



Retrospective Cohort Study

Comparison between hepatocellular carcinoma prognostic scores: A 10-year single-center experience and brief review of the current literature

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) represents the most common primitive liver malignancy. A relevant concern involves the lack of agreement on staging systems, prognostic scores, and treatment allocation algorithms.

AIM

To compare the survival rates among already developed prognostic scores.

METHODS

We retrospectively evaluated 140 patients with HCC diagnosed between February 2006 and November 2017. Patients were categorized according to 15 prognostic scoring systems and estimated median survivals were compared with those available from the current medical literature.

RESULTS

The median overall survival of the cohort of patients was 35 (17; 67) mo, and it was statistically different in relation to treatment choice, ultrasound surveillance, and serum alpha-fetoprotein. The Italian Liver Cancer (ITA.LI.CA) tumor staging system performed best in predicting survival according to stage allocation among all 15 evaluated prognostic scores. Using the ITA.LI.CA prognostic system, 28.6%, 40.7%, 22.1%, and 8.6% of patients fell within stages 0-1, 2-3, 4-5 and > 5 respectively. The median survival was 57.9 mo for stages 0-1, 43 mo for stages 2-3, 21.7 mo for stages 4-5, and 10.4 mo for stage > 5. The 1-, 3-, and 5-year survival

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rates were respectively 95%, 65%, and 20%, for stages 0-1; 94.7%, 43.9% and 26.3% for stages 2-3; 71%, 25.8% and 16.1% for stages 4-5; and 50%, 16.7% and 8.3% for stage > 5. At the same time, although statistically significant in prognostic stratification, the most commonly used Barcelona Clinic Liver Cancer system showed one of the most relevant differences in median survival, especially for stages A and C, when compared to the medical literature. In fact, 10.7%, 59.3%, 27.1%, 1.4%, and 0% of patients were stratified into stages 0, A, B, C, and D respectively. The median survival was > 81.1 mo for stage 0, 44.9 mo for stage A, 21.3 mo for stage B, and 3.1 mo for stage C. The 1-, 3-, and 5-year survival rates were respectively 86.7%, 60%, and 46.7% for stage 0; 91.6%, 50.6%, and 20.5% for stage A; 73.7%, 23.7% and 13.2% for stage B; and 2%, 0% and 0% for stage C.

CONCLUSION

Survival analysis shows excellent prognostic ability of the ITA.LI.CA scoring system compared to other staging systems.

Key Words: Hepatocellular carcinoma; Prognostic score system; Prognostic factors; Survival analysis; Barcelona Clinic Liver Cancer score system; Italian Liver Cancer score system

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Core Tip: Italian Liver Cancer tumor staging system seems a promising prognostic score system with a good applicability and reproducibility for patients with hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma: General aspects

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide, and the third cause of cancer-related mortality^[1]. It is the second most frequent liver malignancy following liver metastasis and the most frequent primitive liver neoplasm, accounting for more than 850000 new diagnoses each year and more than 800000 deaths^[2]. Incidence and death rates are increasing steadily (about 2%-3% per year)^[3,4]. HCC usually arises in patients affected by liver cirrhosis, regardless of the etiology^[5,6]. As chronic liver disease represents the leading risk factor for developing HCC, ultrasound surveillance in this condition is crucial to increase early detection rates and improve the overall survival in treated patients^[7,8]. Current unmet clinical needs involve proper staging, prognosis, and treatment allocation of HCC patients. Both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer recommend staging systems that take into account tumor stage, liver function, and physical status in the form of the Barcelona Clinic Liver Cancer (BCLC) staging classification^[9-13]. Also, patients' characteristics, features of the nodules, and liver function drive the choice of treatment, which might be curative (e.g., liver resection, liver transplantation, radiofrequency ablation, microwave ablation, percutaneous ethanol injection) or merely palliative (transarterial chemo-embolization/radioembolization, or specific protein kinases inhibitors such as sorafenib or lenvatinib). However, since the clinical management for HCC can be challenging, treatment should be defined and individualized by a multidisciplinary team composed of hepatologists, hepatobiliary surgeons, interventional radiologists, surgical and medical oncologists.

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HCC staging systems

In the last 30 years, several staging systems have been proposed for the prognosis stratification and treatment choices of HCC. The tumor node metastasis^[14,15] system does not take into account patient characteristics (*e.g.*, liver function tests), thus not allowing for an appropriate prognostic stratification, especially for patients with large tumors^[16,17]; therefore, other systems have been developed. For example, the BCLC is the most widely accepted and used in clinical practice although many others in past times (*i.e.* Okuda Staging System^[18], Cancer of the Liver Italian Program (CLIP) staging system^[19], Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire [GRETCH] staging system^[18,20]) and more recently (*i.e.* Japanese Integrated Staging [JIS] score^[21], Tokyo Scoring System, Hong Kong Liver Cancer [HKLC] classification^[22,23], Model to Estimate Survival in Ambulatory HCC patients [MESIAH] staging score^[24,25], albumin-bilirubin [ALBI] grading system^[26], ALBI-based BCLC staging system, ALBI-T score^[27], model to estimate survival for HCC patients [MESH] scoring system^[28], NIACE score system^[29] and Italian Liver Cancer Group [ITA.LI.CA] score system) allowed physicians allocate all possible presentations of HCC cases. In addition, other scores aimed toward driving treatment procedures have been developed to improve and provide more effective and customized therapy for specific groups of patients; consensus on their use, however, is still to be reached. Meaningful examples are represented by the needle and syringe program (NSP) scoring system^[30], hepatoma arterial-embolization (HAP) scoring system^[31], the Selection for Transarterial chemoembolization Treatment (STATE) scoring system and START strategy^[32] and tumor size and number, baseline alpha-fetoprotein (AFP), Child-Pugh and objective radiological response (SNACOR) staging system^[33]. The main features of the above-mentioned scoring system are reported in **Table 1**.

