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Review Article

Staging and Prognostication Systems in Hepatocellular Carcinoma

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Abstract: Liver cancer is the second most common cause of mortality among all cancers in the world. A holistic prognostic classification in hepatocellular carcinoma has not been unified yet. Many prognostic scoring systems have been made from different centres, some of which have been validated in large series. Even then, universally acceptable scoring systems are still an unmet need in this disease because the prognostic indices are variable with different groups from different regions who were under study. In this review, a comprehensive detailing of common prognostic scoring systems in hepatocellular carcinoma is dealt with, underlining their strengths and weaknesses.
Keywords: Hepatocellular carcinoma, Prognosis, Staging, Okuda, Barcelona clinic, TNM, CLIP.

INTRODUCTION

Different staging systems have been described for hepatocellular carcinoma (HCC). Even then, a solid unifying system has never been proposed for use in this disease condition. Staging plays an important part in prognostication of patient condition whereby, targeted therapy can be offered to improve survival or quality of life. Unlike other staging systems used in various malignancies, in patients of HCC, the need to define underlying liver dysfunction along with cancer characteristics provides a holistic approach to prognosis. Staging systems are defined as clinical or pathologic scoring systems. The first attempt at defining a staging system was initiated at Kampala, Uganda in 1971 by Vogel and colleagues [1]. All staging systems that have been made hence mainly concentrated on biochemical markers and tumoral characteristics, paving way for diagnosis and prognosis of HCC based on non biopsy methods. The initial staging systems concentrated mostly on alfa-fetoprotein (AFP) levels. In a study by Tangkijvanich et al, HCC patients were divided into three groups based on AFP levels [normal AFP < 20IU/ml, moderately elevated AFP 20 to 399 IU/ml and markedly elevated AFP > 400 IU/ml]. They found that patients with marked elevation in AFP tend to have larger tumors, bilobar involvement, are massive or diffuse in type and with portal vein thrombosis. Bilobar tumor involvement and presence of hepatitis B surface antigen were predictive of high AFP. But further studies failed to consider AFP as the sole prognostic marker in HCC patients due to lack of sensitivity and specificity (at cut-off 20ng/mL, sensitivity 60%, positive predictive value 9% to 50%; sensitivity and specificity 94% and 99.9% respectively in hepatitis B patients, with positive predictive value 5%) [2,3].

CLINICAL BASED SYSTEMS

The prognostic score of Okuda (Table 1), introduced in 1985 utilized tumor characteristics and the degree of underlying liver dysfunction. The system uses four factors that represent advanced disease, including presence or absence of ascites, serum albumin, bilirubin and tumor occupation of more than or less than 50% of liver and classified patients of HCC into three stages with median survival 11.5 months (Stage I), 3 months (Stage II) and 0.9 months (Stage III). It has its shortcoming in the fact that it did not classify well, patients with early HCC and also the ability to stratify patients based on duration of survival in patients with good prognosis was weak.

The Cancer of Liver Italian Program (CLIP, Table 2) scoring system was designed in 1998 and included the Child Pugh stage, AFP level, presence or absence of portal vein thrombosis and tumor morphology, taking into account liver function and tumor character together. The weakness of CLIP system was that it did not adequately stratify (even though better than Okuda staging) patients with early stage HCC. CLIP score was developed using retrospective analysis on mostly patients of cirrhosis in whom univariate analysis identified predictors of overall survival which were then included into a Cox regression model using loco regional therapy as the stratification factor. The score ranges from 0 to 5. The score has been validated in many studies and was also found to be a

good predictor of HCC recurrence in a Chinese study [4, 5].

Table 1: Okuda staging of Hepatocellular Carcinoma

Criteria	Positive	Negative
Tumor Size	>50%	<50%
Ascites	Clinically present	Clinically absent
Albumin	< 3 mg/dL	>3 mg/dL
Bilirubin	>3mg/dL	<3 mg/dL
Stage		
I	No positives	
II	1-2 positives	
III	3-4 positives	

Table 2: Cancer of Liver – Italian Program Scoring System for Hepatocellular Carcinoma

Parameter	Scoring		
	0	**1**	**2**
Child-Pugh stage	A	B	C
Tumor mrphology	Uninodular and extension ≤50%	Multinodular and extension ≤50%	Massive or extension >50%
AFP (ng/dL)	< 400	≥ 400	
Portal vein thrombosis	No	Yes	

The Barcelona Clinic Liver Cancer (BCLC, Table 3) classification was proposed in 1999 and has been considered the standard of prognostication and treatment stratification by the American Association of Study of Liver. It utilizes the Okuda staging along with Child Pugh scores, extend of primary tumor and local complications (importance of tumor size and number of nodules and presence of vascular invasion) that incorporates liver function and physiological factors. The patients are divided into four stages, A to D (early, intermediate or late stages) and corresponding treatment regimes were defined for each stage that spanned from curative resection or transplant to palliative end of life care. It has been shown that utilization of BCLC system prognosticated HCC better than most systems that were utilized at the time. Even though the BCLC has gained widespread acceptance, it lacks discrimination within the intermediate (Stage B) patients. Tumor burden in stage B can encompass four small tumors to near total replacement of liver by tumor provided there is preservation of liver function, without vascular invasion, extrahepatic spread or poor performance status. BCLC staging over stages patients with HCC, for example, in a patient with a 2 cm tumor, but with Child C status the management could only be palliative care as per treatment stratification. Even for patients who fall into BCLC-B category, most of the time, the treatment regimes are directed as for BCLC-C patients in real life clinical practice. Redefining BCLC-B patients and revising the treatment modality in such patients are an unmet need. The system also requires portal hypertension assessment which leads to complexity in its administration [6].

