Overview of Staging Systems for Hepatocellular Carcinoma and Implications for Interventional Radiology

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Hepatocellular carcinoma (HCC) is an aggressive malignancy that commonly occurs in the setting of underlying chronic liver disease and cirrhosis. It is the fifth most common diagnosed cancer, and the second leading cause of cancer death worldwide.¹ In the United States, the annual incidence of HCC was estimated to be at least 6 per 100,000 in 2010,² and it is projected to increase further in individuals born between 1945 and 1965 due to the high prevalence of hepatitis C virus (HCV) infection in this age group.³

Staging Systems and Prognostic Factors

Multiple staging systems have been developed to predict prognosis, none of which have been universally adopted. All staging systems incorporate features that have been identified as significant factors for survival: tumor size, extension of tumor into adjacent structures, severity of underlying liver disease, and the presence of metastatic disease, with some systems also incorporating performance status. Commonly used systems are the Barcelona Clinic Liver Cancer (BCLC),⁴ American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor–node–metastasis (TNM) system,⁵ and the Cancer of the Liver Italian Program (CLIP)⁶ score. Recently, an evidence-based score, the albumin–bilirubin grade (ALBI),⁷ and a variation of the ALBI, the platelet–albumin–bilirubin grade (PALBI),⁸ have been described, which may allow for a more objective assessment of underlying liver dysfunction in a variety of treatment settings.

Tumor, Node, Metastasis Staging System

The TNM staging system by the AJCC, which is identical to that of the UICC, was most recently revised in 2010.⁵ Although the presence or grade of cirrhosis is not integrated into the final tumor stage, the Ishak score for liver fibrosis score is included as a clinically important prognostic factor.

The Ishak score encompasses six stages of fibrosis, ranging from fibrous expansion of some portal areas to probable or definite cirrhosis. As part of the TNM system, a score of 0 is given for fibrosis scores of 0 to 4 (none to moderate fibrosis), and a score of 1 is given for fibrosis scores of 5 to 6 (severe fibrosis or cirrhosis).⁹ The AJCC/UICC system has been found to be most accurate in stratifying outcomes in patients undergoing surgical resection or transplantation.¹⁰ However, in patients with severe underlying liver disease, prognosis is mainly determined by underlying liver function, and systems that incorporate the degree of liver cirrhosis demonstrated improved ability to determine prognosis compared with the TNM system in nonsurgical patients.

Okuda System

The Okuda system was the first system to incorporate anatomical tumor features with the degree of underlying liver dysfunction. It was published in 1985,¹¹ incorporating tumor size (more or less than 50% liver involvement) and three measures of cirrhosis severity (presence of ascites, serum albumin and bilirubin levels), with patients stratified into three disease stages. In the original publication by Okuda et al,¹¹ survival for 229 untreated patients with Okuda stages I, II, and III was 8.3, 2.0, and 0.7 months, respectively. While it became widely adopted after its initial description, the increased detection rate of small tumors occupying significantly less than 50% of the liver parenchyma and the identification of other prognostic factors have diminished the use of this staging system.

CLIP Score

The CLIP score was described in 1998 and derived from a retrospective cohort of 435 patients, with subsequent prospective validation in 196 patients with cirrhosis and HCC.⁶ It incorporates tumor-related aspects including tumor morphology, serum α -fetoprotein levels, and portal vein

thrombosis in combination with the Child-Pugh (C-P) score as a marker for liver cirrhosis severity.⁶ A prognostic score ranging from 0 to 6 is assigned. Several studies suggested that the CLIP score performed better at predicting survival than the TNM, Okuda, or C-P systems.^{12–14} Variations of the CLIP score have been reported, incorporating the Model of End-Stage Liver Disease (MELD) score,¹⁵ or laboratory parameters such as serum levels of the vascular endothelial growth factor (VEGF) or the insulin-like growth factor-1 (IGF-1). Combining the CLIP score with VEGF has been termed *V-CLIP*,¹⁶ while the combination of IGF-1 and CLIP has been referred to as *I-CLIP*.¹⁷

GRETCH Score

The Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH) score was described in 1999 and derived from a cohort of 761 HCC patients from 24 medical centers in France, Belgium, and Canada.¹⁸ A total of five prognostic factors are incorporated into the score—the Karnofsky index, serum bilirubin, serum alkaline phosphatase, α -fetoprotein level, and portal venous obstruction, and patients are stratified into three groups. The GRETCH score is not widely used.

