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TOPIC HIGHLIGHT

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Staging systems of hepatocellular carcinoma: A review of literature

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem with a high incidence and mortality all over the world. Natural history of HCC is severe and extremely variable, and prognostic factors influencing outcomes are incompletely defined. Over time, many staging and scoring systems have been proposed for the classification and prognosis of patients with HCC. Currently, the non-ideal predictive performance of existing prognostic systems is secondary to their inherent limitations, as well as to a non-universal reproducibility and transportability of the results in different populations. New serological and histological markers are still under evaluation with promising results, but they require further evaluation and external validation. The aim of this review is to highlight the main tools for assessing the prognosis of HCC and the main concerns, pitfalls and warnings regarding its staging systems currently in use.

Key words: Hepatocellular carcinoma; Natural history; Prognosis; Staging; Barcelona clinic liver cancer

Core tip: Hepatocellular carcinoma is a major health problem, with a heterogeneous natural history that makes it difficult to identify accurate prognostic factors. The aim of this review is to highlight the main tools for assessing the prognosis of HCC and the main concerns, pitfalls and warnings regarding its staging systems currently in use.

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INTRODUCTION

Hepatocellular carcinoma (HCC) has an increasing incidence worldwide, and it is the leading cause of death in patients with cirrhosis[1]. It is the fifth most common cancer and the third most common cause of cancer-related death[2].

Despite intensive surveillance programs, considerable recent therapeutic advances and use of potentially radical treatments, prognosis and life expectancy remain poor in this setting[3]. Curative treatments are applicable for early stage tumors only, and include resection, liver transplantation and percutaneous ablation, while transarterial chemoembolization (TACE) and sorafenib are regarded as non-curative treatments able to improve survival in intermediate and advanced stages, respectively[4].

NATURAL HISTORY OF HCC

According to the definition by Sackett *et al*[5], natural history is the course of a disease from its biological onset to its recovery or permanent disability or death.

The natural history of HCC is extremely severe, as confirmed by mortality rates overlapping the incidence of the tumor[6]. In addition, it is extremely heterogeneous, due to the complex interplay between the biological characteristics of the tumor and the frequent presence of an underlying chronic liver disease, as showed by a recent meta-analysis which analyzed the survival rates of the placebo and untreated arms of several randomized controlled trials (RCTs) on HCC patients[7].

According to this study, the survival rates were 17.5% at 1 year and 7.3% at 2 years, with a significant heterogeneity among all studies ($P < 0.0001$) both for 1-year and 2-year survival. By meta-regression analysis, impaired performance status (PS), B and C Child-Pugh classes, and presence of portal vein thrombosis (PVT) were independently associated with a poor survival.

The natural history of early HCC can not be evaluated by RCTs for ethical reasons, although a milestone paper published in 1989 showed that overall survival (OS) of asymptomatic patients with HCC and cirrhosis was 96% and 50% at 1- and 2-year, respectively[8].

A recent study analyzed a cohort of 320 patients affected by HCC and not suitable for curative or palliative treatments, confirming the heterogeneous behaviour of untreated HCC[9]. The overall median survival was 6.8 mo, and the 1-year survival was 32%. The 1-year survival according to barcelona clinic liver cancer (BCLC) classes was 100%, 79%, 12% and 0%, for BCLC A, B, C and D, respectively, with a significant difference in survival among each BCLC class.

STAGING SYSTEMS AND PROGNOSTIC SCORES IN ONCOLOGY

Staging systems assess and describe the extent of tumor burden in the originally primary organ and its spread throughout the body.

They have a key role in the management of all cancers, allowing an accurate prognostic stratification of the tumor and the choice of the best therapeutic approach according to the stage. Furthermore, they are useful for grouping patients homogeneously in clinical trials and scientific research, and to make comparable patients of different clinical studies.

Correct tools for the prognostic stratification of cancers

An ideal staging system should be simple, easy and quick to be determined as soon as possible after diagnosis; it should provide information on prognosis and guide therapeutic decisions. In contrast to classical staging systems, which consider only the inherent characteristics of the tumor, prognostic scores include also all the variables that influence the patient's prognosis, over the tumor extension. Each staging system and prognostic score must be reproducible and externally validated, in order to be recommended and used on a large scale. Internal validation is an estimate of the internal reproducibility and answers the question asking if "The score can be properly applied to the patient population from which it was derived".