Proposed in 1999 and updated in 2003, the BCLC staging classification analyzes tumor size, presence of metastasis, portal hypertension, Child-Turcotte-Pugh score, total bilirubin and performance status, stratifying patients into five groups: Stage 0 (very early HCC), stage A (early HCC) which is divided into four subgroups A1-A4; stage B (intermediate HCC); stage C (advanced HCC); stage D (end-stage HCC). The recommended therapy changes according to the stage: Surgical resection is indicated from stage 0 to A2, liver transplant or local ablation procedures from stage A2 to A4, transarterial chemoembolization (TACE) for stage B, sorafenib for stage C, and supportive care for stage D^[34-36]. The median survival for the various stages is over 60 mo for BCLC 0-A, 20 mo for BCLC B, 11 mo for BCLC C and less than 3 mo for BCLC D. Despite its widespread application, the BCLC staging classification has some limitations, especially the strictness in treatment recommendation and the fact that it includes considerably heterogeneous populations in the same stage (principally stage B and C)^[37,38]. Because of the heterogeneity of patients in the intermediate stage (B) of BCLC, several authors have attempted to create subclassifications within this stage to provide more precise prognostic information and allow a more tailored therapeutic approach. In 2012, Bolondi *et al*^[39] proposed a four-class substaging from B1 to B4, based on characteristics such as Child-Turcotte-Pugh score, beyond Milan and up-to-7 criteria, Eastern Cooperative Oncology Group (ECOG) PS and portal vein thrombosis^[35], thus modifying treatment approach according to BCLC scheme^[39]. In 2014, the staging system proposed by Bolondi *et al*^[39] was validated in an Asian population-based study. A year later, the Japanese Society of Transcatheter Hepatic Arterial Embolization (JSTHAE) proposed an alternative subclassification of BCLC stage B, based only on Child-Turcotte-Pugh score and the 4-of-7 cm criterion (total of ≤ 4 tumor nodule, with maximum diameter ≤ 7 cm)^[40-42]. During the same year, researchers from the Kindai University developed other substaging criteria, which appear to perform appropriately; however, external validation is needed^[43]. Another subclassification for intermediate HCC based on the one proposed by Bolondi *et al*^[39] was designed by a Taiwanese group in 2015; however, it has not been validated in Western cohorts of patients. In 2016, a study was conducted to assess whether the ALBI grade could substitute the Child-Turcotte-Pugh score in the BCLC staging system. Concerning the prediction of the clinical outcome of HCC, the ALBI grade performed similarly to the Child-Turcotte-Pugh score when integrated into the BCLC staging system^[44,45]. A few months later, the ITA.LI.CA study group developed and validated its own prognostic system, trying to overcome the shortcomings of previous scores. In particular, 5183 Italian HCC patients (mainly hepatitis C virus infected patients with good performance status and compensated cirrhosis) from the ITA.LI.CA dataset were included in the analysis for internal validation, while other 2651 patients from Taipei (mainly chronic hepatitis B virus infected patients) were recruited for external validation to test the general application of the system. The ITA.LI.CA prognostic system features parameters such as tumor burden (assessed *via* the

Table 1 Description of main features of prognostic score systems for hepatocellular carcinoma

Score system	Parameters taken into account	Classes/ levels	1-, 2-, 3-, or 5-yr survival rates/median survival	Ref.
BCLC	Tumor size; presence of metastasis; portal hypertension; Child Pugh score; total bilirubin; performance status	Stage 0 (very early HCC); stage A (early HCC, subdivided into A1-A4); stage B (Intermediate HCC); stage C (advanced HCC); stage D (end-stage HCC)	5-yr survival rates: 50%-70% for BCLC 0-A; 2-yr survival rates: 63% for BCLC B; 1-yr survival rates: 82%, 44% and 11% for BCLC B, C and D respectively	Llovet <i>et al</i> ^[34] , Mazzaferro <i>et al</i> ^[35] , Weinmann <i>et al</i> ^[36] , Barman <i>et al</i> ^[37] , Yopp <i>et al</i> ^[38]
Okuda staging system	Tumor size (tumor > 50% of the liver; presence of ascites; albumin < 3 g/dL; bilirubin > 3 mg/dL)	Stage I (0 factors); stage II (1-2 factors); stage 3 (3-4 factors)	1-yr survival rates: 57% for stage 1, 20% for stage 2 and 3% for stage 3 respectively	Maida <i>et al</i> ^[18]
CLIP staging system	Tumor size; tumor morphology (uninodular, < 50%; multinodular, < 50%; massive or > 50%); Child-Turcotte-Pugh score; alpha-fetoprotein levels (< or ≥ 400 ng/mL); presence of portal vein thrombosis	One point each parameter (total score ranging from 0 to 6)	1-yr survival rates: 86% for CLIP 0, 76% for CLIP 1, 57% for CLIP 2, 38% for CLIP 3, 22% for CLIP 4, 9% for CLIP 5 and 0% for CLIP 6 respectively; 2-yr survival rates: 69% for CLIP 0, 53% for CLIP 1, 25% for CLIP 2, 7% for CLIP 3, 10% for CLIP 4 respectively; 3-yr survival rates: 58% for CLIP 0, 39% for CLIP 1, 15% for CLIP 2, 6% for CLIP 3, 5% for CLIP 4	[19]
GRETCH staging system	Serum bilirubin; alkaline phosphatase; alpha-fetoprotein; evidence of portal obstruction; Karnofsky score	Stage A (low risk); stage B (intermediate risk); stage C (high risk)	1-yr survival rates are 79%, 31% and 4% for stage A, B and C, respectively	Maida <i>et al</i> ^[18] , Cammà <i>et al</i> ^[20]
Japanese integrated staging score	LCSGJ TNM (presence of single mass; dimension < 2 cm absence of vessel invasion); Child-Pugh score	Total JIS score is the sum of LCSGJ TNM (I to IV are assigned 0 to 3 points) and Child Turcotte-Pugh score (A, B or C are assigned 0, 1 or 2 points)	2-yr survival rates are 94.5%, 88.9%, 78.2%, 52.7%, 30.3% and 15.3% for JIS 0 to JIS 5	Kudo <i>et al</i> ^[21]
Tokyo scoring system	Serum albumin; serum bilirubin; tumor size; number of nodules, each of which is attributed a score	Total Tokyo score is the sum of: 0 points for serum albumin levels > 3.5 g/dL, serum bilirubin levels < 1 mg/dL, tumor size < 2 cm and ≤ 3 tumors; 1 point for serum albumin levels 2.8-3.5 g/dL, serum bilirubin levels 1-2 mg/dL and tumor size 2-5 cm; 2 points for serum albumin levels < 2.8 g/dL, serum bilirubin levels > 2 mg/dL, tumor size > 5 cm and > 3 tumors.	1-yr survival rates: 100% for score 0, 97.6% for score 1, 94.2% for score 2, 84.6% for score 3, 73.8% for score 4-6; 2-yr survival rates: 98.1% for score 0, 90.5% for score 1, 81.7% for score 2, 70.5% for score 3, 52.4% for score 4-6; 3-yr survival rates: 96.2% for score 0, 90.5% for score 1, 63.5% for score 2, 47.4% for score 3, 33.3% for score 4-6; 5-yr survival rates: 52.8% for score 0, 37.3% for score 1, 27.9% for score 2, 19.2% for score 3, 16.7% for score 4-6	Tateishi <i>et al</i> ^[54]
MESIAH staging score	Tumor size; number of nodules; vascular invasion; extrahepatic metastasis; age; serum albumin; AFP levels; MELD score	Each of the parameters is assigned a specific coefficient.	Along with the score is provided a tailored probability of survival at 1, 3, 6, 12, 24 and 36 mo	Kinoshita <i>et al</i> ^[24] , Choi <i>et al</i> ^[25]
ALBI grading system	Serum bilirubin (μmol/L); serum albumin (g/L).	ALBI grade 1 corresponds to a score ≤ -2.60. ALBI grade 2 corresponds to a score > -2.60 and ≤ -1.39. ALBI grade 3 corresponds to a score > -1.39.	In European patients, the median survivals reported in the study were 24.7 mo for ALBI grade 1, 11.4 mo for ALBI grade 2 and 4.9 mo for ALBI grade 3.	Ogasawara <i>et al</i> ^[26]
ALBI-based BCLC staging	The procedure to calculate the BCLC stage stays the same, but, instead of Child-Turcotte-Pugh grade A, B and C, ALBI grade 1, 2 and 3 are employed respectively.	An ALBI score 1 can be present in BCLC stage 0, A, B and C; ALBI score 2 can be present in BCLC stage A, B and C; ALBI score 3 is	1-yr survival rates: 91.3% for ALBI- based BCLC 0, 85.8% for ALBI- based BCLC stage A, 72.6% for ALBI- based BCLC stage B, 32.9% for ALBI- based BCLC Stage C, 26.6% for ALBI- based BCLC stage D. 2-yr survival rates: 79.7% for ALBI- based BCLC 0,	Chan <i>et al</i> ^[45]

