JBUON 2019; 24(1): 150-157
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparison of 10 prognostic staging systems in patients with advanced hepatocellular carcinoma

Lei Wang[1]*, Yutao Xian[2]*, Zhengqiang Yang[2]

[1]Department of Vascular Surgery, Northern Jiangsu People's Hospital, the Clinical Medical School of Yangzhou University, Yangzhou, Jiangsu province, China; [2]Department of Interventional Radiology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu province, China.

*These authors contributed equally to this work.

Summary

Purpose: *To compare the performance of 10 currently staging systems (TNM, Okuda, GETCH, CLIP, CUPI, JIS, CIS, MELD, mJIS, mCLIP) for predicting survival in advanced hepatocellular carcinoma (HCC) patients.*

Methods: *FA total of 133 consecutive advanced HCC patients between January 2014 and December 2014 were enrolled in the study. The Kaplan–Meier method compared by the log-rank test was used to estimate the survival distribution. Ranking of staging systems was done by using the concordance index (c-index) to compare the discriminatory capacity. The area under the curve (AUC) was performed to assess the mortality prediction.*

Results: *The median survival of all 133 patients was 7.5 months. The survival rates at 6, 12, 18 and 24 months were 56%, 30%, 19% and 15%, respectively. CIS and CUPI systems had better performances in survival distribution. CIS, TNM and CLIP systems were the top three ranking staging systems. CIS had the best mortality prediction at 6, 18 and 24 months and CLIP had the best mortality prediction at 12 months.*

Conclusions: *The CIS system was the most informative staging system for predicting survival in advanced HCC patients with mainly hepatitis B virus etiology.*

Key words: *comparison, HBV, hepatocellular carcinoma, prognostic factor, staging system*

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related death and the fifth most common cancer worldwide [1,2]. The majority of HCC patients are diagnosed at an advanced stage because of the presence of portal vein tumor thrombus (PVTT) or extrahepatic metastasis (EHM) [3]. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, most of these patients are classified into the same stage (BCLC-C) [4].

However, the severity of advanced HCC varies greatly and patient survival varies widely. Many staging systems had been developed, including TNM seventh edition [5], Okuda [6], Group d'Etude et de Traitement du Carcinome Hepatocellulaire prognostic classification (GETCH) [7], Cancer of the Liver Italian Program (CLIP) [8,9], Chinese University Prognostic Index (CUPI) [10], Japan Integrated Staging (JIS) [11,12], China Integrated Score (CIS) [13], the Model for End-stage Liver Disease (MELD) [14], modified JIS (mJIS) [15] and modified CLIP (mCLIP) [16]. Many studies have compared and ranked these staging systems according to their prognostic value [17-23], but the results were not consistent and remains controversial.

Correspondence to: Zhengqiang Yang, PhD. Guangzhou Rd no.300, Nanjing, Jiangsu province, China
Tel: +86 13770335028, E-mail: yangzhengqiang@jsph.org.cn
Received: 10/06/2018; Accepted: 14/07/2018

This study focused on advanced HCC patients, mainly associated with hepatitis B virus (HBV). The aim of this analysis was to compare the accuracy of the 10 staging systems for predicting survival in advanced HCC patients. Additionally, we explored whether the best staging system could be improved by inclusion of prognostic factors identified in the multivariate analysis.

Methods

Patient selection

From January 2014 to December 2014, a consecutive series of 281 newly diagnosed HCC patients were admitted to our center. Among them, a total of 133 HCC patients with PVTT and/or EHM were enrolled into this study. The diagnosis of HCC was made according to the American Association for the Study of Liver Disease (AASLD) guidelines [24]. PVTT was diagnosed using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). EHM was diagnosed using CT, MRI, positron emission tomography (PET)/CT, bone scans or any combinations of them.

The eligibility criteria were: (1) newly diagnosed patients without previous treatment for HCC; (2) the presence of PVTT and/or EHM; (3) Child-Pugh class A or B; (4) Eastern Cooperative Oncology Group (ECOG) performance status 0-2; (5) no other malignancies present.

