Current HCC Staging Systems: Their Uses and Limitations

28

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28.1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer, the third most common cause for cancer death in the world [1]. Because of the high recurrence rate and poor prognosis, the prognostic assessment and selection of treatment strategy in HCC patients are quite important [1–3], and a precise stratification system for the prognosis of HCC patients is required.

In patients with HCC, the prediction of prognosis is complex compared with most solid tumors. It is well known that the prognosis and treatment of HCC depend on the tumor burden in addition to patient's underlying liver disease and liver functional reserve [4, 5]. However, the latter is not integrated in the tumor lymph node metastasis (TNM) staging system, which is generally accepted as a standard approach for prognostication in many cancer clinical staging systems. Therefore, staging systems based on information regarding both tumor factors and host factors such as liver function have been required to accurately classify HCC patients undergoing various therapeutic options [4–7].

An accurate staging system could contribute to prognostication, guiding management decision, comparing different treatment modalities, and comparing treatment outcomes among different institutions [4]. Nowadays, many staging and scoring systems based on both tumor factors and host factors have been proposed for the classification and prognosis of patients with HCC [6–9].

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However, there is no consensus on which is the best prognostic staging system for HCC until now, because there is considerable geographic and institutional variation in both risk factors attributable to the underlying liver diseases and the management of HCC. For example, most of HBV-related HCC patients are particularly prevalent in Africa and Asia, in contrast, most of HCV-related HCC patients are prevalent in western countries, Taiwan and Japan [10, 11]. Other strong risk factors exist, such as alcohol, metabolic syndrome. The characteristics of HCC and screening program which can increase the chance of curative treatment and improve survival also vary with geographic location.

The aim of this review is to focus on the currently available staging systems which integrated tumor factors and host factors for assessing the prognosis of HCC, their uses and limitations.

28.2 Staging Systems of HCC

Generally, the TNM staging that include the extension of the tumor burden in the original primary organ and its spread throughout the body is exhaustive for most solid tumors. Currently, the TNM staging which proposed from the Liver Cancer Study Group of Japan (LCSGJ) and from the AJCC/International Union Against Cancer (UICC) are available for HCC [12–14]. Both of them were developed based on the analysis of patients who received hepatic resection. In 1983, the LCSGJ first introduced an HCC Tumor Node Metastasis (TNM) scheme, which has subsequently been revised, most recently from 5th to the 6th edition in 2015. On the other hand, Vauthey et al. [15] developed a simplified staging system for HCC in 2002, which was adopted as the TNM staging system of AJCC/UICC after minor changes. It has been revised and now, 7th edition was available. These 2 staging systems have some similarities; for example, patients with distant metastasis are assigned to the highest stage, and those with hepatic lymph node metastasis are assigned to the second highest stage. In contrast, the major differences between LCSGJ TNM and AJCC/UICC TNM are the cutoff value for tumor size and its application in prognostic classification [14].

Both the LCSGJ-stage and the AJCC-stage were developed based on a survival analysis of patients who underwent hepatic resection. Although these TNM staging systems are appropriate for patients who will undergo hepatic resection, however, many authors have noted that TNM staging dose not accurately predict outcome for HCC patients undergoing various therapeutic options, because it does not consider liver function status [9].

Thus, nowadays, many staging and scoring systems based on both tumor factors and host factors such as liver function have been proposed for the classification and prognosis of patients with HCC (Table 28.1). In this review, these staging systems are conveniently divided into four categories.

1. Conventional staging systems

These were very famous and pioneering staging systems which attempted to combine tumor factor and liver function, however, not suitable at the present day. Okuda staging and the Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH) staging belong to this category. These often made way to the development of more accurate staging systems and functions as the standard for comparison.

2. Staging systems for treatable condition

The staging systems classified into this category are considered to be suitable for estimating the prognosis of HCC patients who are in treatable condition such as surgery or other locoregional therapy. In this category, the Cancer of the Liver Italian Program (CLIP) score and the Japan Integrated Staging (JIS) score are well-known staging systems, and many staging and scoring systems have been proposed for the classification and prognosis of these population.

3. Staging systems for advanced condition

These staging systems are applicable for advanced HCC who were not amendable to surgery or locoregional therapy. Chinese University Prognostic Index (CUPI) and Advanced Liver Cancer Prognostic System (ALCPS) belong to this category. The advent of effective systemic treatment options are needed for this population with such advanced HCC.

4. Staging systems for treatment recommendation

These staging systems provide treatment algorisms. The Barcelona clinic liver cancer (BCLC) staging is well known and provides treatment algorisms and recommendations, and the prognostic value has been externally validated in many countries. Very recently, the Hong Kong Liver Cancer (HKLC) classification was constructed to developed treatment guidance for Asian patients.

These categories and components of each staging system are showed in Table 28.2.

28.3 Statistical Approach for Comparison of the Staging Systems

To compare the prognostic ability of each staging system with different numbers of parameters, statistical analyses were used in many literatures. The area under the receiver

Table 28.1 Current HCC staging systems

Model	Author	Country	Year	Case number	Patient population	Treatment modality
						Curative[a]/noncurative[b]/palliative
Okuda	Okuda [85]	Japan	1985	850	All	157/464/229
CLIP	CLIP investigators [49]	Italy	1998	435	All	150/97/182 (6 cases unknown)
GRETCH	Chevret [48]	France	1999	761	All	83/277/401
BCLC	Llovet [80]	Spain	1999	[c]	All	–
CUPI	Leung [78]	China	2002	926	All	96 (surgical)/289 (non surgical)/ 541
JIS	Kudo [57]	Japan	2003	722	All	n.d.
JIS family						
Modified JIS	Nanashima [60]	Japan	2004	101	Surgery	101/0/0
SLIDE	Omagari [64]	Japan	2004	177	All	71/92/14
bm-JIS	Kitail [66]	Japan	2008	1924	All	892/934/98
Tokyo	Tateishi [67]	Japan	2005	403	Radiotherapy, surgery	403/0/0
BALAD	Toyoda [74]	Japan	2006	2600	All	1473/959/168
ALCPS	Yau [79]	China	2008	1470	Advanced	0/632/838
TIS	Hsu [68]	Taiwan	2010	2030	All	927/769/334
HKLC	Yau [85]	China	2014	3856	All	1489/1611/756
MITS	Tokumitsu [77]	Japan	2015	234	Surgery	234/0/0