BCLC Staging Classification

The BCLC staging classification was published in 1999 and incorporates the extent of the primary tumor, performance status, vascular invasion and extrahepatic spread, and the extent of underlying liver function as approximated by the C-P score.⁴ Patients are stratified into five disease stages, ranging from 0 to D, with each disease stage associated with a specific therapy and prognosis. Patients with early-stage disease (0 and A) are asymptomatic and candidates for radical and potentially curative therapies such as surgical resection or transplantation; patients in intermediate disease stages are asymptomatic with multinodular HCC and are commonly treated with locoregional therapies such as TACE; patients with advanced disease stages have symptomatic tumors with vascular invasion and/or extrahepatic spread but with preserved liver function and are typically treated with kinase inhibitors such as Sorafenib; and patients with terminal disease stages are typically treated with supportive therapy only.

The BCLC system is tied to treatment guidelines, which distinguishes it from the previously described systems. It is endorsed by the American Association for the Study of Liver diseases (AASLD) and the European Association for the Study of the Liver (EASL), and has emerged as the most widely used staging system in the Western hemisphere. Its use in the Asian population has been challenged. HCC in Western countries is most often due to underlying cirrhosis secondary to hepatitis C, alcohol, or increasingly nonalcoholic hepatic steatosis, while endemic hepatitis B infection is the most common cause in most Asian countries and Africa.¹⁹ The BCLC system has been criticized as not being able to accurately reflect cancer progression and prognosis in patients with HCC secondary to underlying HBV infection. Asian HCC patients tend to be younger with better preservation of liver

function compared with the often significant cirrhosis in HCV-related HCC seen in Western patients.²⁰ In addition, higher case volume and surgical expertise has led to a more aggressive surgical approach in most Asian centers.²¹ As a result, multiple different scoring systems have been developed in Asia.

Model for End-Stage Liver Disease Score

The Model for End-Stage Liver Disease (MELD) score was developed and validated in patients with chronic liver disease who underwent transjugular intrahepatic portosystemic shunt (TIPS) placement. The initial cohort consisted of 231 patients who underwent elective TIPS placement at four medical centers in the United States and was published in 2000.²² The goal was to predict patient survival and identify patients whose liver-related mortality post-TIPS would be 3 months or less. The model was then prospectively validated in an independent set of 71 patients from the Netherlands. While the original model included serum bilirubin, serum creatinine, INR, and etiology of liver disease (cholestatic vs. alcoholic vs. other causes), the etiology of liver disease was subsequently removed secondary to difficulties in classifying patients with multiple etiologies of liver disease. With the original equation, the MELD score can range from negative values to infinity. However, to avoid confusion, the MELD score has been modified to range from a minimum of 6 to a maximum of 40 points. In patients with liver cirrhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction and decreased 3-month survival.²³ Due to its accuracy in predicting short-term survival in patients with cirrhosis, the MELD score has been utilized by the United Network for Organ Sharing since 2002 for prioritization of patients awaiting liver transplantation in the United States. A modification of the MELD score, the MELD-Na score incorporates serum sodium to account for the severity of hyponatremia in patients with advanced cirrhosis.²⁴

Chinese University Prognostic Index

The Chinese University Prognostic Index (CUPI) was described in 2002.²⁵ It was derived from a cohort of 926 Chinese patients with HCC, and combined four factors—total bilirubin, alkaline phosphatase, α -fetoprotein, and asymptomatic disease at presentation—with the TNM system to stratify patients into three risk classes. Most patients had liver disease secondary to underlying HBV infection, potentially limiting application in other cohorts.

