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REVIEW ARTICLE

Staging systems of hepatocellular carcinoma: A review

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Abstract

Staging of hepatocellular carcinoma (HCC) is necessary for guiding prognostication, management, and research purposes that further aid in the improvement of existing clinical and epidemiological health services. Though there are some new staging systems for HCC developed in different parts of the world, there is no globally accepted staging system that allows for comparison of current management protocols among heterogeneous populations. In this review, we discuss the evolution and applicability in clinical practice of different clinical staging systems of HCC—Okuda, CLIP (Cancer of the Liver Italian Program) score, MESIAH (Model to Estimate Survival In Ambulatory HCC patients) score, ITA.LI.CA (Italian Liver Cancer) score, BCLC (Barcelona Clinic Liver Cancer) staging, HKLC (Hong Kong Liver Cancer) staging, and the Alberta algorithm. This review aims to highlight the main criteria for assessing the prognosis of HCC that these different staging systems take into account, their strengths and limitations for use in modern clinical practice. Despite the limitations of the BCLC staging system, it remains the most validated and reliable system for prognostication. However, there is a need to update the BCLC staging system to include recent data on locoregional and systemic therapies for HCC, expanded criteria for transplantation, and systemic therapy for hepatitis C infection.

Keywords Alberta algorithm · BCLC staging · CLIP score · HKLC staging · ITA.LI.CA · MESIAH score

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and the third most common cause of cancer-related mortality [1]. It is the fastest-rising cause of cancer-related death in the United States with an overall survival rate of less than 12% [2]. Cirrhosis of the liver is the most significant risk factor for developing HCC [3]. Overall, 75% to 80% of cases of primary liver cancer are attributable to cirrhosis due to persistent viral infections (hepatitis B and C viruses) [4]. Other significant risk factors include alcoholic liver disease and nonalcoholic steatohepatitis (NASH). Given the limited frequency of liver tumor reporting in the National Cancer Registry Program of the Indian Council of Medical Research (ICMR), an estimated annual incidence of HCC in cirrhotic patients is 1.6% [5]. Although the Western literature reports that the incidence of HCC in NASH-associated cirrhosis is less frequent than the incidence of HCC in hepatitis C virus (HCV)-associated cirrhosis (2.4% vs. 6.8%) [6], the data is sparse about the natural history of HCC arising from NASH in the Indian subcontinent [7]. Diagnosis of NASH is made in biopsy specimen demonstrating steatosis and any stage of fibrosis or lobular inflammation or ballooning degeneration. Various population-based studies in India reported prevalence as high as 16% for nonalcoholic fatty liver disease (NAFLD) and that at least 32% of NAFLD-affected individuals have histological features suggestive of NASH [8, 9]. The less common causes are hereditary hemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis, porphyria, and Wilson's disease [10]. Professional societies, including the Indian National Association for the Study of the Liver (INASL) [11], the American Association for the Study of Liver Diseases (AASLD), the National Comprehensive Cancer Network (NCCN), and the European Association for the Study of the Liver (EASL), recommend HCC surveillance in at-risk patients, including all patients with cirrhosis.

Staging plays an important role to prognosticate and manage HCC and is also useful for research purpose. In spite of development of multiple staging systems for HCC in different

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parts of the world including some new ones, no universally accepted staging system exists even today that helps in comparing the management options in different population [12]. Hence, we wish to review the evolution and clinical application of seven staging and scoring systems of HCC, namely—Okuda, CLIP (Cancer of the Liver Italian Program) score, MESIAH (Model to Estimate Survival In Ambulatory HCC patients) score, ITA.LI.CA (Italian Liver Cancer) score, BCLC (Barcelona Clinic Liver Cancer) staging, HKLC (Hong Kong Liver Cancer) staging, and the Alberta algorithm.

Current treatment options for HCC

Currently, the available treatment options for HCC include surgical resection, liver transplantation, minimally invasive locoregional therapies including percutaneous ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE). The Milan criteria guide the decision to provide liver transplantation [13]. However, there has also been recent research to consider selection criteria beyond Milan in specific subsets of patients [14, 15]. Radiofrequency ablation (RFA), microwave ablation, and cryoablation kill the tumor cells with the use of extremes of temperature delivered to the tumor with the help of needle electrodes [16]. As HCC derives its blood supply from the hepatic artery, transarterial injection with a mixture of lipiodol, chemotherapeutic drugs and gelfoam or microspheres (conventional TACE), or drug-eluting beads (DEB-TACE) or Yttrium 99 (TARE) leads to tumor necrosis on delivery at the site of the tumor [17]. Selective internal radiation therapy (SIRT) induces tumor cell death by beta ray emission [18].

Systemic therapy against HCC with Sorafenib, an oral tyrosine kinase inhibitor that blocks the rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway and the receptors for vascular endothelial growth factor and platelet-derived growth factor, is recommended in the advanced-stage HCC patients and has shown to improve the survival outcomes in this patient group [19, 20]. Several other molecular targets such as Lenvatinib [21], Regorafenib [22], Nivolumab [23], Cabozantinib [24], and Ramucirumab [25] have since been studied for their potential benefits. Although novel antiviral drugs for hepatitis B virus (HBV) such as Tenofovir and Entecavir have reported benefits for suppressing HBV replication, they are not known to prevent the risk of HCC in cirrhotic patients in total [26]. Meanwhile, antiviral regimens against HCV including Sofosbuvir, Ledipasvir, Daclatasvir, and Ribavirin have proven efficacious in preventing decompensation of liver and may reduce tumor recurrence after curative therapy [27].