CLIP The Cancer of the Liver Italian Program, *GRETCH* The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire, *BCLC* The Barcelona Clinic Liver Cancer, *CUPI* Chinese University Prognostic Index, *JIS* The Japan Integrated Staging, *bm-JIS* biomarker-JIS, *ALCPS* Advanced Liver Cancer Prognostic System, *TIS* The Taipei Integrated Score, *HKLC* The Hong Kong Liver Cancer, *MITS* The Mathematical Integrated model for Tumor Staging, *n.d* not described

[a]Curative: surgical resection, liver transplantation and local ablation

[b]Noncurative: transarterial therapy, Radiation therapy, and systemic therapy such as Sorafenib

[c]Derived from the results of a study of the outcomes of radical therapy and/or the natural history of untreated HCC patients

operating characteristic curve (AUC) [16–22], linear trend chi-square score [17, 21, 23–29], likelihood ratio chi-square score [8, 17, 23–36], and Akaike information criteria within a Cox proportional hazards regression model were used to compare the predictive ability of each staging system in many literatures [8, 22–26, 28–45]. Recently, Harrell's C-index was also used in several reports [22, 32, 39, 40, 43, 46].

28.4 Conventional Staging Systems

28.4.1 Okuda Staging System (Table 28.3)

The staging system proposed by Okuda et al. (Okuda) in 1985 is the first attempt to successfully combine the anatomical features of the tumor to the degree of the underlining liver disease [47]. 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. Although the Okuda system was the first integrated system for classifying HCC patients, tumor burden which is evaluated by only tumor extension ($\leq$ or >50 % of the entire liver) was too rough, considering recent developments in imaging modality and the use of adequate surveillance programs. Therefore, the Okuda system often makes way to the development of more accurate staging systems and functions as the standard for comparison.

28.4.2 The Groupe D'Etude et de Traitement Du Carcinome Hépatocellulaire (GRETCH) System (Table 28.4)

The GRETCH system was proposed by the French group Goupe d'Etude et de in 1999 [48]. 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. On the basis of a multivariate Cox model in validation cohort, five prognostic factors were

Table 28.2 The categories and components of each staging system

Variables	Conventional staging		Staging for treatable condition									Staging for advanced condition		Staging for treatment recommendation	
	Okuda	GRETCH	CLIP	JIS	JIS family			Tokyo	TIS	MITS	BALAD	CUPI	ALCPS	BCLC	HLKC
					mJIS	SLIDE	bmJIS								
Bilirubin	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Albumin	•		•	•	•	•	•	•	•	•	•			•	•
ICGR15					•	•				•					
ALP		•										•	•		
Portal hypertension														•	
Ascites	•		•	•	•	•	•		•	•		•	•	•	•
Presence of symptoms and/or general status		•										•	•	•	•
Child-Pugh score			•	•			•		•				•	•	•
Liver damage score					•	•				•					
Tumor size	•		•	•	•	•	•	•	•	•		•	•	•	•
Morphological features			•											•	
Numbers of nodules				•	•	•	•	•	•	•		•		•	•
Vascular invasion[a]				•	•	•	•					•			
Portal vein thrombosis		•	•	•	•	•	•					•	•	•	•
Distant metastasis				•	•	•	•					•	•	•	•
TNM				•	•	•	•					•			
AFP		•	•				•		•		•		•		
AFP-L3							•				•				
DCP						•	•				•				

ALP alkaline phosphatase, *ICGR15* indocyanine green retention rate at 15 min, *TNM* tumor node metastasis, *AFP* alpha-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a]Involving any branch of portal or hepatic vein

Table 28.3 Okuda staging system

	Score	
	0	1
Tumor size	≤ 50 % of the liver	>50 % of the liver
Albumin (g/dL)	≥ 3	<3
Bilirubin (mg/dL)	<3	≥ 3
Ascites	Absent	Present

Table 28.4 GRETCH score

	Score			
	0	1	2	3
Karnofsky index	≥ 80 %			<80 %
Bilirubin (μmol/L)	<50			≥ 50
ALP	<2 × ULN		≥ 2 × ULN	
AFP (μg/L)	<35		≥ 35	
Portal vein thrombosis	Absent		Present	

GRETCH The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire, *ALP* alkaline phosphatase, *AFP* alpha-fetoprotein

selected: Karnofsky index, serum bilirubin, serum alkaline phosphatase, serum alpha-fetoprotein, and ultrasonographic evidence of portal obstruction. Patients are classified into three risk groups according to these factors, and the author reported that the overall survival differs markedly for the three groups in both training and validation cohort. However, half of the patients (401/761, 53 %) in this study received no specific therapy, therefore, this score may not be suitable for predicting the survival of HCC patients nowadays, considering recent developments in treatment modality and the use of adequate surveillance programs. Thus, it is not a well validated or a widely used staging system.

28.5 Staging Systems for Treatable Condition

28.5.1 The Cancer of the Liver Italian Program (CLIP) Score (Table 28.5)

The CLIP score was derived in 1998 from a retrospective evaluation of 435 Italian patients with HCC treated at 16 Italian institutions [49] for the purpose of producing a more sensitive prognostic index than the Okuda staging system. It includes four variables as the Child-Pugh stage, Tumor morphology, AFP level, Portal vein thrombosis. 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 [50]. After that, the CLIP score was developed using an appropriate method and has been externally validated over the world [16–18, 30, 37–41, 51, 52]. It is generally accepted that the CLIP score is suitable for use in HCC patients with intermediate-advanced tumors or those receiving non-surgical treatments. In fact, investigators from Korea [53], Canada [51], Italy [17, 30], France [37], Taiwan [38, 52], the United States [54], and Germany [39] recently demonstrated that the CLIP score provides better prognostic value than other staging systems in HCC patients who received specific treatment modalities, including TACE or radioembolization, systemic chemotherapy with intermediate-advanced tumors. Although studies from Japan [18] and Taiwan [16] have shown that the CLIP score provides a superior predictive value compared to other staging systems for HCC patients undergoing surgical resection, however, there were HCC patients with large size advanced tumor or those receiving major hepatectomy. Therefore, this score may not be suitable for predicting the survival of the early stage HCC, which are susceptible to percutaneous or minor hepatectomy.

