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Original Article

Comparison Between the CLIP and Okuda Staging Systems for Prediction of Survival Time of Patients with Hepatocellular Carcinoma in Eastern Taiwan

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Abstract

Objective: Prediction of the survival time for patients with hepatocellular carcinoma (HCC) by a clinical staging system could influence treatment planning. The aim of this study was to evaluate the predictive power of the Cancer of the Liver Italian Program (CLIP) and the Okuda staging system in the prognosis of patients with HCC in eastern Taiwan.

Materials and Methods: We performed a retrospective chart review of patients admitted from 1986 to 2000 with a diagnosis of HCC. Parameters for staging with the Okuda and CLIP systems were collected. The median survival time and 5-year survival curves were obtained using the Kaplan-Meier method. The discriminatory ability of the systems was also compared.

Results: A total of 342 cases were included in the study. The median survival time of patients at Okuda stage I (24.3% of patients), II (56.1%) and III (19.6%) was 16.8, 5.0 and 1.9 months, respectively. The respective 5-year survival rates were 19.0%, 5% and 0%. The median survival times of patients with CLIP scores of 0 (10.2% of patients), 1 (16.1%), 2 (23.1%), 3 (24.9%), 4 (15.2%), 5 (7.9%) and 6 (2.6%) were 32.7, 10.3, 6.7, 4.7, 2.5, 1.9 and 0.8 months, respectively. The respective 5-year survival rates were 23%, 14%, 10%, 1.1%, 0%, 0% and 0%. The CLIP classification showed more prominent discriminatory ability than the Okuda classification, as confirmed by statistical methods.

Conclusion: The CLIP system is more accurate in identifying patients at both extremes of better and worse prognoses than the Okuda classification, and can be used to stratify patients for prospective therapeutic trials for HCC in eastern Taiwan. (*Tzu Chi Med J* 2009;21(1):34–39)

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common cause of cancer death in Taiwan [1]. The global annual incidence and mortality are around half a million, making HCC the fifth most common human malignancy [2]. In clinical practice, patients with HCC have a poor prognosis despite recent advances in diagnosis and treatment [3]. Small lesions found in cancer screening programs are usually asymptomatic and can be treated with surgical resection, transplantation [3] or local ablation procedures [4,5]. However, HCC may invade hepatic blood vessels at relatively early stages, and the accompanying cirrhosis may compromise liver function and limit the safety of treatment procedures [6,7]. Thus the prognosis of patients with HCC is determined not only by tumor morphology, but also by vascular invasion and liver functional reserve.

An estimate of prognosis during the diagnosis period is important in the planning of treatment. An ideal staging system for estimation of prognosis should be simple, accurate, reproducible and inexpensive to implement, and should use objective parameters. The Okuda staging system for HCC has been used for many years [8], but factors like vascular invasion, and α-fetoprotein (AFP) levels are not considered, and new systems are therefore emerging [9–13]. Some systems which use parameters such as performance status are inaccurate and difficult to assess in retrospective studies because of interpersonal variation. After reviewing several recently developed prognosis indicator systems in the literature, the Cancer of the Liver Italian Program (CLIP) classification system [9] seemed to be most commonly used and suitable for a retrospective cohort.

HCC is a cancer with high mortality in eastern Taiwan [1]. The lack of reference data from a prognostic predictive system in this area makes clinical decisions for suitable treatment difficult. In this retrospective study, we analyzed our patients to validate the predictive value of the CLIP classification, and compared its discrimination power with that of the Okuda staging system.

2. Materials and methods

A computer search was done of the hospital records of inpatients who had been admitted with a main diagnosis of HCC from 1986 to 2000. A total of 493 cases were identified. Data collected included patient's age, sex, ethnic origin, social habits, laboratory results, diagnostic methods, hepatitis markers, imaging studies, treatment modalities, and outcome. The CLIP and Okuda classification variables are defined in Table 1. Patients who died during their first admission were also included. Patients with incomplete data for the CLIP (79 cases) and Okuda staging systems (72 cases) were excluded.

