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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Barcelona clinic liver cancer nomogram and others staging/scoring systems in a French hepatocellular carcinoma cohort

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Abstract

AIM
To compare the performances of the Barcelona clinic liver cancer (BCLC) nomogram and others systems (BCLC, HKLC, CLIP, NIACE) for survival prediction in a large hepatocellular carcinoma (HCC) French cohort.

METHODS
Data were collected retrospectively from 01/2007 to 12/2013 in five French centers. Newly diagnosed HCC patients were analyzed. The discriminatory ability, homogeneity ability, prognostic stratification ability Akaike information criterion (AIC) and C-index were compared among scoring systems.

RESULTS
The cohort included 1102 patients, mostly men, median age 68 [60-74] years with cirrhosis (81%), child-Pugh A (73%), alcohol-related (41%), HCV-related (27%). HCC were multinodular (59%) and vascular invasion was present in 41% of cases. At time of HCC diagnosis BCLC stages were A (17%), B (16%), C (60%) and D (7%). First line HCC treatment was curative in 23.5%, palliative in 59.5%, BSC in 17% of our population. Median OS was 10.8 mo [4.9-28.0]. Each system distinguished different survival prognosis groups ($P < 0.0001$). The nomogram had the highest discriminatory ability, the highest C-index value. NIACE score had the lowest AIC value. The nomogram distinguished sixteen different prognosis groups. By classifying unifocal large HCC into tumor burden 1, the nomogram was less powerful.

CONCLUSION
In this French cohort, the BCLC nomogram and the NIACE score provided the best prognostic information, but the NIACE could even help treatment strategies.

Key words: Barcelona clinical liver cancer; Hong kong liver cancer; NIACE; CLIP; Hepatocellular carcinoma

Core tip: Barcelona clinic liver cancer (BCLC) nomogram was compared with BCLC, HKLC systems, CLIP, and NIACE scores for survival prediction in a HCC French cohort. 1102 patients were retrospectively included, with cirrhosis (81%), child-Pugh A (73%). Hepatocellular carcinoma (HCC) were multinodular (59%) and with vascular invasion (41%). At time of HCC diagnosis, patients were mainly BCLC-C (60%). First line HCC treatment was curative (23.5%) or palliative (59.5%). Median OS was 10.8 mo [4.9-28.0]. BCLC nomogram had the highest discriminatory ability, the highest C-index value. NIACE score had the lowest akaike information criterion value. In this French cohort, BCLC nomogram and NIACE score provided the best prognostic information.

INTRODUCTION

Survival prediction and therapeutic strategy for hepatocellular carcinoma (HCC) are based on Barcelona classification of liver cancer staging system (BCLC) in the West[1,2]. It has become the reference classification by its prognostic value, its simplicity, and its treatment algorithm based on randomized clinical studies[3]. However, HCC staging systems remain a controversial issue. Asian countries, in which HCC is mainly related to HBV, have their own staging systems and therapeutic recommendations[4]. The BCLC system has been criticized; the major issue is that stages B and C HCC include a broad spectrum of tumors with a single therapeutic option[5-7], and for some authors other treatments are possible[8-11]. Subsequently, changes have been made compared to the initial version of the BCLC system[12] with the transfer of single and large HCC > 50 mm from intermediate to early stages[3], enhancing the heterogeneity within this group[13]. Older scores such as CLIP[14] showed a better prognostic value than the BCLC system in large Asian and Western HCC cohorts[15,16]. Therefore, a new classification has been proposed, the HKLC system[17], which offers another stratification, and new therapeutic proposals with surgery and chemoembolization to treat more advanced HCC. Other scores, independent of the BCLC system[7,18,19] or additional to the BCLC system[20,21] have been proposed in recent years. NIACE score (tumor Nodularity, Infiltrative nature of the tumor, serum Alpha-fetoprotein level, Child-Pugh stage, ECOG performance status)[22] determines subgroups of different survival prognosis irrespective of the BCLC stage[23], or HCC treatment modalities[24]. This score has been validated either in European or Asian cohorts[25,26]. Recently, Hsu *et al*[27] proposed a simple nomogram, determined from a large HCC cohort mainly related to HBV in order to improve the prognostic value of the BCLC system.