Table 3: The Barcelona Clinic Liver Cancer Scoring System

Stage	PST	Tumor stage	Underlying Liver Function
Stage A: early HCC			
A1	0	Single	No PHTN, Normal TB
A2	0	Single	PHTN and Normal TB
A3	0	Single	PHTN and Abnormal TB
A4	0	3 tumors < 3cm	Child Pugh A - B
Stage B: intermediate HCC	0	Large multinodular	Child-Pugh A-B
Stage C: advanced HCC	1-2	Vascular invasion or extrahepatic spread	Child-Pugh A-B
Stage D: end-stage HCC	3-4	Any	Child C
TB – Total Bilirubin, PST- Performance Status Test, PHTN – Portal Hypertension			

Leung and co-workers established the Chinese University Prognostic Index (CUPI, Table 4) in 2002 based on retrospective analysis of 926 Chinese patients at a single centre in Hong Kong. They derived a Cox regression model based on TNM staging and forward analytics of 18 other significant clinical variables; the

outcome was death within 3 months of diagnosis. They found that TNM staging (only the tumor extend was utilized from TNM, rather than the complete staging system) was highly significant in predicting mortality at 3 months and the presence of asymptomatic disease, AFP level, total bilirubin, serum alkaline phosphatise and clinical presence of ascites were all found to be significant predictors of death (most of the variables that were already part of the time tested Okuda scoring system). The strength of CUPI is that is easily applicable for use in clinical practice; it utilized a weighted scoring system that yielded better prognostication scores to predict outcome. Since CUPI was made in Asian population cohort, the majority of whom had hepatitis B related liver disease, the prospective validation of this system among Asian countries revealed good results. It was not seen as a useful tool in patients of Western regions where hepatitis C is the commonest cause of chronic liver disease. [7].

Table 4: The Chinese University Prognostic Index scoring system for Hepatocellular Carcinoma

Chinese University Prognostic Index (CUPI)	
TNM Stage	
I and II	-3
IIIa and IIIb	-1
IVa and IVb	0
Asymptomatic disease on presentation	–4
Ascites	3
AFP ≥500 ng/mL	2
Total bilirubin (μmol/L)	
< 34	0
34-51	3
>52	4
Alkaline phosphatase ≥200 IU/L	3
CUPI Stages: score ≤1 (Low risk); 2-7 (Intermediate risk); ≥8 (High risk)	

The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH, Table 5) was proposed by the French group in 1999 that uses objective measures along with performance status to predict survival outcomes. In their analysis they found 5 variables that predicted survival at one year – Karnofsky performace score, total bilirubin, alkaline phosphatase, AFP and presence of portal hypertension by ultrasound imaging. The GRETCH system is easy to use and relies on simple parameters that do not require sophisticated investigations. This system however did not prove superior to other currently utilized scoring system and is not widely used world over [8, 9].

Table 5: The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH) scoring system for Hepatocellular Carcinoma

French Classification (GRETCH – Scoring System)				
Score	**0**	**1**	**2**	**3**
Karnofsky index (%)	≥ 80			< 80
Serum bilirubin (μmol/L)	< 50			≥ 50
Serum alkaline phosphatase (ULN)	< 2		≥2	
Serum alpha-fetoprotein (μg/L)	< 35		≥35	
Portal obstruction (ultrasonography)	No	Yes		

PATHOLOGY BASED SYSTEMS

The TNM staging was developed by the American Joint Committee on Cancer (AJCC, Table 6) and the International Union for Cancer Control (UICC) in 1954. The revised 7th Congress took place in 2010. This system takes into account, the primary tumor characteristics (T), presence or absence of lymph nodal involvement (N) and distal metastases (M). In HCC, additional features of histologic grade (G) and fibrosis score (F) as per Ishak criteria, is also included, but the two latter features do not influence the staging. Simplification of TNM staging for HCC was made in 2002 (known as sT system) and focussed on T component definition to encompass tumor number, size and vascular invasion. The analytical study that yielded sT system identified micro or macrovascular invasion (large portal vein branch), severe fibrosis or cirrhosis, tumor size and number to be independent predictors of poor outcome. The TNM staging per say does not help in deciding on treatment modality in patients of HCC and is more concerned with post surgical recurrence and prognosis and hence, has little value in clinical practice, also because it does not predict outcome. It does not consider the underlying severity of liver disease and/or portal hypertension, nor does it address outcomes following therapies such as liver transplantation and ablation and this is the system's major pitfall [10, 11].