The study protocol was approved by the Ethics Committee of our center and adhered to the Declaration of Helsinki and its later amendments. All patients had signed informed consent.

Table 1. Baseline characteristics of 133 patients with advanced HCC

Characteristics	*Number*	*Percents*	*Characteristics*	*Number*	*Percents*
Age, years			Tumor size (cm)		
<55	61	45.86	<10	41	30.83
≥55	72	54.14	≥10	92	69.17
Gender					
Male	105	78.95	Type of PVTT		
Female	28	21.05	None	22	16.54
Etiology			Type I	34	25.56
HBV	98	73.68	Type II	41	30.83
HCV	2	1.50	Type III	36	27.07
Alcohol	5	3.76			
Others	27	20.30	Site of EHM		
Cirrhosis			None	90	67.67
Yes	51	38.35	Node	16	12.03
No	82	61.65	Lung	22	16.54
ECOG score			Bone	4	3.01
0 & 1	125	93.98	Adrenal gland	4	3.01
2	8	6.02	Others	4	3.01
Symptoms					
Absent	34	25.56	Laboratory tests		
Present	99	74.44	Alanine aminotransferase (≥50U/L)	63	47.37
Ascites			Aspartate aminotransferase (≥50U/L)	85	63.91
Absent	96	72.18	Alkaline phosphatase (≥200IU/L)	44	33.08
Present	37	27.82	Albumin (≥40g/L)	46	34.59
Child-Pugh class			Total bilirubin (≥19umol/L)	62	46.62
A	87	65.41	White blood cell count (≥6*10^9/L)	56	42.11
B	46	34.59	Neutrophil count (≥4*10^9/L)	53	39.85
Tumor location			Lymphocyte count (≥1*10^9/L)	46	34.59
Single lobe	79	59.40	Neutrophil-Lymphocyte Ratio (≥4)	37	27.82
Multiple lobes	54	40.60	Platelets count (≥125*10^9/L)	76	57.14
Tumor number			Prothrombin time (≥14s)	35	26.32
Single	81	60.90	α-fetoprotein (≥400ng/mL)	66	49.62
Multiple	52	39.10			

HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; ECOG: Eastern Cooperative Oncology Group; PVTT: portal vein tumor thrombus; EHM: extrahepatic metastasis

Data collection

All data needed to stage patients in the 10 staging system and that could be associated with the prognosis were retrospectively reviewed from the patient medical records. A series of demographic, laboratory, radiologic and clinical data were carefully collected, including age, gender, etiology, liver cirrhosis, ECOG performance status score, symptoms, liver function, Child-Pugh class, intrahepatic tumor characteristics and the extent of PVTT/EHM. The duration of patient survival was calculated from the date of enrollment to death or December 31, 2016.

Karnofsky performance status (KPS) was deducted on the basis of following estimation: ECOG 0= KPS 100%, ECOG 1= KPS 80-90%, ECOG 2= KPS 60-70% [25]. The extent of PVTT was classified into three types: (1) type I, a tumor thrombus was limited to segmental branches; (2) type II, a tumor thrombus involving the right and/or left branch; (3) type III, a tumor thrombus invaded the main portal vein trunk or above. The type of EHM was classified as nodal and distant metastasis.

Table 2. Multivariate analysis of predictive factors for overall survival

Factors	*HR (95% CI)*	*P*
Type of PVTT		
Type I	1.00	-
Type II	2.29 (1.34-3.93)	0.002
Type III	1.85 (1.39-2.46)	0.00003
Type of EHM		
Nodal	1.00	-
Distant	1.14 (1.04-1.26)	0.008
Child-Pugh class		
A	1.00	-
B	1.93 (1.30-2.87)	0.002

HR: hazard ratio; CI: confidence interval; PVTT: portal vein tumor thrombus; EHM: extrahepatic metastasis

Based on the tumor characteristics and liver function, patients with advanced HCC were treated with sorafenib, transarterial chemoembolization or best supportive care. All the treatments were selected by a multidisciplinary team.