The aims of this study were to assess and compare the performances of the BCLC nomogram and others staging and scoring systems (BCLC, HKLC, CLIP and NIACE) for survival prediction in a large European multicenter HCC cohort.

MATERIALS AND METHODS

This retrospective study was conducted in five French centers (Marseille, Nancy, Bordeaux, and Rennes). During a period of seven years, from January 2007 to December 2013, all HCC patients treated or not, have been included in this study.

HCC diagnosis was based on the identification of the typical hallmark of HCC (EASL - AASLD criteria)[28] and, if a patient did not have a typical HCC on imaging or a cirrhotic liver, or if there was discordant results between non-invasive criteria (such as fibrometer and fibroscan), a biopsy was required. The analyzed data (clinical, biological, radiological, therapeutic options, response to treatment and follow-up) were prospectively collected and retrospectively analyzed using the same methodology in the different centers. This study was approved by local ethics committee.

HCC were ranked at diagnosis and during follow-up according to their morphologies (nodular or infiltrative HCC) assessed by multi-sliced contrast-enhanced CT and/or MRI. Liver cancers were either nodular HCC, that is an arterially enhancing mass with clear demarcation and washout in the portal venous phase, or infiltrative HCC, that is an ill-defined tumor with no distinct margination of any portion, characterized by inhomogeneous areas of enhancement on the arterial phase images and corresponding areas of washout on more delayed phases of contrast enhancement. These tumors may be more visible among the surrounding liver parenchyma at diffusion- and T2- weighted MR images and are frequently associated with vascular invasion[29-32]. Early (BCLC A) and intermediate (BCLC B) HCC without vascular invasion, considered as infiltrative tumor as opposed to encapsulated tumors, were tumor with non-smooth tumor margins (*i.e.,* tumor with focal extranodular extension beyond the tumor capsule or focal infiltrative margin), or those with peritumoral enhancement[33-35], or those associated with biliary dilatation. Two liver imaging "senior experts" radiologists reviewed images retrospectively.

Patients' classification according to staging and scoring systems

Following categories were used for the BCLC classification: BCLC A HCC was defined as patients having solitary tumor > 2 cm or no more than 3 tumors not exceeding 3 cm in diameter, PS 0, Child-Pugh grade A or B.

BCLC B HCC encompassed patients with multiple tumors beyond 3 cm, PS 0, Child-Pugh grade A or B.

BCLC C encompassed any tumor with radiologically evident or histologically proven macrovascular invasion (portal vein, hepatic vein, inferior vena cava) and/or patients with lymph nodes and/or distant metastases and/or patients with cancer related - symptoms, with preserved liver function.

BCLC D encompassed tumors leading to a very poor performance status (PS 3-4), or patients with severe liver impairment (Child-Pugh B9 grade) and tumors beyond the transplantation threshold. Child-Pugh C patients were excluded because the NIACE score did not incorporate Child-Pugh C grade.

The HKLC classification, the CLIP score and the BCLC nomogram were applied to each patient before treatments initiation.

The NIACE score was calculated with all parameters collected before treatments initiation, as follows: 1x (Nodular numbers 0 if < 3, 1 if ≥ 3) + 1.5x (Infiltrating tumors: 0 if no, 1 if yes) + 1.5x (Alpha-fetoprotein level: 0 if < 200, 1 if ≥ 200 ng/mL) + 1.5x (Child-Pugh grade: 0 if A, 1 if B) + 1.5x (ECOG PS score 0 if 0, 1 if ≥ 1).

Treatments

Treatment and follow-up modalities were applied similarly in all centers.

Surgery: In general, patients with resectable tumors were selected for surgery if they had a performance status of 0 with both Child-Pugh grade A or B7, and on the basis of their functional hepatic reserve (indocyanine green retention rate at 15 min < 15%) and on the estimated remnant liver volume, regardless of HCC morphologies. Our protocols for the assessment of FHR and determination of surgical extent include biochemical liver function tests, blood cell count, IGR R15, and triphasic liver CT with volumetry. Gastroesophageal endoscopic findings were also taken into consideration for cirrhotic livers.

