

## Staging systems for hepatocellular carcinoma: Current status and future perspectives

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is considerable geographic and institutional variation in both risk factors attributable to the underlying liver diseases and the management of HCC. Therefore, although many staging and/or scoring systems have been proposed, there is currently no globally accepted system for HCC due to the extreme heterogeneity of the disease. The aim of this review is to focus on currently available staging systems as well as those newly reported in the literatures since 2012. Moreover, we describe problems with currently available staging systems and attempts to modify and/or add variables to existing staging systems.

**Key words:** Hepatocellular carcinoma; Staging system; Scoring system; Prognosis

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**Core tip:** Hepatocellular carcinoma is a major health concern worldwide with extreme heterogeneity of the disease. This makes it difficult to identify globally accepted staging systems or treatment algorithms for hepatocellular carcinoma. Clinicians should use currently available staging systems or treatment algorithms carefully while understanding their features and limitations.

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### Abstract

Hepatocellular carcinoma (HCC) is a major health concern worldwide and the third cause of cancer-related death. Despite advances in treatment as well as careful surveillance programs, the mortality rates in most countries are very high. In contrast to other cancers, the prognosis and treatment of HCC depend on the tumor burden in addition to patient's underlying liver disease and liver functional reserve. Moreover, there

### INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health concern worldwide and the third cause of cancer-related death<sup>[1,2]</sup>. Approximately 90% cases of HCC

Table 1 Okuda

Stage	Ascites		Tumor size		Albumin		Bilirubin
	(+)	(-)	> 50% (+)	< 50% (-)	< 3 g/dL (+)	> 3 g/dL (-)	> 3 mg/dL (+)
I (mildly advanced)		(-)	(-)			(-)	(-)
II (moderately advanced)					One or two (+)		
III (very advanced)					Three or four (+)		

are attributable to underlying liver diseases, such as chronic hepatitis B, chronic hepatitis C, alcohol abuse, nonalcoholic steatohepatitis (NASH) or aflatoxin exposure<sup>[3]</sup>. Approximately 80% of HCC cases arise in eastern Asia and sub-Saharan Africa, where the main risk factor is chronic hepatitis B in addition to exposure to aflatoxin B1. In contrast, in North America, Europe and Japan, chronic hepatitis C is the main risk factor, in combination with alcohol abuse<sup>[1]</sup>. NASH has also recently emerged as a relevant risk factor<sup>[2]</sup>.

Despite advances in treatment, such as the use of surgical resection, transplantation, percutaneous ablation and transarterial chemoembolization (TACE) and the administration of multikinase inhibitor sorafenib, as well as careful surveillance programs, the mortality rates in most countries are very similar to the incidence of HCC, thus reflecting the poor prognosis of this disease and subsequent lack of effective treatments<sup>[2]</sup>.

In contrast to that observed for other cancers, the prognosis and treatment of HCC depend on the tumor burden in addition to patient's underlying liver disease and liver functional reserve, both of which affects survival and treatment selection. Moreover, there is considerable geographic and institutional variation in both risk factors attributable to the underlying liver diseases and the management of HCC. This background highlights the extreme heterogeneity of HCC. Therefore, developing a robust staging system and/or identifying prognostic marker for HCC is urgently required.

Staging systems and/or prognostic scores for cancer can be used to evaluate the extent of the tumor burden in the primary organ and the degree of spread to the lymph nodes or other organs. It is thus necessary to accurately predict the patient's prognosis, determine the optimal therapeutic approach and group patients homogeneously for objective comparisons in clinical trials. Moreover, such markers should be simple, reliable and reproducible for clinical use based on clinically available data<sup>[4-7]</sup>.

With regard to HCC, due to the aforementioned heterogeneity, staging systems and/or prognostic scores must account for the tumor burden, underlying liver disease and liver functional reserve, thus indicating the unique required characteristics of such markers. As a result, although a number of staging systems for HCC have been proposed and developed, there is currently no globally applicable staging system.

In this review, we focus on currently available staging systems as well as those newly proposed in the literatures since 2012. Moreover, we describe attempts to modify and/or add variables to existing staging systems.

## CURRENTLY AVAILABLE STAGING SYSTEMS

### Okuda staging system (Table 1)

The Okuda staging system was proposed by a Japanese group in 1984<sup>[8]</sup>. This system is derived from a retrospective cohort of 600 HCC patients treated at Japanese institutions and is the first to combine tumor extension with the liver functional reserve. It incorporates the tumor size ( $\leq$  or  $>$  50% of the entire liver), presence or absence of ascites, serum albumin level ( $\leq$  or  $>$  3.0 g/dL) and serum bilirubin level ( $\leq$  or  $>$  3.0 mg/dL), in which patients are classified into three stages based on these variables (I: not advanced, II: moderately advanced, III: very advanced). Subsequently, the same group validated the Okuda system in 850 HCC patients<sup>[9]</sup>. In that study, the median survival was 11.5 mo for the stage I patients, 3.0 mo for the stage II patients and 0.9 mo for the stage III patients. Among the patient cohort, hepatic failure (45% in surgically treated cases, 38.5% in non-surgically treated cases) was the leading cause of death followed by gastrointestinal bleeding. The authors underlined the importance of assessing the hepatic functional reserve.

Although the Okuda system was the first integrated system for classifying HCC patients, there are major concerns with this system. For example, one variable, tumor extension ( $\leq$  or  $>$  50% of the entire liver), is too rough, considering recent developments in imaging techniques and the use of adequate surveillance programs. Moreover, this system does not include variables such as the degree of vascular invasion or extent of extrahepatic metastasis, both of which affect patient outcomes. Therefore, the Okuda system often makes way for newer staging systems and functions as the standard for comparison<sup>[7]</sup>.

### Cancer of the Liver Italian Program score (Table 2)

The Cancer of the Liver Italian Program (CLIP) score was proposed by an Italian group, the CLIP investigators, in 1998 for the purpose of producing a more sensitive prognostic index than the Okuda

**Table 2** Cancer of the Liver Italian Program

Variables	Scores		
	0	1	2
Child-Pugh stage	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	-	+	

AFP: Alpha-fetoprotein.

staging system<sup>[10]</sup>. This score is derived from the results of a retrospective cohort of 435 HCC patients treated at 16 Italian institutions. This model incorporates four covariates (Child-Pugh grade, tumor morphology, serum alpha-fetoprotein (AFP) level and portal vein thrombosis), assigning a linear score (0/1/2) to each covariate. Patients are subsequently classified into seven groups according to the sum of these scores (0-6). Overall, the differences in survival based on this score are proper.

Subsequently, the same group externally validated the CLIP score in 196 HCC patients enrolled in a randomized clinical trial and confirmed the greater predictive accuracy of this score compared with the Okuda staging system<sup>[11]</sup>.

Although the CLIP score was developed using an appropriate method and has been externally validated, several limitations have been reported. First, half of the patients (235/435, 54%) in the above study received locoregional treatments, such as PEI or TACE, while only 12 patients (2.8%) underwent surgical resection. Therefore, this score may not be suitable for predicting the survival of HCC patients who undergo surgical resection. Second, the covariate "massive" tumor morphology is subjective, without specific size criteria. Therefore, its objectivity and reliability in predicting outcomes may be compromised<sup>[4,7]</sup>. Third, in this study, information regarding underlying liver diseases, which affect patient outcomes, was lacking. Fourth, in the validation study conducted by the same group, the differences among the patient populations assigned to the CLIP 2-3 and 4-6 groups were not significant. In fact, the authors grouped patients with a CLIP score of 4-6 into one group<sup>[4,11,12]</sup>.

