VOLUME 28 · NUMBER 17 · JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Advanced Hepatocellular Carcinoma: Which Staging Systems Best Predict Prognosis?

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Submitted December 3, 2009; accepted March 9, 2010; published online ahead of print at www.jco.org on May 10, 2010.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007, and the Gastrointestinal Meeting of the American Society of Clinical Oncology, Orlando, FL, January 25-27, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2817-2889/$20.00

DOI: 10.1200/JCO.2009.25.9895

ABSTRACT

Purpose
The purpose of cancer staging systems is to accurately predict patient prognosis. The outcome of advanced hepatocellular carcinoma (HCC) depends on both the cancer stage and the extent of liver dysfunction. Many staging systems that include both aspects have been developed. It remains unknown, however, which of these systems is optimal for predicting patient survival.

Patients and Methods
Patients with advanced HCC treated over a 5-year period at Memorial Sloan-Kettering Cancer Center were identified from an electronic medical record database. Patients with sufficient data for utilization in all staging systems were included. TNM sixth edition, Okuda, Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), Chinese University Prognostic Index (CUPI), Japan Integrated Staging (JIS), and Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH) systems were ranked on the basis of their accuracy at predicting survival by using concordance index (c-index). Other independent prognostic variables were also identified.

Results
Overall, 187 eligible patients were identified and were staged by using the seven staging systems. CLIP, CUPI, and GETCH were the three top-ranking staging systems. BCLC and TNM sixth edition lacked any meaningful prognostic discrimination. Performance status, AST, abdominal pain, and esophageal varices improved the discriminatory ability of CLIP.

Conclusion
In our selected patient population, CLIP, CUPI, and GETCH were the most informative staging systems in predicting survival in patients with advanced HCC. Prospective validation is required to determine if they can be accurately used to stratify patients in clinical trials and to direct the appropriate need for systemic therapy versus best supportive care. BCLC and TNM sixth edition were not helpful in predicting survival outcome, and their use is not supported by our data.

J Clin Oncol 28:2889-2895. © 2010 by American Society of Clinical Oncology

INTRODUCTION

In contrast to other cancers, the prognosis and treatment options for patients with hepatocellular carcinoma (HCC) depend not only on the tumor stage but also on the extent of liver dysfunction.[1] A staging system is needed to help predict survival outcome and may be helpful for deciding optimal medical care, especially in this era of complexity of added choice for the treatment of advanced HCC,[2] for which best supportive care may be a more appropriate therapeutic approach in the more advanced cases. Additionally, there is a continued need to appropriately interpret data from clinical trials in patients with advanced HCC. Identification of relevant prognostic factors for both the liver cancer and liver function has led to the development of staging systems that include both. Reported staging systems for HCC include TNM sixth edition,[3] Okuda,[4] Barcelona Clinic Liver Cancer (BCLC),[5] Cancer of the Liver Italian Program (CLIP),[6,7] Chinese University Prognostic Index (CUPI),[8] Japan Integrated Staging Score (JIS score),[9,10] and the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire Prognostic classification (GETCH).[11] The utility of most of these staging systems in predicting survival in patients with advanced HCC seen by medical oncologists for consideration of systemic therapy is often limited. The characteristics of patients with advanced disease might significantly differ from a population of patients balanced between early and advanced disease, for which the available staging systems were originally developed. Whether any one staging system is more informative in patients with advanced HCC, and whether additional

variables not included in these systems have prognostic significance, is unknown.

Objectives

The aim of this analysis was to compare the accuracy of each staging system in predicting survival for patients with advanced HCC evaluated by medical oncologists for consideration of systemic therapy. This analysis was also designed to identify independent prognostic factors for patients with advanced HCC and to determine if the utility of the staging system identified as the best for the population of advanced HCC could be improved by the inclusion of additional prognostic factors identified in a multivariate analysis.