Patients without clinically significant portal hypertension and with normal serum bilirubin value were first considered for resection. Patients who underwent surgery *vs* radiofrequency ablation were as expected younger with less cirrhosis and larger tumor size. In cirrhosis, candidates for resection were carefully selected to diminish the risk of post-operative liver failure[36]. Portal hypertension (presence of either esophageal varices (EV), or splenomegaly with platelet count below 100000/mm^3) was considered as a contraindication for liver resection, but in BCLC A HCC patients with well-preserved liver function, and IGR at 15 min < 15%, not suitable for radiofrequency ablation (RFA) or transplantation, a minor hepatic resection was proposed[37-39]. Surgery was made after endoscopic treatment of EV.

Some BCLC C HCC patients were selected for hepatectomy according to the following selection criteria: PS 0, Child-Pugh A with bilirubin level ≤ 1.0 mg/dL, single nodule with limited portal vein thrombosis (*i.e.,* with second-order branch and third-order branch)[8].

Radiofrequency ablation: Applied in patients with resectable tumor ≤ 50 mm of diameter or within the Milan criteria (single tumor ≤ 50 mm or up to three

tumors ≤ 30 mm in diameter).

Patients who underwent both radiofrequency ablation and chemoembolization *vs* radiofrequency ablation alone had larger tumor size.

Chemoembolization: Multinodular HCC with enhancing lesions, PS 0, Child-Pugh grade A or B7, were treated by TACE, regardless of HCC morphologies. Patients were treated by conventional TACE using the same inclusion/exclusion criteria in the different centers. TACE (Trans Arterial Chemoembolization) was performed in a standard fashion with a selective injection of a mixture of epirubicin (50 mg) and lipiodol (10 mL), followed by embolization with Gelfoam fragments. A second TACE was carried out 6 to 8 weeks later unless clear progress or serious adverse events occurred. Other TACE procedures were planned "on demand", according to the results of radiological and AFP assessments made every 12 wk. The EASL criteria, based on a bi-dimensional measurement of the tumor's enhanced viable component, were used to evaluate tumor response[40,41].

Patients with segmental vein thrombosis were left in the analysis because, in most centers, this is not considered as a contraindication for TACE[42,43].

Patients excluded from this retrospective analysis were: patients who received TACE as a bridge for liver transplantation; Child-Pugh C patients, and patients treated by liver transplantation.

Sorafenib
The initial sorafenib dose was determined according to different factors, such as Eastern Cooperative Oncology Group Performance Status and liver function. Child-Pugh A patients received 400 mg twice a day and Child-Pugh B patients 200 mg, twice a day. A reduction in the sorafenib dose or a temporary interruption was allowed, depending on the type and severity of any adverse event (grade 2 or higher on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0). Sorafenib treatment was continued unless intolerable toxicity or clinical disease progression was observed. CT and/or MRI were used to evaluate the tumor response every 3 mo.

Patients had received Sorafenib since 2008; fifty six patients had received other palliative treatments before 2008 including tamoxifen or pravastatin (*n* = 23), or chemotherapy with doxorubicin (*n* = 20), and others drugs in clinical trials (*n* = 13).

Statistical analysis
Continuous data are expressed as median [quartile 1 - quartile 3] and categorical data are expressed as rates. Normality of the data was assessed by Shapiro-Wilks test. Overall survival was the endpoint used. The time of survival was defined as the time interval between the diagnosis of hepatocellular carcinoma and death or time of last follow-up. Proportionality of the subdistribution hazards was assessed by both inspecting Schoenfeld-type residuals and testing correlation of these residuals with time[44]. In case of proportionality of hazards across time, survivals between groups were compared using log-rank test; generalized Wilcoxon test was used in case on non-proportionality of hazards[45]. Discriminatory ability of each staging system was performed using χ^2 linear trend test (LT) and the Akaike information criteria (AIC): the higher is the LT and the lower is the AIC, the higher is the discriminatory ability of the model. Homogeneity of each staging system was performed using likelihood ratio (LR) calculated using the Cox regression model: the higher de LR, the lower is the difference among the patients classified into the same group by each staging system. The C-index was also used to determine the performance of the model. The larger the C-index, the more accurate the prognostic prediction was[46]. All p-values were considered significant at α-level = 0.05. All calculations were performed using the SAS V9.1 statistical software (SAS Institute Inc. Cary, NC).

