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Restaging Patients With Hepatocellular Carcinoma Before Additional Treatment Decisions: A Multicenter Cohort Study

Alessandro Vitale ,[1] Fabio Farinati,[1] Giulia Noaro,[1] Patrizia Burra,[1] Timothy M. Pawlik,[2] Laura Bucci,[3] Edoardo G. Giannini ,[4] Chiara Faggiano,[5] Francesca Ciccarese,[6] Gian Lodovico Rapaccini,[7] Maria Di Marco,[8] Eugenio Caturelli,[9] Marco Zoli,[5] Franco Borzio,[10] Rodolfo Sacco,[11] Giuseppe Cabibbo,[12] Roberto Virdone,[13] Fabio Marra ,[14] Martina Felder,[15] Filomena Morisco,[16] Luisa Benvegnù,[17] Antonio Gasbarrini,[18] Gianluca Svegliati-Baroni,[19] Francesco Giuseppe Foschi,[20] Andrea Olivani,[21] Alberto Masotto,[22] Gerardo Nardone,[23] Antonio Colecchia,[24] Fabio Fornari,[25] Massimo Marignani,[26] Susanna Vicari,[27] Emanuela Bortolini,[28] Raffaele Cozzolongo,[29] Alessandro Grasso,[30] Camillo Aliberti,[31] Mauro Bernardi,[3] Anna Chiara Frigo,[32] Mauro Borzio,[33] Franco Trevisani,[3] and Umberto Cillo[1]; on behalf of the Italian Liver Cancer (ITA.LI.CA) group

Prognostic assessment of patients with hepatocellular carcinoma (HCC) at the time of diagnosis remains controversial and becomes even more complex at the time of restaging when new variables need to be considered. The aim of the current study was to evaluate the prognostic utility of restaging patients before proceeding with additional therapies for HCC. Two independent Italian prospective databases were used to identify 1,196 (training cohort) and 648 (validation cohort) consecutive patients with HCC treated over the same study period (2008-2015) who had complete restaging before decisions about additional therapies. The performance of the Italian Liver Cancer (ITA.LI.CA) prognostic score at restaging was compared with that of the Barcelona Clinic Liver Cancer, Hong Kong Liver Cancer, and Cancer of the Liver Italian Program systems. A multivariable Cox survival analysis was performed to identify baseline, restaging, or dynamic variables that were able to improve the predictive performance of the prognostic systems. At restaging, 35.3% of patients maintained stable disease; most patients were either down-staged by treatment (27.2%) or had disease progression (37.5%). The ITA.LI.CA scoring system at restaging demonstrated the best prognostic performance in both the training and validation cohorts (c-index 0.707 and 0.722, respectively) among all systems examined. On multivariable analysis, several variables improved the prognostic ability of the ITA.LI.CA score at restaging, including progressive disease after the first treatment, Model for End-Stage Liver Disease at restaging, and choice of nonsurgical treatment as additional therapy. A new ITA.LI.CA restaging model was created that demonstrated high discriminative power in both the training and validation cohorts (c-index 0.753 and 0.745, respectively). *Conclusion:* Although the ITA.LI.CA score demonstrated the best prognostic performance at restaging, other variables should be considered to improve the prognostic assessment of patients at the time of deciding additional therapies for HCC. (HEPATOLOGY 2018;68:1232-1244).

Abbreviations: ABL, ablation; AIC, Akaike Information Criterion; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; C, concordance; CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer; HR, hazard ratio; IAT, intra-arterial therapy; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OTHER, other treatments; PD, progressive disease; SOR, sorafenib.

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Prognostic assessment for patients with hepatocellular carcinoma (HCC) is extremely complex, as it depends on several factors including tumor stage, liver functional reserve, general patient conditions, as well as treatment choice.[1] Although the Barcelona Clinic Liver Cancer (BCLC) classification has been endorsed by American and European guidelines for HCC management,[2,3] its prognostic performance is usually lower than that of other prognostic scores, such as the Cancer of the Liver Italian Program (CLIP).[4] Moreover, the BCLC classification is often not followed in Asia, where other systems such as the Hong Kong Liver Cancer (HKLC) staging system are more often used.[5] Recently, our group proposed the Italian Liver Cancer (ITA.LI.CA) prognostic system, which was developed in a large Italian cohort of patients with HCC and validated both in an independent Italian data set as well as in a large population of patients from Taiwan.[6] Of note, the ITA.LI.CA score demonstrated the best prognostic performance compared with other available HCC prognostic systems, with other investigators having independently confirmed its superiority.[7]

Prognostic staging can be even more complicated in patients with HCC who have received a first treatment and are being restaged. Prognostic assessment of already-treated patients is more difficult than that of naïve patients for several reasons. Specifically, radiological restaging is technically more challenging because of the need to evaluate and differentiate remnant viable tumor from previously treated areas.[8] In addition, dynamic variables such as the response to first treatment and changes in tumor characteristics as well as alterations in baseline liver function and the time elapsed from the first treatment may also have a prognostic role.[9,10]

To date, all available prognostic systems have been developed and validated only in treatment-naïve HCC populations. As such, the prognostic accuracy of these systems to restage patients at the time of making decisions about additional therapies remains unsettled. In fact, to the best of our knowledge, no study has compared the performance of prognostic systems in this setting. Therefore, the objective of the current study was to evaluate the prognostic utility of restaging patients before additional treatment decisions for HCC. In

ARTICLE INFORMATION:

From the [1]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [2]Department of Surgery, Wexner Medical Center at The Ohio State University, Columbus, OH; [3]Department of Medical and Surgical Sciences, Division of Semeiotics, Alma Mater Studiorum – University of Bologna, Bologna, Italy; [4]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Policlinico San Martino, Genoa, Italy; [5]Department of Medical and Surgical Sciences, Division of Internal Medicine, Alma Mater Studiorum – University of Bologna, Bologna, Italy; [6]Division of Surgery, San Marco Hospital, Zingonia Italy; [7]Division of Internal Medicine and Gastroenterology, Complesso Integrato Columbus, Università Cattolica del Sacro Cuore, Rome, Italy; [8]Division of Medicine, Bolognini Hospital, Seriate, Italy; [9]Division of Gastroenterology, Belcolle Hospital, Viterbo, Italy; [10]Department of Medicine, Division of Radiology, Fatebenefratelli Hospital, Milan, Italy; [11]Division of Gastroenterology and Metabolic Diseases, University Hospital of Pisa, Pisa, Italy; [12]Biomedical Department of Internal and Specialistic Medicine, Division of Gastroenterology, University of Palermo, Palermo, Italy; [13]Division of Internal Medicine 2, Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy; [14]Internal Medicine and Hepatology, Department of Experimental and Clinical Medicine, University of Firenze, Florence, Italy; [15]Bolzano Regional Hospital, Division of Gastroenterology, Bolzano, Italy; [16]Department of Clinical Medicine and Surgery, Unit of Gastroenterology and Hepatology, University of Naples, "Federico II," Naples, Italy; [17]Department of Molecular Medicine, University of Padova, Padova, Italy; [18]Division of Internal Medicine and Gastroenterology, Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy; [19]Division of Gastroenterology, Polytechnic University of Marche, Ancona, Italy; [20]Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy; [21]Division of Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [22]Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy; [23]Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Naples "Federico II," Naples, Italy; [24]Department of Surgical and Medical Sciences, Gastroenterology Unit, Alma Mater Studiorum – University of Bologna, Bologna, Italy; [25]Gastroenterologia, Ospedale Saliceto, Piacenza, Italy; [26]UOS Malattie delle vie Biliari e del Fegato, UOC malattie dell'Apparato Digerente e del Fegato, AO S.Andrea, Università "Sapienza," Rome, Italy; [27]U.O.C. Gastroenterologia, Ospedale Bentivoglio, Bologna, Italy; [28]U.O. Medicina VI Epatologia e Gastroenterologia, Ospedale San Paolo, Università degli Studi di Milano, Milan, Italy; [29]UOC di gastroenterologia Ospedale De Bellis IRCCS Castellana Grotte, Italy; [30]SC Gastroenterologia ASL 20 Ospedale Pietra Ligure, Italy; [31]Radiology, Padua University Hospital, Padua, Italy; [32]Biostatistic Unit, Padua University, Padua, Italy; [33]U.O.C. Gastroenterologia, ASST Melegnano-Martesana, Melegnano, Italy.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Alessandro Vitale
Department of Surgery, Oncology and Gastroenterology
University of Padua, Via Giustiniani 2
35128 Padova, Italy
E-mail: alessandro.vitale@unipd.it
Tel: +393358247099

addition, we sought to define the prognostic system that performed the best in the restaging setting. Lastly, we examined whether the prognostic performance of available systems improved with the addition of other independent prognostic variables available only at the time of restaging.

Patients and Methods

DEFINITIONS

First therapy was defined as the therapeutic approach adopted by clinicians to treat baseline HCC at the time of the initial diagnosis. Duration of first therapy varied, as there was a wide range of initial therapy for HCC, including resection/ablation (i.e., single procedure/multiple ablations), transarterial chemoembolizations (i.e., single or multiple), or systemic therapy such as sorafenib (i.e., "continuous" until/if stopped). Evaluation of response to first-line treatment generally occurred 1-3 months after completion of first-line therapy. In the case of sorafenib, evaluation was performed after the first 2 months of systemic therapy. Response to the first-line treatment was categorized into four subgroups according to modified Response Evaluation Criteria In Solid Tumors criteria[8]: complete response (CR), partial response, stable disease, and progressive disease (PD). Patients with CR were further stratified into two subgroups: early tumor recurrence (within 2 years after first-line therapy) and late recurrence (>2 years).

The time of restaging depended on the response to the first-line therapy. Among patients who had a complete response, restaging typically occurred at the time that recurrence was diagnosed. In contrast, among patients who had an incomplete response, time of restaging corresponded to the time of response evaluation to the first-line therapy, as this was the time point at which decisions to perform additional therapies (i.e., repeat or change the first therapy) were made.

STUDY GROUPS

The ITA.LI.CA database included prospectively collected data on 6,669 consecutive patients with HCC who were managed in 24 Italian institutions between January 1987 and March 2015. Beginning in 2008, the ITA.LI.CA database compilation changed, requiring the registration of all parameters not only at baseline (cancer diagnosis) but also at the time of each treatment. Among the 3,263 patients enrolled in the ITA.LI.CA database from January 2008, 1,559 (47.8%) were selected who had been evaluated and managed since HCC diagnosis by the same ITA.LI.CA center. Given the objective of the current study, 322 patients who received only best supportive care (BSC) since the time of HCC diagnosis were excluded. To avoid potential bias, 12 patients who underwent liver transplantation (LT) as first-line treatment for HCC were also excluded. The remaining 1,225 patients had restaging and a new treatment after a first nontransplant treatment. After exclusion of 29 cases who did not have complete follow-up data or were lost to follow-up, a total of 1,196 patients were included in the final analytic cohort (Supporting Fig. S1).

In the final cohort, 201 patients underwent liver resection (LR), 481 ablation procedures (ABL), 495 intra-arterial therapy (IAT), 51 sorafenib (SOR), and 31 other treatments (OTHER) as first therapy.

In addition, to test the generalizability of the survival models evaluated in the ITA.LI.CA database (training cohort), an independent cohort of consecutive Italian patients with HCC enrolled in the same period was analyzed. EpaHCC (Epatologia HCC) is an ongoing, multi-institutional, in-field, large cohort of newly diagnosed HCCs created specifically to validate different prognostic systems of HCC. The EpaHCC project is supported by AIGO (Associazione Italiana Gastroenterologi Ospedalieri). Among the 1,798 cases available at the time of analysis, 921 (51.2%) patients who were evaluated and managed since HCC diagnosis by the same EpaHCC center were identified; 225 patients who received only BSC since the time of HCC diagnosis were excluded. To avoid any bias, 13 patients who underwent LT as first treatment for HCC were also excluded. The remaining 683 patients had restaging and an additional treatment after a first nontransplant treatment. After exclusion of 35 cases who did not have complete follow-up data or were lost to follow-up, a total of 648 patients were included in the final analytic cohort (Supporting Fig. S1). There was no overlap among the patients enrolled in the training and in the validation cohorts.