system		related to BCLC stage D	69.2% for ALBI- based BCLC stage A, 46% for ALBI- based BCLC stage B, 14.5% for ALBI- based BCLC stage C, 15.1% for ALBI- based BCLC stage D. 3-yr survival rates: 71.5% for ALBI- based BCLC 0, 69.2% for ALBI- based BCLC stage A, 26.4% for ALBI- based BCLC stage B, 7.2% for ALBI- based BCLC stage C, 15.1% for ALBI- based BCLC stage D. 5-yr survival rates: 50% for ALBI- based BCLC 0, 30.1% for ALBI- based BCLC stage A, 10.2% for ALBI- based BCLC stage B, 2.9% for ALBI- based BCLC stage C, 2% for ALBI- based BCLC stage D.	
ALBI-T score	ALBI grade; LCSGJ TNM staging system	The final score, ranging from 0 to 5, is obtained by adding the ALBI grade to the TNM stage and then subtracting 2	The reported median survival were 137.7 mo for ALBI-T score 0, 83.2 mo for ALBI-T score 1, 53.4 mo for ALBI-T score 2, 27.4 mo for ALBI-T score 3, 5 mo for ALBI-T score 4 and 1.4 mo for ALBI-T score 5	Hiraoka <i>et al</i> ^[27]
MESH scoring system	Tumor burden (within/beyond Milan criteria); vascular invasion; metastasis; Child-Pugh score; Performance Status; serum AFP; ALP	The sum of the points obtained in the various sections leads to the final MESH score (ranging from 0 to 6).	1-yr survival rates: 89.5% for MESH 0, 82.5% for MESH 1, 74% for MESH 2, 45.2% for MESH 3, 21.4% for MESH 4, 5.7% for MESH 5, 0% for MESH 6; 2-yr survival rates: 72.9% for MESH 0, 52.8% for MESH 1, 74% for MESH 2, 49.4% for MESH 3, 12.8% for MESH 4, 3.7% for MESH 5; 3-yr survival rates: 53.3% for MESH 0, 52.8% for MESH 1, 36% for MESH 2, 14.8% for MESH 3, 8.2% for MESH 4, 1.4% for MESH 5; 5-yr survival rates: 38.6% for MESH 0, 28% for MESH 1, 14.9% for MESH 2, 5.1% for MESH 3, 3.5% for MESH 4, 0% for MESH 5	Liu <i>et al</i> ^[28]
NIACE score system	Number of nodules (N); infiltrative HCC (I); serum AFP levels (A); Child-Turcotte-Pugh grade (C); ECOG PS (E)	The sum of the points obtained in the various sections leads to the final NIACE score (ranging from 0 to 7).	The reported median survivals are 44 mo for NIACE 0, 22 mo for NIACE 1, 20 mo for NIACE 1.5, 14 mo for NIACE 2.5, 9 mo for NIACE 3, 7 mo for NIACE 4, 4 mo for NIACE 4.5, 4 mo for NIACE 5.5, 3 mo for NIACE 6 and 3 mo for NIACE 7	Adhoue <i>et al</i> ^[29]
ITA.LI.CA score system	Tumor burden (assessed <i>via</i> the ITA.LI.CA tumor staging); performance status test; Child-Pugh score; AFP concentration	Each is assigned an amount of points that finally contribute to the total prognostic score (from 0, best prognosis, to 13, worst prognosis)	The median survival was reported to be 61 mo for patients in quartile 1 (ITA.LI.CA score ≤ 1), 38 mo for patients in quartile 2 (ITA.LI.CA score 2-3), 23 mo for patients in quartile 3 (ITA.LI.CA score 4-5) and 8 mo for patients in quartile 4 (ITA.LI.CA score > 5)	Farinati <i>et al</i> ^[46] , Yoo <i>et al</i> ^[47] , Borzio <i>et al</i> ^[48]
NSP scoring system	Tumor number (N); tumor size (S); prothrombin time (P)	The sum of the points obtained in the various sections leads to the final NSP score. Using a threshold score of 1 allows to identify 2 subgroups with different prognosis	1-yr survival rates are 88.4% for NSP ≤ 1 and 62.7% for NSP > 1 ; 3-yr survival rates are 57% for NSP ≤ 1 and 16.9% for NSP > 1 ; 5-yr survival rates are 30.2% for NSP ≤ 1 and 20.4% for NSP > 1	Zhang <i>et al</i> ^[30]
HAP scoring system	Serum levels of albumin; serum AFP; bilirubin; maximum tumor diameter; 1 point is assigned for serum albumin levels < 3.6 g/dL, serum AFP > 400 ng/dL, serum bilirubin > 0.99 mg/dL (17 mmol/L) and for a maximum tumor diameter > 7 cm	HAP A (low risk) for a total score 0, -HAP B (intermediate risk) for a total score 1; HAP C (high risk) for a total score 2; HAP D (very high risk) for a total score > 2	1-yr survival rates: 64.7% for HAP A, 50% for HAP B, 38.5% for HAP C, 25% for HAP D; 2-yr survival rates: 17.6% for HAP A, 10.3% for HAP B, 10.3% for HAP C, 10% for HAP D	Kadalayil <i>et al</i> ^[31]
STATE scoring system and START strategy	Up-to-7 criteria; serum albumin level; C reactive protein values. A neoplasia within Up-to-7 criteria is assigned 0 points, while a neoplasia beyond the criteria subtracts 12 points. C reactive protein values < 1 mg/dL are attributed 0 points, whereas values ≥ 1 mg/dL subtract 12 points	2 groups of patients presenting different prognosis were identified: STATE score < 18 and ≥ 18	Median survival of 20.5 mo for patients with a STATE score ≥ 18 . Median survival of 6.1 mo for patients with a score < 18	Hucke <i>et al</i> ^[32]
SNACOR staging system	Tumor size (S); tumor number (N); baseline AFP (A); Child-Turcotte-Pugh class (C); objective radiological response (OR). No points are assigned for tumors < 5 cm, a number of tumors < 4 , a baseline AFP < 400 ng/mL, a Child-Turcotte-Pugh class A and for complete response or partial response after TACE. 1 point is assigned for tumors ≥ 5 cm and for a Child-Turcotte-Pugh class B; 2 points are assigned for a number of tumors ≥ 4 ; 3 points are assigned for a baseline AFP ≥ 400 ng/ml and for stable disease or progressive disease after TACE	The final SNACOR score is the sum of the points obtained for the previous features and ranges from 0 to 10	1-yr survival rates: 80.9% for SNACOR 0-2, 69.4% for SNACOR 3-6, 40% for SNACOR 7-10; 2-yr survival rates: 55.3% for SNACOR 0-2, 38.9% for SNACOR 3-6, 20% for SNACOR 7-10; 3-yr survival rates: 42.6% for SNACOR 0-2, 26.4% for SNACOR 3-6, 6.7% for SNACOR 7-10; 5-yr survival rates: 24.5% for SNACOR 0-2, 16% for SNACOR 3-6, 3.3% for SNACOR 7-10	Mähringer-Kunz <i>et al</i> ^[33]

AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; ECOG: Eastern Cooperative Oncology Group; GRETCH: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; HAP: Hepatoma arterial-embolization; HCC: Hepatocellular carcinoma; HKLC: Hong Kong Liver Cancer; ITA.LI.CA: Italian Liver Cancer; JIS: Japanese Integrated Staging; LSCGJ: Liver Cancer Study Group of Japan; MELD: Model for End-Stage Liver Disease; MESH: Model to estimate survival for hepatocellular carcinoma patients; MESIAH: Model to Estimate Survival in Ambulatory hepatocellular carcinoma patients; NSP: Needle and syringe programmes; SNACOR: Tumour size and number, baseline alpha-fetoprotein, Child-Pugh and objective radiological response; STATE: Selection for Transarterial chemoembolization Treatment; TACE: Transarterial chemoembolization; TNM: Tumor-node-metastasis.

ITA.LI.CA tumor staging), performance status test, Child-Turcotte-Pugh score and AFP concentration, and each is assigned a number of points that finally contribute to the total prognostic score (from 0, best prognosis, to 13, worst prognosis). The ITA.LI.CA tumor staging system, taking into account features such as the diameter of the largest nodule, the number of nodules, vascular invasion or metastasis, classifies patients in stages: 0 (very early), A (early), B (intermediate, divided into B1, B2, and B3) and C (advanced). The median survival was reported to be 61 mo for patients with ITA.LI.CA score ≤ 1 , 38 mo for patients with ITA.LI.CA scores 2-3, 23 mo for patients with scores 4-5 and 8 mo for patients with more than 5 points. In the validation cohorts, the ITA.LI.CA score proved to have the best discriminatory ability among other staging systems such as BCLC, CLIP, JIS, HKLC, and MESIAH^[46]. Compared to the BCLC classification, the ITA.LI.CA prognostic system allows a more thorough analysis of tumor burden, subclassifying intermediate patients into three groups (B1, B2, B3) rather than grouping them as stage B. Furthermore, the ITA.LI.CA prognostic system differentiates patients with intrahepatic or extrahepatic metastasis, who studies proved to have different prognosis^[47]. Finally, external and independent validation studies proved ITA.LI.CA to offer the best predictive ability in terms of calibration, discriminatory ability, and monotonicity of gradients in both treated and untreated patients^[13,48].

MATERIALS AND METHODS

A total of 140 patients diagnosed with HCC and treated at our Liver Clinic (University Hospital of Trieste) between February 2006 and November 2017, were retrospectively enrolled. Follow-up was censored on June 30, 2018. The following variables were analyzed before the first active treatment: Gender, age, etiology of liver disease, presence of portal vein thrombosis and ascites, Child-Turcotte-Pugh classification, Model for End-Stage Liver Disease score, Karnofsky score, and ECOG PS score. Laboratory tests conducted featured serum levels of albumin, total and direct bilirubin, aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total proteins, creatinine, hemoglobin, sodium, potassium, white blood cells, red blood cells, platelets, international normalized ratio and activated partial thromboplastin time. The diagnosis of HCC was based on typical imaging features of HCC in computed tomography or magnetic

resonance imaging. Liver biopsy was the technique of choice for diagnosing in case previous imaging studies did not allow diagnostic certainty. Imaging was further employed to obtain information on the number of lesions, tumor diameter, presence of metastasis, and Milan and up-to-7 criteria fulfillment. Depending on their characteristics, patients underwent different therapeutic procedures: Surgical resection, radiofrequency ablation, transarterial chemoembolization (TACE), systemic therapy (sorafenib), or supportive care. Patients were then classified according to different prognostic systems, namely ITA.LI.CA, BCLC (and its subclassifications), CLIP, JIS, HKLC, Tokyo score, Okuda, GRETCH, NIACE, MESH, ALBI (and scores derived from it), HAP, STATE, SNACOR, NSP.

Continuous variables were reported as median (interquartile range) according to the results of the Shapiro-Wilk test. Discrete variables were reported as number (percentage). Between-group comparisons of discrete variables were performed using Pearson's Chi-square test and those of continuous variables using Mann-Whitney *U* test. The overall survival was defined as the time from the date of diagnosis of HCC to the date of death or data censoring (June 30, 2018). Kaplan-Meier survival curves were employed to estimate the median overall survival, and the log-rank test was used to compare differences in survival. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, United States).