### **Barcelona clinic liver cancer classification (Figure 1)**

The barcelona clinic liver cancer (BCLC) classification was first proposed by the Barcelona Clinic Liver Cancer group in 1999<sup>[13]</sup>. This model is derived from the results of a study of the outcomes of radical therapy and/or the natural history of untreated HCC patients<sup>[14-16]</sup>. It is comprised of four elements (tumor extension, liver functional reserve, physical status and cancer-related symptoms). Tumor extension incorporates the number of tumors, tumor size and presence of portal vein invasion or extrahepatic metastasis. Meanwhile, the liver functional reserve is substituted for the Child-

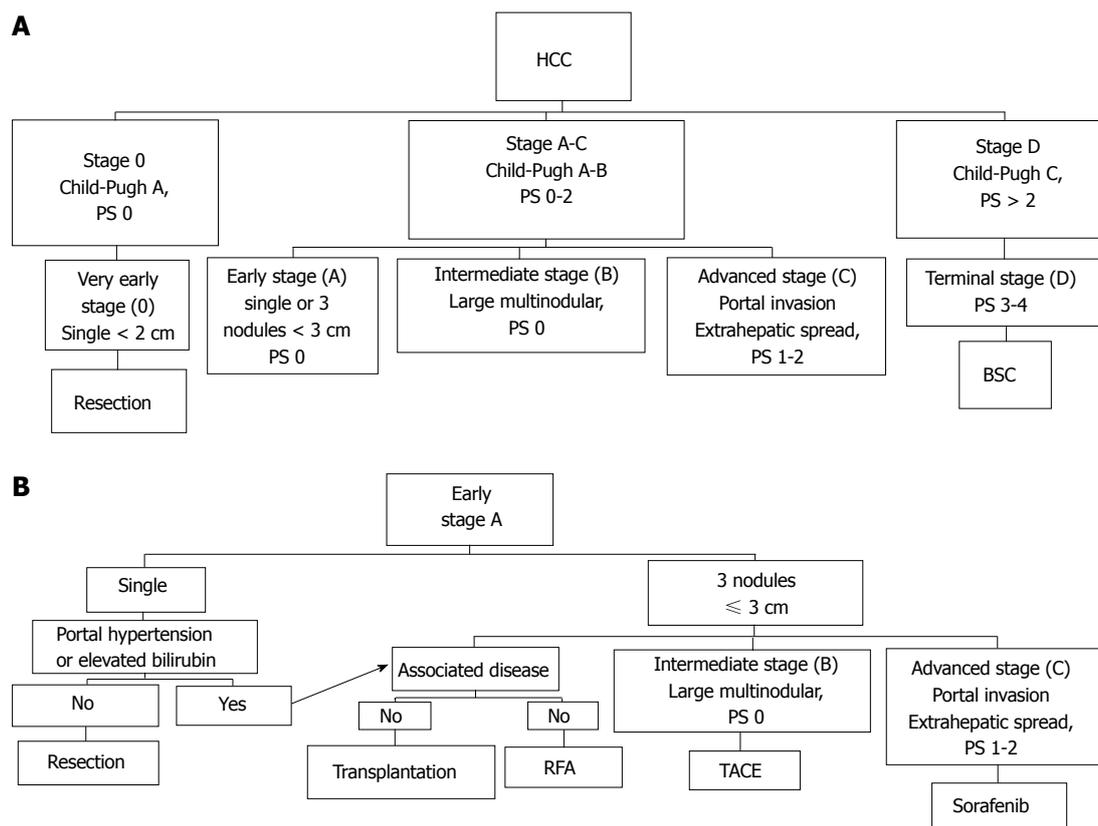
Pugh grade, and the physical status is determined according to the ECOG performance status. Patients are subsequently assigned to five categories (0, A, B, C and D) based on these elements. A BCLC stage of 0 (defined as very early stage disease) comprises patients exhibiting a well-preserved liver function (Child-Pugh A) diagnosed with one asymptomatic nodule measuring less than 2 cm, without vascular invasion or satellites. A BCLC stage of A (defined as early-stage disease) includes patients with a Child-Pugh A or B status diagnosed with one nodule of any size or a maximum of three nodules measuring < 3 cm. A BCLC stage of B (defined as intermediate-stage disease) corresponds to patients with a Child-Pugh grade A or B status diagnosed with multiple nodules without vascular invasion or extrahepatic metastasis. Patients with a Child-Pugh grade of A or B, vascular invasion or extrahepatic metastasis and cancer-related symptoms (PS 1-2) are classified as having BCLC C disease (defined as advanced-stage disease). Finally, patients with a Child-Pugh grade of C, in any tumor stage and cancer-related symptoms (PS > 2) are classified as belonging to the BCLC D disease (defined as terminal stage disease)<sup>[1,13]</sup>.

The notable feature that distinguishes the BCLC system from other staging systems for HCC is the assignment of treatment recommendations for each stage based on the best treatment options currently available<sup>[4,13]</sup>. That is, for patients with a stage 0 and A status, curative treatment options, such as surgical resection, liver transplantation and ablation, are recommended. Meanwhile, TACE is recommended for patients with a stage B status, sorafenib, multikinase inhibitor, is recommended for patients with a stage C status and best supportive care is recommended for patients with a stage D status.

The BCLC classification was updated by incorporating the category of stage 0 (very early stage) and the use of chemoembolization for stage B (intermediate stage) patients in 2003 and further modified to include sorafenib as a first-line treatment option for stage C (advanced stage) patients in 2008<sup>[17,18]</sup>.

Currently, the BCLC classification is endorsed as the standard system for HCC management by the American Association for the Study of Liver Disease, American Gastroenterology Association, European Association for the Study of Liver and the European Organization for the Research and Treatment of Cancer<sup>[3,19]</sup>. However, the BCLC classification has some limitations.

First, stage B (intermediate stage) includes a considerable heterogeneous population of HCC patients with varying degree of tumor extension, liver functional reserve and disease etiology, thus resulting in prognostic heterogeneity and preventing the determination of the optimal treatment regimen<sup>[20,21]</sup>. Second, the variable ECOG PS is somewhat subjective. Hence, the reliability of this system in predicting patient outcomes is compromised. Third, the one-to-



**Figure 1** Barcelona clinic liver cancer classification. A: BCLC classification; B: BCLC classification. HCC: Hepatocellular carcinoma; BCLC: Barcelona clinic liver cancer; TACE: Transarterial chemoembolization.

one correspondence treatment recommendations for each stage of the BCLC system may be not suitable for use in actual clinical practice (*i.e.*, resection or liver transplantation after TACE, the combination of TACE with RFA and/or the combination of TACE with sorafenib, TACE for patients with BCLC 0 or A status and resection for patients with BCLC B or C status).

**GRETCH system (Table 3)**

The GRETCH system was proposed by the French group Goupe d’Etude et de in 1999<sup>[22]</sup>. This system is derived from the finding of a prospective cohort of 761 HCC patients (516 training cohort, 255 validation cohort) treated at 24 Western medical centers. It incorporates five prognostic factors (the Karnofsky index, serum bilirubin, serum alkaline phosphatase (ALP) and serum AFP levels and ultrasonographic portal obstruction) based on a multivariate Cox model. Patients are classified into three risk groups (A: low risk of death, B: intermediate risk of death, C: high risk of death) according to these factors. The overall survival differs markedly for the three groups, with a one-year survival rate in group A of 72% (training cohort) and 79% (validation cohort), compared to 34% (training cohort) and 31% (validation cohort) in group B and 7% (training cohort) and 4% (validation cohort) in group C.

The strength of this system is that it is based on baseline characteristics that are routinely available at

diagnosis and the scores allocated to the respective predictive factors are based on the estimated Cox regression coefficient.

However, half of the patients (401/761, 53%) in this study received no specific therapy, while only 56 patients (7.4%) underwent surgical resection. Therefore, this score may not be suitable for predicting the survival of HCC patients who undergo surgical resection. In addition, evaluating portal obstruction using ultrasound is somewhat out of touch with the current times, considering recent advances in imaging techniques.

**Chines University Prognostic Index (Table 4)**

The Chines University Prognostic Index (CUPI) was proposed by a Hong-Kong group in 2002<sup>[23]</sup>. This score is derived from the results of a cohort of 926 HCC patients (713 training set, 213 validation set) treated at a single Hong-Kong hospital. This score is obtained by adding five prognostic factors (serum bilirubin, ascites, serum ALP, serum AFP and asymptomatic disease on presentation) based on a multivariate Cox model to the TNM staging system. Patients are subsequently divided into three groups (low risk, intermediate risk and high risk) according to the sum of the weights of the six prognostic factors. The differences in the three-month survival among different risk groups classified using this system are highly significant (low-risk group: 85.7%, intermediate-risk group: 56.4% and high-risk

**Table 3 GRETCH**

Weight	0	1	2	3
Karnofsky index (%)	≥ 80			< 80
Serum bilirubin (μmol/L)	< 50			≥ 50
Serum ALP	< 2 × ULN		≥ 2 × ULN	
Serum AFP (μg/L)	< 35		≥ 35	
Portal obstruction (US)	-		+	

AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; US: Ultrasound.

**Table 4 Chines University Prognostic Index**

Variable	Weight
TNM stage	
I and II	-3
IIIa and IIIb	-1
IVa and IVb	0
Asymptomatic disease on presentation	-4
Presence of ascites	3
AFP ≥ 500 ng/mL	2
Total bilirubin (μmol/L)	
< 34	0
34-51	3
≥ 52	4
ALP ≥ 200 (IU/L)	3

≤ 1: Low risk; 2-7: Intermediate risk; ≥ 8: High risk. AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase.

group: 20.2%). Moreover, the authors demonstrated that the CUPI system is more discriminant in predicting survival than the conventional TNM staging system, Okuda system or CLIP score.

In 2011, the group validated the CUPI system in another cohort of 595 HCC patients with predominant HBV infection<sup>[24]</sup>.