28.5.2 CLIP Family

Staging systems based on the CLIP score are conveniently classified into "CLIP family" in this review. In recent years, Kaseb et al. [55] proposed the VEGF-CLIP (V-CLIP) score based on the VEGF, which was the major mediator of angiogenesis in the setting of HCC. The authors integrated the VEGF into the CLIP score, and they reported that the V-CLIP score provides superior predictive accuracy compared to the conventional CLIP score. The same group proposed the insulin-like growth factor-1 (IGF-1) CLIP (I-CLIP) [56] score based on findings demonstrating that the IGF-1 value, which reflects the synthetic function of the liver. The authors added the IGF-1 to the CLIP score and created the V-CLIP score. They also reported that the I-CLIP score provides superior predictive accuracy compared to the conventional CLIP score.

28.5.3 The Japan Integrated Staging (JIS) Score (Table 28.6)

Kudo et al. [57] originally proposed the JIS score, which is defined by the LCSGJ TNM stage and the Child-Pugh classification. It is derived from a cohort of 722 HCC patients treated at two Japanese institutions. Patients with a Child-Pugh grade A, B, and C status are allocated a score of 0, 1, and 2, respectively, and 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. Subsequently, patients are classified

Table 28.5 CLIP score

	Score		
	0	1	2
Tumor morphology	Uninodular and extension ≤50 %	Multinodular and extension ≤50 %	Massive or extension >50 %
Child-Pugh classification	A	B	C
AFP (ng/mL)	<400	≥400	
Portal vein thrombosis	Absent	Present	

CLIP The Cancer of the Liver Italian Program, *AFP* alpha-fetoprotein

Table 28.6 JIS score

	Score			
	0	1	2	3
TNM stage by LCSGJ	I	II	III	IV
Child-Pugh classification	A	B	C	

JIS The Japan Integrated Staging, *TNM* tumor node metastasis, *LCSGJ* Liver Cancer Study Group of Japan

into six groups (0–5) based on the sum of these scores. Using 4525 patients with HCC at five institutions, the same group validated the JIS score as a good prognostic staging system than the CLIP score [31]. Other studies from Japan have also demonstrated that the JIS score to be the best prognostic model in HCC patients who receive various treatment modalities [8, 16, 32, 44]. Toyoda et al. [44] showed that the JIS system was the most suitable after 1990, when early detection and early treatment of HCC became common, although the CLIP staging systems proved to be more suitable before 1991. After 1990, surveillance of patients at high risk for development of HCC caused by chronic viral hepatitis or cirrhosis and early detection of HCC were very common in Japan, because of development of various scanning modality as well as indication of highly sensitive tumor markers [58, 59]. The discriminating power of JIS system is, therefore, particularly suitable for countries such as Japan, where many small HCC are detected and diagnosed at early stages and treated with radical therapies. However, it has not been well validated in countries outside of Japan, especially in a western patient population.

28.5.4 JIS Family (Table 28.7)

Integrated staging systems based on the Japanese TNM stage by LCSCJ are conveniently classified into "JIS family" in this review.

28.5.4.1 Modified JIS Score

Nanashima et al. [60] proposed m-JIS score, which combined TNM staging system by LCSGJ and the degree of the liver damage (Table 28.8) instead of Child-Pugh classification, and reported that this system was better predictor of prognosis than JIS score in HCC patients who underwent hepatic resection [45]. Ikai et al. [61] validated this system using the records of 42,269 patients diagnosed with HCC that were registered between 1992 and 1999 in a nationwide Japanese database. This suggested that the degree of liver

Table 28.7 JIS family

	Score			
	0	1	2	3
Modified JIS score				
TNM stage by LCSGJ	I	II	III	IV
Liver damage classification	A	B	C	
SLiDe score				
TNM stage by LCSGJ	I	II	III	IV
Liver damage classification	A	B	C	
DCP (mAu/mL)	<400	≥400		
bm-JIS score				
TNM stage by LCSGJ	I	II	III	IV
Child-Pugh classification	A	B	C	
No of elevated tumor marker (AFP, AFP-L3, DCP)	0	1	2–3	

JIS The Japan Integrated Staging, *TNM* tumor node metastasis, *LCSGJ* Liver Cancer Study Group of Japan, *AFP* alpha-fetoprotein, *AFP-L3* Lens culinaris agglutinin-reactive alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

Table 28.8 Liver damage classification by LCSGJ

Item	Liver damage grade		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	3.0–3.5	<3.0
ICG R15 (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

LCSGJ Liver Cancer Study Group of Japan, *ICGR15* indocyanine green retention rate at 15 min

damage could evaluate and classify liver function more precisely than the Child-Pugh classification for early HCC or surgical population. The degree of liver damage classification was proposed by the LCSGJ, and incorporates the ICGR15 test, which is an estimation of indocyanine green clearance, instead of encephalopathy in the Child-Pugh classification system. ICGR15 test has been widely used in the field of surgery in Japan as a useful marker of hepatic function [62, 63]. However, ICGR15 are not routinely assessed in other parts of the world, thus, the m-JIS score has not been validated in countries outside of Japan.

28.5.4.2 SLiDe Score

Omagari et al. [64] proposed SLiDe score, which combined TNM staging system by LCSGJ, the degree of the Liver damage and DCP (SLiDe). They showed that there was clear discrimination among the survival curves plotted for patients with different SLiDe scores, and this system could predict the outcome of HCC patients more precisely than the CLIP and JIS scoring systems in these population. Nanashima et al. [65] validated this system in 207 HCC patients who undergone hepatic resection. However, SLiDe score does not seem to be very suitable for worldwide use at present, because it uses some parameters that are not routinely assessed in other parts of the world such as ICGR15 test and DCP. Therefore, this classification should be further validated in other large study populations.

28.5.4.3 Biomarker-JIS Score

The JIS staging classification was further modified by Kitai et al. [66]. They proposed biomarker-combined JIS (bm-JIS) which combined TNM staging system by LCSGJ, the Child-Pugh classification, and three tumor markers for HCC, namely AFP, lens culinaris agglutinin-reactive AFP (AFP-L3), and des carboxyprothrombin (DCP). They validated the bm-JIS score as a good prognostic staging system than the conventional JIS sore [33, 34, 66], BALAD score [33], and BCLC system [34]. Although this scoring system validated in a relatively large population of HCC patients in Japan, this system has now been externally validated from but still requires validation in a western patient population, because measuring all of these three tumor markers in routine clinical practice are uncommon worldwide.