The increasing incidence of NASH-induced HCC, especially in the Indian subcontinent [28], warrants active surveillance for the development of HCC in NAFLD patients, promoting the use of lipid-lowering medications, such as statins, and lifestyle modifications to control metabolic syndrome. Several novel medications including obeticholic acid, liraglutide, elafibranor, cenicriviroc, and aramcholare emerge with the potential to treat NASH and further prevent the development of HCC. However, their effectiveness has to be studied in future clinical trials [29, 30].

Evolution of different clinical staging systems of HCC

The various staging systems developed globally have considered various pretreatment parameters to stage the disease, and a few of them also proposed treatment guidelines for each stage of the disease. Vauthey et al. categorized them as clinical, pathological, and transplant staging systems depending on the reason they were developed [31]. The 18 HCC staging systems have been used globally at the time of the American Hepato-Pancreato-Biliary Association (AHPBA), consensus conference held in 2010 [31]. The in-use clinical staging systems were Okuda, IHPBA (International Hepato-Pancreato-Biliary Association), CLIP, BCLC, revised BCLC, CUPI (Chinese University Prognostic Index), American Liver Tumor Study Group-modified Tumor-Node-Metastasis classification (ALTSG), and Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH). The pathological staging systems were the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC), Liver Cancer Study Group of Japan (LCSGJ) staging system, Japanese Integrated Staging (JIS) score (includes the LCSGJ), Modified JIS New Liver Cancer Study Group of Japan, TNM Early HCC prognostic score, and the Tokyo score. The UNOS-modified TNM staging system, UCSF extended criteria, and the Pittsburgh scoring system are the transplant criteria used in the management of HCC. The use of regional staging systems that preclude a comparison between different centers was discouraged, and most staging systems studied had poor performance when used in patients with a broad spectrum of disease. According to expert consensus, the BCLC staging system provided reasonable guidelines to manage patients with advanced-stage HCC [32]. The AJCC/UICC system was useful in patients undergoing hepatic resection or liver transplantation [32].

The Okuda, CLIP, MESIAH, and ITA.LI.CA are score-based staging systems to predict survival, and the BCLC, HKLC, and Alberta are staging systems that guide treatment decision. The GRETCH, the ALTSG TNM staging systems, and the CUPI are the other clinical staging systems that have been developed. These systems, however, are neither well-validated nor widely adopted (Fig. 1, Table 1).

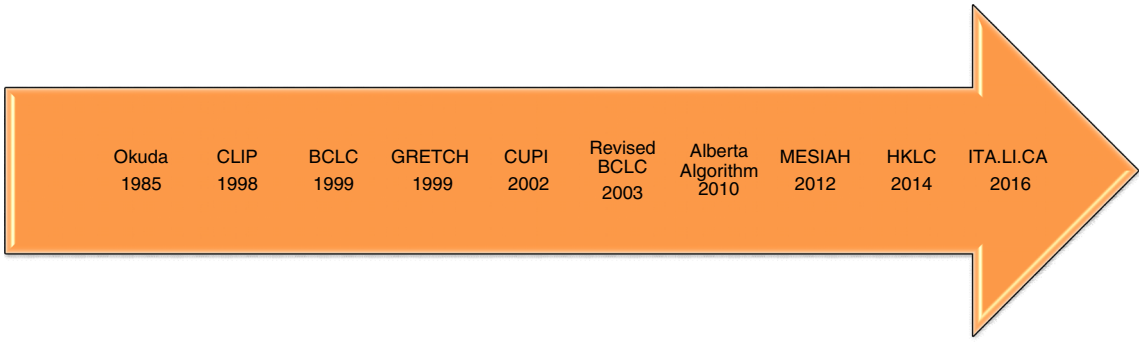

Fig. 1 Timeline for development of various clinical HCC staging systems. *CLIP* Cancer of the Liver Italian Program score, *BCLC* Barcelona Clinic Liver Cancer, *GRETCH* Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire, *CUPI* Chinese University Prognostic Index, *MESIAH* Model to Estimate Survival in Ambulatory HCC patients, *HKLC* Hong Kong Liver Classification, *ITA.LI.CA* Italian Liver Cancer

Staging systems guiding treatment decision

The Barcelona Clinic Liver Cancer classification

The Barcelona Clinic Liver Cancer (BCLC) system (Fig. 2) was constructed by a group of investigators based on the results obtained in the setting of several cohort studies and randomized controlled trials [33]. Since its inception in 1999, it clarifies the decision-making process regarding the management of patients having cirrhosis and HCC according to the tumor burden, liver function, and physical condition [34]. Tumor extent is estimated based on the size and number of the tumors and portal vein invasion or extrahepatic spread. The performance scale (PS) measures the daily living ability of an affected patient, and the scale proposed by the Eastern Cooperative Oncology Group (ECOG) is commonly used by clinicians to assess the functional status of patients affected by HCC [35]. The liver functional reserve is determined by the Child-Turcotte-Pugh (CTP) score. Hepatic venous pressure gradient (HVPG) greater than 10 mmHg is the best predictor of the development of portal venous hypertension [36].