Although the CUPI has a strength in that the prognostic factors in this system are readily available in daily clinical practice and are determined based on the estimated Cox regression coefficient, there are various concerns. First, this score was derived from a cohort of HCC patients with predominant HBV infection (79% of the whole cohort), as the authors adequately mentioned. Therefore, this system may be not suitable for application in Western populations with predominant HCV infection or a history of alcohol abuse. Second, the cohort was composed of a large proportion of patients who received only best supportive care (58.4%, vs resection 10.4%). Hence, this system is not preferable for assessing patients who undergo curative treatment, such as surgical resection or RFA.

**TNM classification (Table 5)**

The TNM classification was developed by the American Joint Committee on Cancer (AJCC) and International Union for Cancer Control (UICC) and has been updated regularly since the first edition was published in 1977. The 7<sup>th</sup> edition has become widespread since 2010<sup>[25]</sup>. The TNM classification assesses the extent of the

**Table 5 American Joint Committee on Cancer /TNM 7<sup>th</sup> edition**

Primary tumor	Description		
T1	Single tumor without vascular invasion		
T2	Single tumor with vascular invasion or multiple tumors, none > 5 cm		
T3a	Multiple tumors, any > 5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumors with direct invasion of adjacent organs or perforation of visceral peritoneum		
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III A	T3a	N0	M0
Stage III B	T3b	N0	M0
Stage III C	T4	N0	M0
Stage IV A	Any T	N1	M0
Stage IV B	Any T	Any N	M1

primary tumor (T) as well as the presence of lymph node involvement (N) and/or extrahepatic metastasis (M). It also includes the histologic grade (G) and fibrosis score (F), which do not affect staging. The current AJCC/UICC 7th edition is a modification of the following simplified staging system<sup>[26]</sup>.

**Simplified staging**

The Simplified Staging system was proposed by Vauthey *et al.*<sup>[27]</sup> in 2002. It is derived from the finding of a cohort of 557 HCC patients who underwent surgical resection at four centers (United States, France and Japan). The authors identified independent prognostic factors (major vascular invasion, microvascular invasion, severe fibrosis/cirrhosis, multiple tumors and a tumor size greater than 5 cm) using a multivariate analysis. Based on these variables, they reclassified the AJCC T classification in use at the time, creating the simplified T classification (sT1: single tumor with no vascular invasion, sT2: single tumor with microvascular invasion or multiple tumors, none measuring < 5 cm, sT3: multiple tumors (any measuring > 5 cm) with major vascular invasion). While the original AJCC T classification failed to stratify patients into distinct prognostic groups, the simplified T classification divides patients into independent prognostic groups (five-year survival rates: stage I 55%, stage II 37% and stage III 16%, *P* < 0.001).

However, both the AJCC/UICC and simplified system are limited to patients who undergo surgical resection and lack factors related to the liver functional reserve<sup>[28]</sup>. Therefore, these systems may be not suitable for application in patients not indicated for surgical resection or with a reduced liver functional reserve.

**Japan Integrated Staging (Table 6)**

The Japan Integrated Staging Score (JIS score) was proposed by Kudo *et al.*<sup>[29]</sup> in 2003. It is derived from

**Table 6 Japan Integrated Staging Score**

T factors	I : Single;	II : Size < 2 cm;	III: No vascular invasion	
T1			Fulfilling 3 factors	
T2			Fulfilling 2 factors	
T3			Fulfilling 1 factors	
T4			Fulfilling 0 factors	
Stage I			T1N0M0	
Stage II			T2N0M0	
Stage III			T3N0M0	
Stage IV A			T4N0M0 or any TN1M0	
Stage IV B			Any TN0-1M1	
Scores				
Variables	0	1	2	3
Child-Pugh grade	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

LCSGJ: Liver Cancer Study Group of Japan.

a cohort of 722 HCC patients treated at two Japanese institutions. The authors combined the Child-Pugh grade and the TNM stage based on the criteria of the Liver Cancer Study Group of Japan (LCSGJ), thus creating the JIS score. Patients with a Child-Pugh grade A, B and C status are allocated a score of 0, 1, and 2, respectively. Patients with the TNM stage by LCSGJ of stage I, II, III and IV are allocated to score of 0, 1, 2 and 3, respectively. Patients are subsequently classified into six groups (0-5) based on the sum of these scores. Statistically significant differences are observed between the survival curves for almost all JIS scores, whereas no differences are observed between the patients with CLIP scores 3, 4, 5 and 6.

Thereafter, the same group externally validated the JIS score in 4525 HCC patients treated at five Japanese institutions in 2004<sup>[30]</sup>. Their findings showed that the JIS score could be used to correctly identify the patient subgroup among early, intermediate, advanced and end-stage HCC patients. Moreover, the authors demonstrated that the JIS score exhibits a better prognostic ability when using the likelihood ratio test and Akaike Information Criteria (AIC) than CLIP score.

Although the JIS score is readily available and relatively objective, it has not been validated in a Western population.

### Estrogen receptor classification

The estrogen receptor (ER) classification was proposed by Villa *et al.*<sup>[31]</sup> in 2003. This system is derived from a cohort of 96 unresectable HCC patients treated at a single Italian institution. Based on the prognostic relevance of identifying of ER transcripts in individuals with HCC, the authors classified patients into two groups according to the presence or absence of the ER in HCC specimens. Consequently, the overall survival rate is significantly higher among patients with the wild-type ER (wt ER) (MST: 36 mo) than among those with the variant-ER (w ER) (MST: 13 mo) ( $P < 0.0001$ ).

Although the ER classification is a simple prognostic model for assessing HCC patients, this system has

**Table 7 Stage, Liver damage and des-gamma-carboxy prothrombinscore**

Parameter/score	0	1	2	3
Liver damage by LCSGJ	A	B	C	
Stage by LCSGJ	I	II	III	IV A or IV B
DCP (mAU/mL)	< 400	≥ 400		

LCSGJ: Liver Cancer Study Group of Japan; DCP: Des-gamma-carboxy prothrombin.

a flaw in that it requires the use of a liver biopsy. In addition, the evaluation of the ER is not readily available in daily clinical practice.

### Stage, Liver damage and des-gamma-carboxy prothrombin score (Table 7)

The Stage, Liver damage and des-gamma-carboxy prothrombin (DCP) score (SLiDe score) was established by Omagari *et al.*<sup>[32]</sup> in 2004. This score is derived from the analysis of a cohort of 177 HCC patients treated at a single Japanese institution. The authors identified liver damage according to the LCSGJ criteria, the TNM stage according to the LCSGJ criteria and the serum level of DCP as independent prognostic factors using a Cox proportional hazard model. The authors then assigned a linear score (0, 1, 2 and 3) to these three variables to create the SLiDe score. Patients are classified into seven groups (0-6) based on the sum of these scores. The discriminatory value of the survival curves between each group (SLiDe score 0-1, 2, 3 and 4-6) is evident, and the prognostic ability of the SLiDe score is superior to that of the CLIP score and JIS score as judged according to AIC.

In 2009, the same group validated the SLiDe score in another cohort of 207 HCC patients who underwent surgical resection<sup>[33]</sup>. The authors subsequently showed that there were significant survival differences between the score 0-1, 2-3 and 4-5 groups ( $P < 0.005$ ).

However, the SLiDe score has some shortcomings. First, the original study population ( $n = 177$ ) was relatively small. Second, the variables DCP and ICG R15, which reflect the degree of liver damage according to the LCSGJ criteria, are not routinely examined worldwide.

### Tokyo score (Table 8)

The Tokyo score was established by Tateishi *et al.*<sup>[34]</sup> in 2005 for the purpose of providing a more precise prognostic system for patients with early-stage HCC. This score is derived from the results of a cohort of 403 HCC patients who received percutaneous ablation (PEIT or PMCT) at a single Japanese institution. The authors identified the following four independent predictors for survival using a Cox proportional hazard analysis: the serum albumin level (3.5 g/dL and 2.8 g/dL), serum bilirubin level (1 mg/dL and 2 mg/dL), tumor size (2 cm and 5 cm) and tumor number (1-3 vs > 3). Scores

**Table 8 Tokyo score**

	Score		
	0	1	2
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Total bilirubin (mg/dL)	< 1	1-2	> 2
Tumor size (cm)	< 2	2-5	> 5
Tumor number	≤ 3		> 3

are assigned to each of the four factors according to the estimated regression coefficient, and the total score is defined as the sum of each subscore. Distinct survival curves are observed for each group based on the Tokyo score, with five-year survival rates of 78.7%, 62.1%, 40%, 27.7% and 14.3% for scores 0, 1, 2, 3 and 4-6, respectively. The authors then validated the Tokyo score in a testing sample consisting of 203 HCC patients who underwent surgical resection at the same institution using the AIC and Harrell’s C index and demonstrated that the predictive ability of the Tokyo score is equal to that of the CLIP score and better than that of the BCLC classification.

Although the Tokyo score is useful for predicting the outcomes of HCC patients who are candidates for curative treatment, such as surgical resection and percutaneous ablation, it may be not suitable for use in patients with advanced stages of disease, as the authors adequately mentioned.