Using survival time as an outcome measure, important criteria for assessing the internal validation of a prognostic system are homogeneity, discrimination and monotonicity[10]. Homogeneity is the characteristic whereby the difference in survival time is small among patients classified into the same staging group, while discriminatory ability is the feature by which there are much greater differences in the survival times among patients classified into different groups. Finally, monotonicity is defined as the property of a staging system by which the mean survival time for a group classified as favourable by that system is always longer than the mean survival times experienced in less favourable groups (monotonicity of gradients). Besides, external validation is an estimate of transportability of the results, and answers the question asking if "It is possible to apply the results of a prognostic study to any single patient". It is assessed by validation studies that are performed on populations other than, but related to the one from which the prognostic score was originally derived.

STAGING OF HCC

Generally, the extension of the tumour burden in the original primary organ and its spread throughout the body, is *per se* exhaustive for the staging of most solid tumors. Nevertheless, unlike other tumors, HCC usually occurs on a background of a liver disease, making the level of management complexity unique among all malignancies.

It is well known that the functional impairment of the underlying liver disease has a significant impact on prognosis, irrespective of the tumour stage[4]. For this reason, systems that include the anatomical characteristics of the tumor only, such as the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system that stratifies patients using a Tumor-Node-Metastasis (TNM) classification, do not have *per se* a good predictive capability[11,12] (Table 1). Thus the TNM, along with all other systems that enclose it, represents a group of models useful for assessment of tumor extension only, but inadequate as prediction models.

Therefore, many staging and scoring systems for the classification and prognosis of patients with HCC have been proposed over time (Figure 1).

Okuda staging system

The staging system proposed by Okuda *et al*[13] in 1984 (Table 1) is the first attempt to successfully combine the anatomical features of the tumor to the degree of the underlining liver disease. A distinction is made by three stages, considering the volume of the tumor (occupancy extended to $\leqslant$ or $>$ 50% of the liver) together with the main indices of liver function (albumin, bilirubin, presence of ascites). This system has been widely adopted and used throughout the world for over two decades. However, the development of more advanced diagnostic

Table 1 Comparison of classifications

Okuda staging system[13]

	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

CLIP score[14]

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

GRETCH score[21]

	Score			
	0	1	2	3
Karnofsky index	≥ 80%			< 80%
Bilirubin (μmol/L)	< 50			≥ 50
Alkaline phosphatase	< 2 X ULN		≥ 2 X ULN	
Alpha-fetoprotein (μg/L)	< 35		≥ 35	
Portal vein thrombosis	Absent	Present		

BCLC[16]

	Stage				
	0 (very early)	A (early)	B (intermediate)	C (advanced)	D (end stage)
ECOG Performance Status	0	0	0	1-2	3-4
Liver function	Child-Pugh A-B	Child-Pugh A-B	Child-Pugh A-B	Child-Pugh A-B	Child-Pugh C
Tumor stage	Single	Single or 3 nodules < 3 cm	Multinodular	Vascular invasion or extrahepatic spread	Any

CUPI[23]

VARIABLE		Weight
TNM stage	Ⅰ and Ⅱ	-3
	Ⅲ	-1
	Ⅳ	0
Total Bilirubin (μmol/L)	< 34	0
	34-51	3
	≥ 52	4
Ascites		3
Alpha-fetoprotein > 500 ng/mL		2
Alkaline phosphatase > 200 IU/L		3
Asymptomatic disease on presentation		-4

JIS[24]

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

Tokyo[22]

	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
Numbers of nodules	≤ 3	-	> 3

AJCC/UICC TNM staging system 7th ed[12]

Group	Description		Stage grouping		
T1	Single tumor without vascular invasion	STAGE Ⅰ	T1	N0	M0
T2	Single tumor with vascular invasion or multiple tumors, none > 5 cm	STAGE Ⅱ	T2	N0	M0
T3a	Multiple tumors, any > 5 cm	STAGE ⅢA	T3a	N0	M0
T3b	Single tumor or multiple tumors of any size involving a major branch of portal or hepatic vein(s)	STAGE ⅢB	T3b	N0	M0

