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Review

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Prognostic Scores and Survival Rates by Etiology of Hepatocellular Carcinoma: A Review

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Abstract

Hepatocellular carcinoma (HCC) is a common cancer and ranks sixth among all malignancies worldwide. Risk factors for HCC can be classified as infectious or behavioral. Viral hepatitis and alcohol abuse are currently the most common risk factors for HCC; however, nonalcoholic liver disease is expected to become the most common cause of HCC in upcoming years. HCC survival rates vary according to the causative risk factors. As in any malignancy, staging is crucial in making therapeutic decisions. The selection of a specific score should be individualized according to patient characteristics. In this review, we summarize the current data on epidemiology, risk factors, prognostic scores, and survival in HCC.

Keywords: Cancer; Hepatocellular; Survival; Mortality

Introduction

Hepatocellular carcinoma (HCC) is a highly prevalent cancer globally, occupying the sixth place and was the third leading cause of cancer death worldwide in 2020 [1]. The prevailing etiology varies by country. Viral hepatitis and alcohol consumption are the most important risk factors for the development of HCC [2]. In countries where vaccination against hepatitis B virus (HBV) is widely available, alcohol-related HCC can be more prevalent [3]. In the last decades, nonalcoholic fatty liver disease (NAFLD) has become a more prevalent risk factor for HCC in the United States due to the rise of obesity and metabolic syndrome in this country [4]. Early detection of HCC is likely beneficial, and prognosis can be calculated using tumor characteristics, clinical parameters, or both. We summarize current data on HCC survival and prognostic scores and show our own analysis using patients from The Cancer Genome Atlas (TCGA).

Epidemiology

HCC accounts for 70% of primary liver cancers and is the sixth most common cancer worldwide [1-3, 5]. It is the third leading cause of cancer-related deaths in the world [2-4]. It is more common in men and the average age at diagnosis is 50 - 70 years [2, 3]. Africa and Asia account for 80% of all HCC cases, with Asia bearing approximately 72.5%. This is thought to be due to their high rates of HBV infection, as well as high rates of aflatoxin exposure [1, 2, 6]. Limited access to HBV screening, vaccination, and treatment also plays a role [7]. Eastern and Central Europe are the regions with the highest prevalence of alcohol-associated HCC [8, 9].

Socioeconomic status is an important factor, and within the same country, there is a disparity between the extremes of social classes [2]. In the United States, a multi-racial/multiethnic country, the incidence of HCC historically was higher among Asians until 2012, when Hispanics surpassed them. The incidence of HCC in these two groups is nearly double that of non-Hispanic whites. Hispanics who were born in the United States have higher rates or alcohol consumption, hepatitis C virus (HCV) infection, and NAFLD, which illustrates that race is not the only factor at play. Asian Americans, on the other hand, have lower incidence of HCC than their non-American counterparts, likely due to lower rates of HBV infection and high access to HBV vaccination at birth [2, 10, 11].

Risk Factors

HCC risk factors can be categorized as infectious or behavioral [12, 13]. The most common infectious risk factors are HBV or HCV infection.

The incidence of HCC in patients with chronic HBV in-

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fection is 44%, and in HCV infection, 21%. Patients with high alcohol consumption have up to 26% risk of developing HCC. Other risk factors include non-alcoholic liver disease, tobacco smoking, aflatoxin-contaminated food intake, diabetes, and obesity [1, 10, 12].

Other less common risk factors are alpha 1-antitrypsin deficiency, Wilson's disease, hereditary hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis [12, 13].

Development of HCC involves hepatic damage, which includes hepatocyte inflammation, necrosis, and regeneration [13]. Having more than one risk factor can contribute to the development of HCC; for example, patients with HBV who are exposed to aflatoxins have a 60-fold increased risk of developing HCC compared to those without exposure. This is due to the role of HBV as a modulator in the binding of aflatoxins to DNA and the resulting mutations in the TP53 suppressor gene [12].

In the case of NAFLD, steatosis is caused by the lipid buildup in the liver caused by high caloric intake and poor physical activity, even in the absence of excessive alcohol consumption. Advanced steatosis along with insulin resistance, hyperinsulinemia, adipose tissue remodeling, oxidative damage, genetic factors, and epigenetic changes activate oncogenic signaling and promote HCC development [13, 14]. Modification of these underlying processes may prevent HCC incidence, as shown in the metanalysis done by Facciorusso et al that confirmed that statins decrease HCC occurrence by reducing liver fibrosis progression, mainly due to their immunomodulatory effects [15].