**BALAD score (Table 9)**

The Bilirubin, Albumin, Lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3), AFP and DCP Score (BALAD score) was constructed by Toyoda *et al*<sup>[35]</sup> in 2006 for the purpose of providing a simple and objective staging system that requires no imaging studies or pathological or clinical evaluations<sup>[35]</sup>. This score is derived from the findings of a cohort of 2600 HCC patients treated at five Japanese institutions. The authors adopted three tumor markers (AFP-L3 > 15%, AFP > 400 ng/dL, DCP > 100 mAU/mL) as factors reflecting tumor progression. The authors also used two serum markers (serum bilirubin and albumin) as factors indicating the liver functional reserve, according to the Tokyo score<sup>[34]</sup>. Patients are classified into six categories based on the sum of the scores assigned to these factors. Survival curves determined according to the BALAD score are well distributed, and the discriminative ability of the BALAD score is comparable to that of the CLIP score and JIS score.

Although the BALAD score is a simple and objective tool that requires the use of only a serum sample, without imaging, pathological or clinical assessments, it is not easy to measure the AFP-L3 and DCP values in routine clinical practice worldwide.

**Memorial Sloan-Kettering Cancer Center nomogram (Table 10)**

The Memorial Sloan-Kettering Cancer Center (MSKCC)

**Table 9 BALAD score: Scoring of remnant liver function**

	Score		
	0	1	2
Serum bilirubin (mg/dL)	< 1.0	1.0-2.0	> 2.0
Serum albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
	0	1	2
Bilirubin-albumin score	A	B	C
Number of elevated tumor markers	0	1	2
			3

A: 0-1 points; B: 2-3 points; C: 4 points.

nomogram was generated by Cho *et al*<sup>[36]</sup> in 2008 for the purpose of identifying the optimal staging system for HCC patients who undergo surgical resection<sup>[36]</sup>. This system is derived from the findings of a cohort of 184 HCC patients treated at a single institution in the United States (MSKCC). The authors identified seven prognostic factors (patient age, serum AFP level, operative blood loss, resection margin status, tumor size, satellite lesions and vascular invasion) for their novel prognostic nomogram. This nomogram demonstrates a superior concordance index of 0.74 (95%CI: 0.68-0.8) compared to that of eight other contemporary staging systems (AJCC/TNM 1997 edition, International Hepato-Pancreto-Biliary Association staging system, AJCC/TNM 2002 edition, Vauthey Simplified Staging, Okuda, BCLC, CLIP and JIS).

However, the study population (*n* = 184) was relatively small, and this nomogram is not suitable for application in patients treated with RFA, TACE or systemic therapy.

**Advanced Liver Cancer Prognostic System (Table 11)**

The Advanced Liver Cancer Prognostic System (ALPCS) was constructed by Yau *et al*<sup>[37]</sup> in 2008 for the purpose of creating an optimal staging system for classifying advanced HCC patients not indicated for surgical resection or locoregional therapy. This system is derived from the analysis of a cohort of 1470 advanced HCC patients (1109 training set, 361 validation set) treated at a single center in Hong Kong. The authors identified 11 prognostic factors (ascites, abdominal pain, weight loss, Child-Pugh grade, ALP, serum total bilirubin, serum AFP, serum urea, tumor size, portal thrombosis and lung metastasis) using a multivariate Cox model. A point is given for each prognostic factor determined according to the relative magnitude of the regression coefficient of the final Cox model. Patients are subsequently divided into three groups (score ≤ 8: good prognostic group, 9-15: intermediate prognostic group, ≥ 16: poor prognostic group) based on the sum of the scores assigned to each factor (range: 0-39). Survival curves for each prognostic group created according to this system show clear differences, with a median OS of 7.9, 3.2 and 1.4 months for the good, intermediate and poor prognostic groups, respectively (*P* < 0.0001). The median OS

**Table 10** Memorial Sloan-Kettering Cancer Center nomogram: Prognostic factors

Age
Estimated blood loss
Margin
Satelites
Vascular invasion
Size
Log (alpha-fetoprotein)

and three-month survival rates in the validation set ( $n = 320$ ) are similar to those obtained for the training set, with a median OS of 7.5, 3.2 and 1.2 months for the good, intermediate and poor prognostic groups, respectively ( $P < 0.0001$ ). Moreover, the authors demonstrated that the discriminatory ability of the ALPCS (AUC 0.77) is significantly better than that of the Okuda system (AUC 0.66) and CLIP score (AUC 0.71).

However, the ALPCS system was constructed based on the results for a cohort of HCC patients with predominant HBV infection (73% of the whole cohort). Therefore, this system needs to be validated in a Western population with predominant HCV infection and/or a history of alcohol abuse. In addition, many prognostic factors are included in this system ( $n = 11$ ), making calculating the total score somewhat complicated in daily clinical practice.

#### China Integrated Score (Table 12)

The China Integrated Score (CIS) was established by Zhang *et al.*<sup>[38]</sup> in 2010. This score is derived from a cohort of 220 patients (166 training set, 54 validation set) with unresectable HCC treated at a single institution in China. The authors identified three prognostic factors (TNM stage, serum AFP and Child-Pugh grade) using a Cox proportional hazard regression model. Patients are classified into six groups (0-5) based on the sum of the scores assigned to the three covariates. The survival curves for a prospective validation cohort of 54 HCC patients were found to be clearly distributed among the groups, with a median survival rate of 9.0, 2.3, 2.1 and 0.6 mo in the patients classified with CIS stages 2, 3, 4 and 5, respectively. The discriminatory ability of the CIS is comparable to that of the CLIP score. According to this system, the authors subsequently proposed a set of guidelines for selecting the optimal treatment in patients with unresectable HCC based on this system.

However, the study population ( $n = 220$ ) was relatively small. Therefore, the CIS needs to be externally validated in a large scale, prospective study.

#### Taipei Integrated Score System (Table 13)

The Taipei Integrated Score System was proposed by Hsu *et al.*<sup>[39]</sup> in 2010. This system is derived from the investigation of a cohort of 2030 HCC patients

**Table 11** Advanced liver cancer prognostic system

Characteristics		Points	
Ascites	Yes	2	
	No	0	
Abdominal pain	Yes	2	
	No	0	
Weight loss	Yes	2	
	No	0	
Child-Pugh grade	A	0	
	B	2	
	C	5	
ALP (IU/L)	> 200	3	
	≤ 200	0	
Total bilirubin (mmol/L)	> 50	3	
	33-50	1	
	≤ 33	0	
Urea (mmol/L)	> 8.9	2	
	≤ 8.9	0	
Portal vein thrombosis	Yes	3	
	No	0	
Tumor size	Diffuse	4	
	> 5 cm	3	
	≤ 5 cm	0	
Lung metastases	Yes	3	
	No	0	
AFP (ng/mL)	> 400	4	
	≤ 400	0	
Prognosis	Score	3-mo survival rate	
	Good	0-2	> 0.81
		3-6	0.72-0.8
		7-8	0.66-0.69
	Intermediate	9	0.63
		10-12	0.51-0.59
13-14		0.42-0.47	
Poor	15	0.38	
	16	0.33	
	17-19	0.21-0.29	
	20-22	0.1-0.17	
	≥ 23	< 0.1	

AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase.

undergoing different treatment modalities at a single institution in Taiwan. The authors adopted the calculated total tumor volume (TTV) as a surrogate marker of the tumor burden and combined the TTV with four cirrhosis associated models (Child-Pugh grade, MELD, MELDNa and MELD-Na) to create the TTV-based staging system. The TTV was categorized into four groups (< 50 cm<sup>3</sup>, 50-250 cm<sup>3</sup>, 250-500 cm<sup>3</sup> and > 500 cm<sup>3</sup>), and single-digit values were assigned to each TTV group (0: < 50 cm<sup>3</sup>, 1: 50-250 cm<sup>3</sup>, 2: 250-500 cm<sup>3</sup> and 3: > 500 cm<sup>3</sup>). A total of 12 new staging models were created and patients were classified into seven groups (0-6) based on these methods. Among the 12 TTV-based staging systems, the TTV-Child-Pugh grade-AFP combination model provides the lowest AIC value. Moreover, the TTV-Child-Pugh grade-AFP model shows superior prognostic value compared with the four current staging systems (CLIP, BCLC, JIS and Tokyo). In particular, the TTV-Child-Pugh grade-AFP model has the smallest AIC value among patients receiving non-curative treatment.

**Table 12 China Integrated Score**

Variables	Scores				
	0	1	2	3	4
TNM stage	≤ III	IVA	IVB		
Child-Pugh grade	A	B	C		
AFP (mg/L)	≤ 400	> 400			
CIS score	0	1-2	3	4	5
	PEI or TACE	Herbs + TACE	TACE herbs	Chemotherapy	Symptomatic RCT

CIS: China Integrated Score; TACE: Transarterial chemoembolization; AFP: Alpha-fetoprotein; PEI: Percutaneous ethanol injection; RCT: Randomized controlled trials.