Initially, the patients were stratified into four stages—the early-stage (A) patients with asymptomatic early tumors who are suitable candidates for radical therapies, such as resection, transplantation, and percutaneous treatments; the intermediate-stage (B) patients with asymptomatic multinodular HCC; the advanced-stage (C) patients with symptomatic tumors and/or an invasive tumor pattern (vascular or extrahepatic spread); and the end-stage (D) patients with extremely grim prognosis. Subsequently, a BCLC very early stage (0) was added to the classification which included patients with well-preserved liver functional reserve and asymptomatic with a single tumor of size less than 2 cm [37].

Table 1 Comparison of different hepatocellular carcinoma staging systems: tumor and patient characteristics and liver function

Staging system	Tumor characteristics						Patient characteristics		Liver function status						
	Size	Number	PVI	Metastasis	Nodes	AFP	PS	Age	CTP	Albumin	Serum bilirubin	Serum Cr	PT/INR	Ascites	ALP
Okuda	✓									✓	✓			✓	
CLIP	✓		✓			✓			✓	✓	✓		✓	✓	
BCLC	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
HKLC	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
Alberta algorithm	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
MESIAH score	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓		
GRETCH score			✓			✓	✓(Karnofsky index)				✓				✓
CUPI	✓			✓	✓	✓					✓			✓	✓
ITA.LI.CA	✓	✓	✓	✓		✓	✓(ECOG)		✓	✓	✓		✓	✓	

PVI portal venous invasion, *AFP* alphafetoprotein, *PS* performance status, *CTP* Child-Pugh score, *Cr* creatinine, *ALP* alkaline phosphatase, *PT/INR* prothrombin time/international normalized ratio, *CLIP* Cancer of the Liver Italian Program score, *BCLC* Barcelona Clinic Liver Cancer, *GRETCH* Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire, *CUPI* Chinese University Prognostic Index, *MESIAH* Model to Estimate Survival in Ambulatory HCC patients, *HKLC* Hong Kong Liver classification, *ITA.LI.CA* Italian Liver Cancer

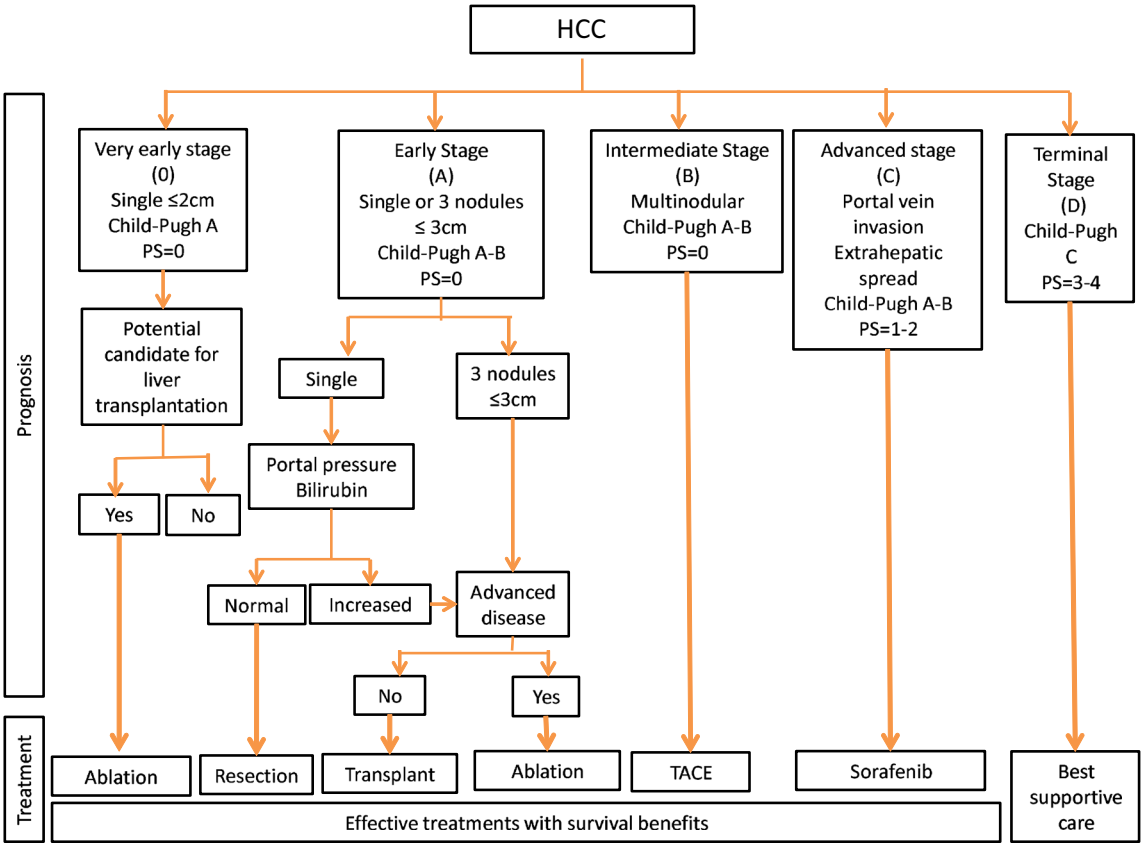

Fig. 2 The Barcelona Clinic Liver Cancer classification. *HCC* hepatocellular carcinoma, *PS* performance status, *TACE* transarterial chemoembolization

The BCLC staging system is relatively unique given its incorporation of stage-based treatment recommendations [38]. The treatment options for the more limited disease include ablation, transplantation, and resection. Chemoembolization and systemic therapies are reserved for the intermediate stage. Best supportive care is offered for end-stage patients. TACE is the mainstay for the treatment of inoperable intermediate-stage HCC [3] (large or multinodular HCC with preserved hepatic function, no evidence of vascular invasion or extrahepatic spread and absence of cancer-related symptoms). Sorafenib was recommended as the first-line treatment option for advanced-stage (C) patients as a modification to the classification in the year 2008 [39].