The institutional review boards of the participating institutions approved the study. According to Italian law, no patient approval was needed for this retrospective study. Patients gave written consent for every diagnostic and therapeutic procedure, as well as for use of data for medical purposes. Informed consent was obtained as usual for medical, surgical, and radiological

treatments, but not specifically for patient data to be used in this retrospective study.

Clinical and treatment-related variables, such as age, sex, etiology of underlying liver disease, and presence of ascites and hepatic encephalopathy, main serological parameters (total bilirubin, creatinine, prothrombin time and/or INR, α–fetoprotein, albumin, sodium), tumor radiological characteristics (number and size of lesions, vascular invasion, extrahepatic metastases), Eastern Cooperative Oncology Group performance status (ECOG PS), and main treatment strategy were recorded. ECOG PS was prospectively assessed by clinicians of the ITA.LI.CA and EpaHCC groups. For each patient, the following composite variables were also calculated and recorded: Child-Pugh score, albumin-bilirubin (ALBI) grade, BCLC stage, HKLC stage, CLIP score, and ITA.LI.CA score.[5,6,11-14] Tumor number and size, major vascular invasion, and patterns of metastatic disease were assessed by computed tomography or magnetic resonance imaging. Specifically, vascular invasion was classified as intra- and extrahepatic, according to the HKLC staging system criteria.[5] Intrahepatic vascular invasion was defined as the neoplastic invasion of intrahepatic branches of the portal vein, left or right portal vein, or main hepatic veins. Extrahepatic vascular invasion included main portal trunk and inferior vena cava involvement.

STATISTICAL ANALYSIS

Baseline characteristics were examined based on frequency distribution; continuous data were presented as median values (interquartile range) unless indicated otherwise. Univariate comparisons were assessed using Student *t* test, Wilcoxon rank-sum test, or chi-square test as appropriate. Missing data relative to study covariates involved less than 10% of patients in all circumstances. Thus, missing values were imputed using the maximum likelihood estimation method.[15] Overall survival was defined from the date of restaging of HCC to the date of death, last follow-up evaluation, or data censoring (December 31, 2015). Kaplan-Meier survival curves were used to estimate median overall survival and 1-, 3-, 5-, and 10-year overall survival in the main study groups (training and validation cohorts). The survival curves were also stratified according to ITA.LI.CA prognostic system quartiles, as well as main BCLC, HKLC, and CLIP stages. The log-rank test was used to compare differences in survival curves. To graphically describe the prognostic performance of the ITA.LI.CA score and to test its prognostic calibration at restaging, patients were divided into four subgroups corresponding to the original quartiles at the twenty-fifth, fiftieth, and seventy-fifth percentiles of the risk score in the paper from Farinati et al.[6] Thus, quartile 1 coincided with ITA.LI.CA score ≤1, quartile 2 with score 2-3, quartile 3 with score 4-5, and quartile 4 with score >5.

To compare the prognostic performance of the ITA.LI.CA prognostic score with that of other systems, the Akaike Information Criterion (AIC), as well as the Concordance (C)-index and the test for trend chi-square, was used.[16,17] The lower the AIC value, the higher the discriminatory ability of the staging system. The higher the C-index and the test for trend chi-square, the higher the discriminatory ability and monotonicity of gradients of the staging system. To assess if the ITA.LI.CA score performs better than other systems, we used the likelihood ratio test.

Univariable and multivariable Cox survival analyses were performed to identify baseline, restaging, or dynamic variables able to improve the performance of main prognostic staging systems (BCLC, HKLC, CLIP, and ITA.LI.CA). A prognostic score was generated using the independent variables obtained by multivariable analysis weighed according to the estimated regression coefficient of the final model. The reference category of each prognostic factor was assigned a value of zero. A simplified version was derived from the original model by linear transformation of the coefficients (coefficients * 3, rounded). Details on how the ITA.LI.CA restaging model was developed are described in the Supporting text.

In all analyses, a two-tailed *P* value <0.05 was considered statistically significant. All analyses were performed in JMP 9.0.1 package (1989-2010 SAS Institute Inc.), STATA13.0 (Copyright 1985-2013 StataCorp LP), and R.app GUI 1.51 (S. Urbanek & H.-J. Bibiko, R Foundation for Statistical Computing, 2012).

Results

CHARACTERISTICS OF THE STUDY GROUP

The characteristics of the population at the time of initial HCC presentation and at the time of restaging are reported in Table 1. The majority of patients

TABLE 1. Patient Characteristics at Baseline and at Restaging

Variables		At the Time of First HCC Presentation Number (%) Median (IQR)	At Restaging Number (%) Median (IQR)	*P* Value
Gender	Female	293 (24.5)		
	Male	903 (75.5)		
Age (years)	Median	69 (62-75)		
Aetiology				
	Alcohol	407 (34.0)		
	HBsAg	161 (13.5)		
	Anti-HCV	727 (60.8)		
Time between baseline and restaging clinical evaluations (months)	Median	10.2 (5-21)		
ECOG PS	0	987 (82.5)	729 (61.0)	<0.001
	1	172 (14.4)	353 (29.5)	
	2	31 (2.6)	83 (6.9)	
	>2	6 (0.5)	31 (2.6)	
MELD	Median	9 (8-11)	9 (8-11)	<0.001
	>10	303 (25.3)	352 (29.4)	0.014
Child-Pugh class	A	922 (77)	865 (72.3)	<0.001
	B	267 (22.5)	306 (25.6)	
	C	7(0.5)	25 (2.1)	
ALBI grades	1	268 (22.4)	224 (18.7)	0.006
	2	880 (73.6)	896 (74.9)	
	3	48 (4.0)	76 (6.4)	
Diameter of the largest viable lesion (cm)	Median	3.0 (2.0-4.1)	2.5 (1.8-3.8)	<0.001
Nodular pattern	Single lesion	682 (57.0)	578 (48.3)	<0.001
	Up to 3 lesions	293 (24.5)	279 (23.3)	
	>3 lesions	221 (18.5)	339 (28.4)	
VI	Intrahepatic	32 (2.6)	72 (6.0)	<0.001
	Extrahepatic	25 (2.0)	65 (5.4)	
AFP (ng/mL)	Median	20 (6-442)	74 (8- 606)	<0.001
Metastatic disease	Yes	24 (2.0)	91 (7.6)	<0.001
Treatment administration	LT	-	41 (3.4)	<0.001
	LR	201 (16.8)	37 (3.1)	
	ABL	418 (34.9)	164 (13.7)	
	IAT	495 (41.4)	446 (37.3)	
	SOR	51 (4.3)	253 (21.2)	
	Other	31 (2.6)	79 (6.6)	
	BSC	-	176 (14.7)	
Response to the first treatment	Late recurrence	239 (20.0)		
	Early recurrence	382 (31.9)		
	PR	358 (29.9)		
	SD	84 (7.0)		
	PD	133 (11.2)		

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; IAT, intra-arterial treatment; IQR, interquartile range; LR, liver resection; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PD, progressive disease; PR, partial response; SD, stable disease; SOR, sorafenib; VI, vascular invasion.

