegaly is often seen on physical examination [3].

Chronic exposure of the liver to injury from viral hepatitis, alcohol abuse or NASH causes repeated hepatocyte damage and sets up a vicious cycle of cell death and regeneration which eventually results in cirrhosis. The resultant genomic instability leads to initiation of HCC. Step wise accumulation of multiple genetic events including gene rearrangements,

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somatic mutations, copy number alterations, epigenetic changes and growth factor pathway alterations eventually lead to tumor progression and metastases [4].

Liver function tests are used to detect, specifically diagnose, and predict the severity of liver disease. Markers of hepatocellular carcinoma can be done through liver function tests, liver function tests usually include alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), serum bilirubin, prothrombin time (PT), international normalized ratio (INR), total protein and albumin. These tests can help determine the area of the liver where damage may occur and, depending on the pattern of elevation, can help set up a differential diagnosis. There are several staging systems for liver cancer. The Barcelona Clinic Liver Cancer (BCLC) Staging System is widely used to stage primary liver cancer. The system is used to predict the patient's chance of recovery and to plan treatment [5, 6].

This literature review aims to understand the demographic profile of hepatocellular carcinoma patients. This review will explore influencing factors such as gender, symptoms, causes, staging BCLC and liver function test results in hepatocellular carcinoma patients. By knowing the profile of hepatocellular carcinoma, it is hoped that more appropriate and efficient interventions can be carried out to overcome liver cancer, both in terms of prevention, early detection, and treatment.

2. Review Content

2.1. Definition and Epidemiology of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a primary liver tumor. Hepatocellular carcinoma accounts for more than 90% of primary liver tumors. Hepatocellular carcinoma (HCC) is a type of liver cancer that originates from hepatocytes, the main functional cells of the liver, caused by abnormal cell growth and malignant transformation that occurs in the liver that can lead to death [7]. According to the WHO Global Cancer Observatory (GCO) report, there are an estimated 866,136 new cases of liver cancer worldwide in 2022. Hepatocellular carcinoma is the most common type of liver cancer, accounting for about 75-85% of all liver cancer cases [1].

Sex disparity has been observed in HCC of male predominance with a 2-5 times higher incidence, regardless of the etiology of HCC . The sex disparity in HBV/HCV-related HCC can be explained by the cross-talk between sex hormone and HBV/HCV. Animal and human studies indicated that sex disparity may originate from different sexual hormones serving different roles: androgen as tumor promoter and estrogen as tumor suppressor. Two meta-analyses demonstrated that sex disparity exists in the obesity and HCC association, in that obese men had higher risk of HCC than obese women. The similarity between men and women in Asian studies may result from the high prevalence of HBV/HCV infections, which contributed to the most HCC cases in Asia [8, 9, 10, 11].

2.2. Pathophysiology of Hepatocellular Carcinoma

The pathophysiology of hepatocarcinoma is multifactorial because various factors contribute directly or indirectly to hepatocarcinoma. Several studies have been conducted and the underlying risk factors for carcinoma are liver cirrhosis due to several etiologies, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, hereditary hemochromatosis, diabetes, overweight, smoking, and alcohol consumption. Whatever the causative factor of hepatocarcinoma, increased liver cell turnover caused by chronic injury and regeneration in the form of inflammation and oxidative DNA damage causes malignant transformation of hepatocytes. This can cause genetic changes, such as chromosome changes, activation of cell oncogenes or inactivation of tumor suppressor genes [12].

2.3. Clinical Manifestation of Hepatocellular Carcinoma

Hepatocarcinoma manifestations can vary widely, from asymptomatic to with clear symptoms and signs, accompanied by liver failure. Signs and symptoms can be; (1) pain or discomfort in the right upper abdomen; (2) signs of liver failure, such as weakness, weight loss, anorexia, and jaundice; (3) hepatomegaly, in patients with cirrhosis of the liver with complaints of right upper abdominal pain, an enlarged liver will be palpable; (4) variceal bleeding due to portal vein thrombosis/portal hypertension, esophageal variceal bleeding; (5) location that does not improve; (6) palpable mass; and (7) bruit/friction rub [13].