**Table 13 Taipei Integrated System**

Variables	Scores			
	0	1	2	3
Total tumor volume (cm <sup>3</sup> )	< 50	50-250	250-500	> 500
Child-Pugh grade	A	B	C	
AFP (ng/mL)	≤ 400	> 400		

AFP: Alpha-fetoprotein.

Although the TTV-based staging system is a useful and reliable system based on the findings of a large cohort of HCC patients with early to advanced stage disease undergoing various treatment modalities, this system is associated with several concerns. First, the TTV is estimated based on the assumption that all tumors are spherical. Therefore, the TTV value may not be accurate in cases involving tumors that are infiltrative or numberless. Second, this system was constructed based on the results for a cohort of HCC patients with predominant HBV infection (55% of the whole cohort) and must therefore be externally validated in Western population.

**Eastern staging system (Table 14)**

The Eastern staging system was established by Yang *et al.*<sup>[40]</sup> in 2011. This system is derived from the analysis of a cohort of 958 HCC patients with predominant HBV infection (91.8%) who underwent surgical resection at a single institution in China. The authors identified 10 independent prognostic factors, including macroscopic vascular invasion, multiple tumors, the PS1-2 status, microscopic vascular invasion, extrahepatic spread, a maximum tumor size of > 5 cm, a serum albumin level of < 35 g/L, a serum AST level of > 40 U/L, a serum total bilirubin level of > 17 μmol/L and the presence of cirrhosis, using a Cox proportional hazard regression analysis. Based on these variables, the authors established a new staging system for classifying resectable HCC patients, named the Eastern staging system, in which the patients are classified into five groups (stage 1-5) according to the sum of the

**Table 14 Eastern stage**

Variables	Score	
	0	1
Macroscopic vascular invasion	-	+
Tumor number	Solitary	Multiple
PS	0	1-2
Microscopic vascular invasion	-	+
Extrahepatic spread	-	+
Maximum tumor size (cm)	≤ 5	> 5
Albumin (g/L)	≥ 35	< 35
AST (U/L)	≤ 40	> 40
Total bilirubin (μmol/L)	≤ 17	> 17
Presence of cirrhosis	-	+
	Cumulative score	
Stage I	0-1	
Stage II	2-3	
Stage III	4-5	
Stage IV	6-7	
Stage V	8-10	

AST: Aspartate transaminase.

score (0-10) allocated to each prognostic factor. The Eastern staging system exhibits significant differences in the probability of survival of the patients in different stages ( $P < 0.001$ ). The Eastern staging system provides the highest likelihood ratio according to the  $\chi^2$  and linear trend  $\chi^2$  tests (543.51 and 414.97) among six other staging systems (Okuda, CLIP, BCLC, CUPI, AJCC/TNM and JIS), indicating superior homogeneity and monotonicity of the gradients. Moreover, the AUC of the Eastern staging is higher at each time point than that of the other six staging systems (1, 3 and 5 years: 0.846, 0.811 and 0.815, respectively).

However, the Eastern staging system is associated with some limitations. First, it was derived from a cohort of HCC patients with predominant HBV infection, as the authors adequately mentioned. Hence, this system must be externally validated in a Western population. Second, the weight for survival of each prognostic factor was not taken into account when identifying the prognostic factors.

**Portal vein tumor thrombus classification (Table 15)**

The portal vein tumor thrombus (PVTT) classification was proposed by Shi *et al.*<sup>[41]</sup> in 2011. This system is derived from the investigation of a retrospective cohort of 441 HCC patients with macroscopic PVTT treated with partial hepatectomy at a single institution of China. The authors proposed the PVTT classification based on the extent of tumor thrombosis in the portal vein, as follows: Type I 0 Tumor thrombus formation on microscopy, Type I tumor thrombosis involving segmental branches of the portal vein or above, Type II tumor thrombosis involving the right/left portal vein, Type III tumor thrombosis involving the main portal vein trunk and Type IV tumor thrombosis involving the superior mesenteric vein. The one-, two- and three-year survival rates for Types I to IV PVTT are 54.8%, 33.9% and 26.7%, 36.4%, 24.9% and 16.9%, 25.9%,

**Table 15 Portal vein tumor thrombus classification**

Types
Type I 0: Tumor thrombus formation found under microscopy
Type I : Tumor thrombi involving segmental branches of portal vein or above
Type II : Tumor thrombi involving right/left portal vein
Type III: Tumor thrombi involving the main portal vein trunk
Type IV: Tumor thrombi involving the superior mesenteric artery

**Table 16 A prognostic model for hepatocellular carcinoma patients within the Milan criteria undergoing non-transplant therapies**

Variables	Scores		
	0	1	2
Total bilirubin (mg/dL)	< 1.5	≥ 1.5	
AFP (ng/mL)	< 100	≥ 100	
Ascites	-	Mild	Moderate to severe

AFP: Alpha-fetoprotein.

12.9% and 3.7%, 11.1%, 0% and 0%, respectively ( $P < 0.0001$ ). The discriminatory ability of the PVTT classification is superior to that of the AJCC/TNM staging system, CLIP score and JIS score.

Although the PVTT classification appears to be useful for predicting the outcomes of HCC patients with surgically treated macroscopic PVTT, it has some limitations. First, it was derived from a cohort of HCC patients with predominant HBV infection (87.5% of the whole cohort) and needs to therefore be externally validated in a Western population. Second, the use of surgical resection with or without portal thrombectomy for HCC associated with PVTT is not a global standard. In fact, in the BCLC classification, sorafenib is recommended as the first-line treatment for HCC patients with PVTT (Stage C). Therefore, this system may be not suitable for use in all HCC patients with PVTT.

### Staging systems proposed since 2012

Several staging systems have been newly proposed since 2012. However, many of these systems have not been externally validated.

### Prognostic model within the Milan criteria for patients undergoing non-transplant therapy (Table 16)

Lee *et al.*<sup>[42]</sup> proposed a prognostic model based on the serum bilirubin level, AFP level and severity of ascites in patients meeting the Milan criteria treated with non-transplant therapy in 2012<sup>[42]</sup>. This system is derived from the findings of a cohort of 1106 HCC patients (49% HBV infection, 553 deviation set, 553 validation cohort) receiving treatment at a single institution in Taiwan. The authors constructed a new system based on three independent prognostic factors identified in a multivariate Cox model of the deviation set. Subsequently, the predictive accuracy was confirmed

**Table 17 Model to Estimate Survival in Ambulatory hepatocellular carcinoma patients score**

### MESIAH score

$$\begin{aligned}
 &= 0.232 * (\text{age in decades}) \\
 &+ 0.099 * (\text{MELD}) \\
 &- 0.391 * (\text{serum albumin level}) \\
 &+ 0.290 * (\text{tumor size}) \\
 &+ 0.153 * (\text{tumor number}) \\
 &+ 1.122 * (\text{vascular invasion}) \\
 &+ 1.130 * (\text{extrahepatic metastasis}) \\
 &+ 0.082 * (\text{serum AFP level}) \\
 &+1
 \end{aligned}$$

AFP: Alpha-fetoprotein. MESIAH: Model to Estimate Survival in Ambulatory HCC patients score; HCC: Hepatocellular carcinoma.

in the validation set, irrespective of the treatment strategy (curative or non-curative).

However, evaluations of the amount of ascites are subjective and affected by the use of diuretics, as the authors adequately mentioned. Therefore, objective assessments of ascites are required.

### MESIAH score (Table 17)

The Model to Estimate Survival in Ambulatory HCC patients score (MESIAH score) was developed by Yang *et al.*<sup>[43]</sup>, from the Mayo group, in 2012. This score is derived from a cohort of 477 HCC patients (derivation cohort) treated at the Mayo Clinic and 904 HCC patients (validation cohort) treated at a Korean institution. The authors identified independent predictors for survival in a multivariate Cox model (age, MELD score, serum albumin level, tumor size, tumor number, vascular invasion and extrahepatic metastasis), thus creating a new risk score. Following internal validation, the prognostic value of the MESIAH score was confirmed in the validation cohort, with a concordance statistics of 0.82, which is higher than that for the CLIP score (0.75) and JIS score (0.78). The derivation cohort differed from the validation cohort with regard to the underlying liver disease (derivation cohort: HBV 18%, HCV 81%, validation cohort: HBV 75%) and treatment modality (derivation cohort: transplantation 31%, resection 17%, TACE 25%, validation cohort: resection 13%, TACE 57%). Conversely, however, it can be said that the predictive accuracy of MESIAH is highly stable, irrespective of the underlying liver disease and/or treatment modality.