T4	Tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum	STAGE ⅢC	T4	N0	M0
N1	Regional lymph node metastasis	STAGE ⅣA	Any T	N1	M0
M1	Distant metastasis	STAGE ⅣB	Any T	Any N	M1

AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer; CLIP: Cancer of the Liver Italian Program; GRETCH: Groupe d' Etude et de Traitement du Carcinome Hépatocellulaire; BCLC: Barcelona clinic liver cancer; CUPI: Chinese University Prognostic Index for hepatocellular carcinoma; JIS: Japan Integrated Staging Score; TNM: Tumor Node Metastasis; ECOG: Eastern Cooperative Oncology Group; LCSGJ: Liver Cancer Study Group of Japan.

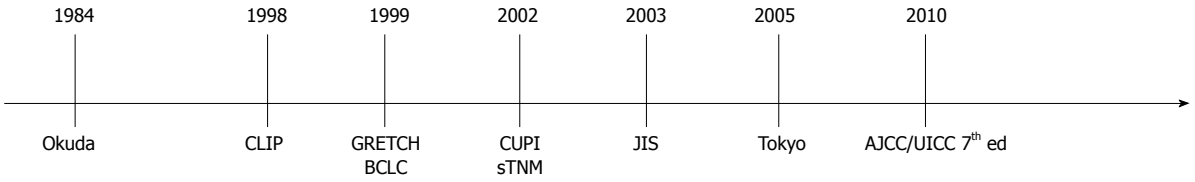

Figure 1 Timeline of hepatocellular carcinoma staging system. AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer; CLIP: Cancer of the Liver Italian Program; GRETCH: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; BCLC: Barcelona Clinic Liver Cancer; CUPI: Chinese University Prognostic Index; JIS: Japan Integrated Staging Score; TNM: Tumor Node Metastasis.

techniques over the years has permitted an increasing detection of small tumors, with an occupancy of the entire liver well below 50%, which are poorly discriminable within the two dimensional groups proposed by Okuda. In addition other prognostic variables not included in that model were identified, leading to the development of more accurate staging systems (Table 2).

Cancer of the Liver Italian Program score

Cancer of the Liver Italian Program (CLIP) is a simple scoring system designed by an Italian group with the aim of overcoming the main limitations of the TNM and Okuda.

It has been derived from a retrospective cohort study of 435 patients[14] and then externally validated comparing its discriminatory ability and predictive power with the one of the Okuda staging system by a randomized trial that prospectively enrolled 196 patients with cirrhosis and HCC[15]. The CLIP includes the liver function according to Child-Pugh score, the morphology of the tumor (uninodular, multinodular, massive), its extension in the liver, the levels of Alpha-fetoprotein and the eventual presence of PVT. The combination of the different variables places all patients into 6 categories (Table 1). Although it was built with a correct methodology and externally validated, this score presents some limits, including the absence of general well-being assessment of the patient, and the inability to identify the early stages, which are susceptible to percutaneous or surgical therapies.

BCLC staging classification

The BCLC staging classification for HCC is currently the only staging system that includes an integrated assessment of liver disease, tumor extension, and presence of constitutional symptoms, providing in the meantime an indication of the first-line treatment. It classify stages of disease into five subgroups, from 0 to D, each associated with a specific therapy and prognosis (Table 1)[16]. Stage 0 is defined as very early stage disease, and is featured by a single nodule ≤ 2 cm without tumor invasion into surrounding tissues, in asymptomatic patients with preserved liver function. Stage A, or early disease, is classified as a solitary HCC of any size, or in maximum 3 nodules, each of them ≤ 3 cm, in asymptomatic patients with Child-Pugh A or B. Stage 0 and A can be effectively treated with curative therapies, such as surgical resection, liver transplantation, or by percutaneous ablation methods, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). These treatments allow to reach a complete response[17], with potential long-term curative effect and a 5-year survival better than 40%-70%. It must be emphasized that tumor size (< 5 cm) has been recently removed as a contraindication for radical therapy in single nodule HCC. However, in this particular case, the choice of the surgeon is finally decisive in defining a tumor as resectable. Stage B, or intermediate disease, consists of multinodular tumor, without macrovascular invasion or extrahepatic spread (ES), in asymptomatic patients with well-preserved liver function, and PS lower than 2. This subset of patients may be treated with TACE, which has proven a significant increase in survival compared with best supportive care (median survival, 20 mo *vs* 16 mo)[18].