The occurrence of multiple symptoms in HCC patients is common, and may include pain, fatigue, weight loss, and obstructive syndromes such as ascites and jaundice. Patients with HCC are usually asymptomatic during the early stages of disease. Unfortunately, 80% of patients with HCC will be diagnosed with advanced stage disease. Between 90–95% of HCC patients will present with the triad of right upper quadrant pain, palpable mass, and weight loss. Patients

typically present with an enlarged, irregular, and nodular liver. Other physical findings include hepatic bruits (25%), ascites, splenomegaly, jaundice, wasting, and fever. Liver function tests and jaundice may not appear until late in the disease trajectory because of the organ's functional reserve capability [14].

2.4. Etiology of Hepatocellular Carcinoma

Hepatitis B, hepatitis C, alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease are the etiological factors for the development of hepatocellular carcinoma [15].

2.4.1. Hepatitis B, Hepatitis C, and Cirrhosis

Chronic liver disease and cirrhosis are the main causative factors of hepatocarcinoma, where hepatitis virus and alcohol are the most common causative factors of liver cirrhosis. The majority of hepatocarcinoma patients occur in patients with a history of liver disease such as hepatitis B (HBV) or hepatitis C (HCV). Hepatitis B and C infections are the cause of 80% of hepatocarcinoma cases worldwide and are the most important cause of hepatocarcinoma cases (A global view of hepatocellular). In the world population, hepatitis B infection is associated with the main cause of hepatocarcinoma. Liver cell damage occurs due to the integration of viruses that cause DNA damage [15]. This infection is common in people who are not vaccinated against hepatitis B, with the highest prevalence occurring in East Asian and African countries [16, 17].

The risk of hepatocarcinoma also increases due to liver cirrhosis. Liver cirrhosis experienced by patients is caused by chronic viral hepatitis, inherited metabolic diseases such as non-alcoholic fatty liver disease (NAFLD), genetic hemochromatosis, or in some cases alpha-1-antitrypsin deficiency, and also caused by chronic alcohol abuse [18]. In most cases, hepatocarcinoma develops into a sequelae of chronic hepatitis that occurs after patients experience cirrhosis due to hepatitis B and C infections [17].

2.4.2. Non-Alcoholic Liver Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease is excess fat in the hepatocytes in the absence of a history of alcohol. NAFLD mostly occurs in the setting of metabolic syndrome. Metabolic syndrome occurs in patients with insulin resistance, hypertension, hypertriglyceridemia, and abdominal obesity, which increases cardiovascular risk. NAFLD is now a leading cause of HCC worldwide, especially in western countries. 13% of patients noted to have HCC without background cirrhosis were noted to have NAFLD. The incidence of HCC is expected to increase by 122% in the United States due to the increase in obesity and diabetes between 2016 and 2030 [19, 20].

2.4.3. Alcohol

United States and Europe, alcoholic cirrhosis is the second most common risk factor. Based on a meta-analysis conducted by the World Cancer Research Fund, it was found that there was an increased risk of 4% per 10g of alcohol intake per day. Based on a retrospective cohort study conducted on 450 patients with alcoholic cirrhosis, it was found that older age (≥55 years) and thrombocytopenia (platelets <125,000/mm3) were independent risk factors for developing hepatocarcinoma [17].

2.4.4. Aflatoxins

Aflatoxin B1 is a mycotoxin produced by Aspergillus flavus and Aspergillus parasiticus. This is mostly found in Sub-Saharan Africa and Southeast Asia, where the fungus contaminates grains. Carcinogenesis is mostly through the mutation of the tumor suppressor gene (p53). Aflatoxin B1 is associated with increased risk for HCC in patients with chronic hepatitis B virus [21].

2.5. Staging BCLC of Hepatocellular Carcinoma

Liver cancer staging is the process of classifying liver cancer based on various factors. It helps determine the severity of the disease, potential prognosis and the best treatment plan after diagnosis. There are more than 18 staging systems, each with a different purpose and their own advantages and disadvantages. For example, Okuda and CLIP are score-based staging systems to predict survival whereas BCLC guides treatment decisions. In addition to liver cancer staging systems, scoring systems such as Child-Pugh and MELD are used to assess liver function [22].