More recently, the same group validated this score in another cohort of 1969 HCC patients with predominant HBV infection (74.6%) treated at a Korean institution<sup>[44]</sup>. The discriminatory ability of the MESIAH score, as evidenced by the C-statistics, LR $\chi^2$  value and AIC, is better than that of the BCLC, CLIP, JIS and Tokyo.

However, calculating the MESIAH score is somewhat complicated in daily clinical practice.

Considering the advantages of superior predictive accuracy and objectivity of the prognostic factors,

**Table 18** Alpha-fetoprotein staging

AFP (ng/mL)	Stage
< 10	N (normal)
10-150	A
150-500	B
> 500	C

AFP: Alpha-fetoprotein.

independent of the underlying liver disease and treatment modality, the MESIAH score is one of the most promising staging systems for evaluating HCC patients.

### AFP staging (Table 18)

The AFP staging was proposed by Burnet *et al.*<sup>[45]</sup> in 2013 against a background in which a substantial proportion of HCC patients in Kentucky have no underlying liver disease<sup>[45]</sup>. This score is derived from the findings of a cohort of 518 HCC patients (272 cirrhotic, 246 non-cirrhotic) treated at a single institution in the United States. The authors defined the AFP stage based on the report by Muscari *et al.*<sup>[46]</sup>, as follows: stage N (AFP < 10 ng/mL), stage A (10 < AFP < 150 ng/mL), stage B (150 < AFP < 500 ng/mL) and stage C (AFP ≥ 500 ng/mL). Survival curves determined according to the AFP stage for each prognostic group show clear survival differences ( $P < 0.0001$ ), similar to the BCLC classification. In particular, in non-cirrhotic patients, the AFP staging system has a lower  $P$  value than the BCLC classification.

However, this study is associated with some limitations. First, there is no information regarding the treatment modality, which affects patient outcomes. Second, the survival differences among patient populations assigned to AFP stage B and C are not significant. Third, although the authors stated that the AFP stage is more suitable for assessing non-cirrhotic HCC patients, no comparative analyses with the BCLC classification have been carried out.

### Hepatoma arterial-embolisation score (Table 19)

The hepatoma arterial-embolisation (HAP) score was developed by Kadalayil *et al.*<sup>[47]</sup> in 2013. This score is derived from a cohort of 281 HCC patients (114 training set, 167 validation set) who received TACE at three institutions in England. The authors identified four prognostic factors (a serum albumin levels of < 36 g/dL, serum AFP level of > 400 ng/mL, serum bilirubin level of > 17 μmol/L and maximum tumor diameter of > 7 cm) using a multivariate Cox model. Patients are classified into four groups (HAP A-D) based on the sum of the scores assigned to the prognostic factors. The survival curves for both the training and validation sets stratified according to the HAP score were clearly distributed ( $P < 0.001$ ), and the authors demonstrated that the HAP score provides

**Table 19** Hepatoma arterial-embolisation score

Variables	Points
Albumin < 36 g/dL	1
AFP > 400 ng/mL	1
Total bilirubin > 17 μmol/L	1
Maximum tumor diameter > 7 cm	1

AFP: Alpha-fetoprotein.

superior predictive value compared to the Okuda, MELD, BCLC and Child-Pugh grade based on the AUC.

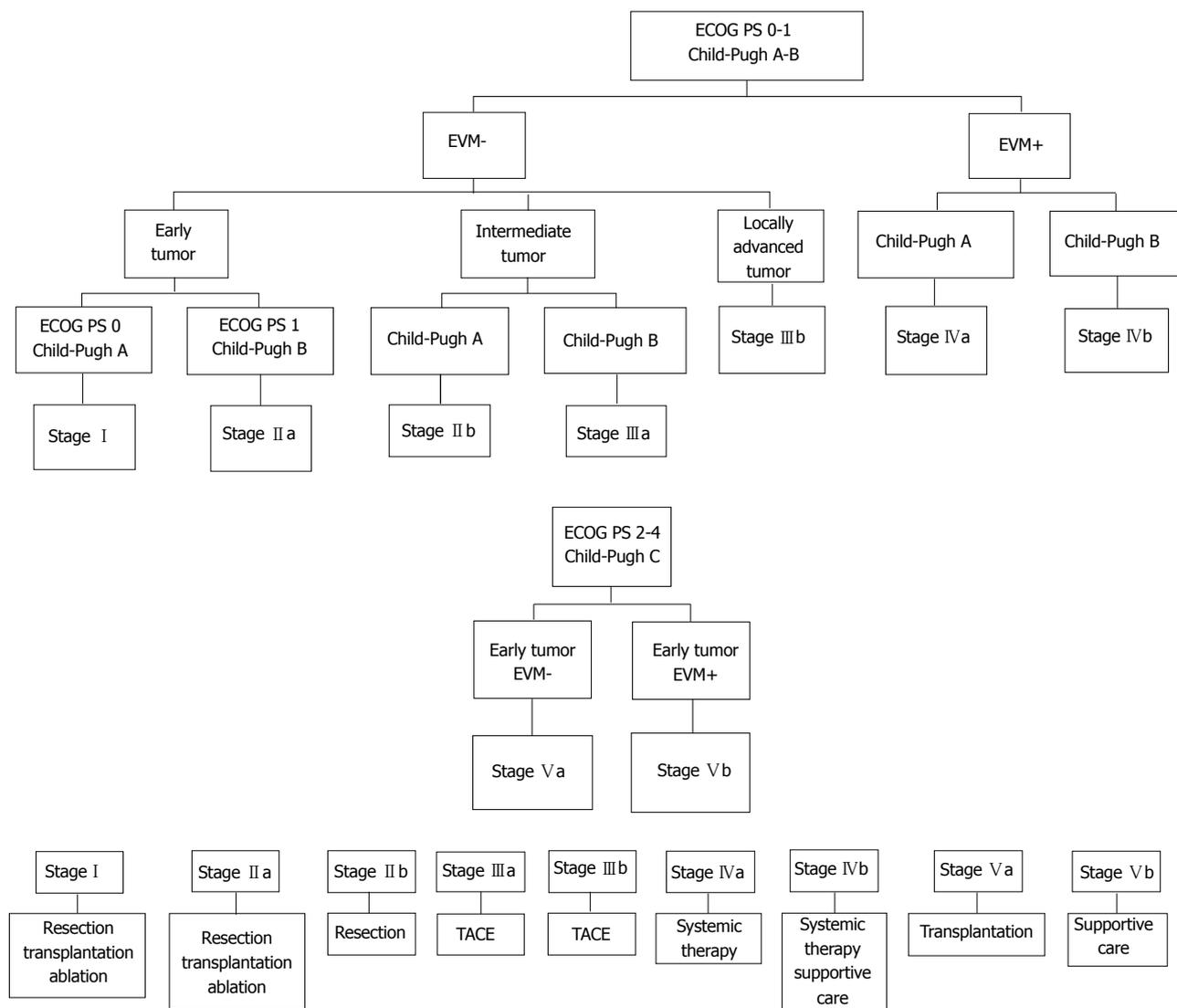
However, the HAP score has not been externally validated.

### 5-gene score

The 5-gene score was proposed by Nault *et al.*<sup>[48]</sup> in 2013. This score is derived from a cohort of HCC patients who underwent surgical resection at two French institutions and several institutions in the United States, Italy, Spain, Japan and China. The authors constructed the 5-gene score based on findings showing that the expression patterns of five genes (*TAF9*, *RAMP3*, *HN1*, *KRT19* and *RAN*) had strong prognostic relevance. This score was found to be significantly associated with the disease-specific survival and rate of early tumor recurrence in both the training cohort ( $n = 189$ ) and validation cohort ( $n = 125$ ). The authors further validated the 5-gene score in HCC patients with predominant HCV infection in Europe and the United States and HCC patients with predominant HBV infection in Asia. However, this score is not readily available in daily clinical practice.

### Hong Kong Liver Cancer classification (Figure 2)

The Hong Kong Liver Cancer (HKLC) classification was developed by a Hong Kong group in 2014<sup>[49]</sup>. This system is derived from the results of a large cohort of 3856 HCC patients (1968 training set, 1888 test set) with predominant HBV infection treated at single institution in Hong Kong. Four established prognostic factors (ECOG PS, Child-Pugh grade, liver tumor status and presence of extrahepatic vascular invasion or metastasis) were selected when building the system using the training set according to a multivariate Cox regression model. Patients are classified in five main stages and nine substages (stages I-Vb) based on these prognostic factors. The constructed staging system and treatment guidelines were subsequently assessed in the test set for internal validation. This classification is based on five main stages with distinct survival outcomes, which were very similar between the training set and the test set. This classification exhibits better prognostic value than the BCLC classification, with an AUC at one year of 0.851, three years of 0.8 and five years of 0.83 for the HKLC classification, compared to an AUC at one year of 0.804, three years of 0.8 and five years of 0.795 for the BCLC classification. In the



**Figure 2 Hong Kong Liver Cancer classification.** EVM: Extrahepatic vascular invasion/metastasis; ECOG: Eastern cooperative oncology group; TACE: Transarterial chemoembolization.

authors' analysis, the C-index for the HKLC was 0.739, which is higher than that for the BCLC classification (0.703). Notably, the HKLC classification is able to better stratify patients in the BCLC B and C stages into distinct groups, with better survival outcomes based on more aggressive treatment recommendations than that observed in the BCLC treatment algorithm.