Patients with mild related symptoms and/or macrovascular invasion or ES are classified as stage C (advanced stage). According to two pivotal RCTs[19,20], the standard of care in this group is Sorafenib, an inhibitor of Raf kinase and vascular endothelial growth factor receptor. Patients with cancer symptoms related to advanced liver failure, tumor growth with vascular involvement, ES, or physical impairment (PS > 2), are classified as stage D (end stage disease). They can not benefit from any specific cancer therapy and could only receive the best available supportive care. Although it is not an ideal staging system and has several gaps, the BCLC has been endorsed by EASL and AASLD as the standard staging system for

Table 2 Variables included in the main prognostic systems

Variables	Prognostic scores						
	Okuda[13]	CLIP[14]	GRETCH[21]	BCLC[16]	CUPI[23]	JIS[24]	Tokyo[22]
Child-Pugh score		X		X		X	
Ascites	X				X		
Albumin	X						X
Total Bilirubin	X		X		X		X
Alkaline phosphatase			X		X		
Alpha-fetoprotein		X	X		X		
Tumor size	X	X		X			X
Numbers of nodules		X		X			X
TNM stage					X	X	
Portal vein thrombosis		X	X	X			
Metastasis				X			
Portal hypertension				X			
Presence of symptoms and/or General Status			X	X	X		

CLIP: Cancer of the Liver Italian Program; GRETCH: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; BCLC: Barcelona Clinic Liver Cancer; CUPI: Chinese University Prognostic Index; JIS: Japan Integrated Staging Score; TNM: Tumor Node Metastasis.

patients with HCC, and it is currently the most used in Western countries.

Other staging systems in western countries

The GRETCH (Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire) score was derived by a prospective cohort of 761 patients with hepatocellular carcinoma from 24 medical centers in France, Belgium and Canada enrolled during a period of 30 mo (Table 1)[21]. Five prognostic factors were selected: Karnofsky index, serum bilirubin, serum alkaline phosphatase, serum alpha-fetoprotein > 35 pg/L, and ultrasonographic evidence of portal obstruction. Three risk groups with different 1-year survival rates were derived, and then independently validated in the test sample. However, it is not a well validated or a widely used staging system.

Other staging systems in eastern countries

The lower survival of Asian patients with HCC seems to be due not only to the different ethnic origin, but also to a different etiologic distribution and to a different and more severe natural history of liver disease. On this background, many prognostic scores have been built on Asian cohorts. The Tokyo score[22] was developed from a cohort of 403 consecutive Japanese patients with HCC treated by percutaneous ablation, and it is composed by four factors including serum albumin, bilirubin, size and number of tumors (Table 1). In the testing sample, the predictive power of this score resulted equal to CLIP and better than BCLC staging. Unfortunately, the score has been derived on a cohort of patients with early HCC, therefore its predictive ability can be transferred only to patients susceptible to radical therapies, whereas it poorly fits to patients with advanced HCC. The CUPI (Chinese University Prognostic Index for hepatocellular carcinoma)[23] was designed in 2002 by the analysis of a cohort of 926 Chinese patients with HCC, adding five prognostic factors (total bilirubin, presence of ascites, alkaline phosphatase, alpha fetoprotein, and asymptomatic disease on presentation) to the TNM, in order to set up 3 classes of risk with highly significant differences in survival (Table 1). This score was obtained from a monocentric and mono-ethnic cohort of patients, and most of the patients had a liver disease secondary to HBV infection. Therefore, the transportability of data of this score could be limited to this specific subset of patients. Finally, the JIS (Japan Integrated Staging Score)[24] is a score system that combines two existing classifications, named TNM and Child-Pugh (Table 1). It is widely used in Japan but it lacks external validation in Western countries.

