Application of the Intermediate-Stage Subclassification to Patients with Untreated Hepatocellular Carcinoma

25 July 2025

Application of the intermediate stage sub-classification to patients with untreated hepatocellular carcinoma

Short title: Sub-classification of untreated intermediate stage HCC.

Edoardo G. Giannini, MD, PhD, FACG,[1] Alessandro Moscatelli, MD,[1] Gaia Pellegatta, MD,[1] Alessandro Vitale, MD,[2] Fabio Farinati, MD,[3] Francesca Ciccarese, MD,[4] Fabio Piscaglia, MD,[5] Gian Lodovico Rapaccini, MD,[6] Maria Di Marco, MD,[7] Eugenio Caturelli, MD,[8] Marco Zoli, MD,[9] Franco Borzio, MD,[10] Giuseppe Cabibbo, MD,[11] Martina Felder, MD,[12] Rodolfo Sacco, MD,[13] Filomena Morisco, MD,[14] Gabriele Missale, MD,[15] Francesco Giuseppe Foschi, MD,[16] Antonio Gasbarrini, MD,[17] Gianluca Svegliati Baroni, MD,[18] Roberto Virdone, MD,[19] Alberto Masotto,[20] Franco Trevisani, MD,[21] for the Italian Liver Cancer (ITA.LI.CA) group.

[1]Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova, Genova; [2]Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Unità di Chirurgia Epatobiliare e dei Trapianti Epatici, Università di Padova, Padova [3]Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Unità di Gastroenterologia, Università di Padova, Padova; [4]Divisione di Chirurgia, Policlinico San Marco, Zingonia; [5]Dipartimento di Scienze Mediche e Chirurgiche, Unità di Medicina, Alma Mater Studiorum – Università di Bologna, Bologna; [6]Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma; [7]Divisione di Medicina, Azienda Ospedaliera Bolognini, Seriate; [8]Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo; [9]Dipartimento di Scienze Mediche e Chirurgiche, Unità di Medicina Interna, Alma Mater Studiorum – Università di Bologna, Bologna; [10]Dipartimento di Medicina, Unità di Radiologia, Ospedale Fatebenefratelli, Milano; [11]Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Gastroenterologia, Università di Palermo, Palermo; [12]Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano; [13]Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa; [14]Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli; [15]Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma, Parma; [16]Dipartimento di Medicina Interna, Ospedale per gli Infermi di Faenza, Faenza; [17]Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma; [18]Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona; [19]Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo; [20]Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar; [21]Dipartimento di Scienze Mediche Chirurgiche, Unità di Semeiotica Medica, Alma Mater Studiorum – Università di Bologna, Bologna; Italy.

Address for correspondence:
Edoardo G. Giannini, M.D., Ph.D., F.A.C.G.
Gastroenterology Unit, Department of Internal Medicine,
University of Genoa,
Viale Benedetto XV, no.6
16132, Genoa, Italy.
Phone +39 010 353 7950
Fax: +39 010 353 8638
e-mail: egiannini@unige.it

Other members of the ITA.LI.CA group:

Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum - Università di Bologna: Luigi Bolondi, Maurizio Biselli, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Annagiulia Gramenzi, Donatella Magalotti, Anna Pecorelli, Carla Serra, Laura Venerandi; *Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova*: Alessia Gazzola, Francesca Murer, Caterina Pozzan, Veronica Vanin; *Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia*: Paolo Del Poggio, Stefano Olmi; *Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia*: Claudia Balsamo, Elena Vavassori; *Dipartimento di Medicina Clinica e Sperimentale, Università di Padova*: Luisa Benvegnù; *Dipartimento di Malattie Apparato Digerente e Medicina Interna, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia*: Alberta Capelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli; *Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma*: Giulia Bosco; *Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo*: Paola Roselli; *Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo*: Serena Dell'Isola, Anna Maria Ialungo, Elena Rastrelli; *Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova*:, Antonino Picciotto, Vincenzo Savarino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo:* Maria Rosa Barcellona, Calogero Cammà, Giuseppe Cabibbo, Andrea Costantino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo*: Andrea Affronti; *Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano*: Andrea Mega; *Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma*: Emanuele Rinninella; *Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa*: Valeria Mismas; *Dipartimento di Medicina Interna; Ospedale per gli Infermi di Faenza, Faenza*:, Arianna Lanzi, Federica Mirici Cappa, Alessandro Musetto, Elga Neri, Giuseppe Francesco Stefanini, Alessandra Suzzi, Stefano Tamberi, Omero Triossi; *Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma:* Elisabetta Biasini, Emanuela Porro; *Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli:* Maria Guarino; *Clinica di Gastroenterologia, Università Politecnica delle Marche*, *Ancona*: Gianluca Svegliati Baroni, Laura Schiadà; *Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar*: Maria Chiaramonte, Fabiana Marchetti, Matteo Valerio.