The AASLD and the EASL have accepted the BCLC as a standard staging system, but the drawbacks of the BCLC system include the use of subjective components, particularly performance status and heterogeneity of patient prognosis within a given category [40, 41, 3]. The CLIP investigators argue that the BCLC classification groups the patients based on treatment options and that it represents only a treatment decision algorithm but not a prognostic evaluation [42]. It has also been stated by other research groups that the BCLC algorithm does not recognize the potential roles of RFA for very early-stage HCC and TARE. The BCLC staging system provides limited information about the expanding role of liver transplantation in the management of HCC, such as, the improved overall survival in tumors of size less than 2 cm [43]. Also, the expanding role of TARE (in the form of segmentectomy) and combination therapies (ablation plus embolization) for single large tumors and the role of TACE and TARE in patients with PS of 1 or with limited portal venous invasion are not adequately addressed. TARE has been reported as a safe and effective therapy for unresectable tumors [44, 45]. Recent clinical trials evaluated the potential benefit of combining locoregional therapy with molecular therapeutic agents to treat subsets of patients with HCC [46]. Such combination therapies can be targeted towards TACE-refractory patients, i.e., patients with stage progression after two sessions of TACE in the first six months of diagnosis [47]. Recent reports demonstrate the safety and effectiveness of DEB-TACE over conventional TACE in patients with advanced HCC [48].

To address the specific limitations of the BCLC staging system, some authors proposed sub-classifications. Bolondi et al. [49] proposed a sub-classification of stage B (B1–B4, depending on the CTP score, PS, and beyond Milan score 7) in association with different first-line (TACE, TARE, or best supportive care) and alternative treatment options (liver transplantation, ablation, sorafenib, and TACE). Santambrogio et al. proposed simplified BCLC staging (s-BCLC) system with four subclasses of BCLC-A stage [50]. The s-BCLC

incorporated AFP levels to subclassify BCLC-A patients and showed better performance in accurately predicting the survival of patients undergoing hepatic resection for HCC. These BCLC sub-classification models need further external validation to be adopted as a standard staging model.

The Alberta classification

The Alberta classification (Fig. 3) represents an evidence-based approach to the versatile management of HCC that incorporates the BCLC staging system and the Canadian authors' local selection criteria for resection, ablative techniques, liver transplantation, TACE, TARE, and Sorafenib in Alberta [51]. The algorithm recognizes the importance of tumor properties (size, number, extrahepatic spread, and AFP levels), patient characteristics (performance status and candidacy for transplantation), and liver function (CTP class along with elevated portal vein pressure or thrombosis of the portal vein) and links patients to the most appropriate therapy.

The significant changes compared to the BCLC staging system are that the Alberta classification recognizes the potential role of RFA in very early-stage HCC and the role of ^{90}Y radioembolization especially for patients who are not candidates for TACE because of bland PVT. The algorithm also provides an expanded role for liver transplant in patients beyond the Milan [13] criteria. In contrast to the BCLC treatment recommendations, sorafenib therapy is offered only to CTP class A cirrhotic patients with advanced HCC.

The Hong Kong Liver Cancer classification

The HKLC classification (Fig. 4), developed by the Hong Kong group of investigators in 2014, aims to create an improved staging system relative to the BCLC, to identify patients in need of more aggressive treatment [52]. Similar to the BCLC, this classification system includes the CTP score, the Eastern Cooperative Oncology Group performance status (ECOG PS), and the extent of the tumor spread. The study population was a large cohort of patients with HCC predominantly associated with HBV infection. HKLC identifies subsets of BCLC intermediate- and advanced-stage patients for more aggressive treatments than recommended by the BCLC,

