Research Article

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Prognosis of hepatocellular carcinoma: Assessment of eleven staging systems

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Background & Aims: Multiple staging systems have been proposed for hepatocellular carcinoma (HCC). However there is no consensus regarding which system provides the best prognostic accuracy. We aimed to investigate the performance of 11 currently used HCC staging systems.

Methods: Between 2002 and 2013, a large prospective dataset of 3182 HCC patients were enrolled. The baseline characteristics and staging information were collected. Independent predictors of survival were identified. Homogeneity and corrected Akaike information criterion (AICc) were compared between each system.

Results: The median follow-up duration was 17 months. Independent predictors of adverse outcome were serum albumin <3.5 g/dl, bilirubin ⩾1 mg/dl, creatinine ⩾1 mg/dl, alpha-fetoprotein ⩾20 ng/ml, alkaline phosphatase ⩾200 IU/L, presence of ascites, multiple tumor nodules, maximal tumor size >5 cm, presence of vascular invasion, presence of extrahepatic metastasis, and poor performance status (all p <0.001). Significant differences in survival were found across all stages of the 11 systems except between Hong Kong Liver Cancer stage IV and V, Japan Integrated Staging score 4 and 5, and Tokyo score 5 through 8. The Cancer of the Liver Italian Program (CLIP) score was associated with the highest homogeneity and lowest AICc value in the entire cohort. In subgroup analysis, the CLIP score was also superior in patients with hepatitis B- or hepatitis C-related HCC and in patients receiving curative or non-curative treatments.

Conclusions: The CLIP staging system is stable and consistently the best prognostic model in all patients and in patients with different viral etiology and treatment strategy.

Keywords: Hepatocellular carcinoma; Treatment strategy; Staging system; Prognosis.

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; AIC, Akaike information criterion; AICc, corrected Akaike information criterion; AJCC, American Joint Committee on Cancer; Alk-P, alkaline phosphatase; BCLC, Barcelona Clínic Liver Cancer; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; CUPI, Chinese University Prognostic Index; EASL, European Association for the Study of the Liver; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HKLC, Hong Kong Liver Cancer; HR, hazard ratio; INR, International normalized ratio; JIS, Japan Integrated Staging; LCSGJ, Liver Cancer Study Group of Japan; MELD, Model for End-stage Liver Disease; PT, prothrombin time; SD, standard deviation; TACE, transarterial chemoembolization; TIS, Taipei Integrated Scoring System; TNM, Tumor-Node-Metastasis.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality, accounting for more than 700,000 deaths each year [1]. The highest incidence rates of HCC are reported in Southeast Asia and sub-Saharan Africa where hepatitis B virus (HBV) infection is endemic. The incidence of HCC in the United States has also tripled in the past two decades due to chronic hepatitis C virus (HCV) infection [2]. In contrast to other malignancies, the management and prognosis of HCC depend not only on the tumor burden alone but also on patient's underlying liver functional reserve [3]. Identifying important clinical predictors is crucial in developing a robust staging system to fight against this growing global health burden.

The key predictors of prognosis in HCC patients include severity of liver dysfunction, tumor extent, overall health status and treatment modality [4]. The Barcelona Clínic Liver Cancer (BCLC) staging system incorporates these key factors and includes treatment suggestions for different stages [5]. The BCLC system has been integrated in the current American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) HCC management guidelines [6,7]. The recently proposed Hong Kong Liver Cancer (HKLC) staging system offers better prognostic ability and a more aggressive treatment algorithm compared with BCLC system [8]. However, the capability of HKLC in a European cohort has been challenged [9].

Table 1. Components of eleven staging systems for hepatocellular carcinoma.

Staging systems	Liver function	Performance status (Symptoms)	AFP	Tumor status				Other
				Number	Size	Vascular invasion	Metastasis	
BCLC	CTP class	Performance status	No	Yes	Yes	Yes	Yes	
HKLC	CTP class	Performance status	No	Yes	Yes	Yes	Yes	
CLIP	CTP class	No	Yes	Yes	Yes	Yes	No	
TIS	CTP class	No	Yes	Total tumor volume		No	No	
JIS	CTP class	No	No	Yes	Yes	Yes	Yes	
Tokyo	Albumin, bilirubin	No	No	Yes	Yes	No	No	
AJCC TNM-7	No	No	No	Yes	Yes	Yes	Yes	
TNM by LCSGJ	No	No	No	Yes	Yes	Yes	Yes	
Okuda	Ascites, albumin, bilirubin	No	No	No	Yes	No	No	
CUPI	Ascites, bilirubin	Symptoms	Yes	Yes	Yes	Yes	Yes	Alk-P
French	Bilirubin	Karnofsky scale	Yes	No	No	Yes	No	Alk-P

AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; Alk-P, alkaline phosphatase; BCLC, Barcelona Clínic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; CUPI, Chinese University Prognostic Index; HKLC, Hong Kong Liver Cancer; JIS, Japan Integrated Staging; LCSGJ, Liver Cancer Study Group of Japan; TIS, Taipei Integrated Scoring System; TNM, Tumor-Node-Metastasis.