ABSTRACT

Objective: The Barcelona Clinic Liver Cancer (BCLC) intermediate stage (BCLC B) includes a heterogeneous population of patients with hepatocellular carcinoma (HCC). Recently, in order to facilitate treatment decisions, a panel of experts proposed to sub-classify BCLC B patients. In this study, we aimed to assess the prognostic capability of the BCLC B stage re-classification in a large cohort of patients with untreated HCC managed by the Italian Liver Cancer (ITA.LI.CA) Group.

Methods: We assessed the prognosis of 269 untreated HCC patients observed in the period 1987-2012 who were re-classified according to the proposed sub-classification of the BCLC B stage from stage B1 to B4. We evaluated and compared the survival of the various sub-stages.

Results: Median survival progressively decreased from stage B1 (n=65, 24.2%: 25 months) through stages B2 (n=105, 39.0%: 16 months) and B3 (n=22, 8.2%: 9 months), to stage B4 (n=77, 28.6%: 5 months; $P<0.0001$). Moreover, we observed a significantly different survival between contiguous stages (B1 *versus* B2, $P=0.0002$; B2 *versus* B3, $P<0.0001$; B3 *versus* B4, $P=0.0219$). In multivariate analysis, the BCLC B sub-classification ($P<0.0001$), MELD score ($P=0.0013$), and platelet count ($P=0.0252$) were independent predictors of survival.

Conclusions: The sub-classification of the intermediate stage HCC predicts the prognosis of patients with untreated HCC. The prognostic figures identified in this study may be used as a benchmark to assess the efficacy of therapeutic intervention in the various BCLC B sub-stages, while it remains to be established whether incorporation of the MELD score might improve the prognosis of treated patients.

Key-words: cirrhosis; survival; MELD score; staging; intermediate stage.

STUDY HIGHLIGHTS

What is current knowledge?

- Patients with intermediate stage hepatocellular carcinoma have a wide survival range, mainly due to the fact that this stage include a heterogeneous group of patients.
- A panel of experts recently proposed to sub-classify the hepatocellular carcinoma intermediate stage into various sub-stages on the basis of tumor burden, liver function, and performance status.
- As of today, this proposed sub-classification has not been fully validated and its prognostic accuracy in patients with untreated hepatocellular carcinoma is unknown.

What is new here:

- Sub-classification of the intermediate stage, untreated hepatocellular carcinoma has prognostic relevance, being able to identify sub-stages with different survival.
- Use of the Model for End-stage Liver Disease may provide additional prognostic information in the early sub-stages of the intermediate stage.
- The survival figures that have been observed in the various sub-stages may be used to counsel patients, and to provide a benchmark against which potential therapies can be tested.

INTRODUCTION

Despite implementation of surveillance programs for the early diagnosis of hepatocellular carcinoma (HCC), a significant proportion of patients are currently diagnosed with large tumor burden; moreover, even if HCC is diagnosed in a non-advanced stage, some patients may have mildly decompensated liver disease [1-3]. Patients with these characteristics are considered by the Barcelona Clinic Liver Cancer (BCLC) classification as patients with intermediate stage HCC (BCLC B), and their primary therapeutic indication is trans-catheter arterial chemoembolization [4-6]. Nevertheless, some studies have emphasised the fact that the BCLC B stage includes a heterogeneous population of HCC patients, who have varying degrees of both liver function impairment and tumor burden [7-9]. In clinical practice, this finding often translates into the application of different therapeutic approaches – thus providing evidence that a single therapeutic option may not fit all intermediate stage patients – and different survival expectancy [7-11]. Moreover, BCLC B patients represent approximately 30% of patients with HCC, and therefore a rigorous prognostic stratification linked to the most appropriate treatment option is eagerly awaited for this population [12].