RESULTS

Patients' clinical, laboratory, radiological characteristics and treatment choice are summarized in [Table 2](#). The median overall survival was 35 (17; 67) mo, and it was statistically different in relation to treatment choice, ultrasound surveillance and serum AFP ([Table 2](#)).

Using the ITA.LI.CA prognostic system, 28.6%, 40.7%, 22.1% and 8.6% of patients fell within stages 0-1, 2-3, 4-5 and > 5 respectively. The median survival was 57.9 mo for stages 0-1, 43 mo for stages 2-3, 21.7 mo for stages 4-5 and 10, 4 mo for stage > 5. 1-, 3-, and 5-year survival rates were 95%, 65% and 20% for stage 0-1, 94.7%, 43.9% and 26.3% for stage 2-3, 71%, 25.8% and 16.1% for stage 4-5 and 50%, 16.7% and 8.3% for stage >5. The Kaplan-Meier curves are shown in [Figure 1](#).

Using the BCLC staging system 10.7%, 59.3%, 27.1%, 1.4% and 0% of patients fell within stages 0, A, B, C and D respectively. The median survival was > 81, 1 mo for stage 0, 44, 9 mo for stage A, 21, 3 mo for stage B and 3, 1 mo for stage C. 1-, 3-, and 5-year survival rates were 86.7%, 60% and 46.7% for stage 0, 91.6%, 50.6% and 20.5% for stage A, 73.7%, 23.7% and 13.2% for stage B and 2%, 0% and 0% for stage C. The Kaplan-Meier curves are shown in [Figure 2](#).

With BCLC stage A substaging 29 (35%), 25 (30.1%), 5 (6%) and 24 (28.9%) patients fell within stages A1, A2, A3, and A4 respectively. The median survival, 1-, 3-, and 5-year survival rates are shown in [Table 3](#), while Kaplan-Meier curves are shown in [Figure 3A](#). With Bolondi's intermediate BCLC subclassification, 13 (34.2%), 19 (50%), 3 (7.9%), and 3 (7.9%) patients fell within stages B1, B2, B3, and B4 respectively. The median survival 1-, 3-, and 5-year survival rates are listed in [Table 3](#), while the Kaplan-Meier curves are shown in [Figure 3B](#).

Median survivals within different stages and 1-, 3- or 5-year survivals for CLIP scoring system, JIS scoring system, HKLC scoring system, Okuda classification, GRETCH scoring system, NIACE scoring system, MESH scoring system, ALBI score, STATE scoring system, SNACOR staging system, NSP staging system are listed in [Table 3](#). The best prognostic performance was achieved by the ITA.LI.CA score ($P < 0.001$), followed by HKLC, GRETCH, BCLC and CLIP ($P = 0.001$); the other showed less accuracy, with STATE and SNACOR staging systems showing no intergroup differences ($P = 0.322$ and $P = 0.09$ respectively). Also, the comparison between the median survival expected from the original studies and median survival in the study population according to the different scores is also shown in [Table 3](#).

DISCUSSION

The main aim of this study was to assess the prognostic efficacy of different staging systems in the local patient population. Fifteen staging systems were analyzed and subsequently compared to data available from the current literature, showing considerably heterogeneous performances ranging from significant prognostic stratification and comparable median survivals to statistical insignificance and

Table 2 Demographic and biochemical factors, liver function, features of hepatocellular carcinoma nodules, treatments and prognosis of our study cohort

Feature of interest	Study population, <i>n</i> = 140	Intergroup statistical significance
Gender		
Male	109 (77.9%)	
Female	31 (22.1%)	
Age at diagnosis, yr	71.6 (65.6; 75.6)	
Liver disease etiology		
Viral	36 (25.7%)	
Alcoholic	30 (21.4%)	
Metabolic	19 (13.6%)	
Mixed	55 (39.3%)	
Laboratory parameters at diagnosis		
Albumin, g/dL	1.12 (0.94-2.23)	
INR	1.12 (0.94-2.23)	
Total bilirubin, mg/dL	1.06 (0.37-14.47)	
AST, UI/L	41 (11-511)	
ALT, UI/L	32 (7-336)	
ALP, UI/L	99 (40-529)	
GGT, UI/L	69 (11-473)	
Total serum proteins, g/dL	7.3 (5.1-8.9)	
AFP, ng/mL	9.3 (5-110)	
Creatinine, mg/dL	0.89 (0.5-2.99)	
White blood cells, × 10 ³ cells/μL	5.04 (1.51-12.18)	
Red blood cells, × 10 ⁶ cells/μL	4.34 (2.85-6.78)	
Hemoglobin, g/dL	13.5 (8.7-17.8)	
Platelets, × 10 ³ platelets/μL	113 (29-346)	
Sodium, mmol/L	139 (128-145)	
Potassium, mmol/L	4.24 (3.40-6.15)	
Clinical characteristics at diagnosis		
Ascites	11 (7.9%)	
Portal hypertension	64 (45.7%)	
Hepatic encephalopathy	10 (7.1%)	
Portal vein thrombosis	10 (7.1%)	
Metastasis	2 (2.4%)	
Child-Turcotte-Pugh		
Class A	116 (82.9%)	
Class B	22 (15.7%)	
Class C	2 (1.4%)	
MELD score	9 (6-25)	
Karnofsky score		
100	136 (97.1%)	
90	3 (2.1%)	

80	0 (0%)
70	1 (0.7%)
< 70	0 (0%)
ECOG PS	
0	137 (97.9%)
1	3 (2.1%)
> 1	0 (0%)
Number of nodules at diagnosis	
1	91 (65%)
2	31 (22.1%)
3	7 (5%)
4	5 (3.6%)
5	6 (4.3%)
Nodule dimensions	
Nodule diameter, mm	30 (20; 40)
Total tumor volume, cm ³	14.13 (5.45-36.43)
Milan criteria	
Within	99 (71.2%)
Beyond	40 (28.8%)
Up-to-7 criteria	
Within	113 (81.3%)
Beyond	26 (18.7%)
Treatment	
Type	
Surgical resection	28 (20%)
Local ablation	49 (35%)
TACE	54 (38.6%)
Sorafenib	2 (1.4%)
Support	7 (5%)
Number	
< 2	63 (45%)
≥ 2	77 (55%)
Response at 1 mo after treatment	
Complete response	72 (51.4%)
Of whom treated with curative treatment	56 (77.7%)
Partial response	40 (28.6%)
Of whom treated with curative treatment	17 (42.5%)
Stable disease	14 (10%)
Of whom treated with curative treatment	1 (7.1%)
Disease progression	10 (10%)
Of whom treated with curative treatment	1 (10%)
Ultrasound surveillance every 6 mo	
Adhesion to ultrasound surveillance	