Staging systems

All patients were restaged according to the 10 staging systems: TNM (stage I, II, III and IV), Okuda (stage I, II, and III), GETCH (Low, Intermediate, and High), CLIP (score 0-6), CUPI (Low, Intermediate, and High), JIS (score 0-5), CIS (score 0-5), MELD (I: score ≤9, II: score 10-14, and III: score ≥15), mJIS (score 0-5) and mCLIP (score 0-8). The predictive accuracy of these staging systems were compared in three aspects: the differences of survival distributions between subgroups, the discrimination capacity to stratify patients with different outcomes and the prediction of 6-, 12-, 18-, and 24-month mortality.

Statistics

Frequencies and percentages were used for descriptive statistics. Univariate and multivariate Cox regression analysis were performed to identify the factors associated with patient survival. A hazard ratio (HR) with 95% confidence interval (CI) was calculated for each variable. A p value of <0.05 was considered to be significant. The Kaplan–Meier method compared by the log-rank test was used to estimate the survival distributions.

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 better the model about a patient's outcome. The c-indices of the different staging systems were compared by using bootstrap and by applying random resampling. The area under the receiver operating characteristic curve (AUC/ROC) was performed to assess the ability in predicting the risk of mortality.

All statistical analyses were performed using SPSS software (version 22.0; SPSS, Chicago, IL, USA) and R (version 3.3.2; The R Foundation, Vienna, Austria).

Table 3. Patient distribution according to the 10 staging systems

Staging system	*Number*	*Median survival (months)*
TNM (I/II/III/IV)	0/21/69/43	-/16.1/6.9/6.7
Okuda (I/II/III)	28/99/6	12.8/7.3/3.3
GETCH (L/I/H)	11/111/11	8.5/7.6/6.0
CLIP (0/1/2/3/4/5/6)	2/14/21/38/40/16/2	14.6/12.8/7.8/8.6/6.7/2.5/1.2
CUPI (L/I/H)	70/53/10	10.5/6.0/2.8
JIS (0/1/2/3/4/5)	0/0/38/66/27/2	-/-/10.1/7.3/5.4/1.2
CIS (0/1/2/3/4/5)	29/51/26/20/7/0	11.7/8.7/6.9/5.4/2.8/-
MELD (I/II/III)	98/30/5	8.5/4.6/9.3
mJIS (0/1/2/3/4/5)	0/0/43/66/23/1	-/-/10.1/6.9/6.0/1.1
mCLIP(0/1/2/3/4/5/6/7/8)	2/14/19/30/35/19/13/1/0	14.5/12.8/8.4/8.6/6.7/7.0/2.5/2.8/-

GETCH: Group d'Etude et de Traitement du Carcinome Hepatocellulaire; (m)CLIP: (modified) Cancer of the Liver Italian Program; CUPI: Chinese University Prognostic Index; (m)JIS: (modified) Japan Integrated Staging; CIS: China Integrated Score; MELD: Model for End-stage Liver Disease

Results

Baseline characteristics

A total of 105 males and 28 females with a mean age of 58 years were included in this study. The etiology of the background liver disease was HBV in 98 patients. PVTT types I, II and III were diagnosed in 34, 41 and 36 patients, respectively. There were 43 patients with 50 sites of EHM, mainly in the lung and lymph nodes. Baseline characteristics are summarized in Table 1.

Analysis of prognosis

The median follow-up time was 30.7 months (range 0.7-36.1); 20 patients were alive and 113 patients had died at the end of the follow-up period. The median survival time of all 133 patients was 7.5 months and the survival rates at 6, 12, 18 and 24 months were 56%, 30%, 19% and 15%, respectively.