New prognostic markers

To date, a growing attention is focused on the lookout for new prognostic markers able to increase the power of predictor models for HCC.

Several years ago, the role of Estrogen Receptor (ER), defined as wild-type (wtER) or variant (vER)[25], has been described for the biologic characterization of the tumor. A study by Villa *et al*[26] showed that the presence of *wt*ER is directly related with a good prognosis, and the survival is five-fold better in patients with HCC presenting with *wt*ER compared with the ones presenting with *v*ER. Similarly to what happens in breast cancer, the presence of variant forms of ER seems to correlate with lack of hormonal control on the tumor growth, elevated proliferation rate and tumor aggressiveness. Thus, although ER characterization requires an invasive procedure - liver biopsy - it can be useful for an accurate prognosis and as a reliable assessment of sensitivity to treatment also for clinical decision making. More recently, some studies have focused on the impact of new serological markers in predicting prognosis of patients with HCC. For example, low serum vascular endothelial growth factor (VEGF) levels seems to be associated with a longer survival at each stage according to CLIP or BCLC, and the inclusion of baseline plasma VEGF levels increases the precision of the CLIP scoring system for predicting HCC prognosis ("V-CLIP" staging)[27,28]. Likewise, high Insulin-like

Table 3 Comparison of different hepatocellular carcinoma staging system in the literature

Ref.	Country	Year	Case number	Patient population	The best
Levy *et al*[58]	Canada	2002	257	All	CLIP
Kudo *et al*[59]	Japan	2004	4525	All	JIS
Cillo *et al*[41]	Italy	2004	187	All	BCLC
Grieco *et al*[39]	Italy	2005	268	Early to intermediate	BCLC
Marrero *et al*[34]	United States	2005	244	All	BCLC
Nanashima *et al*[60]	Japan	2005	210	Surgery	CLIP
Huang *et al*[61]	Taiwan	2005	599	Surgery	TNM
Toyoda *et al*[62]	Japan	2005	1508	All	JIS
Pascual *et al*[63]	Spain	2006	115	All	BCLC
Georgiades *et al*[42]	United States	2006	172	TACE	Child-Pugh
Cillo *et al*[64]	Italy	2006	195	All	BCLC
Nanashima *et al*[65]	Japan	2006	230	Surgery	Modified JIS
Kondo *et al*[66]	Japan	2007	235	Surgery	JIS
Seong *et al*[67]	South Korea	2007	305	Radiotherapy	TNM
Chen *et al*[40]	Taiwan	2007	382	Surgery	CLIP
Huo *et al*[68]	Taiwan	2007	430	All	CLIP
Cammà *et al*[37]	Italy	2008	406	All	CLIP
Guglielmi *et al*[69]	Italy	2008	112	RFA	BCLC
Collette *et al*[70]	French	2008	538	Advanced	CLIP
Lu *et al*[71]	China	2008	234	Surgery	TNM
Chung *et al*[72]	Japan	2008	290	All	JIS
Lin *et al*[38]	Taiwan	2009	3668	All	CLIP
Hsu *et al*[36]	Taiwan	2010	1713	All	CLIP
Op den Winkel *et al*[73]	German	2012	405	Non-surgical	CLIP
Kim *et al*[35]	South Korea	2012	1717	All	BCLC

CLIP: Cancer of the Liver Italian Program; GRETCH: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; BCLC: Barcelona Clinic Liver Cancer; CUPI: Chinese University Prognostic Index; JIS: Japan Integrated Staging Score; TNM: Tumor Node Metastasis.

growth factor-1 (IGF-1) plasma levels seems to reflect time-to-recurrence, as well as overall survival[29], and the addition of plasma IGF-1 levels to CLIP ("I-CLIP" staging) significantly improves prognostic stratification of patients with advanced HCC[30]. Finally, overexpression of the Forkhead box M1 (*FOXM1*) gene is associated with a poor outcome after OLT[31], and expression of the *AKR1B10* (aldo-keto reductase enzyme) gene reflects a less aggressive tumour behaviour[32]. All these new markers have shown promising results, but require further evaluation and external validation.