PATIENTS AND METHODS

Patients

We retrospectively identified patients with HCC (with International Classification of Diseases code 155.0 for primary liver cancer) who were evaluated by medical oncologists at Memorial Sloan-Kettering Cancer Center. Patients were included if they had confirmed pathology or had fulfilled the European Association for the Study of the Liver[12] radiologic criteria of two imaging studies (ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]) showing a focal lesion greater than 2 cm with arterial hypervascularization or the combined criteria of one imaging study showing a focal lesion greater than 2 cm with arterial hypervascularization and an α-fetoprotein (AFP) level greater than 400 ng/mL. A baseline evaluation that included clinical examination, laboratory studies, and imaging studies (ie, CT or MRI) was required. The baseline was defined as the time of the first evaluation for advanced HCC. Advanced HCC was defined as a liver tumor not eligible for local therapies given the extent of disease or liver tumors that recurred after local therapies. Intrahepatic recurrence after local treatment was considered metastatic disease.[13] Typically, such patients are considered candidates for bland embolization and are treated by hepatobiliary surgeons and interventional radiologists.[14] However, on progression of disease or ineligibility for continued embolization, those patients are referred to medical oncologists for consideration of systemic therapy, clinical trials, or best supportive care, similar to those with advanced disease.

Patients were excluded if there were missing data required for classifying patients in any of the seven staging systems or if there was no follow-up information. Patients with a diagnosis or history of other concurrent malignancies other than treated skin basal cell carcinoma were also excluded.

Data Collection

Institutional review board approval was obtained to retrieve data from the electronic charts needed to stage patients in all seven staging systems. These included demographics, risk factors for developing HCC, clinical data including but not limited to performance status, parameters of liver cirrhosis manifestations (eg, ascites and encephalopathy). For patients in whom only Karnofsky performance status (KPS) was recorded, Eastern Cooperative Oncology Group performance status (ECOG PS) was deducted on the basis of best evidence available, as follows[15]: ECOG 0 = KPS 100%, ECOG 1 = KPS 80% to 90%, ECOG 2 = 60% to 70%, ECOG 3 = KPS 40% to 50%, and ECOG 4 = KPS 10% to 30%. Laboratory data, including different cirrhosis parameters and AFP, were captured. Bilirubin references of the CUPI and GETCH scores were converted from μmol/L to mg/dL by using a metric conversion calculator. For patients on oral anticoagulation, prothrombin time/international normalized ratio values were obtained at the time anticoagulation was interrupted for some reason, including for liver biopsy. The Child-Pugh score was calculated from obtained clinical and laboratory data. TNM fifth edition scores were generated to calculate the CUPI scores. All previous therapies received were recorded. Tumor characteristics that were reported were number of lesions, diameter of largest lesion, extent of disease, lobar involvement, vascular invasion, portal vein thrombosis, organ invasion, nodes status, and metastatic disease status; these were retrospectively recorded from the radiol-

Table 1. Baseline Demographic and Clinical Characteristics of Patients With Advanced HCC

Characteristic	Patients (N = 187)
Age, years	
Median	64
Range	24-88
Sex, %	
Male	75
Female	25
Ethnicity, %	
White	63
African American	12
Asian	20
Hispanic	4
Unknown	1
Cirrhosis, %	
Yes	55
No	45
Etiology, %	
Hepatitis C	30
Hepatitis B	33
Alcohol	30
Other	14
None	24
Symptoms, %	
Present	78
Absent	22
ECOG PS, %	
0-1	80
2-3	20
Abdominal pain, %	
Yes	34
No	66
Weight loss, %	
Yes	33
No	67
Ascites, %	
Yes	18
No	82
Encephalopathy, %	
Yes	2
No	98
Esophageal varices, %	
Yes	21
No	73
Laboratory values, medians	
Total bilirubin, mg/dL	1.1
Albumin, g/dL	3.2
PT	1.06
Platelets, K/μL	179
Alkaline phosphatase, U/L	146
AST, U/L	72
ALT, U/L	45
AFP, ng/mL	355
Total bilirubin, mg/dL	1.1
Albumin, g/dL	3.2
Liver function by Child-Pugh stage, %	
A	67
B	29
C	4

(continued on following page)

Table 1. Baseline Demographic and Clinical Characteristics of Patients With Advanced HCC (continued)