In the multivariate analysis, type II PVTT (HR=2.29; 95%CI, 1.34-3.93;p=0.002), type III PVTT (HR=1.85; 95%CI, 1.39-2.46; p=0.00003), distant metastasis (HR=1.14; 95%CI, 1.04-1.26;p=0.008) and Child-Pugh class B (HR=1.93; 95%CI, 1.30-2.87;p=0.002) had a significant negative association with survival (Table 2).

Comparison of 10 staging systems

Patient distribution and median survival time according to the 10 staging systems are depicted in Table 3. Survival curves were generated for each staging system as well and the results are summarized in Figure 1. Statistical differences within all sub-groups were observed only in CIS and CUPI staging systems.

Ranking of discriminatory ability of staging systems was done by using the c-index (Table 4). On the basis of the c-index, CIS (0.598, 95% CI, 0.453-0.744), TNM (0.590, 95% CI, 0.466-0.715) and CLIP (0.587, 95% CI, 0.476-0.699) were the top three ranking staging systems, and there was no statistically difference within the three c-indices (CIS versus TNM, p=0.88; CIS versus CLIP, p=0.80). Compared with CIS, Okuda (0.567), mCLIP (0.558), CUPI (0.555), GETCH (0.528), JIS (0.523), mJIS (0.495) and MELD (0.491) were all significantly less valuable (p<0.018). Addition of the independent prognostic factor of PVTT type improved the discriminatory ability of CIS with a new c-index of 0.673 compared with 0.598 (bootstrap validated).

Using the 6, 12, 18 and 24 months mortality as the endpoint, the AUC for each staging system is

Table 4. Ranking of 10 staging systems in advanced HCC by using c-index

Rank	*System*	*C-index*	*95% CI*
1	CIS	0.598	0.453-0.744
2	TNM	0.590	0.466-0.715
3	CLIP	0.587	0.476-0.699
4	Okuda	0.567	0.444-0.690
5	mCLIP	0.558	0.450-0.665
6	CUPI	0.555	0.419-0.691
7	GETCH	0.528	0.430-0.625
8	JIS	0.523	0.379-0.668
9	mJIS	0.495	0.350-0.640
10	MELD	0.491	0.379-0.605

HCC: hepatocellular carcinoma; c-index: concordance index; CI: confidence interval; CIS: China Integrated Score; (m)CLIP: (modified) Cancer of the Liver Italian Program; CUPI: Chinese University Prognostic Index; GETCH: Group d'Etude et de Traitement du Carcinome Hepatocellulaire; (m)JIS: (modified) Japan Integrated Staging; MELD: Model for End-stage Liver Disease

Table 5. Comparison of 10 staging systems in advanced HCC by using AUC

System	*6-month AUC*	*12-month AUC*	*18-month AUC*	*24-month AUC*
CIS	0.673	0.614	0.633	0.659
CUPI	0.661	0.615	0.587	0.615
CLIP	0.666	0.640	0.615	0.574
Okuda	0.576	0.587	0.539	0.515
TNM	0.642	0.583	0.611	0.642
mCLIP	0.661	0.630	0.630	0.582
GETCH	0.528	0.533	0.500	0.500
JIS	0.616	0.614	0.619	0.629
mJIS	0.610	0.560	0.605	0.598
MELD	0.580	0.541	0.584	0.562

HCC: hepatocellular carcinoma; AUC: Area Under the Curve; CIS: China Integrated Score; CUPI: Chinese University Prognostic Index; (m)CLIP: (modified) Cancer of the Liver Italian Program; GETCH: Group d'Etude et de Traitement du Carcinome Hepatocellulaire; (m)JIS: (modified) Japan Integrated Staging; MELD: Model for End-stage Liver Disease