STAGING SYSTEMS FOR HCC: WHICH IS THE BEST ONE?

To date several staging systems for HCC have been proposed, but currently none of these has been universally accepted, as pointed out by AASLD guidelines, which emphasize how there is not a worldwide consensus on the use of any given model for stadiation of HCC[33].

Several studies comparing the predictive power of different models have shown conflicting results, both in the general population and in the different subgroups of treatment (Table 3).

According to the analysis performed by Marrero *et al*[34] on a cohort of 244 United States patients of any stage, the BCLC showed the best independent predictive power for survival when compared with the other 6 prognostic systems (TNM, CLIP, CUPI, JIS, GRETCH and Okuda). Similar results were found by an Asian study performed on 1717 treatment-naïve HCC patients, showing as BCLC was the best prognostic model if compared with other 5 systems (CLIP, CUPI, JIS, GRETCH and Tokyo score)[35]. Conversely, a study by Hsu *et al*[36] investigating the prognostic ability of the 5 staging systems (BCLC, CLIP, JIS, TNM and Tokyo score), showed the CLIP was the best long-term prognostic model in a cohort of patient with early to advanced stage HCC. Similarly, a recent study comparing the performance of BCLC, CLIP and GRETCH in a cohort of 406 consecutive patients with cirrhosis and HCC[37], showed the CLIP had the best discriminative capacity in the entire HCC cohort and in the advanced untreatable cases, while BCLC proved to be the best in predicting survival in treated patients. Finally, a subsequent study on a larger cohort of 3868 treated patients confirmed a modest discriminatory ability of CLIP for early HCC[38].

In addition, several studies have been also performed over time in order to weigh the performance of staging and prognostic systems in specific subsets of patients receiving different class of treatments (Table 3).

An Italian retrospective study compared the performance of Okuda, CLIP and BCLC in a cohort of 268 patients treated with non-surgical therapy[39]. Both CLIP and BCLC scores were more effective than the Okuda score in stratifying patients into different risk groups of patients with early-intermediate HCC, even if BCLC showed a better prediction of prognosis in patients with very early stage HCC. Furthermore, a subsequent study compared Okuda, TNM, CLIP, BCLC, CUPI, JIS and

MELD in the prediction of survival among patients with HCC treated with major or minor hepatectomy[40]. Among all the seven staging systems, CLIP and JIS showed the best results. In particular, CLIP had a better discriminatory ability in the subset of patients treated with major hepatectomy, while JIS proved to be the most accurate in the minor hepatectomy group.

Conversely, another retrospective analysis of 187 HCC Italian patients mainly treated with radical therapies (resection and percutaneous ablation) showed that BCLC had the greatest prognostic power among five systems (BCLC, CLIP, GRETCH, CUPI and Okuda) both for the whole study group and for the 2 subgroups of surgical and non-surgical patients[41].

These results do not seem to be confirmed in the group of patients treated with "non-curative" therapies. In this regard, the prognostic accuracy of 12 liver staging systems (nominal and categoric Child-Pugh, Okuda, CLIP, BCLC, MELD, CUPI, JIS, TNM, GRETCH, Liver Cancer Study Group of Japan, and Tokyo score) has been assessed in a cohort of 172 consecutive patients with unresectable HCC treated with TACE[42]. According to the results of this study, nominal Child-Pugh, CUPI, and Tokyo score provided the best prognostic accuracy, and the nominal Child-Pugh was the most accurate among them in predicting survival of patients with unresectable HCC treated with TACE.

As already mentioned, currently there is not an ideal staging and prognostic system for HCC. Anyway, the BCLC seems to be the most comprehensive, since it integrates information about tumor extension, liver function and the presence of constitutional symptoms. It also provides prognostic information and guidance to the therapeutic choices, and it has been endorsed by EASL and AASLD as standard for patients with HCC.