Characteristic	Patients (N = 187)
Tumor characteristic, %	
No. of liver tumors	
0	6
1-5	39
> 5	55
Diameter of largest lesion, cm	6.7
Bilobar disease	
Yes	70
No	30
Extent	
≤ 50%	70
> 50%	30
Vascular invasion	
Yes	36
No	64
Portal vein thromboses	
Yes	30
No	70
Organ invasion	
Yes	4
No	96
T	
0-2	36
3-4	64
N	
Yes	37
No	63
M	
Yes	60
No	40
Previous treatment, %	
No. of previous treatments	
0	43
1	32
≥ 2	25
Surgery	25
Embolization	34
Ablation	14
Chemoembolization	6
Chemotherapy	4
Transplantation	1
Treatment offered, %	
Clinical trial	29
Chemotherapy	33
Best supportive care	38
Staging system	
TNM*	
1-2	6
2	32
3	63
Okuda stage	
1	49
2	40
3	11
BCLC	1
A	1
B	1
C	85
D	13
CLIP score	9
0	9
1	19
2	31
3	23
4	12
5	6
CUPI	38
Low	38
Intermediate	50
High	12
JIS score	0
0	0
1	2
2	8
3	64
4	22
5	3
GETCH	15
Low	15
Intermediate	71
High	14

Abbreviations: HCC, hepatocellular carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; PT, prothrombin time; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; JIS, Japan Integrated Staging; GETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire.
*Sixth edition.

ogy report, with the exception of tumor extent, that was prospectively determined by review of the available baseline CT and/or MRI of the liver by a medical oncologist.

Staging

Collected data was used to restage all patients. This included all patients assessed by the TNM sixth edition (2006), Okuda, BCLC, CLIP, CUPI, JIS, and GETCH systems.

Statistical Analysis

Overall survival was estimated by using the Kaplan-Meier method from the date of initial evaluation for advanced HCC to the date of death or last follow-up. Survival analysis was stratified according to prognostic categories for each of the seven staging systems. Differences in survival among their prognostic strata were tested by using the log-rank test. Independent prognostic factors were identified through stepwise selection in a Cox regression model. Added variables that significantly related to survival in univariate Cox models ($P < .1$) were subsequently included in a multivariate model.

Ranking of staging systems was done by using the concordance index (c-index), which measures the capacity of the different staging systems to discriminate patients with different outcomes: the higher the c- index, the more informative the model is about a patient's outcome. The c-indices of the different staging systems were compared by using bootstrap[16] and by applying random resampling to test the inferences we generated.

Those additional pertinent prognostic variables previously identified were then added to the top-ranked staging system. A new c-index was calculated to quantify the improvement. The c-index of the resulting model was internally validated by using bootstrap to quantify the improvement.

RESULTS

Between July 1, 2001 and June 30, 2006, 513 patients with HCC were seen by medical oncologists at Memorial Sloan-Kettering Cancer Center; of these, 326 patients either did not fulfill the inclusion and exclusion criteria or had incomplete or no follow-up. The remaining 187 patients were staged by using each of the seven different staging systems discussed in the Methods section. Their baseline characteristics are listed in Table 1. Median follow-up was 13.4 months. Of the 187 patients, 137 (73%) had died at the time of the final analysis (May 29, 2007). Of note, 94% of referred patients had advanced tumor stages (32% stage III and 62% stage IV on the basis of TNM sixth edition) with preserved liver function status (66% Child-Pugh A). Despite the advanced tumor stage, 31% of patients were asymptomatic at presentation. At the time of evaluation, 29% of patients entered onto a clinical trial, and 33% received chemotherapy outside of a clinical trial.

Evaluation of Staging Systems

Kaplan-Meier curves were generated for each of all staging systems except TNM fifth edition. Results are summarized in Figure 1.