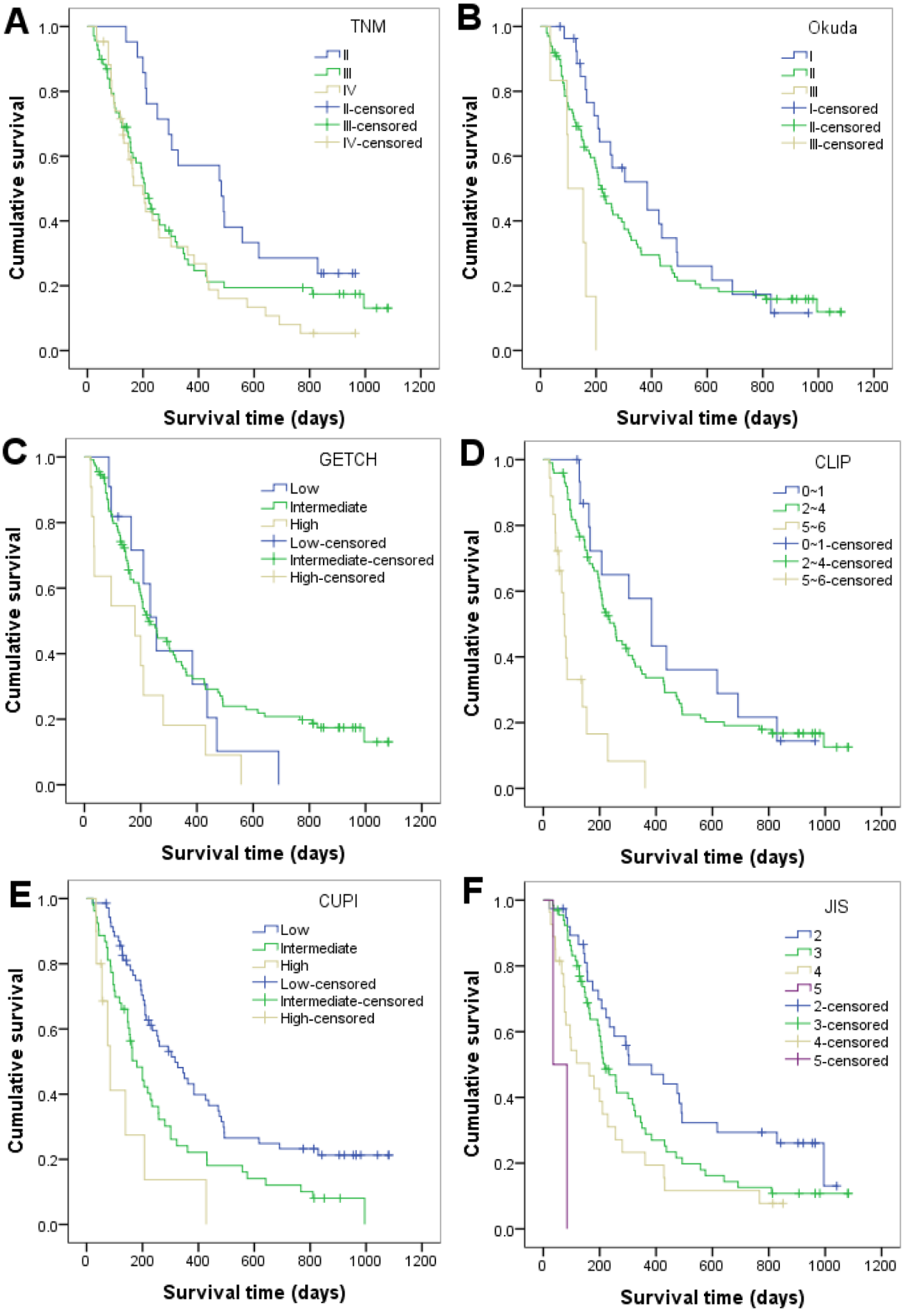

Figure 1. *Continued on the next page*

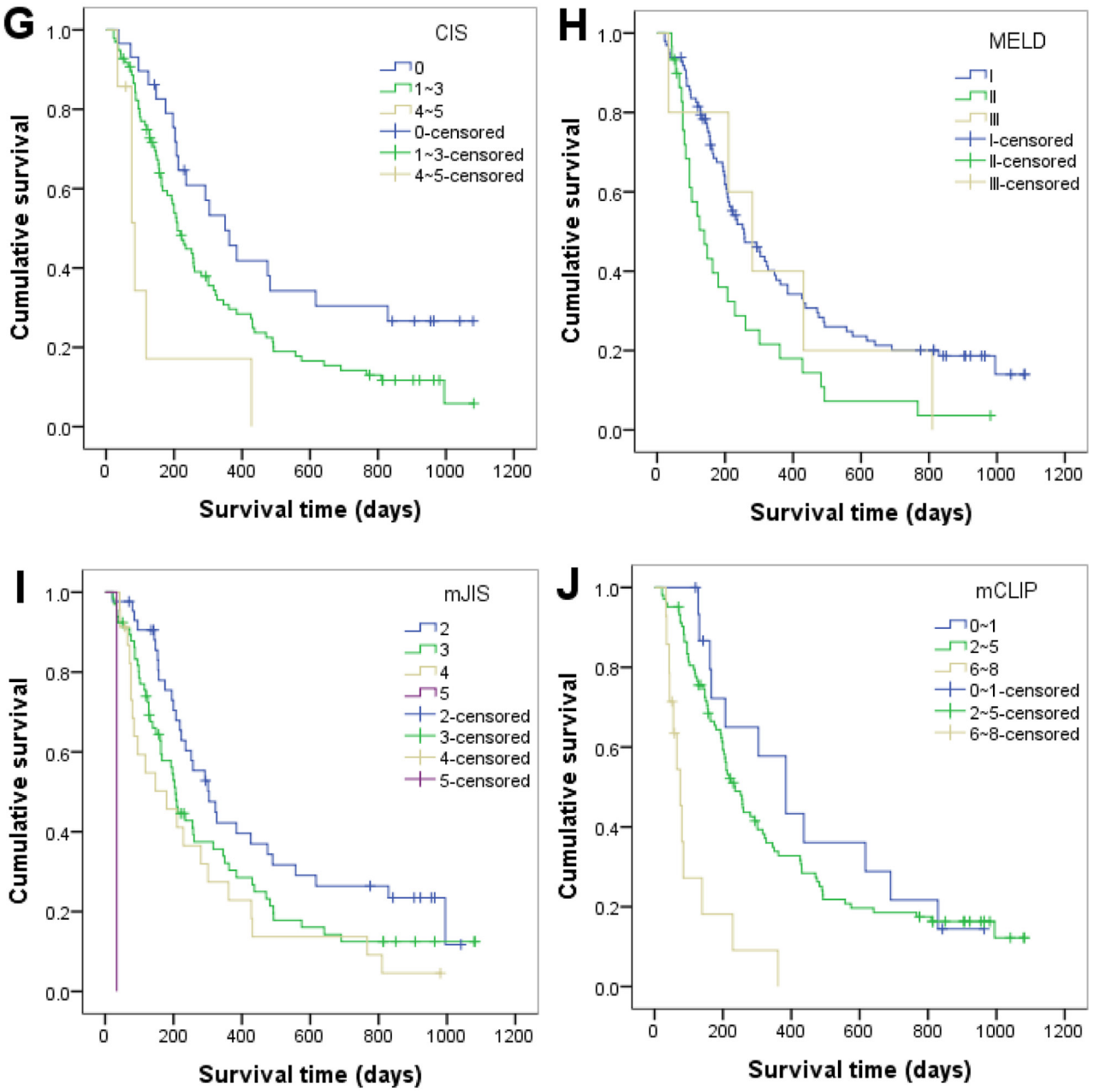

Figure 1. Comparison of survival distribution in patients with advanced hepatocellular carcinoma. **(A)** TNM seventh edition: stage II versus III, p=0.046; stage III versus IV, p=0.410. The difference between stage III and IV was not statistically significant. **(B)** Okuda staging system: stage I versus II, p=0.295; stage II versus III, p=0.009. The difference between stage I and II was not statistically significant. **(C)** Group d'Etude et de Traitement du Carcinome Hepatocellulaire prognostic classification (GETCH): group low risk versus group intermediate risk, p=0.560; group intermediate risk versus group high risk, p=0.023. The difference between group low and intermediate risk was not statistically significant. **(D)** Cancer of the Liver Italian Program (CLIP) staging system: score 0-1 versus 2-4, p=0.624; score 2-4 versus 5-6, p<0.001. The differences between score 0-1 and 2-4 were not statistically significant. **(E)** Chinese University Prognostic Index (CUPI) staging system: group low risk versus group intermediate risk, p=0.003; group intermediate risk versus group high risk, p=0.045. All differences between groups were statistically significant. **(F)** Japan Integrated Staging (JIS) system: score 2 versus 3, p=0.060; score 3 versus 4, p=0.096, score 4 versus 5, p=0.098. The differences between score 2 and 3, 3 and 4, 4 and 5 were not statistically significant. **(G)** China Integrated Score (CIS) staging system: score 0 versus 1-3, p=0.028; score 1-3 versus 4-5, p=0.011. Statistical difference was noted between any