Under surveillance	81 (57.9%)	
Not under surveillance	59 (42.1%)	
Nodule diameter, mm		$P < 0.001$
Under surveillance	25 (20; 35)	
Not under surveillance	34 (25; 45)	
Number of nodules at diagnosis		$P < 0.001$
Under surveillance, < 2 nodules	69 (85.2%)	
Not under surveillance, < 2 nodules	22 (37.3%)	
Choice of curative treatment		$P = 0.037$
Under surveillance	54 (66.6%)	
Not under surveillance	29 (49.2%)	
Survival time, mo		
Overall survival	35 (17;67)	
Survival related to gender		NS
Male	34 (20; 80)	
Female	35 (16; 64)	
Survival related to etiology		NS
Viral	32 (15; 65)	
Non-viral	41 (19; 67)	
Survival related to treatment choice		$P = 0.013$
Curative (surgery/ablation)	48 (18; 68)	
Non-curative (TACE/sorafenib/support)	23 (14; 34)	
Survival related to ultrasound surveillance		$P = 0.002$
Under surveillance	48 (20; 75)	
Not under surveillance	30 (12; 49)	
Survival related to AFP		$P < 0.001$
AFP ≤ 200 ng/mL	55 (34; 75)	
AFP > 200 ng/mL	22 (12; 54)	

AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECGO: Eastern Cooperative Oncology Group; GGT: Gamma glutaryl transferase; INR: International normalized ratio; MELD: Model for End-Stage Liver Disease; TACE: Transarterial chemoembolization.

differences in overall survival. The most relevant differences were found for the BCLC, CLIP, JIS, HKLC, Okuda, and GRETCH staging systems and for the ALBI grade, as reported in [Table 3](#).

Despite the unequivocal statistical significance in prognostic stratification of the CLIP and GRETCH staging systems in the study population, the original studies reported substantially shorter survival for almost every stage, although they were validated in European cohorts. However, the reason behind this difference might be related to the advances in treatment for HCC that took place over time since the 1992 and 1994, when the studies were censored. Despite being statistically significant in the study population, the original studies for the Okuda, JIS, and HKLC staging systems reported notably different median overall survival rates. In this case, although the JIS staging system was proven effective by some studies also for Western patients, the explanation is likely to be found in the patient population recruited for the analysis, since validation was performed using only Eastern cohorts along with other factors such as prevalent etiology and different treatment protocols. Moreover, the worse median survival from the original study for the Okuda staging system can be justified by the higher efficacy that therapeutic procedures have reached since 1984. The shorter median survival of patients from the ALBI original study can be explained by the

Table 3 Patients' allocation and their median survival according to prognostic scores taken into account

Score	Number of patients	Percentage	Median survival in mo	Statistical significance for prognostic stratification	Median survival in the original study in mo
ITA.LI.CA				$P < 0.001$	
0	7	5%	93.5		
1	33	23.6%	57.9		
2	19	13.6%	63.1		
3	38	27.1%	40.6		
4	20	14.3%	25.2		
5	11	7.8%	21.1		
6	5	3.6%	20.8		
7	4	2.9%	10.3		
8	3	2.1%	4.3		
> 8	0	0%			
ITA.LI.CA					
0-1	40	28.6%	57.9		57-61
2-3	57	40.7%	43		43-48
4-5	31	22.1%	21.7		23
> 5	12	8.6%	10.4		9-8
BCLC				$P = 0.001$	
0	15	10.7%	> 81.1		> 60
A	83	59.3%	44.9		> 60
B	38	27.1%	21.3		20
C	2	1.4%	3.1		11
D	0	0%			< 3
BCLC A				$P = 0.022$	
A1	29	20.7%	61.9		43.4
A2	25	17.6%	44.3		28.9
A3	5	3.5%	10.7		25.4
A4	24	17.1%	34.4		22.3
BCLC B (Bolondi)				$P = 0.007$	
B1	13	9.3%	34.7		31.9
B2	19	15.7%	25.2		26.9
B3	3	0.7%	10.4		13.5
B4	3	1.4%	7.8		10.9
CLIP				$P = 0.001$	
0	59	42.1%	50.7		27
1	47	33.6%	53.3		15
2	19	13.6%	20.5		9
3	12	8.6%	17.8		7
4	3	2.1%	3.1		5
> 4	0	0%			3

JIS				$P = 0.049$	
0	27	19.3%	70.8		22.6
1	66	47.1%	44.3		22
2	40	28.6%	42		20.6
3	7	5%	10.4		16.9
4-5	0	0%			12.1-5.9
HKLC				$P < 0.001$	
1	93	67.4%	47		79.7
2a	10	7.3%	19		33.4
2b	18	13%	34.7		32.7
3a	5	3.6%	10.4		12.5
3b	10	7.3%	20.8		5.5
4a	1	0.7%	17.8		3.9
4b	1	0.7%	3.1		1.9
5 (a/b)	0	0%			32.5/1.6
Tokyo				$P = 0.002$	
0	10	7.1%	93.5		
1	48	34.3%	47		
2	41	29.3%	43.6		
3	21	15%	30.3		
4	14	10%	20.8		
5	4	2.9%	10.4		
6	1	0.7%	10.3		
7	0	0%			
8	1	0.7%	0.8		
Okuda				$P = 0.026$	
1	102	72.9%	45.5		15.8
2	36	25.7%	20.5		3.6
3	2	1.4%	0.8		1.3
GRETCH				$P < 0.001$	
A	75	53.6 %	57.6		29.3
B	62	44.3 %	30		7.4
C	3	2.1 %	7.8		2.1
NIACE				$P = 0.001$	
0	77	55 %	45.7		44
1	10	7.1 %	43		22
1.5	39	27.9 %	21.7		20
2.5	5	3.6 %	10.4		14
3	6	4.3 %	16.5		9
4	3	2.1 %	3.1		7
> 4	0	0 %			4
MESH				$P < 0.001$	
0	40	28.6 %	57.9		66