RESULTS

Patient characteristics
Patients' characteristics are indicated in Table 1. The cohort included a total of 1102 patients, the majority of patients were male (86%) and the median age was 68 [60-74] years. Cirrhosis was present in 81% of patients; 73% of them were ranked Child-Pugh grade A. Underlying liver disease was related to alcohol in 41% of the patients, and to viral C hepatitis in 27% of the patients. HCC were multinodular in 59% of the cases and 43% of the patients had at least three nodules. Portal vein thrombosis was present in 41% of the cases, and 43% of HCCs were infiltrating tumors. Baseline ECOG performance status of our population (as expression of symptomatic tumor) was as follows: PS 0 (50%), PS 1-2 (46%), PS 3-4 (4%).

The stratification of patients according to the BCLC system was as follows: BCLC A (17%), BCLC B (16%), BCLC C (60%), and BCLC D (7%).

The primary anti-cancer treatments of patients are shown in Figure 1 and Table 1. twenty-three point five percent of the patients received treatments of curative intent (surgery, RFA ± TACE), while 59.5% of the patients received a palliative treatment (TACE, sorafenib, others systemic treatments) and 17% only best supportive care.

Survival analysis and stage-specific survival
Median overall survival for the entire cohort was 10.8 mo [4.9-28.0], consistent with the median follow-up duration: 10 mo [4.4-22.7]. Eighty-two percent of patients died. Median overall survival according to the BCLC system was as follows: BCLC A 43 mo [36-57],

Figure 1 Flow diagram shows the patient selection criteria. BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; PS: Performance status; TACE: Trans arterial chemoembolization.

Table 1 Patients' characteristics at diagnosis (*n* = 1102) and first hepatocellular carcinoma recorded treatment *n* (%)	
	All patients (*n* = 1102)
Age - Median (Q1-Q3), yr	68 (60-74)
Gender	
Male/Female	943 (86)/159 (14)
Liver disease	
Alcoholism/HCV/HBV/MS/Other	452 (41)/297 (27)/66 (6)/99 (9)/188 (17)
Cirrhosis	895 (81)
Child - Pugh grade	
A/B	653 (73)/242 (27)
Tumor Size (Q1-Q3) mm	43 (20-75)
Multifocal	654 (59)
Nodules	
< 3/⩾ 3	633 (57)/469 (43)
Portal vein thrombosis	452 (41)
Infiltrative HCC	469 (43)
AFP - Median [Q1-Q3], ng/mL	53 (7-1300)
ECOG (PS)	
0/1-2/3-4	553 (50)/506 (46)/43 (4)
BCLC stage	
A/B/C/D	187 (17)/177 (16)/658 (60)/80 (7)
Treatment allocation	
Resection/RFA ± TACE	259 (23.5)
TACE	260 (23.5)
Sorafenib	342 (31)
Other palliative treatments	56 (5)
Supportive care	185 (17)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; MS: Metabolic syndrome; AFP: Alpha-foetoprotein; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BCLC: Barcelona Clinic Liver Cancer; RFA: Radiofrequency ablation; TACE: Trans arterial chemoembolization.

BCLC B 19 mo [17-23], BCLC C 8 mo [7-9] and BCLC D 2 mo [2-3] (*P* (Log-Rank) < 0.0001) (Figure 2A).

The HKLC system differentiated within this cohort between nine subgroups with median overall survival ranging from 43 [36-55] mo for the HKLC group 1 to 3 [2-4] mo for the HKLC group 5b, *P* (Wilcoxon) < 0.0001. However, several subgroups (Ⅱa/Ⅱb, Ⅲb/Ⅳa, Ⅳb/Ⅴb) had a similar overall survival (Figure 3).