Japan Integrated Staging Score

The Japan Integrated Staging score (JIS score) was published in 2003 and combines two existing classifications, the TNM staging by the Liver Cancer Study Group of Japan (LCSGJ) criteria and the C-P system. The system was derived from a cohort of 722 Japanese patients with HCC,²⁶ but it lacks validation in Western countries. A modified JIS score, the MELD-JIS, was described by Huo et al in 2006 in 276 HCC patients who underwent locoregional therapy.²⁷ The C-P class was replaced by the MELD score with a cutoff of less

than 10, 10 to 14, and more than 14 points. Survival analysis in the cohort by Huo et al demonstrated improved discriminatory ability with more accurate outcome prediction compared with the traditional C-P-based JIS score.²⁷

Tokyo System

The Tokyo System was described in 2005, and was derived from 403 patients with HCC treated by percutaneous ablation, with subsequent validation in 203 patients with HCC who underwent partial hepatectomy.²⁸ The score combines four factors—serum albumin, bilirubin, and size and number of tumors. Since the score was derived from a limited set of patients with early disease amenable to aggressive and potentially curative therapy, its applicability to patients with more advanced disease stages has been questioned.

Hong Kong Liver Cancer Staging System

The Hong Kong Liver Cancer (HKLC) staging system is the most recently described staging system. It was published in 2014 based on data from 3,856 Chinese patients with HCC predominantly related to hepatitis B.²⁹ The Hong Kong system uses a combination of the Eastern Cooperative Oncology Group performance status, C-P score, tumor extent, and extrahepatic disease to define a total of nine stages and substages with prognostic implications and treatment recommendations. The authors concluded that the Hong Kong model allowed for identification of patients suitable for more aggressive treatment than the BCLC system. Criticism of the Hong Kong system includes difficulty of use and limited applicability in non-Asian patients.^{20,30} Further validation of this system in Asia and Western countries is required before it can be introduced more widely.

ALBI and PALBI Score

Evaluation of underlying liver function to determine HCC prognosis in patients with chronic liver disease is challenging. The C-P classification has traditionally been used for risk stratification and to determine patient eligibility for treatment of HCC. The C-P score was originally developed in the 1960s to assess the prognosis of patients with portal hypertension undergoing surgery for variceal bleeding.³¹ It has since become widely utilized as a tool to assess presurgical hepatic reserve and to evaluate liver function in patients enrolled in clinical trials. Limitations of the C-P score include the use of interrelated and subjective variables (ascites, encephalopathy), which limit its prognostic ability in particular in patients with advanced HCC. Recently, an international group introduced a new tool to assess liver function, the albumin-bilirubin grade (ALBI).⁷ Based on data from 1,313 Japanese patients with different stages of HCC, bilirubin and albumin were determined to be the only non-tumor-related variables to influence survival in a multivariate analysis. Combination of these two factors into a model resulted in the ALBI score, which is calculated as follows linear predictor: $(\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$ with bilirubin in micromol/L and albumin in g/L. Three separate prognostic groups were determined by cutoff point analysis—ALBI grade I (score -2.60 or lower), grade II

(score higher than -2.60 to -1.39 or lower), and grade III (higher than -1.39). Validation of the model was performed in an international cohort of patients with C-P stage A disease and HCC from Asia, Europe, and the United States, as well as in patients treated with resection ($n = 525$), sorafenib for advanced disease ($n = 1,132$), and patients with chronic liver disease without HCC ($n = 501$).⁷ The ALBI model was discriminatory in all studied groups, and two distinct prognostic groups emerged within the C-P stage A patients evaluated in the study. A modification of the ALBI grade has also been reported, termed the platelet-bilirubin-albumin grade (PALBI), which incorporates the blood platelet count as a surrogate marker for portal hypertension.⁸ —Tables 1 and 2 provide a comprehensive summary.

Other Factors Influencing Survival

Additional factors that influence survival that are not captured by the above-described scoring and staging systems have been described. These include tumor histology, variant estrogen receptors, hepatitis B or C, and gene expression profiling.

Encapsulated, well-differentiated tumors and fibrolamellar tumors have been associated with a better prognosis.³²

Patients with a variant form of a wild-type estrogen receptor tend to have tumors with a more aggressive pattern and shorter doubling times. The presence of the receptor was found to predict survival more accurately compared with the Okuda, BCLC, and CLIP classification systems in a study of 96 patients, of which 44 had the variant receptor.³³

The presence of infectious hepatitis B or C has been associated with a higher tendency for tumor recurrence after surgical resection.^{34–36} This has been attributed to the likely higher frequency of metachronous carcinogenesis in these patients. There are data to suggest that antiviral therapy to suppress viral replication may reduce the HCC recurrence rate and improve outcomes in patients with hepatitis B.³⁷

Certain gene expression profiles have been associated with poor outcome³⁸ or less aggressive tumor behavior.³⁹ Although these approaches hold promise, further investigation is required, and they are not routinely incorporated into clinical practice at this point.