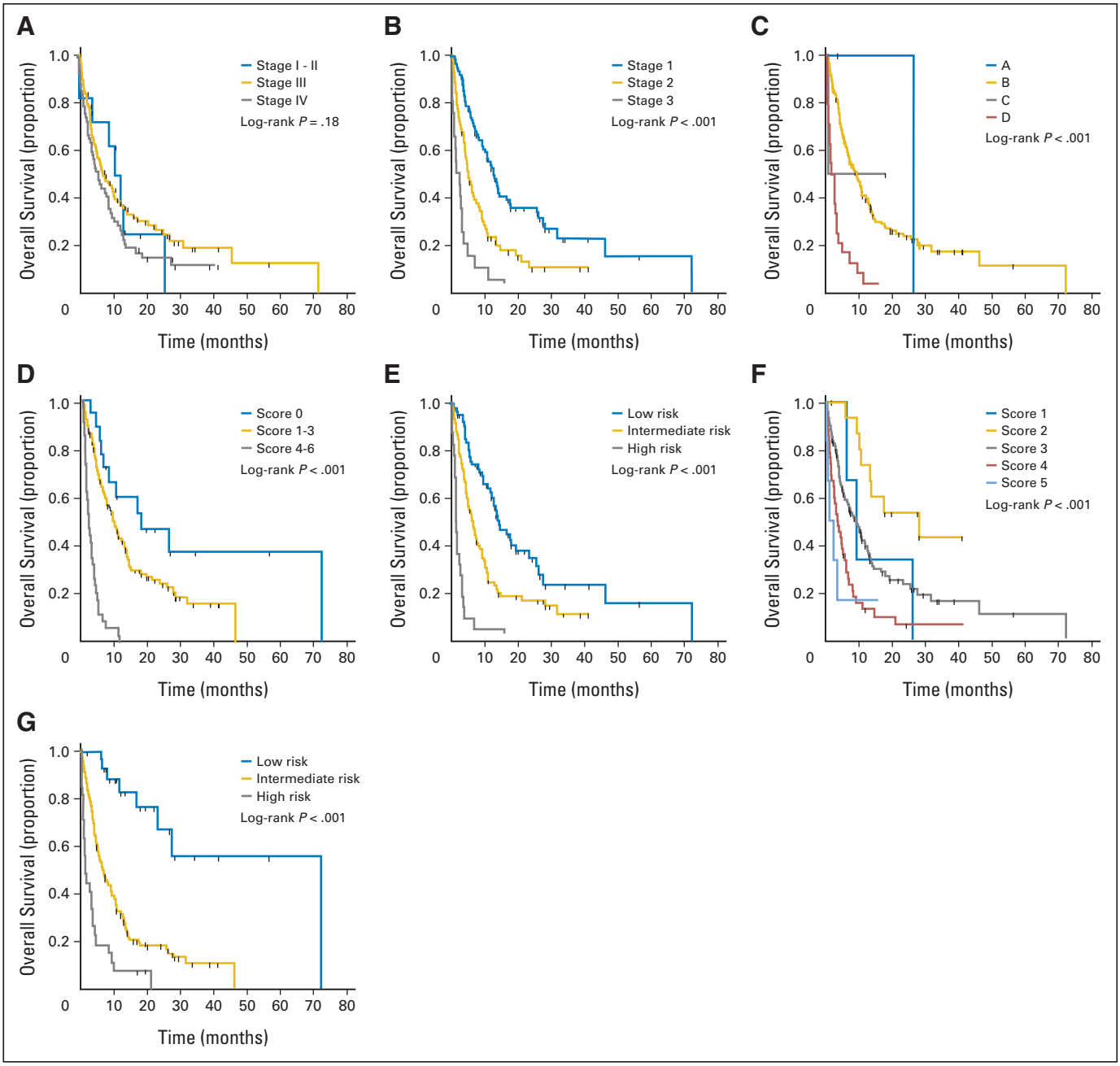

Fig 1. Kaplan-Meier survival curves for patients with advanced hepatocellular carcinoma by staging system: (A) TNM 6th edition, (B) Okuda, (C) Barcelona Clinic Liver Cancer, (D) Cancer of the Liver Italian Program, (E) Chinese University Prognostic Index, (F) Japan Integrated Staging score, and (G) Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire.

Table 2. Ranking of Staging Systems in Patients With Advanced HCC By Using C-Index

Rank	System	C-Index	95% CI
1	CLIP	0.69	0.65 to 0.73
2	CUPI	0.67	0.63 to 0.71
3	GETCH	0.66	0.62 to 0.70
4	Okuda	0.65	0.61 to 0.70
5	JIS	0.63	0.59 to 0.67
6	BCLC	0.58	0.55 to 0.62
7	TNM6	0.47	0.42 to 0.52

Abbreviations: HCC, hepatocellular carcinoma; c-index, concordance index; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS, Japan Integrated Staging; BCLC, Barcelona Clinic Liver Cancer; TNM6, TNM staging, sixth edition.