The CLIP and NIACE scores differentiated within this cohort seven and ten subgroups respectively with a different prognosis, *P* (Wilcoxon) < 0.0001 (Figure 3). CLIP scores ranked 74% of the patients in the first three groups (0 - 1 - 2): 19%, 30% and 25%, respectively. The distribution of patients in the ten subgroups from the NIACE score was more homogeneous (NIACE 0: 14%, 1: 8%, 1.5: 16%, 2.5: 11%, 3: 17%, 4: 12%, 4.5: 9%, 5.5: 8%, 6: 2% and NIACE 7: 3%).

The nomogram values within the cohort are shown in the Figure 4. In summary, the nomogram distinguished sixteen subgroups. Analysis of survival time based on nomogram BCLC values showed a significant difference, *P* (Wilcoxon) < 0.0001, survival time decreased with increasing nomogram values.

Comparison of predictive accuracy for overall survival between the nomogram and the conventional staging and scoring systems
Performances of the nomogram and other staging and scoring systems for survival prediction are indicated in Table 2. The C-index of the nomogram for predicting overall

Table 2 Comparison of predictive accuracy for overall survival between the nomogram and the conventional staging and scoring systems (Barcelona clinic liver cancer, HKLC, CLIP, NIACE)

Score	Discriminatory ability linear trend test		Homogeneity likelihood ratio test		Akaike information criterion	C-index
	LT (χ^2)	*P* value	LR (χ^2)	*P* value		
BCLC Nomogram	93.2169	< 0.0001	500.7218	< 0.0001	10679.513	0.719
NIACE	91.6906	< 0.0001	532.0369	< 0.0001	10648.198	0.718
BCLC	79.0342	< 0.0001	380.4100	< 0.0001	10805.825	0.674
HKLC	71.8861	< 0.0001	455.3169	< 0.0001	10740.918	0.698
CLIP	87.2785	< 0.0001	430.3872	< 0.0001	10749.848	0.716
Nomogram according to BCLC last version	86.1320	< 0.0001	417.4356	< 0.0001	10762.799	0.698

BCLC last version transfer single and large HCC > 50 mm from intermediate to early stages[3]. BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma.

Figure 2 Kaplan-Meier estimated survival curves stratified according to Barcelona clinic liver cancer stages (A) or to Barcelona clinic liver cancer nomogram stratified in 5 classes (0-5), (5-10), (10-15), (15-19), (≥ 20) (B).

survival was 0.719, significantly higher than the BCLC system (0.674), the HKLC system (0.698). The nomogram yielded a higher discriminative ability (LT (χ^2) = 93.2169) than the other systems. The likelihood ratio test showed that the nomogram had an additional homogeneity of survival within each score (500.7218) close to the best value produced by the NIACE score (532.0369), and higher than other systems. Moreover, the nomogram was associated with a lower corrected Akaike information criterion (10679.513) compared with the other systems and close to the best value produced by the NIACE score (10648.198).

DISCUSSION

Our findings indicate that the nomogram has a good stratification ability with regard to prognosis in patients with HCC, within a European HCC cohort, mostly BCLC-C[47,48] compared to other known staging and scoring systems (BCLC, HKLC systems, CLIP score). By specifying the magnitude of each variable within the BCLC system (tumor burden, liver function, general conditions), the nomogram can better predict the survival of patients with HCC. In previous studies, CLIP and NIACE scores showed a better predictive value for survival compared to other staging and scoring systems within two large Asian and European HCC cohorts[15,25,26].

In our study the CLIP score also distinguished between subgroups with significantly different survival, but the majority of patients (74%) were in the first three groups (CLIP 0, 1 and 2), as previously described[15,49,50], limiting its discriminatory capacity.

The HKLC classification proposes another stratification with five groups and nine subgroups in order to enhance prognostic accuracy for HCC; the early stages (Ⅰ, Ⅱa) include BCLC A and B HCC patients, the intermediate stages (Ⅱb, Ⅲa) include BCLC A, B and C HCC patients and the locally advanced stages (Ⅲb) include BCLC B and C HCC patients. Despite a greater number of subgroups, some of them had the same survival (Ⅱa/Ⅱb, Ⅲb/Ⅳa and Ⅳb/Ⅴb), as previously reported[51], reducing the usefulness of this new classification in a European cohort.