Table 6: The AJCC TNM system classification and scoring of Hepatocellular Carcinoma

American Joint Cancer Committee Staging of Hepatocellular Carcinoma			
Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm		
T3a	Multiple tumors more than 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 other than the gallbladder or with perforation of visceral peritoneum		
Regional Lymph Nodes (N)	Regional lymph nodes cannot be assessed		
NX			
N0	No regional node metastasis		
N1	Regional lymph node metastasis		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/ Prognostic Groups			
Stage I	T1	N0	M0
Stage II	T2	0	0
Stage IIIa	T3a	0	0
Stage IIIb	T3b	0	0
Stage IIIc	T4	0	0
Stage IVa	Any T	N1	0
Stage IVb	Any T	Any N	M1
Histologic Grade (G)			
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Fibrosis Score (F)			
F0	Fibrosis score 0-4 (none to moderate fibrosis)		
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)		

The United International Consensus Committee (UICC, Table 7) was established by the International Hepato-Pancreato-Biliary Association. This study group analysed a cohort of patients from the Liver Cancer Study Group of Japan which formed the basis of UICC staging that has not been published or validated. In this system, previous AJCC system was applied to a new cohort of patients utilizing Kaplan Meir survival curves to compare outcomes. In their analysis, they found that only tumor size > 5cm was predictive of poor outcome in patients with vascular invasion. This scoring system does not include liver dysfunction and is mostly applicable to patients who have survived resection and the variables in this scoring system are not fully validated to have significant predictive value since no univariate or multivariate analysis was done [12].

The Japan Integrated Staging (JIS, Table 8a and 8b) system was developed in 2003 by the Liver Cancer Study Group of Japan for prognostication of survival in patients of early HCC, which was found to be better than CLIP scoring system. The system uses a modified TNM staging along with Child Pugh scoring. The score ranges from 0 to 10, with survival rates of 65% to 23% respectively. It is not widely used in Western countries because of lack of validation and its modifications have not been widely utilized outside of Japan. Later on, a modified m-JIS score was calculated from tumor node metastasis and grade of liver dysfunction as per Liver Cancer Study Group of Japan which was found to have better predictive power than CLIP or modified CLIP systems [13, 14].

Table 7: The UICC staging for Hepatocellular Carcinoma

UICC Staging System for HCC	
T Classification	
Morphology – 3 variables Single tumor Size <2 cm No vascular invasion of portal or hepatic vein	
Staging	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0
Stage IVA	T4N0M0 or T any N1 M0
Stage IV B	Any T/N + M1

Table 8a: The J.I.S scoring system of Hepatocellular Carcinoma

The Japan Integrated Scoring System For Hepatocellular Carcinoma				
Variables	**Scores**			
	0	1	2	3
Child-Pugh	A	B	C	
TNM (Liver Cancer Study Group of Japan)	I	II	III	IV

Table 8b: The J.I.S modification of TNM staging for Hepatocellular Carcinoma

The Liver Cancer Study Group of Japan – TNM Modification For JIS Score		
Scoring Parameters	**Original Score**	**Modified Score**
T factor		
T1	Fulfilling 3 factors	
T2	Fulfilling 2 factors	
T3	Fulfilling 1 factor	
T4	Fulfilling 0 factors	
TNM stage		
Stage I	T1N0M0	
Stage II	T2N0M0	
Stage III	T3N0M0	
Stage IVA	T4N0M0, or any TN1M0	
Stage IVB	Any TN0-N1M1	
JIS system		
Stage I	0	0
Stage II	1	1
Stage III	2	2
Stage IV	3	3
CTP class		
Class A	0	-
Class B	1	-
Class C	2	-
MELD score		
10	-	0
10–14	-	1
> 14	-	2

Table 9 represents the SLIDe scoring system (S, stage; Li, liver damage; De, des-gamma-carboxy prothrombin;) for staging and prognostication of HCC. According to the researchers, this scoring system could predict outcome of HCC patients more precisely than CLIP and JIS systems and is useful in assessment as long as definitions of tumor staging and liver dysfunction was followed as per the Japan Cancer Society Criteria. This study has its problems because the number of patients utilized to derive the score was small (n=177) compared to other studies, the cut off value of tumor marker was an arbitrary one without validation and in both stage IVa and IVb stages, the scoring was similar, thereby falsely providing similar outcomes in these groups. The system also did not take into consideration the various treatment options and outcomes based on the same [15].

Table 9: **The SLIDe scoring system for prognosis of Hepatocellular Carcinoma**

The SLIDe Scoring System				
Parameter/score	**0**	**1**	**2**	**3**
Liver damage as per Liver Cancer Study Group of Japan	A	B	C	
Stage Liver Cancer Study Group of Japan	I	II	III	IVa or IVb
Des-γ-carboxy prothrombin (mAU/mL)	< 400	≥ 400		

CONCLUSION

In summary, scoring and prognostic systems in HCC are plenty, but the utility of each varies according to the region of derivation and the cohort from which it has been derived. The proposed systems are currently not universally acceptable and further unifying scoring systems that could help Hepatologists and Oncologists equally in prognosticating the patient, along with providing the best optimizing or curative measures is still an unmet need.

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