Besides the BCLC and HKLC systems, multiple staging systems were proposed without the ability to guide treatment decisions directly. These systems generally claimed to have superior prognostic performance. To date, at least 11 prognostic models have been proposed (Table 1) [10–19]. The pursuits of an optimal staging system for HCC have resulted in heated debates for the past two decades [20]. This lack of consensus may stem from heterogeneity of underlying liver diseases as well as diverse preferences of treatment modalities worldwide [3]. The absence of a consensus on cancer staging may further hinder clinical researches from adequate disease control. In this study, we aimed to identify independent predictors of survival and to compare the prognostic abilities of the 11 existing HCC staging systems.

Patients and methods

Patients

Patients with newly diagnosed HCC admitted to Taipei Veterans General Hospital during more than a decade's period from 2002 to 2013 were retrospectively analyzed. Their baseline information, including demographics, etiologies of underlying liver disease, serum biochemistry, tumor extent, severity of liver cirrhosis and performance status was comprehensively recorded. Patients were followed every 3–6 months until death or dropout from the follow-up program. Recipients of liver transplantation were censored at time of transplantation. The study was approved by the Institutional Review Board of the Taipei Veterans General Hospital and complies with the standards of the Declaration of Helsinki and current ethical guidelines. Patient information was de-identified prior to investigation.

Diagnosis and definitions

The diagnosis of HCC was established according to the AASLD or EASL HCC management guidelines [6,7,21,22]. Staging of HCC was obtained when the diagnosis was confirmed. The staging information for HKLC, Chinese University Prognostic Index (CUPI), and French system was retrospectively determined after chart review [8,14,15]. Vascular invasion was defined as radiological evidence of tumor invasion to intrahepatic vasculatures, portal trunk or abdominal great vessels. Patients who were seropositive for anti-HCV antibody, seronegative for hepatitis B surface antigen (HBsAg), and had no history of alcoholism were classified as HCV-related HCC. HBV-related HCC was defined as seropositive for HBsAg, seronegative for anti-HCV, and without history of alcoholism [23].

Treatment

Patients were reviewed at multi-disciplinary HCC board of Taipei Veterans General Hospital when the diagnosis was confirmed. Information about therapeutic risks and benefits was provided to individual patients. Share-decisions were made between physicians and patients. Written informed consent was obtained prior to initiation of any definite treatment. Radiofrequency ablation, surgical resection, and transarterial chemoembolization were performed under standard procedures as previously described [24–26]. Resection, ablation, and liver transplantation are classified as treatments with curative intents. Other managements are labeled as non-curative treatments.

Statistics

Before survival analysis, the proportionality assumption was assessed graphically and by a test based on Schoenfeld residuals. The Cox proportional hazards model was performed if proportionality assumption was not violated. Parametric survival analysis was employed when proportionality was rejected [27]. Prognostic factors that were possibly linked to overall survival, including sex, severity and etiology of chronic liver diseases, performance status, laboratory parameters and tumoral status were comprehensively included in survival analysis. Continuous variables were dichotomized by the median value for survival analysis with guidance by clinical judgement.

The survival distributions of each staging system were examined by the Kaplan-Meier methods with log-rank tests. Corrected Akaike information criterion (AICc) was obtained to reveal how staging system correlated with patient survival. The AICc was chosen over Akaike information criterion (AIC) to compensate for the different number of parameters in each staging system. Homogeneity was measured by χ^2 test to evaluate the differences in survival among patients in the same stage within each system [28].

Missing values were handled by multiple imputation while a complete case analysis was used as benchmark analysis [29]. Two-tailed χ^2 test and Fisher's exact test was employed to compare categorical data. The Mann-Whitney *U* test was used to evaluate continuous variables. Statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., NC) and IBM SPSS version 21 (IBM, NY). Statistical significance was set as p value less than 0.05 in a two-tailed test.

Results

Patient characteristics and overall survival

A prospective dataset of 3182 patients were enrolled. Baseline demographics and clinical information of these patients are shown in Table 2. The median age was 65 years, with the major-