(75.5%) were male, and the average age was 69 years. The main etiological risk factors for HCC were hepatitis C (61%) followed by alcohol consumption (34%).

The median time between the first HCC presentation and clinical-radiological restaging was 10.2 months. Comparison of baseline characteristics among

patients at the time of restaging demonstrated worsening of both general conditions (i.e., ECOG PS) and liver function (both $P < 0.05$). In particular, there was migration of the Child-Pugh class from class A to B or C ($P = 0.001$); for example, 28% of patients were CHILD B-C at restaging versus 23% at baseline. The median Model for End-Stage Liver Disease (MELD) score of 8 (8-11) remained stable, yet more patients had a MELD score >10 at restaging (29.5% vs. 25.3 %; $P = 0.014$). In addition to the MELD score distribution being different ($P < 0.001$), median ALBI grades were also slightly worse ($P = 0.006$). Regarding tumor burden, although the size of the largest viable lesion was lower (2.5 vs. 3.0 cm, $P < 0{\cdot}001$), there was an increase in multinodular cancers (28.4% vs. 18.5%, $P < 0.001$) and vascular invasion (11.4% vs. 4.6%, $P < 0.001$) at the time of restaging. Furthermore, median alpha-fetoprotein levels (74 vs. 20 ng/mL, $P < 0.001$) were higher and metastatic disease (7.6% vs. 2.0%, $P < 0.001$) was more common at restaging.

Patients more frequently received radical therapies to treat the first HCC (i.e., LR 16.8% and ABL 35.0%) compared with disease at restaging; specifically, disease at restaging was more often treated with IAT, SOR, or BSC (73% of patients; $P < 0.001$). The patient distributions for each HCC prognostic system are shown in Supporting Table S1. Of note, there was an increase in the proportion of patients who had advanced stages of disease at restaging. For instance, the proportion of patients who had an ITA.LI.CA score of 5 doubled (from 6.2% to 11.6%), and the proportion of patients with an ITA.LI.CA score ≥9 increased from 0.8% to 4.9%. In contrast, the proportion of patients with a score of 1 at restaging decreased from 18.4% to 13.1%, and those patients with a score of 2 decreased from 22.2% to 15.7%.

Given the general trend toward progression of cancer stage from baseline to restaging, we sought to better understand disease migration using the ITA.LI.CA system. Table 2 demonstrates patient migration according to the ITA.LI.CA tumor staging and functional score. As demonstrated in Supporting Tables S2-S3, tumor staging included main tumor variables (size and number of nodules, macroscopic vascular invasion, and metastases), and functional score included main patient- and liver function variables (i.e., ECOG PS and Child-Pugh score). At restaging, 37.5% of patients had a worse tumor stage (26% with an upgrade of 1 or 2 stages), 35.3% of patients maintained the same stage, and 27.2 % of patients were down-staged. Considering functional stage, there was no migration among 49.1% of patients, and liver function worsened in 40% of cases.

TABLE 2. Stage Migration Within ITA.LI.CA Tumor Staging and Functional Score

	Number of Points Migrated	Number (%) Median (IQR)
ITA.LI.CA Tumor Staging Migration		
Down-staging	–5	3 (0.2)
	–4	8 (0.7)
	–3	26 (2.2)
	–2	74 (6.2)
	–1	214 (17.9)
	Total	325 (27.2)
Stable disease	0	**422 (35.3)**
Up-staging	1	191 (16.0)
	2	120 (10.0)
	3	82 (6.8)
	4	36 (3.0)
	5	20 (1.7)
	Total	449 (37.5)
ITA.LI.CA functional score migration		
Down-staging	–3	2 (0.2)
	–2	10 (0.8)
	–1	118 (9.9)
	Total	130 (10.9)
Stable disease	0	588 (49.1)
Up-staging	1	361 (30.2)
	2	92 (7.7)
	3	14 (1.2)
	4	10 (0.8)
	5	1 (0.1)
	Total	478 (40.0)

Abbreviations: IQR, interquartile range; ITA.LI.CA, Italian Liver Cancer.

PROGNOSTIC PERFORMANCE OF DIFFERENT SYSTEMS

The median follow-up time was 34.5 months (31.4-35.5). Overall survival at 1-, 3-, 5-, and 10 years was 81%, 56%, 41%, and 29%, respectively, with a median survival of 42 months (37.6-46.7) (Supporting Fig. S2). To examine which staging system had the best prognostic power, each system was applied to the cohort both at the time of the first HCC diagnosis and at restaging (Figs. 1 and 2). The ITA.LI.CA prognostic system had the lowest AIC value among patients (4908.583) and the