Choice of Staging System and Implications for Interventional Radiology

The complexity in treating HCC stems from the interplay between the severity of the underlying liver disease and the heterogeneity of the cancer. Published studies comparing different staging systems vary widely with regard to the preferred treatment modality, tumor stage, severity and etiology of liver disease, pattern of patient referral, and analyzed sample size, and all or a part of these variables could influence the reported outcomes. As a result, no single, standard global staging system has emerged that allows for accurate risk stratification in HCC patients.^{40,41}

For patients undergoing surgical resection, the TNM system allows for the best prognostication in patients with either HBV-predominant HCC or non-HBV HCC undergoing curative resection.^{42,43} With regard to interventional

Table 1 Variables included in the main staging systems

Staging system	Hepatic function	Tumor staging	Performance status	Stages
Okuda ¹¹	Ascites, bilirubin, albumin	Tumor greater or less than 50% of liver	No	I–III
CLIP ⁶	Child-Pugh class, alpha-fetoprotein	Number of nodules, extension >50%, portal vein thrombosis	No	0–2
BCLC ⁴	Child-Pugh class	Number of nodules, tumor size, portal vein invasion, extrahepatic spread	Yes	0, A–D
GRETCH ¹⁸	Bilirubin, alkaline phosphatase, alpha-fetoprotein	Portal vein thrombosis	Yes	0–3
CUPI ²⁵	Ascites, alkaline phosphatase, alpha-fetoprotein, bilirubin	TNM stage	Presence of symptoms	1–3
JIS ²⁶	Child-Pugh class	TNM stage by LSCGJ	No	0–3
Tokyo ²⁸	Albumin, bilirubin	Number of nodules, tumor size	No	0–2
AJCC/UICC TNM ⁵	Fibrosis score	Number of nodules, tumor size, presence of portal vein invasion, presence of metastatic disease	No	T1–T4, N0–N1, M0–M1
HKLC ²⁹	Child-Pugh class	Number of nodules, tumor size, vascular invasion, extrahepatic disease	Yes	I–V
ALBI ⁷	Albumin–bilirubin gradient	None	No	1–3
PALBI ⁸	Platelet–albumin–bilirubin gradient	None	No	1–3
ALBI-JIS ⁵³	ALBI	TNM stage by LSCGJ	No	0–3
ALBI-BCLC ⁵⁴	ALBI	Number of nodules, tumor size, portal vein invasion, extrahepatic spread	Yes	0, A–D

Abbreviations: AJCC, American Joint Committee on Cancer; ALBI, albumin–bilirubin gradient; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; ECOG, Eastern Cooperative Oncology Group; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; HKLC, Hong Kong Liver Cancer Staging System; JIS, Japan Integrated Staging Score; LSCGJ, Liver Cancer Study Group of Japan; PALBI, platelet–albumin–bilirubin gradient; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control.

treatment, several studies have compared the different staging systems for HCC in patients undergoing locoregional therapy. Georgiades et al evaluated the diagnostic accuracy of 12 staging systems—nominal and categorical C-P, Okuda, CLIP, BCLC, MELD, CUPI, JIS, TNM, GRETCH, LSCGJ, and the Tokyo system in 172 North American patients who underwent TACE for HCC.⁴⁴ The authors found that the nominal C-P, CUPI, and Tokyo systems provided the best prognostic accuracy but felt that the CUPI and Tokyo systems were artificially enhanced due to their greater number of staging levels. They concluded that the C-P score was the most basic system with similar accuracy and therefore represented the preferred staging system. Cho et al evaluated seven staging systems—nominal C-P score, Okuda, BCLC, CLIP, MELD-modified CLIP system, JIS, and MELD-modified JIS—in 131 Asian patients who underwent TACE for HCC.⁴⁵ The authors found that the original CLIP system was superior to the other systems with regard to discriminatory ability, including the MELD-modified CLIP and JIS systems. A recent retrospective analysis of