Since survival outcomes can be inevitably confounded by treatment strategies that may be quite different from one center to another[43], It must be noted that the external validation which uses the natural history of untreated HCC cohorts might be the most useful way to compare the prognostic value of each staging system[44,45]. In this regard, the previously mentioned meta-analysis by Cabibbo *et al*[7] which analyzed the survival rates of the untreated and placebo arms of several RCTs on HCC patients, confirmed that many of the prognostic variables of the BCLC (PS, Child-Pugh B-C class, and presence of PVT) are also robust predictors of death in untreated patients. This provides further evidence that the BCLC has a good discriminative capacity as prognostic score, regardless of the treatment strategy applied.

Anyway, it does not represent a perfect model and still it has several unmet points. First, unlike CLIP[14], GRETCH[21] and CUPI[23], the BCLC was not derived from a cohort of HCC patients by a multivariate analysis, and therefore it is not a prognostic model able to predict the mortality of HCC patients, being internally and externally validated just as a staging system. Second, acting as classification model, it presents itself some inherent drawbacks. For example, the intermediate stage (BCLC B) includes an extremely heterogeneous population in terms of both liver function and tumor characteristics. In addition, according to the BCLC, any patient with a PS equal to 1 automatically falls in the advanced stage (BCLC C), even if this condition identifies a "subject capable of performing all the normal daily activities" according the original ECOG (Eastern Cooperative Oncology Group) definition.

In addition, acting as treatment algorithm, the main limitation of the BCLC is represented by its rigidity. First, some prognostic factors, such as the presence of clinically significant portal hypertension, are outlined as contraindications that preclude a therapy, whereas evidences suggest that hepatic resection can be performed successfully, in highly selected cases, even in patients with portal hypertension and multiple hepatic lesions[46,47]. Second, it should be noted that not all patients defined by each stage of BCLC are ultimately candidates for the suggested treatment modality. For instance, TACE can be performed at earlier stages in patients not eligible to RFA or PEI because of tumor location (proximity to the gallbladder, biliary tree, or blood vessel), or failure of previous curative treatments and/or presence of medical comorbidities. Moreover, BCLC algorithm does not provide indications concerning second-line therapies, retreatment choices or combined treatments[48,49].

An important management problem is still represented by the indications for transplantation suggested by BCLC. For example, several lines of evidence show that transplant can get similar results in patients exceeding the Milan criteria, but conform to the "up-to-seven"[50] or the "San Francisco" criteria[51]. Furthermore, transplant is not indicated for end stage disease (BCLC D), which includes, among others, also patients with early tumor but with severe hepatic decompensation (Child-Pugh C). Despite the recommendations of the BCLC suggesting supportive care as the only available therapy, this subset of patients gets anyway the best benefit after transplantation[52,53]. As a result of its rigidity and unmet points, the BCLC is frequently difficult to apply, and its adherence in clinical practice is low[54]. Finally, to date, none of these staging systems have been analyzed or validated taking into account the prognosis of OLT, and therefore can not be recommended in the setting of liver transplantation[55].

CONCLUSION

Currently, the non-ideal predictive performance of existing prognostic systems is secondary to their inherent limitations, as well as to a non-universal reproducibility and transportability of the results in different populations. In addition, other key factors must be considered. First, most of prognostic models are derived by a multiple regression analysis using time-fixed Cox model in order to identify independent factors for mortality. It is already well known as this kind of models may be unreli-

able because of the potential interaction of time-varying predictors. In this context, compared with the time-fixed models, a time-dependent Cox model could have a better potential to estimate prognosis in HCC patients, as already demonstrated by a recent study[56]. Second, as already mentioned, the natural history of HCC is extremely heterogeneous. This is probably secondary to the existence of specific factors not accounted in the prognostic models that can have some impact on patient outcomes. In this regard, the evaluation of gene expression profiling may have an important role in the future to better understand the tumor biology and to improve the predictive power of the models.

In conclusion, due to a non-perfect homogeneity and discrimination (internal validity) and a not absolute transportability of prognostic models in different populations (external validity), currently they are still far away from getting a good confidence in predicting outcome in the individual patient[57]. For these reasons, prognostic models should be used with caution, and staging systems that include integrated therapeutic algorithms should be considered as a general guide only.

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