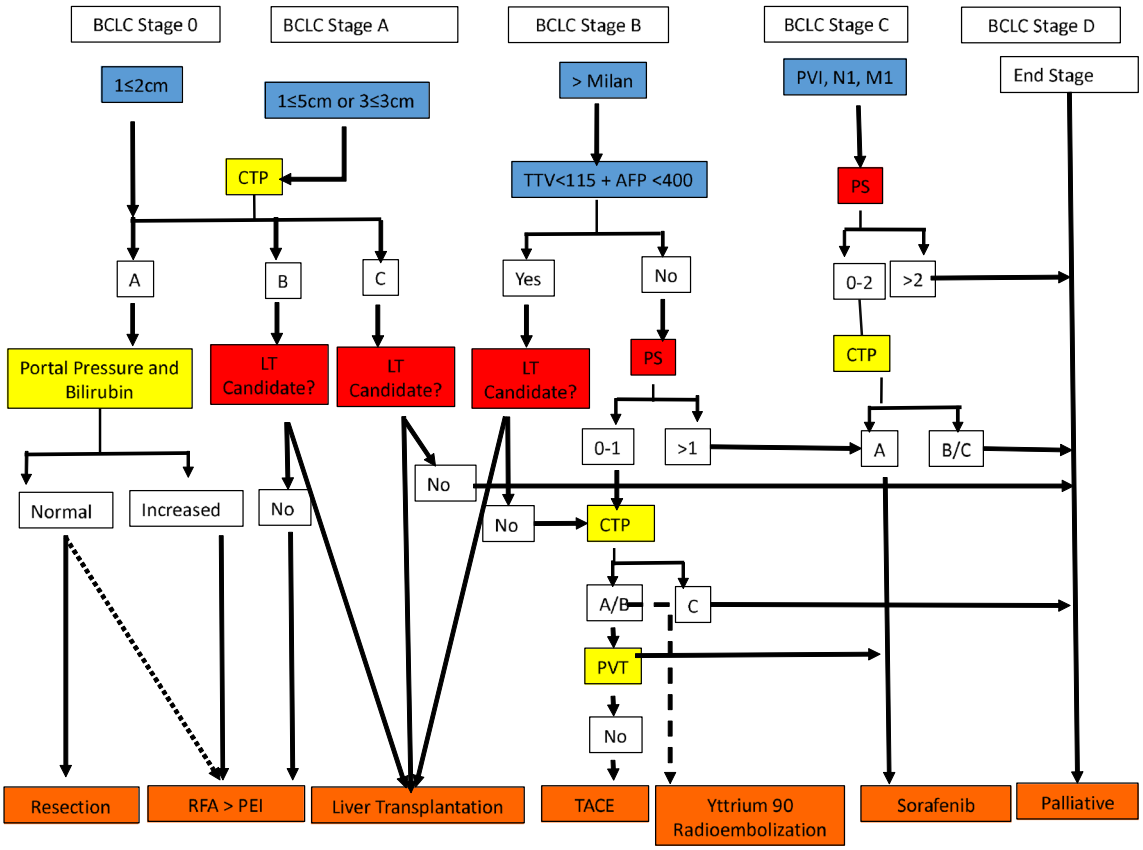

Fig. 3 The Alberta HCC algorithm. Tumor characteristics (blue boxes), patient characteristics (red boxes), and liver function (yellow boxes). The dotted line represents the potential role of RFA in very early-stage HCC. Dashed line recognizes the potential role of 90 Yttrium (Y) TARE, especially for patients who are not candidates for TACE because of bland PVT. *HCC* hepatocellular carcinoma, *LT* liver transplantation, *PS* performance status, *RFA* radiofrequency ablation, *PEI* percutaneous ethanol injection, *PVI* portal venous invasion, *PVT* portal venous thrombosis, *Milan* Milan criteria, *N* lymph node, *TTV* total tumor volume, *TACE* transarterial chemoembolization, *TACE* transarterial chemoembolization