Recently, taking into account the marked heterogeneity of this population, a panel of experts has proposed to sub-classify patients with intermediate stage HCC, suggesting possible treatment options for each sub-stage in order to facilitate treatment decisions in clinical practice.[8] According to these suggestions, BCLC B patient were re-classified into 4 sub-groups on the basis of impairment in liver function assessed by the Child-Pugh score, tumour burden staged according to the Milan and "up-to-seven" *criteria*, and patients' performance status (PS), also including patients with tumour-related PS 1, included in the advanced HCC stage (BCLC C) [7]. This sub-classification was mainly based on experts' opinions derived from the results of studies carried out in BCLC B patients, and its prognostic capability has never been tested. Indeed, few studies assessing the

prognostic power of the BCLC B sub-classification have been recently published, but they report contrasting results likely due to the presence of the confounding effect caused by a non-standardised therapeutic management [13-16]. A reliable assessment of the prognostic ability of the BCLC-B sub-classification can be obtained by analysing the "natural history" of *untreated* BCLC-B patients, and definitively confirmed with a prospective study in which the treatment choice should follow the indications of the algorithm.

In this study our aim was to assess the prognosis of a large population of untreated patients with HCC who were re-classified according to the proposed sub-classification of the intermediate (BCLC B) stage. The evaluation of the outcome of untreated BCLC B patients allows us to test the prognostic capability of the proposed sub-classification without incurring in the potential bias of treatment allocation, thus providing a solid point of reference for comparison of survival once a determined treatment is applied to a definite sub-population.

PATIENTS AND METHODS

Patients

The Italian Liver Cancer (ITA.LI.CA) database currently contains data of 5,136 HCC patients consecutively diagnosed with HCC from 1987 to 2012 at 21 Italian medical institutions in Italy. These data were collected prospectively and updated every 2 years with information on the follow-up of the patients. After data entry by any single centre, the consistency of the dataset was checked by the group coordinator (F.T.) and, when clarification or additional information was needed, it was resubmitted to each centre before statistical evaluation. For the purpose of this study we included all intermediate stage patients (BCLC B) who received no anti-cancer treatment but best supportive care alone or tamoxifen and whose data were available to assess BCLC stage and calculate Model for End-stage Liver Disease (MELD) score (74 patients were excluded due to lack of data for the calculation of the MELD score) [4, 17]. Patients who received tamoxifen (n=101, 37.5%) were included into this study due to the demonstrated lack of any effect of this drug on survival of HCC patients [18]. Moreover, we performed a sensitivity analysis assessing the survival of patients who received best supportive care alone and tamoxifen and found no statistically significant difference in median survival (tamoxifen, 12 months *versus* best supportive care alone, 13 months; *P*=0.148; Supplementary Figure 1). The reasons for treatment withdrawal were various and related to the presence of co-morbidities preventing any therapeutic approach, advanced age, advanced tumour stage, poor residual liver function in patients not candidates for liver transplantation, and refusal of treatment by the patient.

Methods

Common biochemical liver tests and tests used to calculate the MELD score were carried out by conventional methods using commercially available assays. Likewise, test used to identify the

aetiology of liver disease were those available at each centre at the time of patients' inclusion. The MELD score was calculated in all patients according to the original formula proposed by the Mayo Clinic group: 3.78 * $\log_e$ (bilirubin [mg/dl]) + 11.2 * $\log_e$ (I.N.R.) + 9.57 * $\log_e$ (creatinine [mg/dl]) [17, 19]. The presence of cirrhosis was assessed by the physician in charge of the patient according to histological or unequivocal clinical and instrumental evidence, and liver function was evaluated using the Child-Pugh classification [20]. The diagnosis of HCC was made by ultrasound-guided biopsy or by characteristic, contrast-enhanced, radiological imaging results according to the guidelines published at the time of patients inclusion. Cancer size and stage were evaluated by radiological imaging, and PS was assessed according to the Eastern Cooperative Oncology Group (ECOG) [21]. Briefly, an ECOG PS score of 0 is assigned to asymptomatic patients (fully active, able to carry on all pre-disease activities without restriction), a PS score of 1 to symptomatic but completely ambulatory patients (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), a PS of 2 to symptomatic patients who spend less than 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities), a PS of 3 to symptomatic patients who spend more than 50% of the day-time in bed but are not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours), and a PS of 4 to bed-bound patients (completely disabled, cannot carry on any self-care, totally confined to bed or chair).