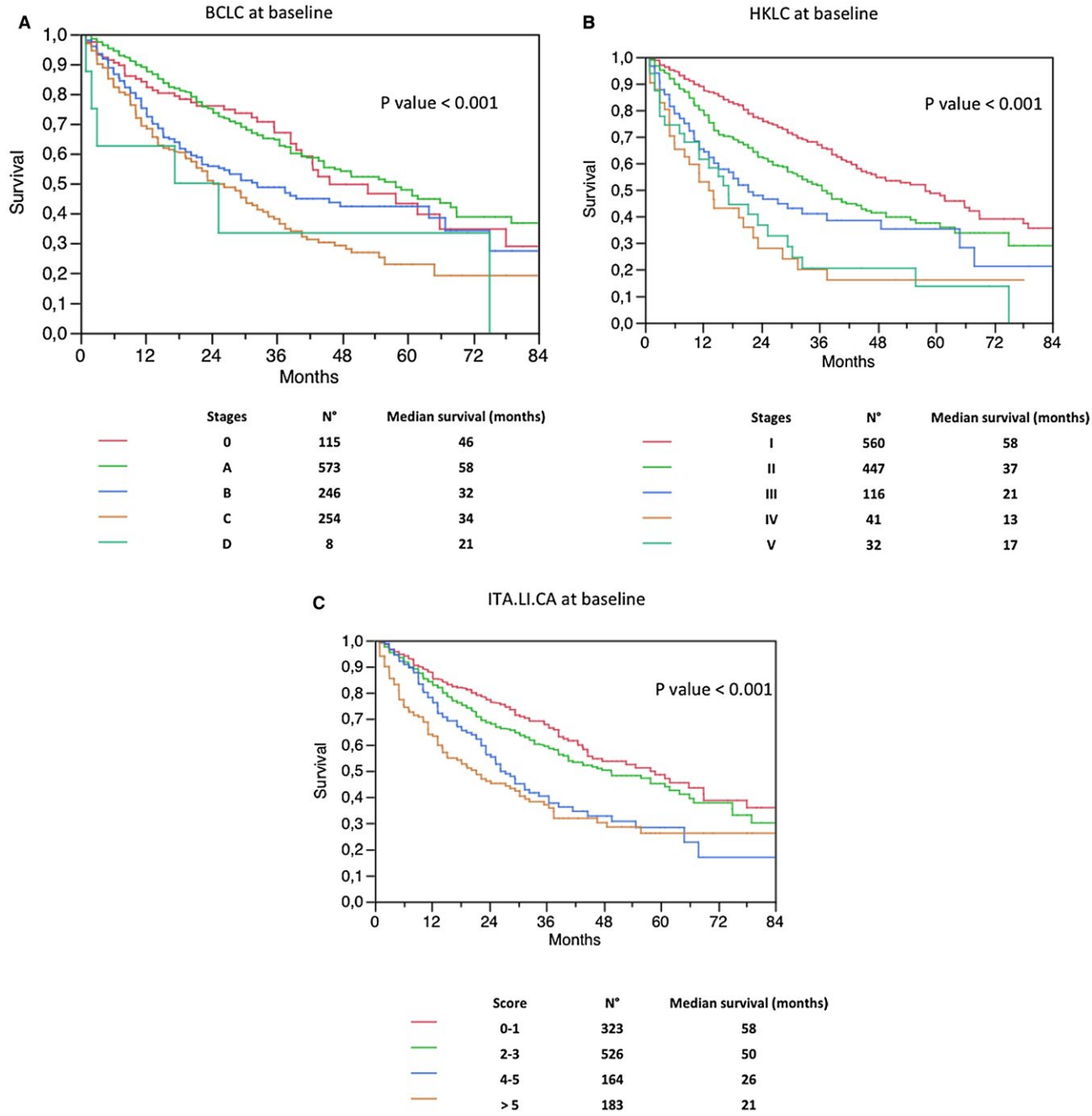

FIG. 1. Survival curves according to BCLC (A), HKLC (B), and ITA.LI.CA score quartiles (C) at baseline in the training cohort.

highest C-index (0.707) at restaging, indicating the best discriminatory ability and monotonicity of gradients (Table 3). The discriminatory ability of the ITA.LI.CA system was demonstrated by the best separation of survival curves among the different prognostic subgroups (Fig. 2). There was good calibration of the ITA.LI.CA score at restaging, with the observed and predicted survival curves largely overlapping (Supporting Fig. S3).

IMPROVING THE PROGNOSTIC PERFORMANCE OF THE ITA.LI.CA PROGNOSTIC SCORE AT RESTAGING

Univariable survival analyses were performed, including all clinical variables collected both at the time of HCC diagnosis and at restaging (Supporting