Trending of HCC Risk Factors Over Time

NAFLD has recently risen to prominence as one of the main causes of HCC in many countries [16]. NAFLD is a variety of liver conditions that can range from mild steatosis to liver damage. Nonalcoholic steatohepatitis (NASH) is the first inflammatory stage phase in NAFLD [16]. Although various disease modifiers, including steatohepatitis, are thought to be the pathophysiological drivers of disease development, there is a growing recognition that this disease activity is dynamic and can wax and wane, varying over time between NAFLD and NASH [17].

Furthermore, an incredibly versatile and dynamic inflammatory microenvironment is supported by NASH in which hepatic lipid buildup triggers metabolic reprogramming. This is characterized by a concomitant accumulation of potentially harmful metabolites and cellular metabolic modifications that favor the growth of liver tumorigenesis [16]. In addition to the lipotoxicity caused by the increased liver triglyceride storage, overnutrition and insulin resistance can directly activate the immune system and cause further damage to the hepatocytes [18, 19]. Extrahepatic factors like alterations of the intestinal mycobiome also play a role in the development of liver inflammation. Ultimately, the hepatocellular stress induces apoptosis, necrosis and necroptosis of the hepatocytes that could lead to HCC [18].

NASH is expected to rank among the most common causes of HCC in the coming years [1, 20-22]. Multiple studies have been performed, looking for molecular and genetic predisposition to NASH. Hepatokines, adipokines, and other hormones are implicated in NAFLD-related HCC. For example, increased serum leptin levels are associated with carcinogenesis in obesity and could represent a risk factor for recurrent phase I/II HCC after curative treatment [23].

The main etiological factor for HCC in Asia and Africa is HBV [24] with some regional exceptions like Japan (HCV 39%) [25] and Egypt (HCV 40-50%) [26]. In the Americas [4, 27] and Europe [24], HCV and alcoholic liver disease are the main etiological factors. Better antiviral treatments and improved HBV vaccination policies worldwide have led to declining rates of HCV and HBV-associated HCC [22, 28, 29]. However, close attention must be paid in patients who have achieved sustained virological response after treatment for HCV infection, because HCC may develop [30].

Prognostic Factors and Staging

Staging HCC involves not only the extent of invasion and spread of the tumor, but also the degree of liver function at the time of the diagnosis [29]. As in any malignancy, it is crucial to have a clinical staging system to assist in making therapeutic decisions. Some of the most frequently used scoring systems in HCC are the tumor, node, and metastasis (TNM), Okuda and Barcelona Clinic Liver Cancer (BCLC) systems, and the Cancer of the Liver Italian Program (CLIP). A new evidence-based score for HCC is the albumin-bilirubin (ALBI) grade which may enable a more accurate evaluation of the severity of liver failure in HCC patients [31, 32].

TNM staging

The TNM staging method is widely used for classification, prognosis, and therapeutic approach, both at the time of initial presentation and after surgical treatment of any solid malignancy [33]. T1 is subclassified into two stages: T1a for solitary tumors less than 2 cm, and T1b for solitary tumors without invasion of the vasculature and more than 2 cm. T2 includes a solitary tumor greater than 2 cm with vasculature invasion or multiple tumors no more than 5 cm. T3 includes patients with multiple tumors or any tumor greater than 5 cm, and T4 includes single or multiple tumors of any size with portal or hepatic vein involvement [34]. This staging score has been validated in patients treated with hepatic resection or transplantation [33]. One of its disadvantages is that it excludes liver function impairment, which has been shown to be a significant prognostic predictor [35].

Okuda system

In 1984, Okuda et al proposed a scoring system that considered ascites, albumin, and bilirubin as well as tumor size [36]. However, their classification of tumor burden as more or less as 50% of liver volume, and the lack of metastases or vascular invasion as criteria make this system inappropriate for clinical practice [36]. Modern diagnostic methods have discovered

Table 1. Okuda Staging System, Developed to Estimate the Survival in HCC

Criteria	0	1
Tumor size	> 50%	< 50%
Ascites	Clinically detectable	Clinically absent
Albumin	< 3 g/dL	> 3 g/dL
Bilirubin	> 3 mg/dL	< 3 mg/dL
Stage		
I	0	
II	1 or 2	
III	3 or 4	

HCC: hepatocellular carcinoma.

that multiple small tumors occupying the entire liver, but still under 50% of its total size, are not effectively classified by this staging system [37] (Table 1).