Cancer stage was assessed using both the Milan criteria and the up-to-seven criterion. The Milan criteria encompass a single tumor ≤5 cm or a maximum of 3 total tumors with none >3 cm, while the up-to-7 criterion combines the number of nodules and the size of the largest tumor, with the sum being no more than 7 [e.g., 3 nodes up to 4 cm in size (3+4=7)] [22, 23].

Intermediate stage patients were further subdivided according to the sub-classification of the BCLC B stage proposed by Bolondi et al. in 4 sub-stages from B1 to B4 (Table 1) [7]. Patients

survival was defined as the time – expressed in months – elapsed from the date of HCC diagnosis and the date of death or the last follow-up information.

Statistical analysis

Continuous data are shown as median value and range, and discrete variables as absolute and relative frequencies. Comparison of continuous data was carried out using the Mann-Whitney *U*-test, and comparison of discrete variable using the Fisher's exact test or the χ^2-test with Yates correction, as appropriate. Cumulative overall survival was estimated by the Kaplan-Meier method, and statistical comparison of survival distribution was analysed by the log-rank test. Associations with a *P*-value ≤0.1 at univariate analysis were entered into a Cox's stepwise multivariate regression analysis where the cut-offs for platelet count and MELD score was the median value of the series, for the year of diagnosis we used two groups (1987-2000 vs 2001-2012), while for age we used the commonly accepted definition of elderly (>65 years), and for alpha-fetoprotein we used both the upper limit of normal (*i.e.*, 10 ng/mL) and an arbitrary cut-off of 400 ng/mL. A *P*–value <0.05 in a two-tailed test was considered statistically significant. Statistical analysis was performed using MedCalc statistical package (MedCalc Software, Mariakerke, Belgium).

Ethics

The ITA.LI.CA database management conforms to the past and current Italian legislation on privacy and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for the study was obtained by the Institutional Review Board of the participating centres.

RESULTS

Baseline cohort characteristics

A total of 269 patients with untreated HCC were included into this study. Patients were prevalently males (n=204, 75.8%), their median age was 69 years (24-95 years), and 171 patients (63.6%) were older than 65 years. The main aetiology of liver disease was infection with hepatitis virus alone (n=154, 57.2%: n=116 hepatitis C virus, n=27 hepatitis B virus, n=11 hepatitis B and C viruses) or with alcohol abuse (n=37, 13.8%). Ascites and hepatic encephalopathy were present in 76 (28.3%) and 12 patients (4.5%), respectively, while 191 patients (66.1%) had esophageal varices. Median albumin, bilirubin, and creatinine levels were 35 g/dL (21-50 g/dL), 1.4 (0.6-14.0 mg/dL), and 1.0 mg/dL (0.5-6.1 mg/dL), respectively, and median INR value was 1.30 (0.91-2.56). Median MELD score was 11 (6-32), and median serum alpha-fetoprotein was 108 mg/mL (6-72,918 ng/mL). In the whole cohort, overall median survival was 13 months. Causes of death were HCC progression in 90 patients (51.1%), liver failure in 38 patients (21.6%), gastrointestinal bleeding in 10 patients (5.7%), infection in 4 patients (2.3%), various causes in 12 patients (6.8%), while in 22 patients the causes of death were not known (12.5%).

Characteristics and survival of patients according to the proposed sub-classification of the intermediate (BCLC B) stage

Patients were subdivided into 4 stages according to the BCLC B sub-classification, from stage B1 to B4 (Table 1). According to this sub-classification, 65 patients were classified B1 (24.2%), 105 patients B2 (39.0%), 22 patients B3 (8.2%), and 77 patients B4 (28.6%). The main characteristics of patients subdivided according the intermediate stage HCC sub-classification are shown in Table 2. Among the demographic, biochemical and clinical parameters, presence of oesophageal varices (P<0.0001), platelet counts (P=0.0225), serum albumin (P<0001) and bilirubin levels (P<0.0001),

INR values (*P*<0.0001), and MELD scores (*P*<0.0001) were significantly different among the various sub-stages.