1	46	32.9 %	43	37
2	30	21.4 %	19.5	21
3	19	13.6 %	20.8	10
4	5	3.5 %	10.4	5
> 4	0	0 %		4
ALBI				<i>P</i> = 0.008
1	43	31.9 %	79.2	24.7
2	87	64.4 %	34.7	11.4
3	5	3.7 %	15.7	4.9
ALBI				<i>P</i> = 0.008
2a	53	39.2 %	44.3	14.5
2b	34	25.2 %	25.2	6.6
BCLC based on ALBI				<i>P</i> = 0.048
0	15	10.9 %	> 81.1	
A	75	54.3 %	44.9	
B	20	14.5 %	22.2	
C	1	0.7 %	3.1	
D	27	19.6 %	21.7	
ALBI-T				<i>P</i> = 0.002
0	12	9 %	93.5	137.7
1	42	31.6 %	63.1	83.2
2	49	36.8 %	42	53.4
3	28	21.1 %	21.3	27.4
4	2	1.5 %	0.8	5
5	0	0 %		1.4
HAP				<i>P</i> = 0.004
A	31	22.2 %	45.7	25.5
B	51	36.4 %	45.7	18.1
C	41	29.3 %	35.7	8.9
D	17	12.1 %	20.6	5.9
STATE				<i>P</i> = 0.322
> 37	8	5.7 %	25.2	20.5 (≥ 18 points)
27-37	17	12.1 %	40.6	
18-27	16	11.4 %	44.9	
< 18	13	9.3 %	20	
Median STATE score	29.1 (range: 2.4 - 45.6)			6.1
SNACOR				<i>P</i> = 0.09
0-2	31	22.1 %	25.2	31.5
3-6	17	12.1 %	19	19.9
7-10	1	0.7 %	10.3	9.2
NSP				<i>P</i> = 0.03
0	63	45 %	79.2	

1	49	35 %	42	
2	11	7.9 %	14.9	
3	10	7.1 %	20	
4	4	2.9 %	22.2	
5	3	2.1 %	5.6	
NSP				$P = 0.002$
0-1	13	9.3 %	47	51.5
> 1	25	17.9 %	20.5	17.3

Comparison with data in original studies which available. NS: Not significant. ALBI: Albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; GRETCH: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; HAP: Hepatoma arterial embolization; HKLC: Hong Kong Liver Cancer; ITA.LI.CA: Italian Liver Cancer; JIS: Japanese Integrated Staging; MESH: Model to estimate survival for hepatocellular carcinoma patients; NSP: Needle and syringe programme; SNACOR: Tumor size and number, baseline alpha-fetoprotein, Child-Pugh and objective radiological response; STATE: Selection for Transarterial chemoembolization treatment.

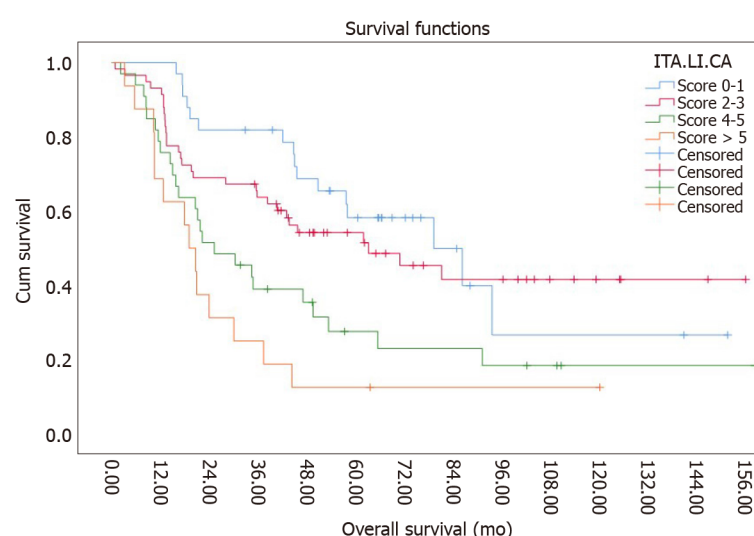


Figure 1 Kaplan-Meier curve for Italian Liver Cancer prognostic score system. $P < 0.001$. ITA.LI.CA: Italian Liver Cancer.

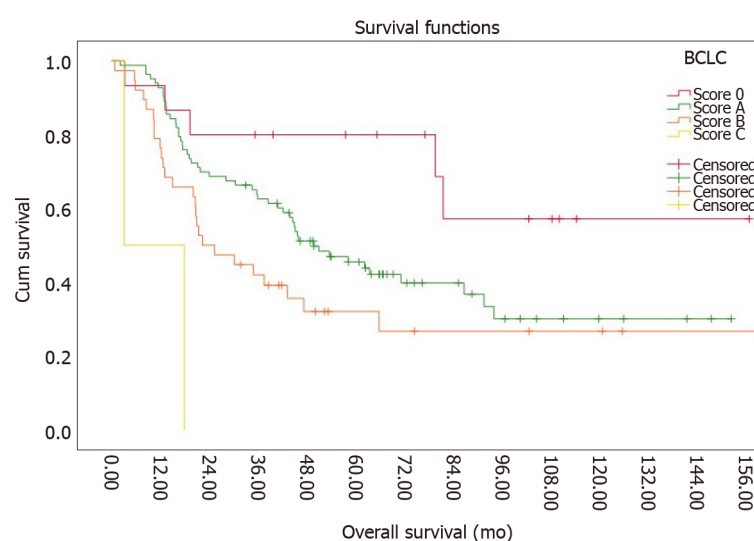


Figure 2 Kaplan-Meier curve for Barcelona Clinic Liver Cancer prognostic score system. $P = 0.001$. BCLC: Barcelona Clinic Liver Cancer.