Table 28.9 Tokyo score

	Score		
	0	1	2
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	<1	1–2	>2
Tumor size (cm)	<2	2–5	>5
Number of nodules	≤ 3	–	>3

28.5.5 TOKYO Score (Table 28.9)

Tateishi et al. [67] proposed the Tokyo score would provide a prediction of prognosis for patients who were candidates for radical therapy, such as percutaneous ablation or surgical resection. A total of 403 patients with HCC treated by percutaneous ablation were used as the training sample to develop the Tokyo Score and validated by 203 independent patients who underwent hepatectomy at the same institution 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.

Investigators from Taiwan [29] reported that the Tokyo score was the most informative staging system in a large cohort (n = 2010) of HCC patients with predominant HBV infection who underwent surgical resection or transarterial chemoembolization. However, the Tokyo score has not been validated in a Western population. Further, external validation of the Tokyo classification in different patient populations is needed.

28.5.6 The Taipei Integrated Score (TIS) System (Table 28.10)

The Taipei Integrated Score System (TIS) was proposed by Hsu et al. [68] in 2010. This system is derived from the investigation of a cohort of 2030 HCC patients undergoing

Table 28.10 TIS

Variable	Score			
	0	1	2	3
Total tumor volume (cm^3)	<50	50–250	250–500	>500
Child-Pugh classification	A	B	C	
AFP (ng/nL)	≤ 400	>400		

TIS Taipei integrated system, *AFP* Alpha-fetoprotein

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. TTV was defined as the sum of the volume of each tumor [(4/3) × 3.14 × (radius of tumor in cm)^3]. Subsequently, they combined the TTV with four cirrhosis-associated models (Child-Pugh grade, MELD, MELDNa and MELD-Na) and/or tumor factors (serum AFP levels and vascular invasion) to create the TTV-based staging system and the prognostic ability of the TTV-based staging system and the four current systems, including the BCLC, CLIP, JIS, and Tokyo score was examined. They reported that the TTV-CTP-AFP model [i.e. The Taipei Integrated Score System (TIS)] provided the best prognostic ability among them and the model was validated in Taiwanese population [35, 36]. The TTV and TTV-based staging systems are also evaluated to predict recurrence of HCC after liver transplantation in many countries [69–73]. However, the TTV value may not be accurate in tumors which are not typically spherical, such as infiltrative or numberless type, because the TTV is estimated based on the assumption that all tumors are spherical.

28.5.7 BALAD Score (Table 28.11)

BALAD score was constructed by Toyoda et al. in 2006 for the purpose of providing a simple and objective staging system that requires no imaging studies or pathological or clinical evaluations [74]. There were five variables in the BALAD score: The Bilirubin, Albumin, Lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3), AFP, and DCP Score. 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 and also used two serum markers (serum bilirubin and albumin) as factors indicating the liver functional reserve. They reported that the discriminative ability of the BALAD score was comparable to that of the CLIP score and JIS score. The BALAD score is a simple and objective tool that requires the use of only a serum sample, without imaging, pathological, or clinical assessments. Although it was considered that measuring the AFP-L3 and DCP values in routine clinical practice worldwide were uncommon, however, this system was externally validated in recent years in countries outside of Japan [75, 76].

Table 28.11 BALAD score

	Score			
	0	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8	
Bilirubin (mg/dL)	<1	1–2	>2	
Bilirubin-albumin score*	A	B	C	
No of elevated tumor marker (AFP, AFP-L3, DCP)	0	1	2	3

*Liver function was categorized by the sum of these 2 points (i.e., bilirubin and albumin) as scores A (0–1 points), B (2–3 points), and C (4 points)
AFP alpha-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

28.5.8 The Mathematical Integrated Model for Tumor Staging (MITS) Score (Table 28.12)

More recently, we developed a novel predictive system based on mathematical product of tumor number and size of largest tumor ($N \times S$ factor) for prognosis of Japanese HCC patients after hepatectomy [77]. We found that cutoff value of $N \times S$ factor at 4 and 9 had high accuracy in predicting recurrence of HCC. Given that the $N \times S$ factor and the degree of Liver Damage classification by LCSGJ were independent risk factors for HCC prognosis by multivariate analysis, we constructed the mathematical integrated model for tumor staging (MITS) score by combining the $N \times S$ factor with the degree of Liver Damage classification. In this population, we showed that the MITS score was more predictable for the prognosis of HCC patients than any of the six well-known clinical staging systems [TNM (LCSGJ), TNM (UICC), JIS score, modified JIS score, CLIP score, and the Tokyo Score]. We found that the $N \times S$ factor-based staging system had high accuracy in predicting HCC prognosis.

There were several limitations in this study: First, it was a retrospective single-center study that enrolled only patients who underwent curative hepatectomy. Second, HCC patients with invasion of major portal or hepatic vein branch were excluded in this study. Third, MITS score integrates the degree of Liver damage classification which incorporates the

Table 28.12 MITS score

	Score		
	0	1	2
Mathematical product of tumor number and size ($N \times S$ factor)	<4	4–9	>9
Liver damage classification	A	B	

MITS The Mathematical Integrated model for Tumor Staging

ICGR15 test instead of Child-Pugh classification system, and ICGR15 are not routinely assessed in other parts of the world or non-surgical populations even in Japan. In this regard, further studies will be needed to evaluate whether the robustness of the $N \times S$ factor-based staging system which may integrate Child-Pugh classification in predicting prognosis could be maintained in a cohort in which the majority of the subjects were HCC patients who received non-surgical treatment.

28.6 Staging Systems for Advanced Condition

28.6.1 Chinese University Prognostic Index (CUPI)(Table 28.13)

The Chines University Prognostic Index (CUPI) was proposed by a Hong-Kong group in 2002 [78]. This score is derived from the results of a cohort of 926 HCC patients treated at a single Hong-Kong hospital. In that study, 19 potential prognostic factors were evaluated in a multivariate analysis using a Cox regression model among 926 Chinese patients, mostly with HBV-associated HCC. Subsequently, five prognostic factors (total bilirubin, presence of ascites, alkaline phosphatase, alpha fetoprotein, and asymptomatic disease on presentation) were selected and added to the TNM, in order to set up 3 classes of risk with highly significant differences in survival. 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 this study, 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 and several validation studies were performed in Asian population with advanced stage of HCC [28, 40, 43, 46]. In recent years, Chan et al. [78] reported an international validation of the CUPI. They reported that the CUPI was demonstrated to be optimal for those undergoing palliative treatment in both Eastern and Western HCC patient population, and they concluded that a more precise staging system for early-stage disease patients is required.