11 staging systems including the BCLC, HKLC, CLIP, Taipei Integrated Scoring System, JIS, Tokyo, TNM, Okuda, CUPI, and GRETCH in 3,182 Asian patients, 890 of who underwent TACE, concluded that the CLIP system was the best prognostic model regardless of underlying etiology or curative versus noncurative treatment.⁴⁶

In 2003, the consensus conference of the American Hepato-Pancreato-Biliary Association (AHPBA) and AJCC concluded that no staging system fulfilled all the needs of physicians treating HCC, and recommended the use of the AJCC/UICC TNM systems for surgical patients and the use of the CLIP staging system for prognosis stratification and treatment guidance in nonsurgical patients with advanced HCC and/or underlying liver disease.⁴⁷ These recommendations were revised in 2010, with the BCLC system now recommended for use in nonsurgical patients, while the TNM system remained the staging system of choice for surgical patients.⁴⁸ The Society of Interventional Radiology Standard of Practice guideline for transcatheter therapy for

Table 2 Components included in the main prognostic systems

Prognostic score										
Component	Okuda ¹¹	CLIP ⁶	BCLC ⁴	GRETCH ¹⁸	JIS ²⁶	CUP ²⁵	Tokyo ²⁸	AJCC/UICC TNM ⁵	HKLC ²⁹	PALBI ⁸
Liver function										
Ascites	X					X				
Albumin	X						X		X	X
Alkaline phosphatase				X		X				
Alpha-fetoprotein		X		X		X				
Child-Pugh class		X	X		X				X	
Portal vein invasion		X	X	X				X	X	
Serum platelet count										X
Total bilirubin	X			X		X	X		X	X
Tumor variables										
Metastasis			X					X	X	
Number of nodules		X	X				X	X	X	
TNM stage					X	X		X		
Tumor size	X	X	X				X	X	X	
Patient status										
Symptoms/General status			X	X		X			X	
Treatment recommendation			X						X	

Abbreviations: AJCC, American Joint Committee on Cancer; ALBI, albumin–bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUP, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; HKLC, Hong Kong Liver Cancer Staging System; JIS, Japan Integrated Staging Score; PALBI, platelet–albumin–bilirubin grade; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control.

hepatic malignancy recommends reporting the clinical status of the patient population and/or tumor stage based on established criteria such as C-P, CLIP, BCLC, Hong Kong Liver Cancer, or United Network for Organ Sharing staging systems.⁴⁹

Since the introduction of the ALBI grade in 2015, multiple groups have provided external validation. Hickey et al reported that the ALBI grade outperformed the C-P class with regard to discriminating survival in patients undergoing TACE or yttrium-90 radioembolization.⁵⁰ A recent multicenter study that included 1,461 intermediate-stage patients treated with chemoembolization from centers in Europe, Asia, and the United States confirmed the independent prognostic value of the ALBI grade.⁵¹ Liu et al compared the performance of the MELD score with the ALBI and the PALBI grade in 3,182 Asian patients with HCC, and concluded that the ALBI and PALBI grades were superior to the MELD score in predicting survival, with the PALBI grade demonstrating the best prognostic performance.⁵² Integration of the ALBI grade into established staging systems has also been described. Hiraoka et al replaced the C-P component of the JIS system with the ALBI grade in 2,584 Japanese patients and found that the ALBI-JIS system was superior for distinguishing patients with better hepatic function, and thus may be a better prognostic tool compared with the conventional JIS system in Japanese patients.⁵³ Chan et al integrated the ALBI score into the BCLC system, and compared performance of the C-P-based BCLC and the ALBI-based BCLC in 3,696 HCC patients from Hong Kong, Japan, and the United Kingdom.⁵⁴ They concluded that the overall prognostic performance was similar, with the ALBI-based BCLC system potentially able to allow for more precise patient selection in clinical trials using systemic agents. While the available data favor the CLIP system for predicting survival in patients undergoing interventional treatment, it is important to remember that only two staging systems, the BCLC and the HKLC systems, integrate treatment recommendations into the staging process. While the CLIP system may be used to provide patients with an accurate prognosis prior to treatment, the BCLC or HKLC system should be used to determine treatment. Of the two, the BCLC system is more widely used in clinical trials as well as in clinical practice in the United States.

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