Survival status was queried by telephone contact with family members of the patients. Status was further verified using the National Death Certificate database, using national identification number, gender and birth date as linking variables. The date of December 31, 2001 was defined as the last census date in this study.

A total of 342 cases with complete data were included in the analysis. Median survival time and 5-year survival curves were obtained by the Kaplan-Meier method. The log-rank test was used to compare the survival rates of patients with different staging scores. Cox's proportional hazards regression was used to analyze the effect of both staging systems on the survival prediction. The likelihood ratio χ^2 test derived

Table 1 — Parameters of the CLIP and Okuda staging systems

Variables	CLIP system	Score	Okuda system	Score
Tumor morphology	Single nodule and ≤50% liver volume	0	≤50% liver volume	0
	Multiple nodules and ≤50% liver volume	1	>50% liver volume	1
	Massive or >50% liver volume	2		
Portal vein thrombosis	No	0		
	Yes	1		
AFP	≤400 ng/mL	0		
	>400 ng/mL	1		
Child-Pugh class	A	0		
	B	1		
	C	2		
Ascites			No	0
			Yes	1
Albumin			>3.0 g/dL	0
			≤3.0 g/dL	1
Bilirubin			≤3 mg/dL	0
			>3 mg/dL	1

CLIP = Cancer of the Liver Italian Program; AFP = α-fetoprotein. Okuda stage I = 0 points; II = 1–2 points; III = 3–4 points.

from analysis of the Cox regression model was used to determine the homogeneity (small differences in survival among cases in the same group of each system) [14]. The linear trend χ^2 test was used to measure the discriminatory ability of each staging system [15] and Akaike's information criterion was used to determine which was the more explanatory-informative system [16].

All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) for Windows, SPSS version 12 (SPSS Inc., Chicago, IL, USA) for Windows, and MedCalc version 9.3.7.0 (MedCalc Software, Mariakerke, Belgium) for Windows.

3. Results

The diagnosis of HCC was made by pathologic examinations in 17.2% of patients and by typical imaging findings, in addition to elevated AFP and clinical course in 82.8%. The clinical characteristics of 342 patients at diagnosis are described in Table 2. The median age at diagnosis was 47.6 years. The majority of patients were male. More than 60% of patients were HBsAg-seropositive, while around one third of patients were anti-HCV-seropositive. Most patients had accompanying liver cirrhosis. Our patients tended to present late in the course because more than half (53.5%) received no treatment.

The statistical analysis of patients according to the CLIP and Okuda prognostic systems for HCC and the Child-Pugh classification for liver cirrhosis (assessment of residual liver function) are shown in Table 3. The CLIP system delimits more subsets of patients with statistically significant differences in median survival times and survival rates than the Okuda system. The 5-year survival curves were plotted using the Kaplan-Meier method according to the CLIP (Fig. 1) or Okuda (Fig. 2) classifications.

To increase the discriminatory ability of the CLIP system, we merged cases with CLIP scores of 4, 5 and 6 in the same group for further statistical analysis. Cox's proportional hazards regression showed good survival prediction for both the CLIP and Okuda classifications (Table 4, Figs. 3 and 4). The CLIP staging system showed higher linear trends and homogeneity likelihood ratio χ^2 values and lower Akaike's information criterion value, confirming that the CLIP classification is statistically better than the Okuda system (Table 5).

Table 2 — Clinical characteristics of 342 patients on admission

	n (%)
Sex	
Female	60 (17.5)
Male	282 (82.5)
Age at diagnosis (yr)	
<60	152 (44.4)
≥60	190 (55.6)
Ethnicity	
Han Chinese	222 (71.4)
Taiwanese Aborigines	29 (9.3)
Unknown	60 (19.3)
HBsAg serostatus	
Negative	129 (37.7)
Positive	206 (60.2)
Unknown	7 (2.0)
Anti-HCV serostatus	
Negative	201 (58.8)
Positive	93 (27.2)
Unknown	48 (14.0)
α-fetoprotein	
0–12.5	76 (22.2)
12.6–400	98 (28.7)
>400	168 (49.1)
Cirrhosis	
No	58 (17.0)
Yes	284 (83.0)
Child-Pugh score	
A	144 (42.1)
B	139 (40.6)
C	59 (17.3)
Ascites	
No	228 (66.7)
Mild	63 (18.4)
Moderate or severe	51 (14.9)
Portal vein thrombosis	
No	247 (72.2)
Yes	95 (28.8)
Treatment	
None	183 (53.5)
Surgery	52 (15.2)
TACE	105 (30.7)
PEIT	41 (12.1)

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; TACE = transcatheter arterial chemoembolization; PEIT = percutaneous ethanol injection.