BCLC (Barcelona Clinic Liver Cancer) staging is a system designed to classify the stage of hepatocellular carcinoma (HCC) based on a series of clinical factors that influence prognosis and treatment options. The BCLC system is one of the most widely used staging systems worldwide for hepatocellular carcinoma, because it takes into account liver function,

patient performance status, tumor severity, and the ability to treat locally or systemically. The following is a detailed explanation of BCLC staging in HCC:

2.5.1. BCLC 0 (Stage 0) - Solitary Tumor, Normal Liver Function

At this stage, the patient has a single small tumor (usually ≤2 cm), without signs of vascular invasion or metastasis. The patient's liver function is still normal, namely with Child-Pugh A (excellent liver function) and good performance status (ECOG 0). The main therapy for patients at this stage is resection or liver transplantation. Liver resection can be considered if the tumor is localized and liver function is still good, while liver transplantation can be chosen if there is a risk of cirrhosis or underlying liver failure. Patients with this stage have a very good prognosis, with a high survival rate after intervention.

2.5.2. BCLC A (Stage A) – Solitary or Multiple Tumors, Good Liver Function

In this stage, patients have a solitary tumor or multiple small tumors (3-5 tumors, each <3 cm) that are confined to one part of the liver, and liver function is still Child-Pugh A or B (relatively good liver function). The patient's performance status is generally good (ECOG 0-1). The mainstay of therapy at this stage can be resection (if the tumor is well localized), local ablation (such as radiofrequency or microwave) or liver transplantation, especially if there is underlying cirrhosis. Local ablation can be an option in patients with multiple inoperable tumors. Patients at this stage generally have a fairly good prognosis, especially if resection or liver transplantation is performed.

2.5.3. BCLC B (Stage B) – Multiple Tumors with Good Liver Function

In stage BCLC B, patients usually have multiple larger tumors, but liver function is still quite good (Child-Pugh A or B). This stage shows no signs of blood vessel invasion or distant metastasis. Patients with this stage are not suitable for resection or liver transplantation. The mainstay of therapy is transarterial embolization (TACE - Transarterial Chemoembolization), which is a procedure to inject chemotherapy drugs directly into the tumor through the arteries that feed the tumor, while blocking blood flow to the tumor. Another alternative is local ablation if possible. The prognosis in stage BCLC B tends to be worse than in previous stages, but TACE can provide good results in controlling the tumor for a certain period of time.

2.5.4. BCLC C (Stage C) - Tumor Spread with Blood Vessel Invasion or Metastasis

At this stage, liver cancer has experienced blood vessel invasion or distant metastasis to other organs. Liver function can vary, but patients often have a poor performance status (ECOG ≥2). The mainstay of therapy at this stage is systemic therapy. Sorafenib, a tyrosine kinase inhibitor drug, is the mainstay of treatment often used to treat advanced HCC. Other options include newer systemic therapies, such as immunotherapy (eg, pembrolizumab) or combination systemic therapies. In patients who still have good performance status, some more aggressive treatment options can be considered. The prognosis for this stage is worse, with lower survival rates, but systemic therapy can help control the tumor and improve the patient's quality of life.

2.5.5. BCLC D (Stage D) – Terminal Liver Disease with Poor Patient Performance

In this stage, patients have very advanced liver disease, often with Child-Pugh C (very poor liver function), and poor performance status (ECOG ≥2). Patients may have liver failure or related complications, such as ascites, variceal bleeding, or hepatic encephalopathy. Treatment for patients with this stage is palliative care to manage symptoms, improve quality of life, and provide psychosocial support. Liver transplantation may be considered in some cases, but only if there is a strong medical indication and the patient has a good enough performance status. The prognosis at this stage is very poor, with very limited life expectancy. Palliative care focuses more on reducing pain and symptoms [23, 24].