CLIP score

The CLIP score measures various tumor characteristics along with the severity of cirrhosis and gives scores between 0 and 6. CLIP scores are useful for prognostication of HCC patients receiving non-surgical treatment, and some studies have shown that it outperforms the TNM, Okuda, or Child-Pugh systems in these patients [38, 39]. This score has certain limitations, such as the lack of an overall health assessment, and the inability to recognize the early stages that are receptive to surgical or less invasive treatments [40] (Table 2).

Table 2. Cancer of the Liver Italian Program Scoring System for HCC, Useful for Prognostication of HCC Patients Receiving Non-Surgical Treatment

Variable	Score
Child-Pugh stage	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension ≤ 50%	0
Multinodular and extension ≤ 50%	1
Massive or extension > 50%	2
Alpha-fetoprotein	
< 400	0
≥ 400	1
Portal vein thrombosis	
No	0
Yes	1

HCC: hepatocellular carcinoma.

Table 3. The Barcelona Classification for Staging and Treatment Strategy, Useful for Patients Undergoing Surgical Resection of HCC

Stage	Description
Early stage (0)	A solitary, ≤ 2 cm tumor in a patient with preserved liver function, no symptoms suggestive of malignancy, and no vascular invasion or extrahepatic dissemination.
Early stage (A)	Single tumor of any size or up to three nodules of less than 3 cm, with no macrovascular invasion, and no cancer-related symptoms.
Intermediate stage (B)	Patients with multifocal HCC who have a performance status of zero and adequate liver function without invasion or spread.
Advanced stage (C)	Presence of vascular invasion and extrahepatic spread, taking into consideration a performance status ≤ 2 and preserved liver function.
End stage (D)	Patients with a performance status of more than 2 with cancer symptomatology and/or impaired liver function without an option for liver transplantation.

HCC: hepatocellular carcinoma.

The Barcelona staging classification

The Barcelona staging classification was introduced in 1999 and is commonly used for patients undergoing surgical resection of HCC [41]. It includes five stages, and integrates tumor stage, liver function, overall physical condition, and disease-related symptoms (Table 3) [42].

ALBI score

The ALBI score is a simple and objective prognostic tool for evaluating liver function in patients with HCC [43]. Using bilirubin and albumin in a formula [(log10 bilirubin (in µmol/L) × 0.66) + (albumin (in g/L) × -0.085)], a score is calculated. The results are classified into three groups: grade I (≤ -2.60), grade II (< -2.60 to ≤ -1.39), and grade (III > -1.39) [43]. This score provides an objective assessment of liver function in HCC, without considering ascites or encephalopathy, as required by the Child-Pugh classification [43, 44].

Risk Estimation of Tumor Recurrence After Transplant (RETREAT) and Model of Recurrence After Liver Transplantation (MoRAL) scores

The RETREAT score provides an estimate of recurrence risk for HCC after liver transplant. It includes microvascular invasion, serum alpha-fetoprotein (AFP) at the time of liver transplant, and the total sum of the biggest tumor diameter for all viable tumors on explant [45]. With a score ranging from 0 to 5, RETREAT was able to categorize the risk of a 5-year post-

liver transplantation recurrence into groups from less than 3% in those with a score of 0, to more than 75% in patients with a score of 5 or more [45].

The MoRAL score provides an accurate risk stratification for recurrence after living donor liver transplantation and has a better predictability of tumor recurrence after liver transplant than conventional models [46].

Choosing a staging system

There is controversy regarding the best staging strategy for predicting survival in HCC patients [47]. For patients who are candidates for surgical resection, the TNM staging system can be more useful [34]. In contrast, the Okuda, Barcelona, and CLIP systems may be more efficient in patients with impaired liver function who are not candidates for surgery or who are being managed clinically [48]. Some experts recommend the TNM system to predict outcomes following resection or liver transplantation, and the BCLC for advanced HCC in which surgical resection is not indicated [49]. The European Society for Medical Oncology (ESMO) guidelines recommend using the BCLC score system to choose the correct treatment for each group of patients [50]. In conclusion, the choice of which scoring system to use should be made considering the individual characteristics of each patient.

New Prognostic Markers and Methods Under Investigation

New indicators to improve the classification of staging and prognosis are being studied. Some of these include vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1) and gene overexpression for cancer cell survival. According to some studies, VEGF overexpression is associated with greater capsule invasion, more microvascular invasion, and poor overall survival [51, 52]. Additionally, IGF-1 is implicated in the development of liver cancer and was found to be a prognostic factor for patients with HCC, especially when it is associated with diabetes mellitus [53]. These molecular and serologic indicators show promise, but further studies are needed to validate the use of these biomarkers.