4. Discussion

HCC is prevalent in Asians because of the high prevalence of viral hepatitis [2,3]. It is the most common cause of cancer death in Taiwan [1]. In reviewing the clinical prognostic predicting systems in the literature, we found that the CLIP system seemed to be optimal. Similar results were confirmed for patients with HCC in eastern Taiwan. Assessment is easy in the CLIP system and it can be used to stratify patients into groups with identical scores to compare different treatment modalities in prospective studies.

In the past, the principal prognostic systems for HCC were the TNM (tumor, node, metastasis) and the Okuda systems, but limitations and criticisms have emerged, mainly related to the incomplete assessment of residual liver function and the lack of many prognostic

Table 3 — Survival of hepatocellular carcinoma patients according to CLIP or Okuda classifications

	n (%)	Median survival in months (95% CI)	Survival rate (%)				*p* of log-rank test
			6 mo	1 yr	3 yr	5 yr	
CLIP score							<0.0001
0	35 (10.2)	32.736 (11.934–44.669)	0.714	0.657	0.486	0.229	
1	55 (16.1)	10.298 (6.802–16.901)	0.673	0.473	0.236	0.139	
2	79 (23.1)	6.736 (4.504–10.628)	0.532	0.367	0.139	0.100	
3	85 (24.9)	4.727 (3.066–6.628)	0.435	0.247	0.059	0.011	
4	52 (15.2)	2.450 (1.769–3.496)	0.192	0.096	0.039	0.000	
5	27 (7.9)	1.934 (1.231–2.471)	0.185	0.111	0.037	0.000	
6	9 (2.6)	0.835 (0.331–1.562)	0.000	0.000	0.000	0.000	
Okuda stage							<0.0001
I	83 (24.3)	16.802 (10.298–27.231)	0.699	0.578	0.325	0.188	
II	192 (56.1)	4.967 (4.099–6.397)	0.453	0.271	0.104	0.052	
III	67 (19.6)	1.934 (1.207–2.231)	0.164	0.105	0.030	0.000	
Child-Pugh							<0.0001
A	144 (42.1)	8.603 (6.397–10.298)	0.611	0.396	0.215	0.131	
B	139 (40.6)	3.430 (2.636–5.000)	0.396	0.302	0.115	0.050	
C	59 (17.3)	1.934 (1.231–2.760)	0.220	0.136	0.034	0.000	
Overall	342 (100)	4.760 (4.000–6.132)	0.456	0.313	0.143	0.074	

CI = confidence interval; CLIP = Cancer of the Liver Italian Program.