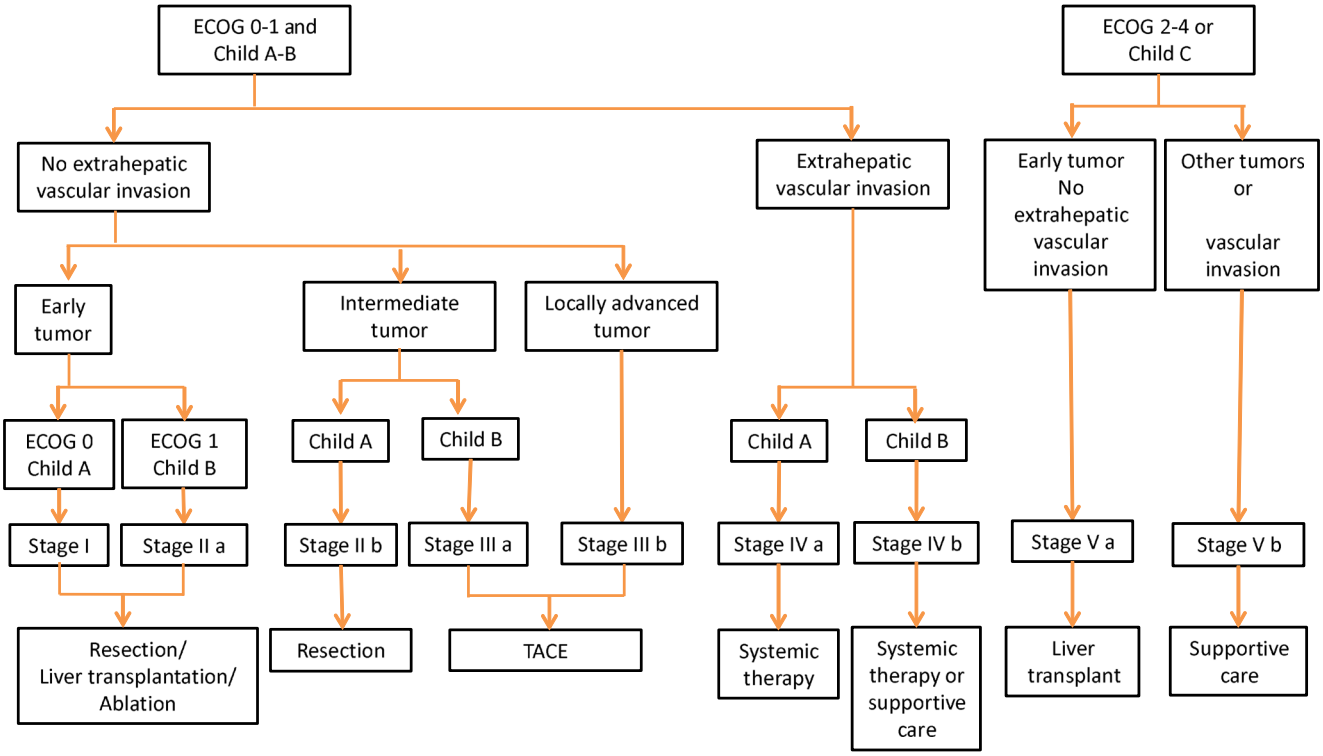

Fig. 4 The HKLC classification. *Early tumor* is ≤ 5 cm, ≤ 3 tumor nodules, and no intrahepatic venous invasion. *Intermediate tumor* is (a) ≤ 5 cm, either > 3 tumor nodules, or with intrahepatic venous invasion or (b) > 5 cm, ≤ 3 tumor nodules, and no intrahepatic invasion. *Locally-advanced tumor* is (a) ≤ 5 cm, > 3 tumor nodules, and with intrahepatic venous invasion or (b) > 5 cm, > 3 tumor nodules, or/and with intrahepatic venous invasion, or (c) diffuse tumor. *HKLC* Hong Kong Liver classification, *TACE* transarterial chemoembolization, *ECOG* the Eastern Cooperative Oncology Group performance status

which improved survival outcomes [52]. Due to the higher incidence and growing expertise in the treatment of the HCC in the Asian population, more aggressive treatments, such as surgical resection, have been adopted. The higher prognostic accuracy and treatment efficacy proposed for the HKLC over the BCLC staging system needs further external validation studies in different cohorts.

Scoring systems to predict survival

Okuda staging system

The Okuda staging system (Table 2) was the first staging system developed three decades ago in Tokyo to analyze the relationship between survival and treatment in 850 patients with HCC. The authors noted that irrespective of the geographic location and the time of diagnosis, the primary clinical features and the prognosis of patients affected with HCC were similar and reported that a staging system should be as simple and practical as possible based on their analysis [53]. They indirectly determined the functional hepatic reserve by taking into account the serum bilirubin and serum albumin levels (as 3 mg/dL and 3 g/dL, respectively) as well as the presence or absence of ascites apart from determining the tumor burden by measuring the tumor size (the separating level being 50%). Stage I was defined as tumor involvement < 50% of the liver, without ascites, > 3 g/dL albumin, and < 3 mg/dL bilirubin. Stage II was assigned when one or two of the following features were positive: tumor size more than 50%, ascites, < 3 g/dL albumin, and > 3 mg/dL bilirubin. Patients with stage III had three or four of these features.

The Okuda staging classified patients appropriately when the diagnosis of HCC happened in the advanced/symptomatic phase and was a useful tool to identify the end-stage patients (stage III), who should not be included in clinical trials as they had a poor prognosis. However, in the later decades, when a diagnosis of HCC happened early due to the improved diagnostics, the Okuda staging was insufficient to stratify patients before radical or palliative therapy [33].

The Cancer of the Liver Italian Program score

The CLIP scoring system [54] (Table 3) for prognosticating HCC patients was proposed by Italian investigators in the year 1998 to verify the value of the known prognostic factors in producing a prognostic index more sensitive than Okuda that accounts for both the liver function and tumor characteristics. The CLIP score incorporated variable factors (CTP score: A, B, or C [55, 56]; tumor morphology: uninodular or multinodular

Table 2 Okuda staging and its elements

Stage	Tumor size > 50%		Ascites		Albumin < 3 g/dL		Bilirubin > 3 mg/dL	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
I	(−)		(−)		(−)		(−)	
II	1 or 2 (+)							
III	3 or 4 (+)							

with extension ≤ 50% or > 50%; alpha fetoprotein [AFP]: levels < 400 or ≥ 400 ng/dL; and presence or absence of portal vein thrombosis [PVT]) into a Cox model and analyzed the overall survival in 435 patients treated with locoregional and systemic therapies. The minimum score was 0 (CTP stage A, uninodular tumor with ≤ 50% extension and no PVT, AFP levels being < 400 ng/dL), and the maximum was 6 (CTP stage C, massive tumor involving > 50% of the liver with PVT, and AFP ≥ 400 ng/dL). Patients with a higher score had a poorer prognosis. The CLIP score was externally validated by randomized clinical trial in the year 2000 [57] by the same collaborative group.

The CLIP investigators state that this scoring system is simple, has increased predictive efficiency, and better defines the prognostic heterogeneity of Okuda stage 2 as it incorporates a higher number of variables with higher discriminant ability. It can identify a subgroup of patients with favorable prognosis who may be candidates for more radical therapy, such as resection. The score can also identify a subset of patients with a worse prognosis but having a median survival long enough to be considered for clinical trials of palliative anti-neoplastic therapy.