However, the HKLC classification is associated with several limitations. First, it was derived from a cohort of HCC patients with predominant HBV infection (80% of the whole cohort) and should therefore be validated in a Western population as well as patients with different disease etiologies, as the authors adequately described. Second, the authors subdivided the BCLC classification into five groups (A1-2, A3-4, B, C and D) when assessing the AUC values for the HKLC and BCLC classifications, which is not appropriate considering the current categories of the BCLC classification (0, A, B, C and D)<sup>[50]</sup>.

Despite these limitations, the HKLC system app-

ears to have a greater impact on the current BCLC classification, addressing the problems with the heterogeneity of the BCLC B and C stages and rigidity of treatment allocation. Regarding the former problem, it is interesting that the HKLC classification is compared with the subclassification of the BCLC B stage proposed by Bolondi *et al.*<sup>[20]</sup>. Regarding the latter problem, the expanded treatment guidelines of the HKLC classification, such as surgical resection for BCLC B patients or TACE for BCLC C patients, should be verified in a large-scale prospective study in addition to HCC patients with etiologies other than HBV infection.

**External validation and comparison of currently available staging systems**

As mentioned above, a number of staging systems and/or scoring systems for HCC have been proposed and established. Several studies have also externally validated and compared the prognostic value of various staging systems.

### **AJCC/TNM 7<sup>th</sup> edition**

Kee *et al.*<sup>[51]</sup> demonstrated that the 7<sup>th</sup> edition of the TNM staging system provides a superior discriminatory value than 6<sup>th</sup> edition of the TNM system based on the findings of a cohort of 8828 HCC patients treated at a single institution in Taiwan<sup>[51]</sup>. Chun *et al.*<sup>[52]</sup> also showed that the 7<sup>th</sup> edition of the TNM system has greater prognostic power than the 6<sup>th</sup> edition of the TNM system based on an analysis of a cohort of 877 HCC patients with predominant HBV infection treated at a single Korean institution<sup>[52]</sup>, and Zhou *et al.*<sup>[53]</sup> showed that the 7<sup>th</sup> edition of the TNM system was the best prognostic model for HCC patients without AFP elevation who undergo surgical resection<sup>[53]</sup>.

However, the prognostic ability of the 7<sup>th</sup> edition of the TNM system is poorer than that of the BCLC classification, particularly in patients with advanced stages of the disease<sup>[54]</sup>. Studies from China have also reported the predictive inaccuracy of the 7<sup>th</sup> edition of the TNM system, although the patient populations were limited to subjects undergoing surgical resection<sup>[55]</sup>. Due to its inherent lacks of factors related to the liver functional reserve, the prognostic relevance of the TNM staging system appears to be limited to HCC patients with early-stage tumors and a preserved liver functional reserve.

### **CLIP score**

Because the CLIP score was originally derived from a cohort of HCC patients who primarily presented with advanced stage tumors, it is generally accepted that the CLIP score is suitable for use in HCC patients with advanced tumors or those receiving non-surgical treatments.

In fact, investigators from Japan, Canada, Italy, France, Taiwan, the United States and Germany recently demonstrated that the CLIP score provides better prognostic value than other staging systems in HCC patients with advanced stage tumors<sup>[56-63]</sup>. In a cohort of HCC patients who received specific treatment modalities, including TACE or radioembolization, systemic chemotherapy and BSC, the CLIP score proved to be the best prognostic model<sup>[64-66]</sup>. However, studies from Japan and Taiwan have shown that the CLIP score provides a superior predictive value compared to other staging systems, even in HCC patients undergoing surgical resection<sup>[67,68]</sup>. Finally, a large-scale study from Taiwan demonstrated that the CLIP score is the best prognostic model in patients with early to advanced stages of disease, irrespective of the use of curative or non-curative treatment<sup>[69]</sup>. These results indicate that the predictive accuracy of the CLIP score is highly stable, independent of the tumor stage, treatment modality, underlying liver disease and geographic differences.

### **BCLC classification**

As expected, several studies from Italy and China have shown that the BCLC classification is the best

prognostic model in HCC patients who receive radical therapy, including surgical resection or percutaneous ablation<sup>[70-74]</sup>. In contrast, investigators from Italy, the United States, Spain, South Korea and Egypt demonstrated that the BCLC classification provides the best prognostic value in HCC patients with early to advanced stage tumors treated with various modalities<sup>[75-79]</sup>. These results indicate that the predictive accuracy of the BCLC classification is highly stable, independent of the tumor stage, treatment modality, underlying liver disease and geographic differences.

With regard to treatment allocation, a large-scale trial from Taiwan ( $n = 3892$ ) showed that the treatment schedules determined according to the BCLC classification are both reasonable and beneficial for survival in patients with HCC<sup>[80]</sup>.

### **CUPI**

Studies from Taiwan and China have demonstrated that the CUPI is the best prognostic model in advanced HCC patients with portal vein invasion or extrahepatic metastasis<sup>[63,81]</sup>.

However, this score has not been validated in either a Western population or in patients with etiologies other than HBV infection.

### **JIS**

A study from Japan showed that the JIS score provides the best prognostic value in HCC patients treated with surgical resection<sup>[82]</sup>. Other studies from Japan have also demonstrated the JIS score to be the best prognostic model in HCC patients who receive various treatment modalities<sup>[83,84]</sup>. However, the JIS score has not been validated in countries outside of Japan.

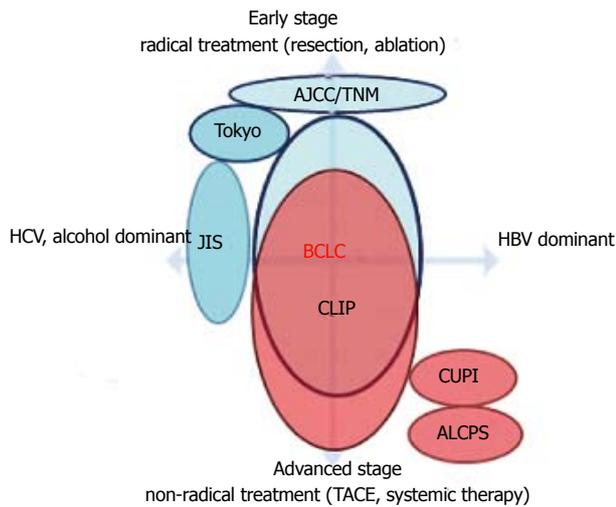
### **Tokyo**

Investigators from Taiwan reported that the Tokyo score was the most informative tool in a large cohort ( $n = 2010$ ) of HCC patients with predominant HBV infection (67%) who underwent various treatment regimens<sup>[66]</sup>. However, the Tokyo score has not been validated in a Western population.

### **ALCPS**

A study from China demonstrated the ALCPS system to be the best prognostic model in advanced HCC patients with predominant HBV infection (88%)<sup>[85]</sup>. However, this score has not yet been validated in a Western population.

Staging systems must to be validated in both Western and Asia-Pacific patient populations, irrespective of the underlying liver disease and etiology, before they can be considered to be globally applicable, as there are significant regional and institutional differences in HCC in terms of etiology, underlying liver disease and feasible treatment modality<sup>[4]</sup>. In this context, among many staging systems BCLC and CLIP can be currently globally applicable staging systems for HCC patients.



**Figure 3** A positioning map of existing validated staging systems. AJCC: The American Joint Committee on Cancer; BCLC: The Barcelona Clinic Liver Cancer; CLIP: The Cancer of the Liver Italian Program; JIS: The Japan Integrated Staging Score; CUPI: The Chines University Prognostic Index; ALCPS: The Advanced Liver Cancer Prognostic System; HBV: Hepatitis B virus.

A positioning map of existing validated staging systems is shown in Figure 3.

### New attempts

In addition to creating new models, investigators have made attempts to modify and/or add other variables, such as biomarkers or the general status, into existing prognostic systems.

### Modifying currently available staging systems:

Huo *et al.*<sup>[86]</sup> proposed the MELD-based model in 2007. In this model, the Child-Pugh grade, which is used in the CLIP, BCLC and JIS scores to assess the liver functional reserve, is replaced with the MELD score, and the authors subsequently created MELD-based modified CLIP, BCLC and JIS scores. These scores have better predictive value than the original scores. Ling *et al.*<sup>[87]</sup> also incorporated the MELD score into the TNM system for use in patients undergoing surgical resection, thus creating the MELD-based TNM staging system and demonstrated that the MELD-based TNM stage provides better prognostic stratification<sup>[87]</sup>.