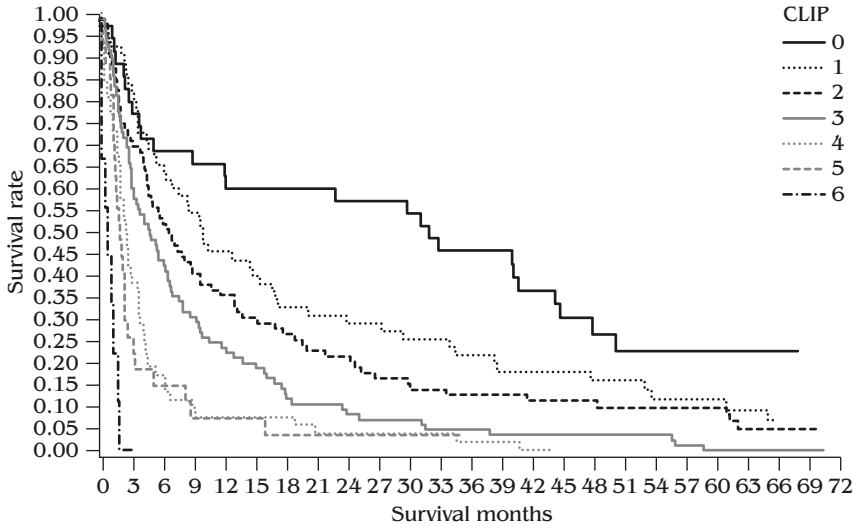

Fig. 1 — Survival curves of patients plotted using the Kaplan-Meier method according to Cancer of the Liver Italian Program (CLIP) scores.

factors [9–13,17–22]. New staging systems for HCC have been developed, including the CLIP (from Italy), the Barcelona Clinic Liver Cancer system (BCLC, Spain) [10], the French classification [11], the Chinese University Prognostic Index (CUPI, Hong Kong) [12] and the Japan Integrated Score (JIS, Japan) [23]. Each has been shown to have predictive power for HCC. These systems share common features of combined assessment of tumor burden with markers of liver function and the addition of many factors that are probably related to the survival time. The residual liver function at the time of diagnosis of HCC has been increasingly emphasized by most investigators. This was also confirmed by our study, demonstrating that the Child-Pugh classification can also predict the outcome of patients with HCC. However, the BCLC and French systems include subjective parameters, such as performance status, which increase interpersonal bias and are difficult to assess in a retrospective fashion. The CUPI and JIS systems include the TNM status, which is complicated, and the exact estimation can be impossible in patients who have not received surgical intervention [13,17].

The CLIP system, originally proposed by the Cancer of the Liver Italian Program, includes tumor characteristics, vascular invasion, and liver function reserve. It has been shown to have high discriminatory power in many retrospective studies [18–20]. Moreover, prospective studies have shown that CLIP is suitable for

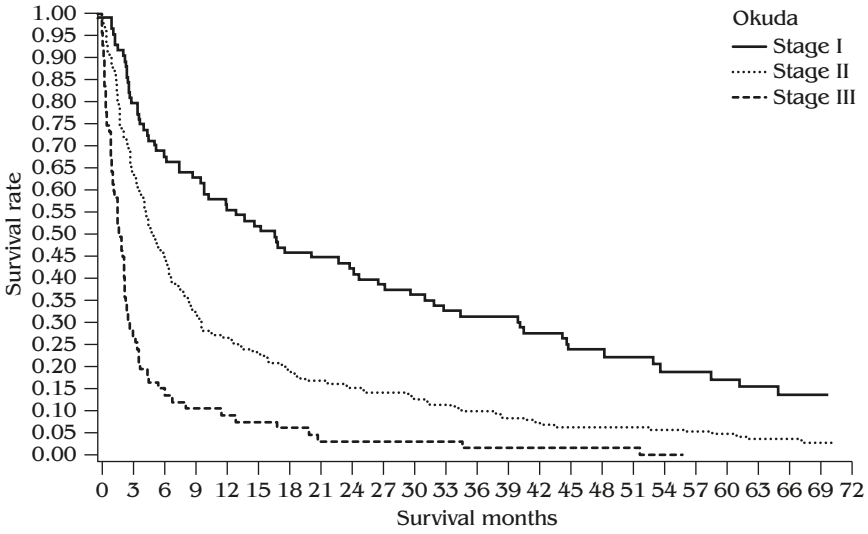

Fig. 2 — Survival curves of patients plotted using the Kaplan-Meier method according to the Okuda stages.

Table 4 — Survival prediction of hepatocellular carcinoma patients according to CLIP or Okuda classifications analyzed by Cox's proportional hazards regression

	Regression coefficient	SE	*p*	RR	95% CI
CLIP	0.4358	0.04815	0.0000	1.5462	1.4077–1.6985
Okuda	0.7083	0.08974	0.0000	2.0305	1.7046–2.4189

CLIP = Cancer of the Liver Italian Program, merging scores 4, 5 and 6; SE = standard error; RR = relative risk; CI = confidence interval.