stages. **(H)** Model for End-stage Liver Disease (MELD) staging system: stage I versus II, p=0.002; stage II versus III, p=0.356. The difference between stage II and III was not statistically significant. **(I)** Modified Japan Integrated Staging (mJIS) system: score 2 versus 3, p=0.071; score 3 versus 4, p=0.278, score 4 versus 5, p<0.001. The differences among score 2, 3 and 4 were not statistically significant. **(J)** Modified Cancer of the Liver Italian Program (mCLIP): score 0-1 versus 2-5, p=0.382; score 2-5 versus 6-8, p<0.001. The difference between score 0-1 and 2-5 was not statistically significant.

listed in Table 5. CIS had the best performance at 6, 18 and 24 months. CLIP had the best performance at 12 months.

Discussion

The population of this study was limited to patients with advanced HCC and HBV etiology. In both univariate and multivariate analysis, tumor stage (type of PVTT, type of EHM) and liver function (Child-Pugh class) were independent factors with significant influence on overall survival. PVTT not only can lead to complications of portal hypertension such as ascites, variceal hemorrhage and worsening liver function, but also can result in progression of disease by direct invasion of adjacent tissues and distant metastasis [26].

The survival duration is very heterogeneous in patients with advanced HCC. It is essential to identify which staging system is most informative in advanced HCC patients for estimating prognosis and guiding treatment. BCLC is the most comprehensive staging system available. But most of patients with advanced HCC are classified into the single BCLC-C stage, which limits any discriminatory abilities. Ten