Table 28.13 CUPI

Variable		Weight
TNM stage	I and II	−3
	III	−1
	IV	0
Bilirubin (μmon/L)	<34	0
	34–51	3
	≥ 52	4
Ascites		3
AFP (ng/mL)	>500	2
ALP (IU/L)	>200 IU/L	3
Asymptomatic disease on presentation		−4

CUPI Chinese University Prognostic Index, *TNM* tumor node metastasis, *AFP* alpha-fetoprotein, *ALP* alkaline phosphatase

28.6.2 Advanced Liver Cancer Prognostic System (ALCPS) (Table 28.14)

The Advanced Liver Cancer Prognostic System (ALPCS) was constructed by Yau et al. [79] in 2008 for the purpose of creating an optimal staging system for classifying advanced HCC patients who were not amendable to surgery or locoregional therapy. This system was derived from the analysis of a cohort of 1470 advanced HCC patients (1109 training set and 361 validation set) treated at a single center in Hong Kong, and developed using 11 prognostic factors with different weights on basis of a multivariate Cox model. They reported that the ALCPS stratified patients in both training and validation sets to different prognostic groups with significant difference in three-month overall survival.

Table 28.14 ALCPS

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

ALCPS Advanced liver cancer prognostic system, *ALP* Alkaline phosphatase, *AFP* Alpha-fetoprotein

Moreover, the score showed significantly better predictive power in known three-month survival status than Okuda score and CLIP score in the validation set.

Although investigators from China demonstrated the ALCPS system to be the prognostic model in advanced HCC patients [21, 41], however, this score has not yet been validated in a Western population. In addition, many prognostic factors are included in this system (n = 11), calculating the total score somewhat complicated in daily clinical practice.

28.7 Staging Systems for Treatment Recommendation

28.7.1 The Barcelona Clinic Liver Cancer (BCLC) Staging (Fig. 28.1)

The Barcelona Clinic Liver Cancer (BCLC) classification was first proposed by the Barcelona Clinic Liver Cancer group in 1999 [80]. This staging system includes an integrated assessment of liver disease, tumor extension, and presence of constitutional symptoms. 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, and might be an appropriate classification system for a patient population evenly distributed among early, intermediate, and advanced stages of the disease. The notable feature of the BCLC system is the assignment of treatment recommendations for each stage based on the best treatment options currently available, and this system has been updated according to the results of investigations that have incorporated strong evidence. The BCLC staging system and treatment allocation is summarized in Fig. 28.1. In 2003, the system incorporated the concept of very early stage (BCLC 0) that included patients with HCC 2 cm with well-preserved liver function [10]. With the description of several cohort studies showing the efficacy of ablation in these patients, the scheme was updated again recognizing ablation as first treatment option. In 2008, the positive results of two randomized controlled trial in advanced HCC, allowed the acknowledgment of sorafenib as the first-line treatment option for stage C (advanced stage) patients [3, 81].

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

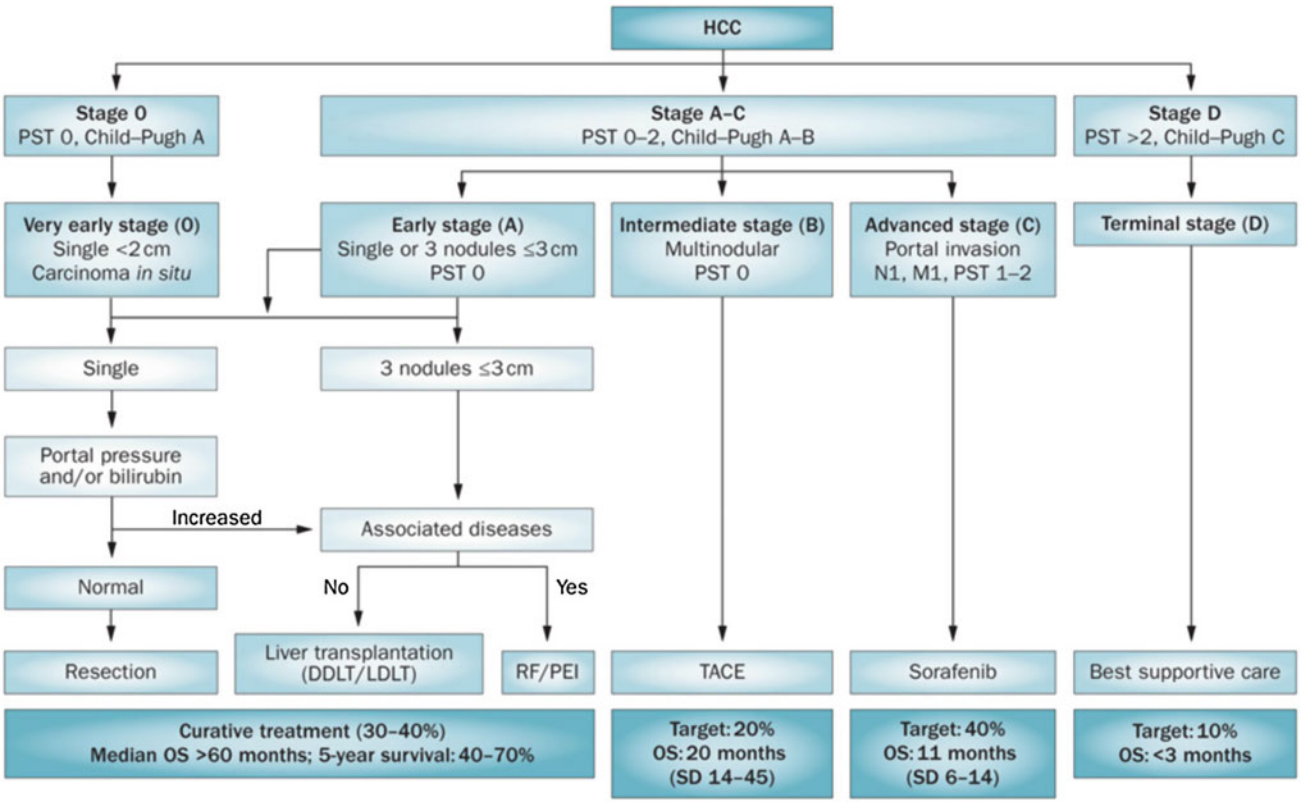

Fig. 28.1 The Barcelona Clinic Liver Cancer (BCLC) staging system for Hepatocellular carcinoma. *M* metastasis classification; *N* node classification; *PST* performance status; *RF* radiofrequency ablation; *PEI* percutaneous Ethanol Injection; *TACE* transarterial chemoembolization. Permission obtained from Elsevier © European Association for the Study of the Liver [88]. Permission from Elsevier

Study of Liver, and the European Organization for the Research and Treatment of Cancer, and it is currently the most used in Western countries [5].