Model to Estimate Survival in Ambulatory HCC patients score

The MESIAH score was developed by the members of the Mayo group in 2012 to predict survival of HCC patients based on objective parameters, including the model of end-stage liver disease (MELD) score, as a gauge of liver dysfunction to provide a refined prognostication and supplementation to the BCLC classification [40]. The dataset included the majority of patients with viral hepatitis having a normal PS score. The MESIAH score can further classify patients with substantially different prognosis, particularly in BCLC B to D patients. The computation of this score may be implemented easily using a spreadsheet program, a web-based worksheet, or a handheld device. The survival model incorporated the age of the patient, the number of tumor nodules, and the size of the largest nodule, vascular invasion, metastasis, serum albumin, AFP levels, and the MELD score. The MESIAH score is calculated by the following equation [40]:

$$\begin{aligned}\left[\text{The MESIAH score} = {}& 0.232*(\text{age in decades}) \right.\\ & + 0.099*(\text{MELD}^{\dagger}) - 0.391*(\text{serum albumin level})\\ & + 0.290*(\text{tumor size}^{\dagger\dagger\dagger}) + 0.153*(\text{tumor number}^{\dagger\dagger})\\ & + 1.122*(\text{vascular invasion})\\ & + 1.130*(\text{extrahepatic metastasis})\\ & \left. + 0.082*(\text{serum AFP level}^{\dagger\dagger\dagger\dagger}) + 1\right]\end{aligned}$$

(†MELD scores=< 13 set to 13;

††Number of nodules : 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = 5, or greater;

†††Size of the largest nodule : 1=<=1, 2 = 1−2, 3 = 2−3, 4 = 3−5, 5 = 5−10, 6 = 10−15, 7 = 15−20, 8=>20 cm;

††††ln(AFP) with AFP capped at 10, 000 units].

Table 3 The Cancer of the Liver Italian Program score and its elements

Variables	Scores		
	0	1	2
CTP score	A	B	C
Tumor morphology	Uninodular and extension ≤ 50%	Multinodular and extension ≤ 50%	Massive or extension > 50%
AFP (ng/dL)	< 400	≥ 400	
Portal vein thrombosis	No	Yes	

AFP alpha-fetoprotein, *CTP* Child-Pugh score

The authors claim that the MESIAH score complements the BCLC and other staging models and that it is a valuable tool to estimate the prognosis of HCC patients in epidemiological research. Since the system was developed from a small dataset of patients where the majority had preserved PS, it may breakdown in patients with abnormal PS. Whether MESIAH may inform treatment decisions, such as the BCLC staging system, remains to be determined.

The Italian Liver Cancer tumor staging and integrated prognostic staging system

The ITA.LI.CA, another novel staging system of HCC, is derived from a prospectively collected multicenter database of over 5000 HCC patients from Italy and Taiwan [58]. While HCV infection was more predominant in the internal validation dataset, HBV infection was more prevalent in the external validation dataset. Almost all patients had good performance status. The tumor stage (Table 4) is defined as a composite variable based on the following four main stages: 0 (very early), A (early), B (intermediate), and C (advanced). In contrast to the BCLC, the ITA.LI.CA tumor staging does not include the CTP score or the ECOG PS. A single tumor of a size larger than 5 cm was considered stage B which was further stratified into three sub-stages, B1, B2, and B3, depending on the size and number of tumor nodules, vascular invasion, and metastasis.

Selecting overall survival as the outcome of interest and using a multivariable survival parametric model estimate based on the ITA.LI.CA tumor stage, functional status, CTP score, and AFP concentration (≤ 1000 or > 1000 ng/mL), a prognostic score (ITA.LI.CA functional score) (Table 4) is derived. The least score (ITA.LI.CA score = 0) corresponds to best prognosis, and the highest score (ITA.LI.CA score = 13) corresponds to worst prognosis [58].

Another unique feature of the ITA.LI.CA prognostic system is that it can be synthesized in a single simplified, user-friendly formula, TS_{FA} (where "TS" is the tumor stage, "F" is the point value of the ITA.LI.CA functional score, and "A" is the AFP value), which not only provides an accurate clinical description of each HCC patient but also has a potential to be used for deciding patient treatment or designing clinical trials [58].

When compared with the most commonly used staging systems, BCLC, CLIP, MESIAH, HKLC, and JIS, the ITA.LI.CA showed the best discriminatory ability and monotonicity of gradients and demonstrated broad applicability in both European and Asian populations. The ITA.LI.CA prognostic staging system, however, needs to be further validated through prospective trials in populations having poor performance status and hepatic decompensation since the study was retrospective, including almost all patients with good performance status with only 2% in the derivation cohort undergoing liver transplantation [59].

Discussion

Clinical staging is essential as it helps in making decisions regarding available treatment options. Management and treatment of HCC must consider two different disease processes reflected by the stage of the tumor and the functional hepatic reserve in the setting of chronic liver disease. Selection of treatment modality is based on tumor characteristics, the general medical condition of the patient, and the liver function status

Table 4 The elements of the ITA.LI.CA tumor staging system and the integrated prognostic score

The ITA.LI.CA tumor staging system							
Number and diameter of largest nodule (cm)						Stage	
A single nodule of ≤ 2 cm						0	
2–3 nodules of ≤ 3 cm or a single nodule of 2–5 cm						A	
2–3 nodules of 3–5 cm or single nodule of > 5 cm						B1	
2–3 nodules of > 5 cm or > 3 nodules of ≤ 5 cm						B2	
> 3 nodules of > 5 cm without an intrahepatic spread or any number of nodules with any size with intrahepatic spread						B3	
Any number of nodules with any size with extrahepatic spread						C	
The ITA.LI.CA integrated prognostic score							
ITA.LI.CA tumor stage	Points	CTP score	Points	ECOG PS	Points	AFP level	Points
0	0	5	0	0	0	≤ 1000 μ/L	0
A	1	6–7	1	1–2	1	> 1000 μ/L	2
B1	2	8–9	2	3–4	3		
B2	3	10–15	3				
B3	4						
C	5						