Table 3. Independent Prognostic Factors for Overall Survival in Patients With Advanced HCC According to Multivariate Analysis

Variable	Hazard Ratio for Death	95% CI	*P*
No. of liver lesions, 1 *v* > 1	0.25	0.089 to 0.720	.009
Bilobar disease, yes *v* no	1.76	1.08 to 2.784	.0166
Abdominal pain, yes *v* no	2.29	1.551 to 3.39	< .001
Esophageal varices, yes *v* no	1.61	1.069 to 2.437	.0227
ECOG PS, 2-3 *v* 0-1	2.95	1.868 to 4.666	< .001
Child Pugh stage, B *v* A	1.88	1.243 to 2.832	.0028
Alkaline phosphatase	1.96	1.007 to 3.817	.04
AFP	1.24	1.106 to 1.393	< .001
AST	3.47	1.799 to 6.686	.002

Abbreviations: HCC, hepatocellular carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, α-fetoprotein.

The Kaplan-Meier curves showed clear different prognostic strata for CLIP, CUPI, GETCH, and Okuda, with high statistical significance (log-rank $P < .001$ in all cases). Although some overlapping of survival curves is observed for JIS and BCLC, overall the difference in survival among different prognostic strata is also highly statistically significant (log-rank $P < .001$ in both cases). Only the TNM sixth edition could not demonstrate survival difference among its prognostic strata (log-rank $P = .18$ for TNM sixth edition).

Comparison of Staging Systems

The comparison of the prognostic ability of the different staging systems was done by using the c-index (Table 2). On the basis of the c-index, CLIP (0.69; 95% CI, 0.65 to 0.73), CUPI (0.67; 95% CI, 0.63 to 0.71), and GETCH (0.66; 95% CI, 0.62 to 0.70) were the top three ranking staging systems, and there was no statistically significant difference among each other (CLIP compared with CUPI, $P = .26$; CLIP compared with GETCH, $P = .17$; and CUPI compared with GETCH, $P = .7$). There was a borderline difference between prognostic ability of Okuda (c-index, 0.65; 95% CI, 0.61 to 0.70) compared with CLIP ($P = .06$). JIS (c-index, 0.63), BCLC (c-index, 0.58), and TNM sixth edition (c-index, 0.47) were all significantly less valuable than CLIP ($P < .004$).

Prognostic Factors

Independent prognostic factors for overall survival identified through multivariate analysis are reported in Table 3. The most significant of those prognostic factors that are not regularly used as part of the different staging systems are performance status, the presence of abdominal pain, and the presence of esophageal varices. Identified laboratory prognostic factors include elevated alkaline phosphatase, AST, and AFP levels.

Improvement of Staging Systems

Addition of the independent prognostic variables of performance status, AST, abdominal pain, and presence of esophageal varices improved the discriminatory ability of CLIP with a new c-index of 0.76 compared with 0.69 (bootstrap validated).

DISCUSSION

Medical oncologists assess patients with advanced HCC. Of particular impact for these patients is information pertaining not only to tumor stage but also to the extent of liver dysfunction.[1] Unlike other cancers, a TNM staging seems insufficient, and multiple other comprehensive prognostic staging systems have been developed. There have been different views to the validity of certain staging systems reflected by the multidisciplinary approach to the management of HCC. Yet it remains unknown which staging system is most informative in patients with advanced HCC in regard to survival outcome and direction of care. As new therapies continue to emerge for HCC, identifying patients who are suited for such therapies versus best supportive care is essential. The interpretation of clinical trials in advanced HCC may also be dependent on which staging system was used. It is also unclear whether additional variables not considered in these systems have prognostic significance.

In our study, we attempted to help define which staging system should be used for the evaluation of patients with advanced HCC who are referred to medical oncology specialists. We retrospectively identified and then compared seven different staging systems in terms of their prognostic abilities by using c-index. We showed that the purely anatomic TNM sixth edition was not useful for predicting overall survival. BCLC has been viewed "as the standard classification that is used for trial design and clinical management of patients with HCC" on the basis of a commentary report,[17p699] supported by two prospective validation studies that had a limited number of patients with metastatic disease,[18-19] which was the subject of this study. BCLC is the most comprehensive staging system available. It is designed with an ability to factor therapeutic choices for patients at different stages of disease. However, it did not score well in our exercise, because we were studying a specific niche of patients with advanced disease who fall under the single C category in BCLC, which limits any discriminatory abilities. BCLC is currently under revision, and a substratification of category C is possible.[20]