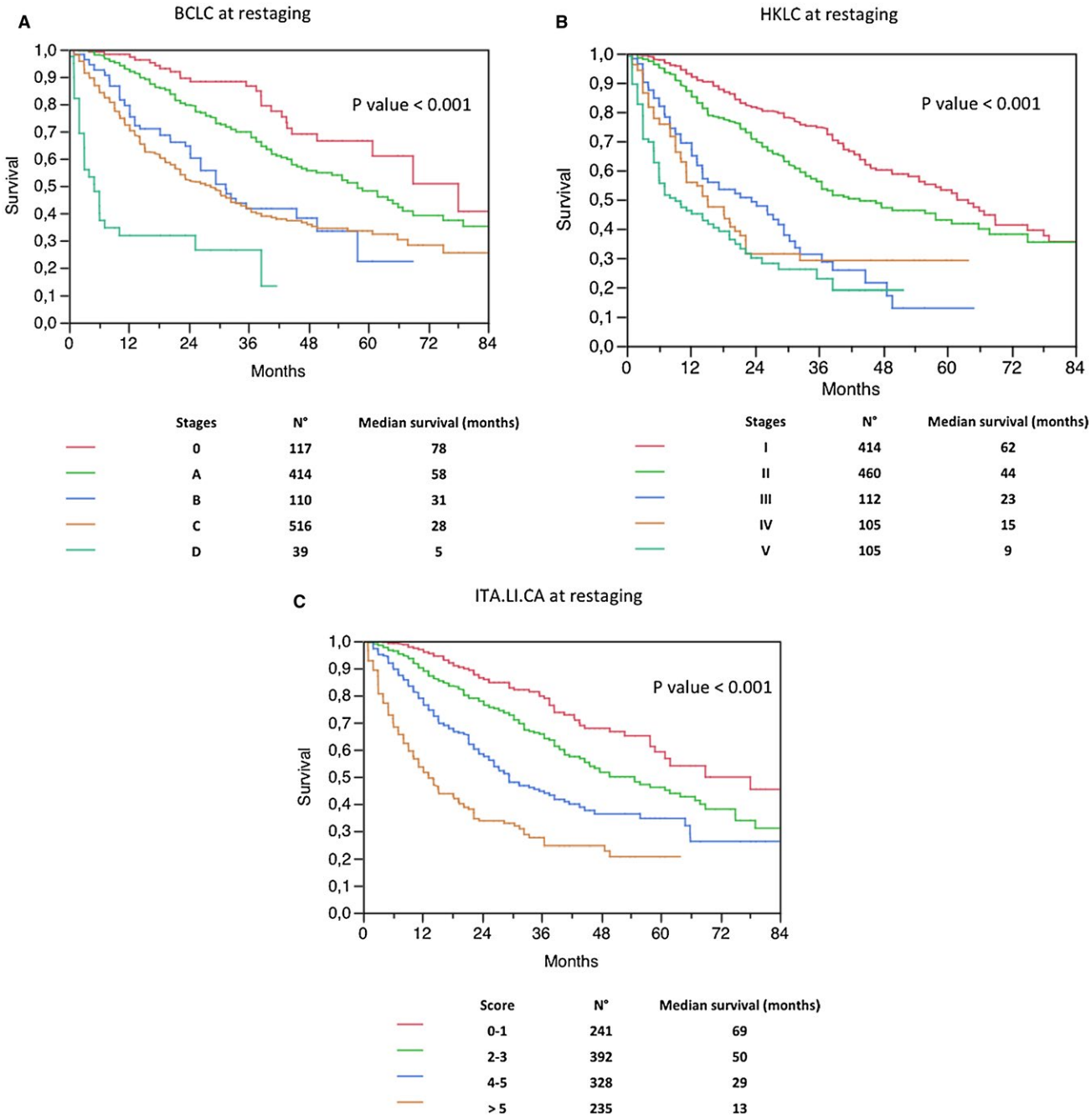

FIG. 2. Survival curves according to BCLC (A), HKLC (B), and ITA.LI.CA score quartiles (C) at restaging in the training cohort.

Table S4). The dynamic trend of some relevant variables were also analyzed (stated as Δ). These analyses demonstrated that not only the final value at restaging but also any change in a number of variable parameters during the follow-up period had an impact on survival. To test whether these variables and the changes associated with survival improved the prognostic performance of the ITA.LI.CA score at restaging, a multivariable analysis was performed. The final model is shown in Supporting Table S5. Although no dynamic variable remained independently associated with prognosis, MELD at restaging (hazard ratio [HR] 1.06, $P < 0.001$), PD after the first treatment (HR 2.07, $P < 0.001$), and nonsurgical treatment after restaging (HR

TABLE 3. Prognostic Ability of Different Prognostic Systems at Baseline and at Restaging

Prognostic system	AIC	C-Index	χ^2 Test	lr Test, *P* Value
ITA.LI.CA at restaging	**4908.583**	**0.7071**	**213.08**	-
HKLC at restaging	4922.160	0.6900	267.25	23.80, <0.001
CLIP at restaging	4960.322	0.6788	168.48	68.05, <0.001
BCLC at restaging	4976.321	0.6659	113.72	86.07, <0.001
HKLC baseline	5054.732	0.6213	116.94	156.37, <0.001
ITA.LI.CA baseline	5071.975	0.6092	89.27	171.58, <0.001
BCLC baseline	5079.535	0.6049	52.48	189.35, <0.001
CLIP baseline	5076.824	0.5839	49.60	184.55, <0.001
ITA.LI.CA restaging model	**4774.709**	**0.7532**	**335.62**	**–109.49, 1.000**

In each column, the Akaike Information Criterion (AIC) have been reported as the first value, the C-index as the second value, and the test for trend chi-square as the third value. The lower the AIC value, the higher the discriminatory ability of the prognostic system. The higher the C-index and the test for trend chi-square, the higher the discriminatory ability and monotonicity of gradients of the prognostic system.
In addition, in each column the ITA.LI.CA score was compared with other systems by using the likelihood ratio test.
Abbreviations: χ^2, chi-square; AIC, Akaike Information Criterion; BCLC, Barcelona Clinic Liver Cancer; C, concordance; CLIP, Cancer Liver Italian Program; HKLC, Hong Kong Liver Cancer; ITA.LI.CA, Italian Liver Cancer; lr, likelihood ratio.

TABLE 4. Construction of a Simple, User-Friendly ITA.LI.CA Restaging Model

Prognostic Factor	Stage, Score, or Value	Estimate ± Standard Error	*P* Value	Points*
MELD at restaging	Per point	0.06 ± 0.01	<0.001	0.2
ITA.LI.CA score at restaging	Per point	0.17 ± 0.02	<0.001	0.5
Response to first treatment	CR, PR, SD	0.82 ± 0.12	<0.001	0
	PD	0.17 ± 0.06	0.0029	2
Treatment after restaging	LT	0		0
	LR	0.75 ± 0.47	0.110	2
	ABL	1.10 ± 0.80	0.001	3
	IAT	1.30 ± 0.96	**<0.001**	4
	SOR	1.73 ± 1.10	**<0.001**	5
	Other	1.78 ± 1.28	**<0.001**	5
	BSC	1.85 ± 1.46	**<0.001**	6

*Points = estimate × 3, rounded.
Abbreviations: BSC, best supportive care; IAT, intra-arterial treatment; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PD, progressive disease; PR, partial response; SD, stable disease; SOR, sorafenib.

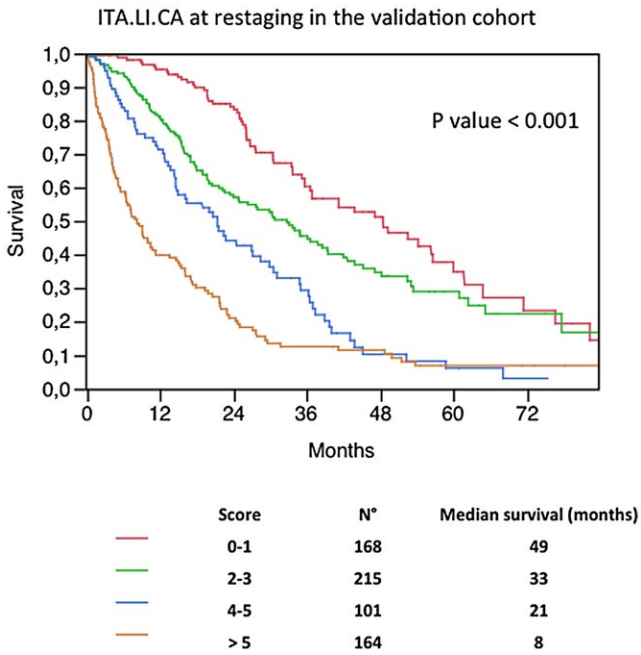

FIG. 3. Survival curve according to ITA.LI.CA score quartiles at restaging in the validation cohort.

from 2.93 with ABL to 6.30 with BSC) maintained their prognostic independence from the ITA.LI.CA score at restaging. The inclusion of these variables improved the C-index of the ITA.LI.CA prognostic score system (0.707 vs. ITA.LI.CA + additional variables, 0.769).