Survival Rates in HCC

The prognosis of HCC correlates closely with tumor stage, with early diagnosis associated with more than 70% survival rates at 5 years, while advanced stages can carry less than 20% survival rates in the same interval [5].

Studies seem to indicate that underlying HBV has the most impact on overall survival, followed by HCV, metabolic disorders, and alcoholic liver disease, in descending order. According to a 2020 study using the Surveillance, Epidemiology, and End Results (SEER) Program from the United States National Cancer Institute, the median survival times after diagnosis of HCC in patients with the aforementioned etiologies were 10.3, 8.3, 7.6 and 6.1 months, respectively [54]. This study found no statistical difference in mortality rates between the HBV and HCV groups. On the other hand, mortality rates were shown to be higher in alcoholic and metabolic-related HCC compared to the viral etiologies [54]. Previous studies showed that this finding can be caused by a delay in diagnosis of alcohol-related HCC, with correspondingly worse liver function and tumor characteristics at the time of detection compared with HCV patients, and not necessarily because alcoholism causes a more aggressive form of HCC [55, 56]. In addition, other factors play a role in survival rates, like treatment choice. For example, according to Sacco et al, patients with nonviral-HCC treated with lenvatinib may survive longer than those with viral etiology [57]. Microwave ablation seems to decrease the rate of long-term recurrence as compared to radiofrequency ablation in patients with HCC [58].

On the other hand, in the SEER study, HBV-related HCC was found to have the most favorable survival rate, which aligns with findings by Chen et al in Taiwan after comparing the two viral etiologies of HCC [2, 56]. However, other international studies failed to replicate these findings, which may be due to confounding factors such as the Taiwanese population having access to a universal healthcare system with HCC surveillance guidelines in place [2, 59, 60].

HCV is believed to be the most frequent etiology of HCC in patients with human immunodeficiency virus infection and tends to present at younger ages compared to patients with isolated HCV infection [61, 62]. Coinfected patients have lower survival rates (74.3%) than monoinfected patients (92%) [61, 63].

Impact of Surveillance on HCC Survival

According to SEER program statistics, the United States is expected to have a continuous increase in the incidence of HCC through 2030 [64]. The impact of HCC surveillance on survival rates has been primarily studied in patients with HBV-related HCC. The ESMO guidelines recommend that surveillance should be considered in non-cirrhotic patients with chronic HBV infection, and in those with HCV infection with liver fibrosis even after achieving sustained virological response following antiviral treatment [50]. According to the American Association for the Study of Liver Diseases (AASLD), there were some promising results about using liver ultrasound alone or plus AFP for improving survival, but more studies are needed to establish the best surveillance strategies [65].

Two randomized controlled trials done in China included the measurement of AFP every 6 months. One of them used AFP in addition to liver ultrasound for HCC surveillance and found an increase in early diagnosis and better curative rates with surgical resection, as well as a 37% lower mortality rate than in the control group. The other study used only AFP and found no benefit in survival rates compared to non-surveillance patients [5, 28]. Other surveillance studies have also found no survival benefit, but they were not randomized, controlled trials [5, 66].

Case volume and type of hospital have also been shown to affect survival rates. Hospitals with a high volume of HCC cases and academic hospital settings are correlated with im-

proved overall survival, probably due to the higher-experienced providers, better interdisciplinary team integration, and overall improved logistics [67]. The specific impact of a multidisciplinary approach in patients with HCC has also been found to have a positive effect on overall survival compared with patients not managed in a multidisciplinary manner, with 5-year survival rates of 71.2% and 49.4%, respectively [29].

Conclusions

HCC is the sixth most common cancer worldwide and it is the third leading cause of cancer-related mortality. Risk factors for HCC can be classified as infectious or behavioral and survival rates vary between them. Currently, viral hepatitis and alcohol use are the most important risk factors for HCC; however, NASH is expected to become the most common cause in the future. Staging in HCC is crucial in making therapeutic decisions; multiple scoring systems have been proposed but the selection should be individualized for better management and prognosis.

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Conflict of Interest

The authors do not have any conflict of interest.

Author Contributions

All the authors contributed to the writing of the manuscript. The paper was edited by CME. Survival analysis of TCGA data was done by ZDC. Critical revisions and final approval were made by CJ.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IGF-1: insulin-like growth factor 1; MoRAL: Model of Recurrence After Liver Transplantation; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; RETREAT: Risk Estimation of Tumor Recurrence After Transplant; SEER: Surveillance, Epidemiology, and End Results; TCGA: The Cancer Genome Atlas; TNM: tumor, node, and metastasis; VEGF: vascular endothelial growth factor

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