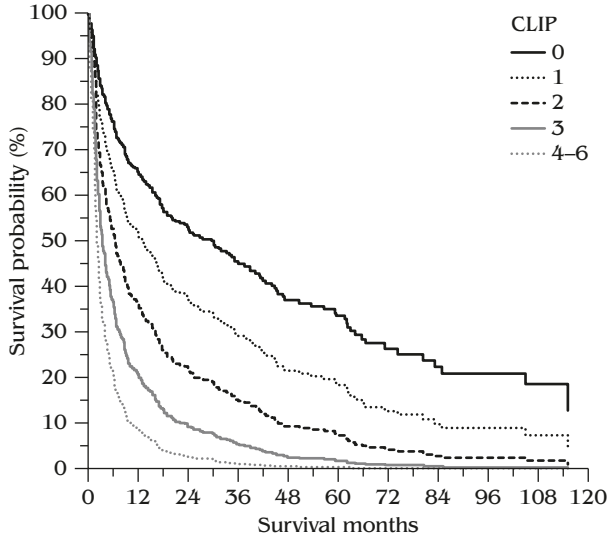

Fig. 3 — Survival probability curves of patients plotted using Cox's proportional hazards regression method according to Cancer of the Liver Italian Program (CLIP) scores, merging scores 4, 5 and 6.

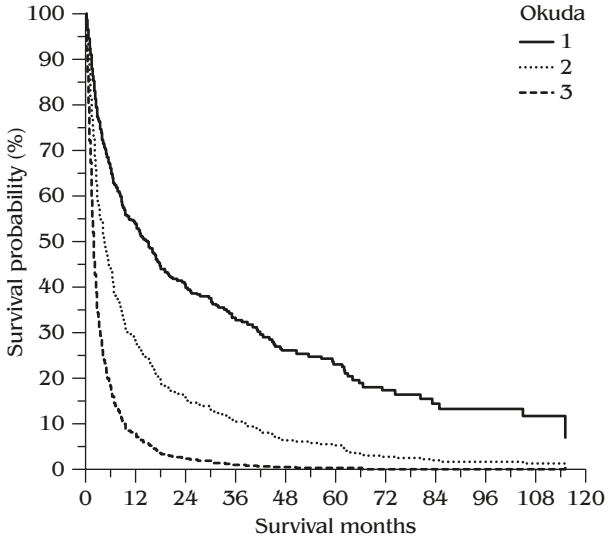

Fig. 4 — Survival probability curves of patients plotted using Cox's proportional hazards regression method according to the Okuda stages.

Table 5 — Comparison of the prognostic stratification* of CLIP and Okuda classifications

	Linear trend χ^2	Homogeneity likelihood ratio test	Akaike's information criterion
CLIP	77.0076	87.2844	3163.74749
Okuda	59.8840	62.0593	3188.97259

*Higher values of discriminatory ability linear trend χ^2 test and homogeneity likelihood ratio χ^2 test and lower value of Akaike's information criterion were associated with better prognostic stratification of the system. CLIP = Cancer of the Liver Italian Program, merging scores 4, 5 and 6.

identifying the prognosis of patients after surgery (23) and transcatheter arterial chemoembolization (24). A modified CLIP score using protein induced by vitamin K antagonist II (PIVKA-II), as proposed by Nanashima et al, showed a better discrimination ability for patient survival (23), but this marker is not universally available or accepted.

Although only a fraction of patients in our study had pathologically proven HCC, most of our patients had typical clinical presentations, compatible imaging findings and elevated AFP levels. The apparently poorer outcomes of our patients probably occurred because we included many patients who died soon after diagnosis, which may be due to inefficient cancer screening efforts and policies. In addition, because percutaneous ethanol injection therapy and radiofrequency ablation can be performed on an outpatient basis (4,5), many patients with smaller tumors were not included in this chart review of inpatients.

The results of our study showed accuracy and predictive power of the CLIP system which were comparable with previous retrospective studies (9,18,19). The CLIP prognosis prediction system can be used to stratify patients diagnosed with HCC in eastern Taiwan for prospective therapeutic trials.

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