staging systems (TNM, Okuda, GETCH, CLIP, CUPI, JIS, CIS, MELD, mJIS and mCLIP) were included into the comparison of survival distribution, discriminatory capacity and mortality prediction. As a result, CIS was the most informative staging system in predicting survival in our study.

CIS was a new staging system based on TNM stage (0-2), Child-Pugh class (0-1) and AFP level (0-1); the CIS score is calculated by summing up each individual score of three items [13], but the type of PVTT is not included. After adding this independent factor, the discriminatory ability of CIS improved significantly.

Many studies comparing staging systems in HCC have reported different ranking of staging systems [17-23,27-30]. However, these studies included patients with multiple stages of HCC or with mainly alcoholic etiology, whereas our study focused on patients with advanced HCC and mainly HBV etiology. We attempted to help define which staging system should be the most informative staging system for predicting survival in our cohort.

This study has some limitations. First, it was a single-center retrospective study. Second, the study sample size was relatively small. Third, the anticancer treatment could be different in the same patient during the follow-up period.

Conclusion

Among the 10 staging system available for HCC (TNM, Okuda, GETCH, CLIP, CUPI, JIS, CIS, MELD, mJIS and mCLIP), CIS was the most informative staging system in predicting survival in advanced HCC in our study. Further prospective and multicenter validation is required to demonstrate whether CIS staging system can be used to stratify patients accurately in clinical trials and help guide treatment.