European population employed as the reference, for all the patients had advanced

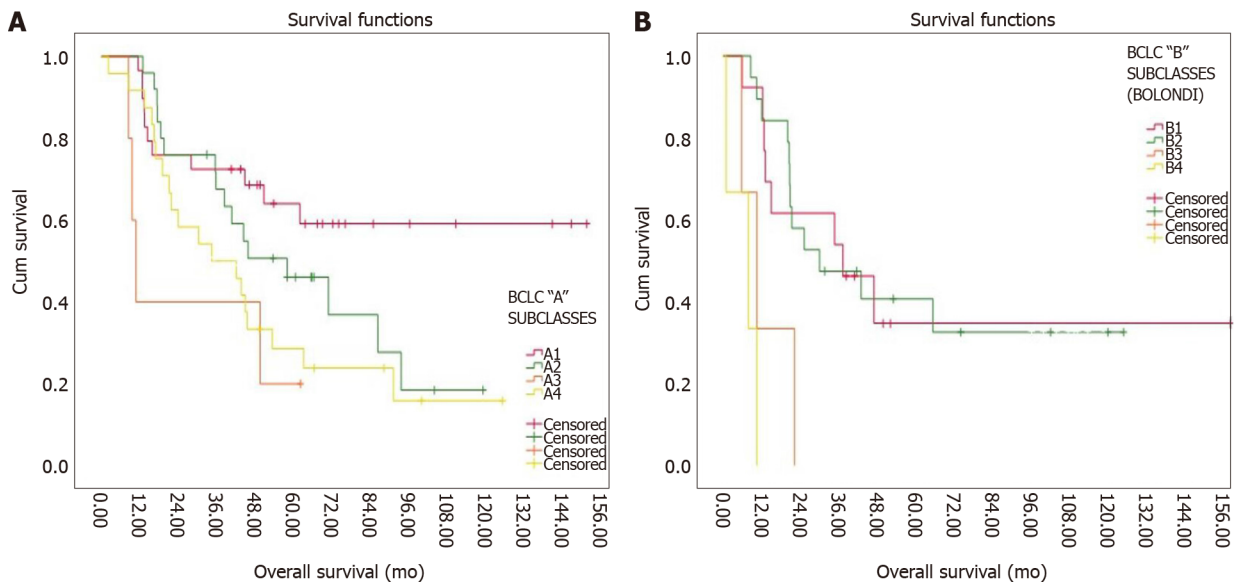


Figure 3 Kaplan-Meier curves. A: Kaplan-Meier curves for Barcelona Clinic Liver Cancer (BCLC) A subclasses. $P = 0.022$; B (right side): Kaplan-Meier curves according to Bolondi's intermediate BCLC subclassification. $P = 0.007$. BCLC: Barcelona Clinic Liver Cancer.

HCC and were treated with sorafenib. Furthermore, if the study population's median survivals are compared with those of the Japanese population of the study, that also included patients who underwent surgical resection, the differences appear much less significant. Despite the difference in survival, however, the ALBI grade showed statistical significance in the study population.

The median survival from the BCLC staging system clearly differs for stages A (and BCLC stage A subclassification) and C in the study population. The difference in survival for stage A might be explained with the heterogeneity in treatment that these patients received in the study population, while the reason for the difference in stage C is to be found in the low number of patients falling within this category in the study population. Nevertheless, BCLC stage B showed similar survivals, and so happened also for the BCLC intermediate subclassification according to Bolondi. The BCLC staging system, BCLC stage A subclassification and Bolondi's BCLC B substaging all resulted statistically significant.

The NIACE staging systems presented median survivals similar to the validation study, and similarly, the MESH staging system presented median survivals comparable to those of the original study, except for stages with lower numbers of patients.

Among all of the staging systems, not only did the ITA.LI.CA show one of the highest statistical significance ($P < 0.001$) for prognostic stratification of the patients, but it also showed almost complete correspondence of median overall survivals for all different stages. Only patients in stage > 5 showed a median survival 2 mo longer than that of the original study (10.4 *vs* 8.9 mo), probably related to the relatively low numerosity of patients in this stage (12 patients, 8.6%). This study further supports the external validation process for the ITA.LI.CA prognostic system in Western patients affected by HCC^[48].

The study also assessed the prognostic performance of scoring systems related to treatment. The median survivals of all three scoring systems (STATE, SNACOR, NSP) in the study population were similar to those of the original studies, but only the NSP system reached inter-group statistical significance.

As could be expected, the median overall survival of patients undergoing ultrasound surveillance every 6 mo was longer than those of patients who were not followed (48 *vs* 30 mo), attributable to an early detection of HCC nodules. In fact, as shown in Table 2, patients undergoing ultrasound surveillance had smaller nodule diameter (25 *vs* 34 mm, $P < 0.001$) and showed lower prevalence of 32 nodules at diagnosis. Also, patients with AFP > 200 ng/mL showed reduced survival if compared to patients with lower AFP levels (22 *vs* 55 mo, $P < 0.001$).

In terms of the treatment regimen, median overall survival was 48 (20; 75) mo for curative (surgery/ablation) treatment and 23 (14; 34) mo for non-curative (TACE/sorafenib/support) treatment. Further analyses were carried out assessing the difference in survival of patients who did and did not receive the treatment

recommended for their stage by the BCLC staging system. For patients treated with surgical resection or TACE, there was no significant difference in survival between the two groups, proving that the BCLC score does not affect the overall survival for the same type of therapy. As could be expected, patients with BCLC stage A who underwent curative treatment (as recommended by the BCLC staging system) presented a significantly better survival compared to those who did not, but at the same time patients with BCLC stage B showed a benefit from curative treatment (not recommended by the BCLC staging system) compared to those who underwent TACE (as recommended), with a median survival of 34.7 mo instead of 22.2 mo. Therefore, the rigorous application of treatment recommendations for each BCLC stage, may shorten patients' survival. In fact, treatment choices based on the sub-classification of the BCLC stage B can furtherly stratify patients and provide the most suitable treatment^[49-53].

CONCLUSION

In conclusion, the study identified the ITA.LI.CA as the most effective staging system in the local population. In addition, the ITA.LI.CA does not propose a treatment algorithm, as opposed to other staging systems such as the BCLC, since numerous variables influence treatment choice, and the use of rigid and categorical flowcharts may not always guarantee the most suitable therapy, as partly shown also in this study. ITA.LI.CA seems a promising prognostic score system with a good applicability and reproducibility for patients with HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma represents the most common primitive liver malignancy.

Research motivation

Currently there is a widespread lack of agreement on staging systems, prognostic scores and treatment allocation algorithms.

Research objectives

Define the prognostic ability of fifteen different prognostic scores.

Research methods

Retrospective study, 10-year enrollment of patients.

Research results

With the Italian Liver Cancer (ITA.LI.CA) prognostic system 28.6%, 40.7%, 22.1% and 8.6% of patients fell within stages 0-1, 2-3, 4-5 and > 5 respectively. The median survival was 57.9 mo for stages 0-1, 43 mo for stages 2-3, 21.7 mo for stages 4-5 and 10.4 mo for stage > 5. 1-, 3-, and 5-year survival rates were 95%, 65% and 20% for stages 0-1, 94.7%, 43.9% and 26.3% for stages 2-3, 71%, 25.8% and 16.1% for stages 4-5 and 50%, 16.7% and 8.3% for stage > 5.

Research conclusions

The median overall survival of the cohort of patients was 35 (17; 67) mo, and it was statistically different in relation to treatment choice, ultrasound surveillance and serum AFP.

Research perspectives

External validation to the ITA.LI.CA staging system.

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