The prognostic value of BCLC staging system has been externally validated in many countries [19, 20, 23–27, 42]. Several investigators from Italy [27] and China [42] have shown that the BCLC classification is the best prognostic model in HCC patients receiving curative therapy. In contrast, studies from Italy [19, 23, 26, 30], the United States [24], Spain [25], South Korea [20] have shown that the BCLC classification provides the best prognostic value in HCC patients with early to advanced stage tumors treated with various modalities. These results indicate that the predictive accuracy of the BCLC classification is highly stable. With regard to treatment allocation, a large-scale trial from Taiwan [82] (n = 3892) showed that the treatment schedules determined according to the BCLC classification are both reasonable and beneficial for survival in patients with HCC.

However, the BCLC classification has some limitations. Although the BCLC treatment schedule recommends that resection be applied only for those very early stage patients without portal hypertension and normal bilirubin levels, however, portal hypertension which is defined as the presence of a hepatic venous pressure gradient >10 mmHg is invasive and not routinely carried out in daily practice worldwide [67]. It might be easier and simpler to use clinical portal hypertension, including esophageal varices or splenomegaly with a platelet count [80]. Indocyanine green retention rate at 15 min as the criteria in selection of the best candidates for resection is also useful [82]. Moreover, BCLC 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 [83, 84].

28.7.2 The Hong Kong Liver Cancer (HKLC) Staging (Fig. 28.2)

Very recently, the HKLC classification [85] was constructed by a Hong Kong group to developed treatment guidance for Asian patients with HCC. This system is derived from the results of a large cohort of 3856 HCC patients predominantly infected by hepatitis B virus (HBV). ECOG PS, Child-Pugh grade, liver tumor status, and presence of extrahepatic vascular invasion or metastasis were selected while developing the system by using the 1968 training set according to a multivariate analysis. Patients are classified into five main stages and nine substages (stages I–V_b) based on these prognostic factors. Subsequently, the HKLC classification was compared with the BCLC classification in terms of discriminatory ability and effectiveness of treatment recommendation in 1888 test set. They demonstrated that the HKLC system had significantly better ability than the BCLC system to distinguish between patients with specific overall survival times. 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. The HKLC system appears 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. Yan et al. [22] reported that the HKLC system was more suitable for predicting prognosis in a Chinese cohort of 668 HCC patients than the BCLC classification. External validation in Western population and/or elsewhere is needed.

28.8 Summary of Staging Classifications

It is currently difficult to establish the staging system that is suitable for all patient populations universally. The best staging system to use may differ according to the detection and treatment conditions of HCC. The validation and comparative studies of each staging system are showed in Table 28.3. Each existing staging system may have been characterized by the patient population based on which it was constructed [10]. For example, the incidence of HCC varies considerably with the geographic area because of differences in the major causative factors. Hepatitis B, which is endemic in developing geographic regions such as Eastern Asia and Sub-Saharan Africa, is the main cause of new HCC cases in such areas. Hepatitis C is the predominant cause of HCC in area such as Southern Europe and Japan. In Northern Europe and the USA, HCC is often related to other factors such as alcoholic liver disease. Several studies have shown that HCC patients with HCV infection or alcoholic liver disease exhibit poorer outcomes than those with HBV infection. This is because HCC patients with HBV infection generally have a better liver functional reserve than those with HCV infection or alcoholic liver disease.

Usefulness of the staging systems will differ depending on distribution of HCC stage at diagnosis. For example, CUPI score and ALCPS were suitable staging systems for advanced stages of the disease and validated in a large cohort of HCC patients in China, these are not suitable in country where the early detection and early treatment of HCC are common. In western patient populations, the BCLC staging system appears to be superior based on findings in several studies (two conducted in Italy, one in Taiwan, and one in North America). The JIS score, the JIS family, and the Tokyo score are the suitable staging systems in Japan, where many smaller tumors are detected based on the established screening system for HCC [13, 86]. However, it is the