Meanwhile, Lin *et al.*<sup>[88]</sup> subdivided the CLIP score into 36 subgroups<sup>[88]</sup>. The authors showed that different prognostic weighting of four predictive factors of the CLIP score (PVT followed by the Child-Pugh grade, AFP and tumor morphology) resulted in heterogeneity of survival within the same score group.

Furthermore, Santambrogio *et al.*<sup>[89]</sup> proposed a simplified BCLC staging system (s-BCLC) for assessing resectable HCC patients. This score is defined by only two groups (AA: BCLC A1 + A2 with a serum AFP level of  $\leq 20$  ng/mL, AB: BCLC A1 + A2 with a serum AFP level of  $> 20$  ng/mL or A3, A4). The authors demonstrated that the s-BCLC is more suitable for prognostic stratification in HCC patients who undergo

surgical resection than the original BCLC or other staging systems.

Regarding the heterogeneity of patients in BCLC stage B, Bolondi *et al.*<sup>[20]</sup> proposed a subclassification of stage B (B1-B4) in 2012, in association with different first-line and alternative treatment options (Table 20). Notably, the authors adopted the up-to-7 criterion in order to distinguish major from minor tumor extension<sup>[90]</sup>. Recently, this subclassification was externally validated in a cohort of HCC patients in both South Korea and Taiwan<sup>[91,92]</sup>.

### Adding biomarkers to existing staging systems:

Kitai *et al.*<sup>[93]</sup> combined the JIS score and three tumor markers (AFP, AFP-L3 and DCP), to create a new staging system, the Biomarker combined JIS (bm-JIS), in 2008. This system is derived from a cohort of 1824 HCC patients treated at five Japanese institutions. The authors showed that the bm-JIS score has better stratification value than the conventional JIS score. The group also externally validated the bm-JIS score in 1173 HCC patients treated at five Japanese institutions<sup>[94]</sup>.

Kaseb *et al.*<sup>[95]</sup> proposed the VEGF-CLIP (V-CLIP) score in 2011 based on findings showing that the VEGF, the major mediator of angiogenesis in the setting of HCC, is associated with the overall survival of HCC patients. The authors added the VEGF (cutoff point: 450 pg/mL) to the CLIP score, thus creating the V-CLIP score. The V-CLIP score stratifies patients into homogenous prognostic groups ( $P = 0.005$ ) and provides superior predictive accuracy compared to the original CLIP score ( $P = 0.005$ ). The same group proposed the insulin-like growth factor-1 (IGF-1) CLIP (I-CLIP) score in 2011 based on findings demonstrating that the IGF-1 value, which reflects the synthetic function of the liver, is an independent prognostic factor for overall survival of HCC patients<sup>[96]</sup>. The authors subsequently integrated the dichotomized IGF-1 level (cutoff point: 26 ng/mL) into the CLIP score, thereby creating the I-CLIP score. The I-CLIP score classifies patients into independent prognostic groups ( $P < 0.0001$ ) and displays a better prognostic ability than the original CLIP score ( $P < 0.0001$ ). Based on these results, Kaseb *et al.*<sup>[97]</sup> established the IGF-1, VEGF-BCLC (IV-BCLC) score in 2011 in which they integrated the IGF-1 value (cutoff point 26 ng/mL) and VEGF value (cutoff point 450 pg/mL) into the BCLC score, to create the IV-BCLC score. The authors demonstrated that IV-BCLC score is more accurate in predicting overall survival and provides better prognostic stratification than the original BCLC score ( $P < 0.0001$ ).

More recently, Kinoshita *et al.*<sup>[98,99]</sup> reported that the addition of the serum CRP level to previously validated staging systems (CLIP, BCLC, JIS, BCLC, Tokyo and TNM according to LCSGJ) improves the prognostic value of each staging system, based on

**Table 20 Barcelona Clinic Liver Cancer B subclassification**

Sub-Stage	B1	B2	B3	B4
Child-Pugh score	5-6-7	5-6	7	8-9 (with severe/refractory ascites and/or jaundice)
Beyond Milan and within Ut-7	In	Out	Out	Any
ECOG (tumor related) PS	0	0	0	0-1
Portal vein thrombosis	-	-	-	-
1 <sup>st</sup> option	TACE	TACE or	Research	BSC
Alternative	Liver transplantaion TACE + ablation	TARE sorafenib	Research trials TACE sorafenib	Liver transplantaion (only if Up-to-7 IN and PS0)

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; BSC: Best supportive care.

results showing an elevated serum CRP level to be independently associated with a poor prognosis in HCC patients.

**Adding the general status to existing staging systems:** Tournoux-Facon *et al*<sup>[100]</sup> reported that the addition of the WHO PS to the CLIP score improves the discriminatory ability compared to that of the original CLIP and BCLC scores in patients treated in the palliative setting (BoBar). The same group also demonstrated that incorporating quality of life data improves the prognostic value of the CLIP, BCLC, GRETCH and BoBar scores in palliative HCC patients<sup>[101]</sup>.

Furthermore, Hsu *et al*<sup>[102]</sup> showed that the modifying the BCLC system according to the ECOG PS enhances the prognostic ability in HCC patients in early to advanced stages of the disease.

**Problems with currently available staging systems and future perspectives**

As mentioned above, many staging systems and scoring systems have been established and refined. However, there is currently no globally accepted system for assessing HCC patients, due to heterogeneity of the extent of tumor extension, underlying liver disease and liver functional reserve. There are several problems regarding currently available staging systems.

First, none of these systems take into account the location of the tumor or its proximity to major vessels, which affect both treatment selection and tumor progression<sup>[7]</sup>.

Second, none of the above systems incorporate the etiology (HBV infection, HCV infection, alcoholism and NASH) or underlying liver disease (LC, hepatitis and a normal liver). Generally, the outcomes of HCC patients differ according to the etiology of the liver disease. Several studies have shown that HCC patients with

HCV infection or alcoholic liver disease exhibit poorer outcomes than those with HBV infection<sup>[7,103,104]</sup>. This is because HCC patients with HBV infection generally have a better liver functional reserve than those with HCV infection or alcoholic liver disease<sup>[50]</sup>. An increasing number of patients develop HCC based on the presence of nonalcoholic fatty liver disease (NAFLD) or NASH, both of which affect the liver functional reserve and patient outcomes. In fact, Reddy *et al*<sup>[105]</sup> demonstrated that HCC patients with NASH undergoing surgical resection display a better liver functional reserve and survival outcomes than those with HCV infection and/or alcoholic liver disease<sup>[105]</sup>. More recently, Kaseb *et al*<sup>[106]</sup> showed that currently available staging systems (Okuda, CLIP, BCLC, CUPI and TNM 6<sup>th</sup> edition) are significantly less predictive of overall survival in HCC patients without cirrhosis or hepatitis, advocating that staging systems should be modified to include factors related to viral hepatitis and cirrhosis in addition to demographics and geographic location.

Third, many staging systems lack optimal treatment allocation, with the exception of BCLC and HKLC. There is also controversy regarding current BCLC treatment recommendations. First, this system does not provide recommendations for second-line therapy or combined treatment, such as resection or liver transplantation after TACE, the combination of TACE with RFA and/or the combination of TACE with sorafenib. Second, it is rigid. In a study from South Korea, many patients with a BCLC 0 (62.9%) or BCLC A (54%) status underwent TACE rather than radical therapies, such as surgical resection or percutaneous ablation, as proposed by the BCLC classification. Moreover, patients with BCLC C stage disease underwent TACE (35.7% of patients) or HAIC (24.6% of patients) rather than receive treatment with sorafenib, which is inconsistent with the recommendations in the BCLC classification<sup>[78]</sup>. More recently, a multicenter Italian study demonstrated that the survival rate of BCLC B patients undergoing TACE (MST: 27 mo) was significantly shorter than that of BCLC B patients who underwent surgical resection (MST: 37 mo) and percutaneous ablation (MST: 36 mo) ( $P < 0.001$ ), indicating that patients with a BCLC B status are often suitable candidates for more aggressive therapies than TACE based on proper patient selection<sup>[107]</sup>. In addition, a multicenter study from Italy showed that liver transplantation could result in survival benefit for HCC patients with BCLC D status<sup>[108]</sup>. These results also suggest the need for careful multidisciplinary evaluations of optimal treatment modalities as recommended by the BCLC classification.

In conclusion, although many staging and/or scoring systems have been proposed, there is currently no globally accepted system for assessing HCC patients due to the extreme heterogeneity of the disease. Clinicians involved in treating HCC patients

should use currently available staging systems or treatment algorithms carefully while understanding their features and limitations. Growing evidence regarding understanding of tumor biology as well as advancements in imaging techniques and treatment modalities will result in the development of better staging systems that refine the process of stratification, survival prediction and treatment allocation in order to optimize the management of HCC patients.

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