AFP alpha-fetoprotein, *CTP* Child-Pugh score, *ECOG PS* the Eastern Cooperative Oncology Group performance status

[31]. Tumor characteristics include, but are not limited to, size, number, tumor burden, venous invasion, and extrahepatic spread. The general condition of the patient takes into account the extent of compromised physical activity described by the ECOG PS scale, tumor-related symptoms, and complications related to chronic liver diseases, such as encephalopathy and ascites. Finally, the hepatic reserve is estimated based on the liver function tests, such as serum albumin, bilirubin, international normalized ratio, and alkaline phosphatase levels. Most of the staging systems take into account the tumor characteristics, hepatic function reserve, and the performance status of the patient. However, there is no globally accepted staging system because all the systems have been developed in different population cohorts and perform well only in similar cohorts.

Furthermore, given the widespread etiology of HCC (predominantly HBV and HCV infections in the Eastern and the Western populations, respectively), there is no single staging model that may be used in all geographic cohorts [1]. Many studies compared various staging models to better discriminate the overall survival in HCC patients [60–71] (Table 5). However, there is no ideal staging and prognostic system for HCC which can be used as a standard globally. There is difficulty in modeling biology of this tumor across a widespread tumor etiology. The BCLC staging system is considered the most comprehensive, taking into account all the clinically essential parameters into consideration and providing prognostic guidance to available therapeutic choices. The later-developed classification systems have their inherent limitations and need further external validation in different population cohorts.

Recent advances in molecular biology have provided a more profound understanding of the tumor biology and carcinogenesis mechanisms and discovery of new tumor markers that have a potential to prognosticate HCC [72]. Novel gene therapies directed towards defective molecular pathways are being identified and have a promising role in the management of HCC [73]. Identification of specific tumor markers to monitor the response to these therapies would further aid the management and prognostication of HCC patients. The use of liquid biopsy technology to assess the circulating tumor DNA in at-risk individuals may improve the detection and surveillance in cirrhotic patients [74]. There has also been increasing interest in the application of radiomic features in tumor prognostication [75]. Considering these recent developments and based on the robust validation data acquired in future clinical trials, the current prognosticating classifications may need to be updated for future applicability.

Table 5 Studies comparing various staging models for overall survival discrimination

Author(s) and year of publication	Type of study, number of patients included	Country	Compared staging systems	Conclusion
Cillo et al. [60], 2004	Retrospective analysis, 187 patients	Italy	Five systems	BCLC system was the best in prognosticating patients treated with potentially radical therapies.
Sirivatanauksorn et al. [61], 2011	Retrospective cohort study, 181 patients	Thailand	Six systems	TNM and CTP determined the survival best in post-surgical resection patients.
Memon et al. [62], 2014	Prospective cohort study, 728 patients	USA	Seven systems	CLIP was most accurate in predicting HCC survival in patients following Y-90 TARE.
Liu et al. [63], 2016	Prospective cohort study, 3128 patients	Taiwan	11 systems	CLIP score is the most accurate prognostic model.
Su et al. [64], 2016	Retrospective prognostic analysis, 307 patients	China	Four systems	China staging system best predicts the overall survival in patients with HCC in the Shandong province of China.
Chen et al. [65], 2017	Retrospective prognostic analysis, 220 patients	China	Seven systems	CLIP score best predicts the 3- and 6-month overall survival rates.
Li et al. [66], 2017	Retrospective study, 1270 patients	Singapore	Two systems	BCLC performs better than HKLC in allocating patients to curative treatment as well as predicting survival.
Zhou et al. [67], 2017	Retrospective cohort study, 249 patients	China	Seven systems	Okuda, CUPI, and Chinese Guangzhou 2001 staging systems are the best for prognosticating HCC patients undergoing radiotherapy.
Wallace et al. [68], 2017	Prospective cohort study, 292 patients	Australia	Two systems	HKLC triages more HCC patients to curative therapies and is associated with better survival.
Sohn et al. [69], 2017	Retrospective cohort study, 1009 patients	USA	Two systems	HKLC system determined prognosis in patients following intraarterial therapy.
Selby et al. [70], 2017	Retrospective prognostic analysis, 766 patients	Singapore	Two systems	HKLC has better performance in guiding treatment.
Parikh et al. [71], 2018	Retrospective cohort study at 4 US health systems	USA	Four systems	Prognostic performance of HKLC and MESIAH is better than that of BCLC.

BCLC Barcelona Clinic Liver Cancer staging, *CUPI* Chinese University Prognostic Index, *CLIP* Cancer of the Liver Italian Programme score, *MESIAH* Model to Estimate Survival in Ambulatory HCC patients, *HKLC* Hong Kong Liver classification, *ITA.LI.CA* Italian Liver Cancer staging, *TNM* tumor node metastasis staging, *Y-90 TARE* Yttrium-90 transarterial radioembolization

In conclusion, despite the limitations of the BCLC staging system, it remains the most validated and reliable system for prognostication. However, there is a need to update the BCLC staging system to include recent data on locoregional and systemic therapies for HCC, expanded criteria for transplantation, and systemic therapy for viral hepatitis.

Compliance with ethical standards

Conflict of interest ST, PDS, MSB, AGS, and SPK declare that they have no conflict of interest.

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