The nomogram showed a higher predictive power for survival within this external European cohort, but there is still some issue. The nomogram is a reliable predictor of survival for patients with HCC, however this nomogram is complex ranging from 0 to 26 points and in our cohort, it distinguished sixteen subgroups. Moreover, it doesn't help clinicians in treatment decision. A simplified stratification into five sub-groups is possible: [0-5], [5-10], [10-15], [15-19], and [≥ 20]; the survival time observed in our cohort was respectively: 35 [30-38] mo, 12 [10-16] mo, 9 [8-10] mo, 4 [3-4] mo, and 2 [2-3] mo, *P* < 0.0001 (Figure 2B). These results should be validated, or other thresholds may be suggested by a specific analysis.

There is another issue with the nomogram after

Figure 3 Overall survival Histograms according to HKLC staging system, CLIP score and NIACE score in our hepatocellular carcinoma cohort.

the adoption of changes in the BCLC system[3], which could affect its discriminatory capacity. Single and large tumors (> 50 mm) were included into the BCLC A group; therefore, they should logically be included in the tumor burden grade 1 and not 2. By applying this rule, the predictive value of the nomogram became lower (c-index: 0.698 *vs* 0.719) (Table 2).

In addition, the prognostic accuracy of the nomogram and the NIACE are close within this cohort. However, NIACE score is not only an additional prognostic score to the BCLC system[22,26], but it can be used as an aid to the decision-making process, distinguishing different prognostic groups among patients treated by surgery or those treated by TACE

or Sorafenib[22,24]. The combination of classification plus scores (BCLC and NIACE) have already showed an additional value for treatment recommendation in a retrospective cohort and prospective validation study should be designed[52].

There are several limitations of the present study including the retrospective study design, its multicenter nature, which may make bias unavoidable. Regarding treatment decision, BCLC treatment recommendations are seldom followed due to great heterogeneity within each stage[48,53,54]. In our study, 33% of patients received treatment outside BCLC recommendations [14% of BCLC A HCC patients (*n* = 27), 28% of BCLC B HCC patients (*n* = 49), and 40% of BCLC C HCC

Performance Status (PS) 3-4: 6.7 points, PS 1-2: 3 points
Child-Pugh-Turcotte CPT C: 8.9 points, CPT B: 5.2 points
Tumor burden (TB) grade 3: 10 points, TB grade 2: 3.7 points, TB grade 1: 1.2 points

Figure 4 Survival time in months according to hepatocellular carcinoma nomogram. Hsu *et al*[27] in our hepatocellular carcinoma cohort.

patients (*n* = 227)]. sixty-two percent of patients undergoing surgery or RFA were ranked as BCLC A HCC, 43% of patients treated by TACE were ranked as BCLC B HCC, and 40% of treated BCLC C patients received a first-line treatment other than sorafenib. Our cohort mainly included advanced HCC, that is a heterogeneous population with limited therapeutic option until now, namely sorafenib with modest survival benefit[55] or inclusion in randomized trials who do not reflect patients in daily clinical practice. In our study like others[56-59] impairment of liver function is the major factors that preclude patient to receive sorafenib. Moreover BCLC-C patients before sorafenib availability have received others non-valuable treatment. Each BCLC stage including a broad spectrum of tumors, a proportion of patients in each stage do not fulfill all the criteria for the treatment allocation, and for some authors other therapeutic options are possible[8,54,60,61]. Therefore treatment recommendations based on new combination of BCLC and scoring systems such as NIACE or other are urgently required.