BCLC (Barcelona Clinic Liver Cancer) staging is used to determine the stage of hepatocellular carcinoma (HCC) development and assist in treatment planning. Most patients are diagnosed at stage A and stage B. Stage A, with small tumors and good liver function, is found in about 25-30% of patients and has a better prognosis. Stage B, with multifocal tumors, is seen in 15-20% of patients and is more often treated with TACE. In stage C, with vascular invasion or distant metastases, the prevalence is about 25-30% and systemic treatment such as sorafenib is needed. Stage D, terminal stage, is found in 10-15% of patients and focuses on palliative care. These data suggest that early detection is essential to improve the prognosis of patients with HCC [25].

2.6. Liver function test of Hepatocellular Carcinoma

SGOT and SGPT are markers of hepatocellular injury. These enzymes participate in gluconeogenesis by catalyzing the transfer of amino groups from aspartate or alanine to α-ketoglutaric acid to produce oxaloacetate and pyruvic acid. SGOT is present as cytosolic and mitochondrial isoenzymes and is found in the liver, heart muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and red blood cells. It is not as sensitive or specific for the liver as SGPT, and elevations in SGOT can also be seen secondary to nonhepatic causes [26]. HCC patients generally have higher levels of SGOT, SGPT, and bilirubin and lower levels of albumin which are associated with liver damage. SGOT and SGPT in HCC patients are generally high and correlate with parenchymal inflammatory processes due to carcinogenesis [27]. Alkaline phosphatase (ALP) is a marker of liver function and is associated with biliary tract disease. It was reported as a prognostic factor for hepatocellular carcinoma (HCC). Patients with HCC with a higher ALP (>81 U/dL) had significantly more major hepatectomies, vascular invasion, and recurrence [28].

Bilirubin is the end product of hemoglobin breakdown, a diagnostic marker of liver disease and hematologic diseases. Due to its antioxidant effects, bilirubin is widely believed to be a protective factor for inflammation, diabetes, cardiovascular disease, metabolic syndrome, and chronic liver disease. Mild unconjugated hyperbilirubinemia may play a role in preventing cardiovascular disease and cancer [29, 30]. Several studies have shown that serum bilirubin levels in HCC patients are much lower than in BLD patients [31].

Albumin is synthesized by liver parenchymal cells at a rate that depends on colloid osmotic pressure and dietary protein intake. The rate of albumin synthesis is also subject to feedback regulation determined by plasma albumin concentration. Traces of albumin can be found in almost all extracellular body fluids. Only small amounts are lost from the body through excretion. Low serum albumin levels can be caused by impaired hepatic synthesis, urinary or enteric losses, or extravascular distribution (e.g., in ascites) [32].

Prothrombin time (PT) measures the rate of conversion of prothrombin to thrombin. Except for factor VIII, all other coagulation factors are synthesized by the liver. Prothrombin time requires factors II, V, VII, and X, and, because these factors are made in the liver, liver function is essential for coagulation [6]. A high PT usually means that there is serious liver damage or cirrhosis [33].

AFP levels profile based on etiology was showed that the AFP level> 400 ng/ml had common etiology of hepatitis B and hepatitis C. High AFP levels in patients with hepatitis infection reflect necroinflammation and regeneration process. High AFP levels in hepatitis B virus infection is associated with mutations in tumor suppressor gene p53 and β-catenin [34].

3. Conclusion

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, with an increasing incidence, especially in men, influenced by risk factors such as alcohol consumption, chronic hepatitis infection, and smoking. Symptoms of HCC include abdominal pain, fatigue, weight loss, and signs of liver failure such as jaundice and ascites. The main causes of HCC are hepatitis B and C infections, with other causes being alcoholic liver disease and NASH. The BCLC staging system is used to determine the stage of the disease and plan treatment, with different therapies depending on the stage of the cancer. Most patients are diagnosed at advanced stages (stages B and C), which have a poor prognosis if not detected early. In Liver function tests, HCC patients generally have higher levels of SGOT, SGPT, bilirubin, PT and AFP and lower levels of albumin which are associated with liver damage.

Compliance with ethical standards

Acknowledgments

The author would like to thank all supervisors and various parties who have helped carry out this research well.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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