CLIP, CUPI, and GETCH staging systems were the most informative regarding survival outcome. CLIP is a commonly used staging system for patients with HCC. The staging system was validated in a population of patients treated prospectively in a clinical trial that tested tamoxifen therapy in HCC that had underlying hepatitis C as the main etiology. Five prognostic strata were defined according to a score derived from the analysis of variables related to cirrhosis (Child-Pugh score), tumor morphology, AFP level, and portal vein thrombosis, as detailed in Appendix Table A1 (online only). The higher the score, the worse the outcome was. A patient with limited metastatic

disease exemplified by, for example, a few lesions in the lung but with a CLIP score of 6 would have a median survival of a few weeks and may be recommended best supportive care rather than systemic therapy.

CUPI was developed in a population of patients with HCC who predominantly had hepatitis B.[8] CUPI parameters include bilirubin, ascites, AFP, alkaline phosphatase, the tumor extent as defined by the TNM staging system, and the absence or presence of clinical symptoms on presentation. CUPI was the only prognostic system, other than BCLC, to introduce a clinical assessment variable. CUPI is strengthened by the weighted scores for each parameter that were derived from the regression coefficients of various factors (Appendix Table A2, online only).

GETCH[11] is based on assessment of total bilirubin, KPS, AFP, alkaline phosphatase, and portal vein thrombosis (Appendix Table A3, online only). The points from Appendix Table A3 range from 0 to 11; in patients with HCC, group A includes those at a low risk of death (score = 0); group B indicates an intermediate risk of death (score = 1 to 5); and group C indicates a high risk of death (score $\geq$ 6). Similar to CUPI, GETCH is powered by the portal vein thrombosis parameter, a critical prognostic factor for HCC.

We independently examined the prognostic importance of independent clinical, pathologic, and laboratory variables. Novel prognostic variables were identified as follows: performance status, abdominal pain, AST level, and esophageal varices. Performance status is a universal prognostic variable that has a clear impact on outcome, abdominal pain may be a manifestation of tumor extent, and the presence of esophageal varices is an indirect measure of the presence of portal hypertension; all are viewed as important prognostic factors of HCC. The presence of an elevated AST level shows one of the highest hazard ratios for poor outcome. Of note, in patients with chronic hepatitis and cirrhosis, an increase in AST/ALT ratio is associated with progressive liver functional impairment.[21,22] Those added variables helped improve the discriminatory ability of the CLIP, one of the three top-ranked models in this retrospective analysis.

Our effort is obviously limited by the retrospective nature of the analysis and the single-institution experience. Our future goal is to help evaluate our hypothesis in a prospective fashion as part of a prospective clinical trial. We were also unable to explain the lack of any meaningful difference between CLIP, CUPI, and GETCH; this lack of difference may be real or limited by the retrospective analysis of the study, or it may be influenced proportionally by the equal contribution of the patients with hepatitis B virus, hepatitis C virus, and alcohol risk factors to the database (Table 1).

A comparison of four staging systems in two French clinical trials in patients with advanced HCC has recently been reported.[22] The authors compared Okuda, CLIP, and BCLC, staging systems that use different statistical tools. CLIP was reported to be the most adaptive scoring system in the setting of advanced disease.

Other multiple studies comparing staging systems in hepatocellular carcinoma have been conducted and have reported different ranking of staging systems.[18,23-27] However, these studies included patients with multiple stages of HCC, whereas our studied population included patients with advanced disease that is not amenable to curative or local therapies. This observation highlights once again that, for different stages of the natural history of a disease, the relevance of certain prognostic factors and the usefulness of staging systems might vary. Patients with advanced HCC who present to a medical oncologist for consideration of systemic therapy have distinct clinical characteristics, tumor extent, and residual liver function.

In summary, CLIP, CUPI, and GETCH were the most informative staging systems in predicting survival in patients with advanced HCC. Prospective validation is required to determine if these staging systems can be accurately used to stratify patients in clinical trials and to help direct medical care. BCLC has limited discriminatory abilities in this population, and we do not recommend its use in this setting. Ongoing revisions of the BCLC with respect to this patient population may change this observation in the future. TNM sixth edition was not helpful, mostly because of a lack of any prognostic parameters of liver dysfunction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Fidel David Huitzil Melendez, Marinela Capanu, Eileen M. O'Reilly, Austin Duffy, Ghassan K. Abou-Alfa
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