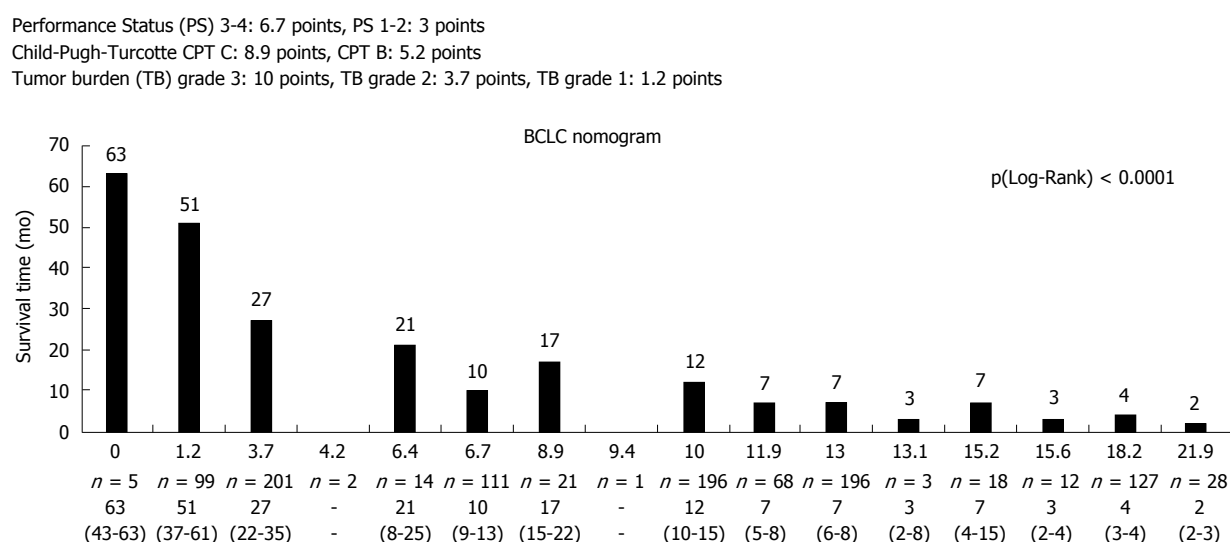In summary, this study confirms the BCLC nomogram as a new HCC reliable prognostic tool; its predictive value on survival is higher compared to known classifications and scoring system. However, the usefulness of this nomogram is limited due to its complexity and the fact that it is not linked to a therapeutic strategy. BCLC system remains the most widely used staging system, however BCLC treatment recommendations are seldom followed suggesting the need for better tools.

COMMENTS

Background
Hepatocellular carcinoma (HCC) prognosis is still a controversial issue. Barcelona Clinic Liver Cancer staging system has limits [heterogeneity of the Barcelona clinic liver cancer (BCLC) subgroups, strict therapeutic algorithm]. Using a nomogram as proposed by Hsu *et al* to improve BCLC system prognostic value is an attractive idea for clinicians.

Research frontiers
Hsu *et al* think that conferring value on each of the three main parameters of the BCLC system ie tumor burden, liver function and performance status (using a multivariate Cox regression model within a large Asian HCC cohort), could improve the individual prognosis of HCC patients. The authors think that prognosis and treatment of HCC should be associated. They assessed the reliability and the usefulness of the BCLC nomogram within a European cohort mainly related to alcohol abuse and HCV hepatitis.

Innovations and breakthroughs
This paper shows that the BCLC nomogram is a reliable tool for HCC prognosis, irrespective of the underlying liver disease, with a better predictive value for survival compared to other scoring or staging systems (CLIP, HKLC).

But its usefulness is limited by its complexity (tumor burden grade 3: 10 points, grade 2 and 1: 3.7 and 1.2 points; Child-Pugh grade C: 8.9 points, Child-Pugh grade B and A: 5.2 and 0 points; PS 3-4: 6.7 points, PS 1-2 and 0: 3 and 0 points) and the lack of therapeutic link. They Suggest an additional score (including other prognostic variables such as AFP serum level and/or tumor morphology) to the BCLC system in order to improve the prognostic information and the therapeutic decision.

Applications

BCLC nomogram provides reliable prognostic information for HCC patients, irrespective of underlying liver disease, but it doesn't guide the therapeutic decision. Conversely a combination of BCLC system and scores may influence HCC prognosis and its therapeutic management.

Terminology

NIACE score (tumor Nodularity, Infiltrative nature of the tumor, serum Alpha-fetoprotein level, Child-Pugh stage, ECOG performance status) determines sub-groups of different survival prognosis irrespective of the BCLC stage, or HCC treatment modalities.

Peer-review

The aim of this study is to compare the performances of several HCC staging systems including the BCLC nomogram in the prediction of survival of a large French HCC cohort. A total of 1102 HCC patients retrospectively recruited from 5 hospitals in different areas. The objective of this study is clear and the statistical studies were well done. The conclusion is logical and adequate.

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