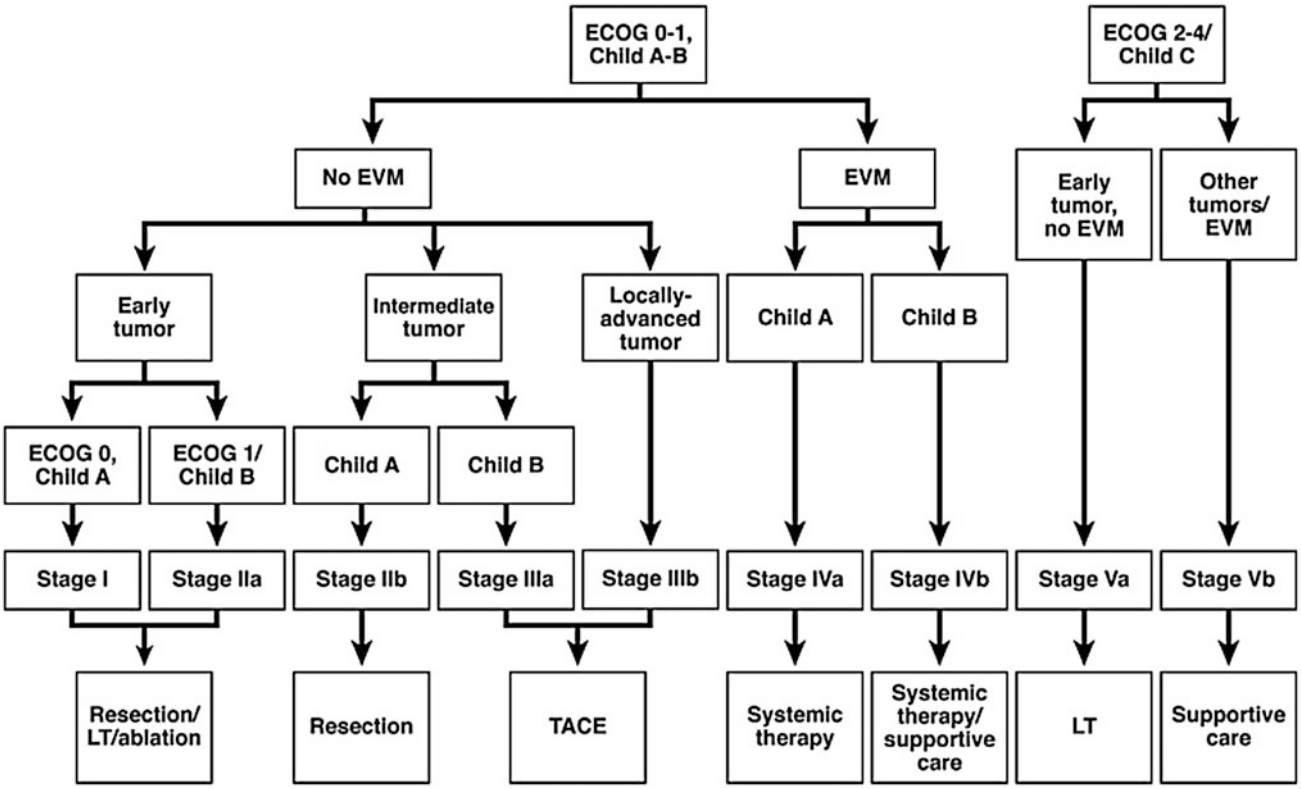

Fig. 28.2 The Hong Kong Liver Cancer (HKLC) prognostic classification scheme. EVM, extrahepatic vascular invasion/metastasis. Early tumor: 5 cm, 3 tumor nodules and no intrahepatic venous invasion; Intermediate tumor: (*1*) 5 cm, either >3 tumor nodules or with intrahepatic venous invasion, or (*2*) >5 cm, 3 tumor nodules and no intrahepatic venous invasion; and Locally advanced tumor: (*1*) 5 cm, >3 tumor nodules and with intrahepatic venous invasion, or (*2*) >5 cm, >3 tumor nodules or/and with intrahepatic venous invasion, or (*3*) diffuse tumor. Modified from Yau et al. [85]. Permission from W. B. Saunders Company

problem that few validation studies of these Japanese staging systems were reported outside Japan (Table 28.15).

Usefulness of the staging systems will also differ depending on the distribution of patients with HCC according to the period. As mentioned above, Toyoda et al. [44] reported that the CLIP staging systems proved to be more suitable before 1990, however, the JIS system was the most suitable after 1990, when early detection and early treatment of HCC became common. When early detection of HCCs becomes more common in many countries, it could lead to the predominance of early-stage HCC patients and Japanese staging systems such as the JIS and the JIS family may become more suitable over the world.

Although the JIS score and JIS family based on the TNM by LCSGJ for HCC were useful in Japan, however, there are some limitations. First, although the Japanese TNM for HCC has been generally accepted as a standard approach for prognostication in Japan, however, it is not always used all over the world. Second, the model included established classifications such as the case for TNM staging can be modified in the future, and different versions may be confused. Third, discrepancies between pre- and postoperative diagnoses in the TNM and the TNM-based staging systems often caused by microvascular invasion detected in resected specimens after hepatectomy. In the first place, the TNM staging was developed based on a survival analysis of surgical patients and their pathological findings, thus, these postoperative histopathological staging systems are appropriate for patients who are scheduled to undergo surgical resection [12, 14]. Although, vascular invasion, one of the TNM staging components, is considered as a prognostic factor, however, peripheral vascular invasion is usually obtained as microvascular invasion in resected specimen and underestimated preoperatively. Thus, pre/postoperative staging discrepancy in the TNM and the TNM-based staging system (the JIS and JIS family) often caused by accompanying newly detected microvascular invasion in the resected liver. In this regard, there is still room for development of novel tumor factor which is simple, robust, and not needed the information on pathological vessel involvement, and the $N \times S$ factor, which consists of mathematical product of tumor number and size of largest tumor, could solve these problems.

One of the goals of staging systems today is to provide an evidence-based treatment guide [80]. All staging

Table 28.15 The validation and comparative studies of each staging system

Suitable model		Country	Year	Case number		Treatment modality	Comparator staging systems
						Cur[a]/Non-cur[b]/Palliative	
CLIP	Levy [51]	Canada	2002	257	ALL	95/29/133	Okuda
	Giannini [30][c]	Italy	2004	81	ALL	25/43/13	Okuda, BCLC, GRETCH
	Chen [16][c]	Taiwan	2007	382	Surgery (major hepatectomy)	382/0/0	Okuda, TNM, BCLC, CUPI, JIS MELD
	Camma [17]	Italy	2008	406	ALL	115/63/228	BCLC, GRETCH
	Collete [37]	French	2008	538	Advanced	0/122/416	Okuda, BCLC
	Cho [53]	Korea	2008	131	TACE	0/131/0	Okuda, BCLC, JIS, Child
	Lin et al. [52]	Taiwan	2009	3668	ALL	662/1768/1438	–
	Noda [18]	Japan	2009	46	Surgery (HCC > 10 cm)	46/0/0	TNM, JIS
	Hsu et al. [38]	Taiwan	2010	1713	ALL	797/655/261	TNM, BCLC, JIS, Tokyo
	Op den Winkel [39]	German	2012	405	ALL	95/263/47	JIS, Okuda, GRETCH, TNM, BCLC, Child
	Shao et al. [40][c]	Taiwan	2012	157	Advanced	0/157/0	GRETEC, CUPI, Okuda, Tokyo, JIS, BCLC, CIS, AJCC
	Lin et al. [41][c]	Taiwan	2012	156	Advanced	0/0/156	TNM, Okuda, CUPI, JIS, Tokyo, ALCPS
	Memon [54]	USA	2014	428	TARE	0/428/0	Okuda, BCLC, GRETCH, CUPI, JIS
GRETCH	Giannini [30][c]	Italy	2004	81	ALL	25/43/13	Okuda, BCLC, CLIP
BCLC	Cillo [23]	Italy	2004	187	ALL	119/40/28	Okuda, CLIP, GRETCH, CUPI
	Giannini [30][c]	Italy	2004	81	ALL	25/43/13	Okuda, CLIP, GRETCH
	Grieco [19]	Italy	2005	268	Early to intermediate	146/103/19	Okuda, CLIP
	Marrero [24]	USA	2005	244	ALL	107/66/71	Okuda, TNM, CLIP, GRETCH, CUPI, JIS
	Pascual [25]	Spain	2006	115	ALL	38/39/38	Okuda, CLIP, BCLC,GRETCH, MELD, Child
	Cillo [26]	Italy	2006	195	ALL	175/9/11	Okuda, CLIP, TNM, JIS,
	Wang [82]	Taiwan	2008	3892	ALL	631/1796/1465	–
	Guglielmi [27]	Italy	2008	112	RFA	112/0/0	Okuda, TNM, CLIP, GRETCH, CUPI, JIS
	Kim [20]	Korea	2012	1717	ALL	357/1188/172	JIS, Tokyo, CLIP, CUPI, GRETCH
	Zhao [42]	China	2015	743	Surgery	743/0/0	TNM, JIS, Tokyo, CLIP, CUPI, Okuda
CUPI	Chan [43]	China	2011	595	ALL	83/206/306	BCLC, CLIP, TNM, Okuda
	Shao [40][c]	Taiwan	2012	157	Advanced	0/157/0	GRETCH, CUPI, Okuda, Tokyo, JIS, BCLC, CIS, AJCC
	Zhang [28]	China	2014	196	Non-surgical treatment	6/114/76	BCLC, CLIP, JIS, CIS, Okuda, TNM
	Chan [46]	China	2014	517	ALL	92/224/201	BCLC, CLIP
	Chan [46]	UK	2014	567	ALL	228/235/104	BCLC, CLIP