In building a simple, user-friendly restaging model, four main prognostic factors were selected: ITA.LI.CA score at restaging, MELD score at restaging, response to first treatment, and treatment modality after restaging. For the final score, each factor was weighted accordingly: ITA.LI.CA score, half point was assigned for each increase point of the score; MELD at restaging, 0.2 point was assigned for each increase point of the score; response to first treatment, two points were assigned for a progressive disease, zero points were assigned for all other cases; treatment modality after restaging, 0 points were assigned for LT, 2 for LR, 3 for ABL, 4 for IAT, 5 for SOR and OTHER, and 6 points for BSC (Table 4). In turn, a simple formula was created to calculate the ITA.LI.CA restaging model:

2 (if progressive disease after first therapy) + 0.2 * (MELD at restaging - 6) + 0.5 * (ITA.LI.CA score at restaging) + treatment choice at restaging (LT = 0; LR = 2; ABL = 3; IAT = 4; SOR = 5; OTHER = 5; BSC = 6).

The discrimination ability of the new ITA.LI.CA restaging model was confirmed by the broad separation

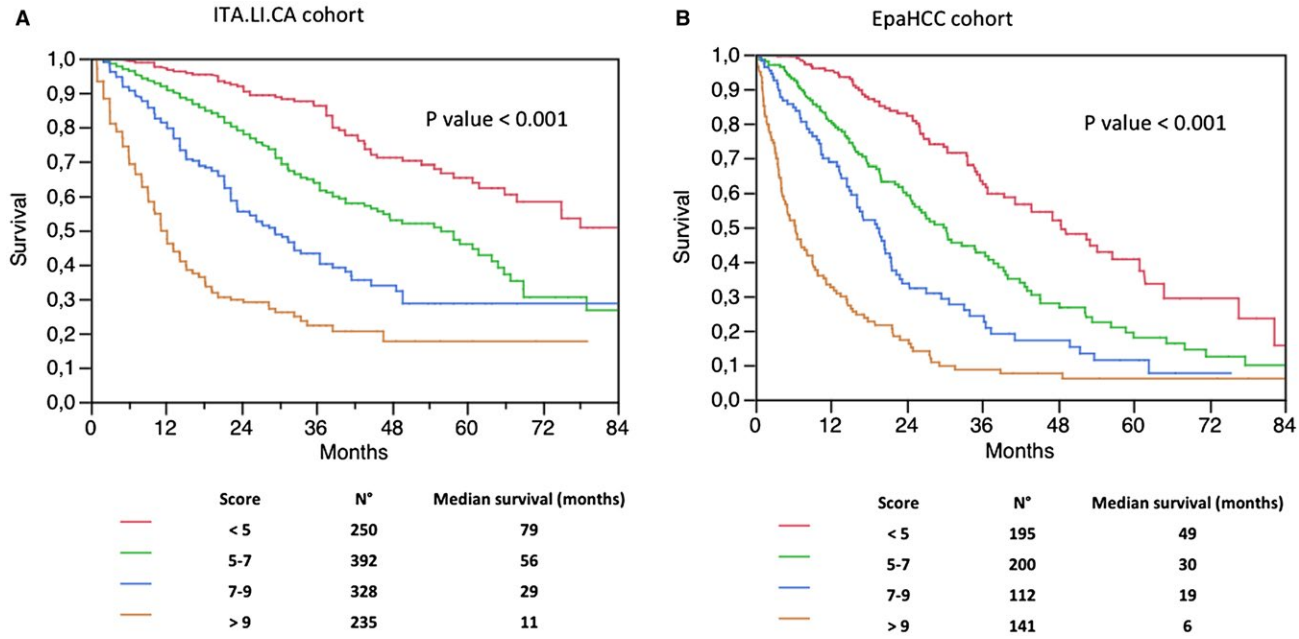

FIG. 4. Survival curves according to the new ITA.LI.CA restaging model quartiles in the ITA.LI.CA (A) and in the EpaHCC (B) cohorts.

of survival curves associated with the different quartiles of the model (Fig. 4A).

VALIDATION OF ITA.LI.CA RESTAGING MODEL

The characteristics of the validation cohort enrolled from the EpaHCC database are described in the Supporting material (Supporting Table S6). To examine which staging system had the best prognostic power, each system was assessed using the validation cohort both at the time of the first HCC diagnosis and at restaging. The ITA.LI.CA prognostic system had the lowest AIC value among patients (3952.010) and the highest C-index (0.723) at restaging, indicating the best discriminatory ability and monotonicity of gradients (Supporting Table S7). The discriminatory ability of the ITA.LI.CA system was demonstrated by the optimal separation of survival curves associated with different prognostic subgroups (Fig. 3). Similar to the training cohort, the ITA.LI.CA restaging model (Table 4) demonstrated the best prognostic performance (C-index = 0.745) in the validation cohort as compared with other available staging systems (Supporting Table S7), with a broad separation of survival curves associated with the different quartiles of the model (Fig. 4B).