Conflict of interests

The authors declare no conflict of interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Fomer A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-55.
3. Park JW, Chen M, Colombo M et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015;35:2155-66.
4. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Sem Liv Dis 1999;19:329-38.
5. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
6. Okuda K, Ohtsuki T, Obata H et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
7. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma: Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 1999;31:133-41.
8. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28:751-5.
9. The Cancer of the Liver Italian Program (CLIP) investigators. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000;31:840-5.

10. Leung TW, Tang AM, Zee B et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: A study based on 926 patients. Cancer 2002;94:1760-9.
11. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitation, and a proposal for a new staging system, the Japan Intergrated Staging Score (JIS score). J Gastroenterol 2003;38:207-15.
12. Kudo M, Chung H, Haji S et al. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology 2003;40:1396-405.
13. Zhang BH, Wang XH, Yue HY, Ling CQ. A new staging system is more discriminant than conventional staging systems for unresectable hepatocellular carcinoma. J Cancer Res Clin Oncol 2010;136:821-7.
14. Wiesner R, Edwards E, Freeman R et al. The United Network for Organ Sharing Liver Disease Severity Score Committee. Model for End-Stage Liver Disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-6.
15. Huo TI, Lin HC, Huang YH et al. The model for end-stage liver disease-based Japan Integrated Scoring system may have a better predictive ability for patients with hepatocellular carcinoma undergoing locoregional therapy. Cancer 2006;107:141-8.
16. Huo TI, Lin HC, Huang YH et al. Proposal of a Modified Cancer of the Liver Italian Program Staging System Based on the Model for End-Stage Liver Disease for Patients with Hepatocellular Carcinoma Undergoing Loco-Regional Therapy. Am J Gastroenterol 2006;101:975-82.
17. Marrero JA, Fontana RJ, Barrat A et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 2005;41:707-16.
18. Cho YK, Chung JW, Kim JK et al. Comparison of 7 staging systems for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. Cancer 2007;112:352-61.
19. Collette S, Bonnetain F, Paoletti X et al. Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials. Ann Oncol 2008;19:1117-26.
20. Huitzil-Melendez FD, Capanu M, O'Reilly EM et al. Advanced hepatocellular carcinoma: which staging systems best predict prognosis? J Clin Oncol 2010; 28:6.
21. Hsu CY, Hsia CY, Huang YH et al. Selecting an optimal staging system for hepatocellular carcinoma: comparison of 5 currently used prognostic models. Cancer 2010;116:9.
22. den Winkel M, Nagel D, Sappl J et al. Prognosis of patients with hepatocellular carcinoma. Validation and ranking of established staging-systems in a large western HCC-cohort. PLoS One 2012;7:e45066.
23. Zhang JF, Shu ZJ, Xie CY et al. Prognosis of Unresectable Hepatocellular Carcinoma: Comparison of Seven Staging Systems (TNM, Okuda, BCLC, CLIP, CUPI, JIS, CIS) in a Chinese Cohort. PLoS One 2014;9:e88182.
24. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
25. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996;32:1135-41.
26. Jiang ZB, Shan H, Shen XY et al. Transjugular intrahepatic portosystemic shunt for palliative treatment of portal hypertension secondary to portal vein tumor thrombosis. World J Gastroenterol 2004; 10:1881-4.
27. Guglielmi A, Ruzzenente A, Pachera S et al. Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. Am J Gastroenterol 2008;103:597-604.
28. Kondo K, Chijiiwa K, Nagano M et al. Comparison of seven prognostic staging systems in patients who undergo hepatectomy for hepatocellular carcinoma. Hepatogastroenterology 2007;54:1534-8.
29. Grieco A, Pompili M, Caminiti G et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: Comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. Gut 2005;54: 411-8.
30. Cillo U, Bassanello M, Vitale A et al. The critical issue of hepatocellular carcinoma prognostic classification: Which is the best tool available? J Hepatol 2004;40:124-31.