(continued)

Table 28.15 (continued)

Suitable model		Country	Year	Case number		Treatment modality	Comparator staging systems
						Cur[a]/Non-cur[b]/Palliative	
JIS	Kudo [31]	Japan	2004	4525	ALL	2023/2306/196	CLIP
	Toyoda [44]	Japan	2005	1508	ALL	598/632/288	CLIP, BCLC
	Kondo [32]	Japan	2007	235	Surgery	235/0/0	CLIP, BCLC, GRETCH, CUPI, mJIS, Tokyo
	Chung [8]	Japan	2008	290	ALL	208/58/24	BCLC, Tokyo
	Chen [16][c]	Taiwan	2007	382	Surgery (minor hepatectomy)	382/0/0	Okuda, CLIP, TNM, BCLC, CUPI, JIS, MELD
m-JIS	Nanashima [45]	Japan	2006	230	Surgery	230/0/0	TNM, JIS CLIP
	Ikai [61]	Japan	2006	42269	ALL	24,421/13,868/3,980	m-CLIP
SLIDE	Nanashima [65]	Japan	2009	207	Surgery	207/0/0	–
bm-JIS	Kitai [33]	Japan	2008	1173	ALL	663/470/36	JIS, BALAD
	Kitai [34]	Japan	2014	4649	ALL	2995/1455/199	JIS, BCLC
Tokyo	Chen [29]	Taiwan	2009	2010	ALL	984/518/478	JIS, CLIP, BCLC, Okuda, TNM
BALAD	Fox [75]	UK	2014	319	ALL	16.1 %/83.9 % (non cur + palliative)	–
	Chan [76]	China	2015	198	ALL	37/87/74	BCLC
ALCPS	Lin [41][c]	Taiwan	2012	156	Advanced	0/0/156	TNM, Okuda, CLIP, CUPI, JIS, Tokyo
	Li [21]	China	2013	208	Advanced	0/10/198	JIS, TNM, CLIP, GRETCH
TIS	Hsu [35]	Taiwan	2012	2203	ALL	1017/1186/0	CLIP, BCLC, JIS
	Chen [36]	Taiwan	2015	467	RFA	467/0/0	BCLC, CLIP, JIS
HKLC	Yan [22]	China	2015	668	ALL	453/205/10	BCLC

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *TARE* transarterial radioembolization, *TNM* Tumor Node Metastasis, *CLIP* The Cancer of the Liver Italian Program, *GRETCH* The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire, *BCLC* The Barcelona Clinic Liver Cancer, *CUPI* Chinese University Prognostic Index, *JIS* The Japan Integrated Staging, *bm-JIS* biomarker-JIS, *ALCPS* Advanced Liver Cancer Prognostic System, *TIS* The Taipei Integrated Score, *HKLC* The Hong Kong Liver Cancer, *MELD* Model for End stage Liver Disease, *CIS* China integrated staging

[a]Cur: surgical resection, liver transplantation, and local ablation

[b]Noncur: transarterial therapy, radiation therapy, and systemic therapy such as Sorafenib

[c]The same literature

classifications have been designed to predict prognosis, many staging systems lack optimal treatment allocation except for BCLC and HKLC. However, BCLC treatment recommendations were not suitable in all situations. For example, some prognostic factors, such as the presence of portal hypertension is contraindications, because there are evidences which suggest that hepatic resection can be performed successfully even in patients with portal hypertension and multiple hepatic lesions in highly selected cases. In addition, this algorithm also does not provide indications concerning second-line therapies, retreatment choices, or combined treatments. Furthermore, there are several differences in indication of Liver transplantation for HCC among countries. In Japan, it is considered that the therapeutic algorithm in the Japanese guidelines for the management of liver cancer is established and superior to the BCLC treatment algorithm in Japanese population [4]. HKLC from China needs further evaluations. Among these countries, treatment situations and options are various in some part, thus, it seems to be currently difficult to establish the unified staging system which provides both optimal treatment recommendation and prediction prognosis for worldwide.

Another goal of staging systems is to develop a globally applicable staging classification [87].

There is currently no globally accepted system for HCC, and thus no common language on which to base treatment decisions and guide research. For practical purposes, staging systems should be simple and based on data that are easily obtainable. Our novel $N \times S$ factor and $N \times S$ factor-based staging system are very simple and obtained anywhere and easily in daily practice, and it may potentially become one of a common score in many countries.

28.9 Conclusion

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 regional differences in tumor extension and underlying liver disease, which affects the patient prognosis, thus, a staging classification needs to be validated in both western and Asia-Pacific patient populations. Although the prognosis of HCC patients is complex for various reasons, simple staging systems available anywhere are needed at first to compare the differences of the prognosis of HCC patients among the nations.

In conclusion, further research efforts are needed for us to gain a full understanding of the factors that affect the prognosis of patients with HCC, and it will allow us to refine staging classifications and improve our therapeutic approach. Growing evidence of tumor biology and development in imaging techniques and treatment modalities against both HCC and liver disease will result in the proportion of better staging systems in the future.

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