Discussion

Over the last 20 years, a static and simplistic vision of HCC clinical management has prevailed in international guidelines.[2,3] According to this view, prognostic assessment has been performed using systems/scores based on variables available at the time of diagnosis. In routine clinical practice, these time-independent algorithms are sequentially applied to the patients during the follow-up, without regard to the fact that most patients with HCC have a complex disease history characterized by multiple consecutive treatments, requiring ongoing reassessment and restaging. With this in mind, we sought to analyze the prognostic relevance of restaging. Specifically, we explored (1) whether, how much, and how frequently patients with HCC change their initial stage after the first treatment, and (2) whether the performance of the most used staging systems changed at restaging after the first treatment. Indeed, the performance of each prognostic system changed compared with the baseline (Table 3). This was largely due to the fact that the oncologic composition of the population varied over

the follow-up, with only 35% maintaining stable disease, whereas most patients were either down-staged by the treatment (about one third) or had disease progression (Table 2). To date, the concept of down-staging in patients with HCC has been exclusively adopted for potential candidates for LT.[18,19] The current study demonstrated that the concept of down-staging can be applied to all patients with HCC and is an important factor that affects the performance of the prognostic system.

Of note, the prognostic performance of the various systems at baseline had a discriminatory power that was worse than previously reported.[6] The reason for these findings may have been related to selection bias. In particular, according to our study design, patients undergoing LT or BSC as initial therapy were excluded, as were patients who experienced an early death after the first therapy, as these patients lacked information on restaging at the time of the second treatment.

The current study also demonstrated that the ITA.LI.CA score[6] had the best prognostic discriminatory power both at the time of initial HCC diagnosis and following primary HCC treatment at the time of restaging. The difference in predictive ability between the ITA.LI.CA and BCLC systems (those more frequently used in Western countries) was clear when examining Figs. 1 and 2.

Of note, when other variables were included in the ITA.LI.CA staging system, the accuracy of the staging system improved at the time of restaging (Supporting Table S5; Table 4). For example, deterioration of liver function (i.e., MELD score at restaging) was an independent prognostic factor of prognosis at restaging. This finding is consistent with a recent ITA.LI.CA study from Cabibbo et al.[20] that examined radically treated patients with hepatitis C virus and HCC. Another relevant variable to consider at restaging after first therapy was progressive disease.[21,22] These factors were probably surrogate markers of biologically aggressive tumors.

Surgery as second therapy was another independent prognostic factor at restaging.

The inclusion of a treatment-related variable in a prognostic model may be criticized, as treatment choice is usually a function of tumor staging, patient functional status, and liver function—all variables already included in the ITA.LI.CA score. We decided, however, to maintain choice of surgical treatment as a variable of the ITA.LI.CA restaging model for three main reasons.

First, the possibility to treat HCC recurrences surgically is a well-known independent prognostic factor already included in several other multivariable survival models of recurrent HCC.[23,24]

Second, a recent study performed in a large cohort of U.S. patients with HCC[25] had emphasized that treatment choice had an important prognostic impact on survival independently from HCC staging classification. A clear therapeutic hierarchy exists, with surgical therapy having the highest impact on survival compared with nonsurgical therapies. In this study, multidisciplinary evaluation of patients with HCC also had an independent impact on survival. Collectively, the data strongly suggest that treatment related variables (i.e., treatment choice, multidisciplinary approach) should be included in prognostic survival models of patients with HCC.

Third, to demonstrate the crucial prognostic role of treatment decision at restaging, we also calculated the C-index (discrimination ability) of a revised restaging model in which the variable "treatment after restaging" was removed. We found that in this revised restaging model, the C-index considerably decreased from 0.753 (Table 3) to 0.726 (restaging model excluding treatment) in the training cohort, and from 0.7448 (Supporting Table S7) to 0.7238 in the validation cohort.

In conclusion, restaging improved the prognostic performance of all systems examined, because a relevant stage migration phenomenon was observed compared with baseline. Among available systems, the ITA.LI.CA score demonstrated the best discriminatory power in predicting survival both at the time of HCC diagnosis and at restaging. Additional variables, such as MELD score at restaging, response to first therapy, and nonsurgical therapy as second therapy, improved prognostic ability when considered in conjunction with the ITA.LI.CA score. A new, simple ITA.LI.CA restaging model was developed, and this new score had the best prognostic ability both in the training and in the validation cohorts. These data may help better predict the prognosis of patients undergoing the first treatment of HCC, as well as those patients in need of restaging thereafter.

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Other members of the EpaHCC group: UOC Gastroenterologia, Ospedale Valduce, Italy: Giancarlo Spinzi, Anna Toldi; UOC di Medicina Interna, Ospedale S.Maria del Prato, Feltre, Italy: Giancarlo Parisi; Dipartimento Medicina, Università di Verona, Italy: Andrea Salmi; U.O.D. Epatologia, Ospedale Civile di Brescia, Brescia, Italy: Angelo Rossini; U.O. di Ecointerventistica, Dipartimento di diagnostica per immagini, P.O. Pineta Grande, Castelvolturno, Italy: Giampiero Francica; UO Gastroenterologia—Ospedale Civile "S. Anna" di Ferrara, Italy: Sergio Boccia; Strutture Complessa di Medicina Interna a indirizzo epatogastroenterologico, Cattedra di Gastroenterologia Seconda Universita` di Napoli— Ospedale Policlinico, Italy: Ilario De Sio; Dipartimento Scienze chirurgiche, oncologiche e gastroenterologiche—Policlinico Universitario Padova ,Italy: Anna Giacomin; UO Medicina Interna I—Ospedale "Civico e Benfratelli," Palermo, Italy: Mario Mitra Mario, Alberto Maranghini Alberto; UOC Gastroenterologia ed Epatologia–Ospedale G. da Saliceto, Piacenza, Italy: Gianmaria Prati; Azienda Ospedaliero Universitaria Pisana—UO Epatologia—Presidio di Cisanello, Pisa, Italy: Filippo Oliveri; U.O. Gastroenterologia Azienda Ospedaliera "G. Salvini" Ospedale di Rho, Italy: Barbara Omazzi; UO Gastroenterologia—Ospedale Infermi, Rimini, Italy: Luigi Solmi; Azienda Ospedaliera S.Andrea, Roma, Italy: Paola Begini, Michela Di Fonzo; Unita` Operativa Gastroenterologia, San Giovanni Rotondo, Italy: Fulvia Terracciano; UO Gastroenterologia-Ospedale San Bortolo, Vicenza, Italy: Alessandro D'Alessandro.

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Author names in bold designate shared co-first authorship.

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