Median survival progressively decreased from stage B1 (25 months) through stages B2 (16 months), B3 (9 months) and B4 (5 months, *P*<0.0001, Figure 1). Moreover, we observed a significantly different survival between contiguous stages [Figure 2A: B1 *versus* B2, *P*=0.0002; Figure 2B: B2 *versus* B3, *P*<0.0001; Figure 2C: B3 *versus* B4, *P*=0.0219).

Table 3 shows the results of the univariate analysis for survival in the whole cohort. A MELD score <11 (*P*<0.0001), the absence of esophageal varices (*P*=0.0003), and being diagnosed after the year 2000 (*P*=0.0009) were associated with a better survival, while low platelet counts (*P*=0.065) and very high alpha-fetoprotein levels (*P*=0.073) were marginally associated with worse survival. In Cox's regression multivariate analysis, the BCLC B sub-classification [Hazard Ratio=2.194 (95% confidence interval, 1.846-2.604), *P*<0.0001], MELD score (Hazard Ratio=1.899, (95% confidence interval, 1.287-2.800), *P*=0.0013], and platelet count [Hazard Ratio=1.499, (95% confidence interval, 1.053-2.132), *P*=0.0252] were independent predictors of survival.

Lastly, we evaluated the prognosis of the various BCLC sub-stages further subdivided according to overall median MELD score. Table 4 shows that the only sub-stage where further break-down of patients according to the MELD score was statistically significant and clinically meaningful was stage B1, with an observed median survival in B1 patients with a MELD score ≤11 of 33 months and in those with a MELD score >11 of 20 months (*P*=0.003). Less impressive, but statistically significant, was the different survivals observed in B2 patients (*P*=0.047). Instead, MELD score did not provide additional prognostic information in B3 and B4 patients.

DISCUSSION

Intermediate stage patients represent approximately 30% of patients with HCC, and their prognosis is quite variable due to the inclusion in the same stage of a population with various degrees of liver dysfunction and different tumour burden [8, 12]. Due to these findings, despite clinical guidelines suggest an unique first-line treatment for this stage, in clinical practice patients are often treated with various therapeutic approaches [9-11]. With the aim to rationalize patients stratification and therefore improve the staging-treatment association, a panel of experts recently suggested to sub-stage patients with intermediate HCC, basing their suggestions on the break-down of patients according to liver function, tumour burden, and tumour-induced impairment of everyday activities [7]. However, this sub-classification has never been fully validated, and the few recent studies that tried to assess its prognostic capability were carried out mainly in patients treated with trans-catheter arterial chemoembolization, reporting contrasting results [13-16].

In this study, the median survival of untreated patients with intermediate stage HCC slightly exceeded one year, a finding consistent – yet with a minimal improvement – both with the results of our previous study carried out in a limited number of untreated, intermediate patients (*i.e.*, 10 months) and the placebo arm of the patients with intermediate stage (BCLC B) included in the SHARP trial (*i.e.*, 11.4 months) [24, 25]. The re-staging according to the proposed sub-classification of the BCLC B stage provided an important prognostic indication, since the median survival progressively, and significantly, decreased across all the sub-stages. Thus, discriminatory ability and gradient monotonicity, two essential performance characteristics of a prognostic system, were fulfilled [26]. As a matter of fact, while untreated stage B1 patients showed a median survival overlapping the one we observed in untreated BCLC stage A patients (*i.e.*, 25 months), the prognosis of stage B4 patients was dismal, with a median survival of 5 months, that was even worse than the one previously observed in untreated stage D patients [24]. All in all, these findings

once again emphasise the marked heterogeneity of BCLC B stage, and provide baseline survival figures that may be used to counsel patients and their families, to assess the efficacy of treatments in each sub-stage, and to discourage anticancer treatment when prognosis is unlikely to be improved by therapy.

As far as patients' distribution among the intermediate sub-stages is concerned, it is worth noting that although we selected patients who were not treated, our results are in keeping with those of the studies that assessed the prognosis of sub-classified BCLC B patients treated with trans-catheter arterial chemoembolization [13, 14, 16]. As a fact, stage B1 and B2 patients represented more than half of the population, with stage B2 being the most numerous stage in our cohort as well as in the previous series. However, despite a similar patients' distribution among the various sub-stages, the comparison of other figures – in particular survival – was difficult to perform among studies. In fact, the series presented by Ha et al. and Wang et al. included patients fit enough to undergo trans-catheter arterial chemoembolization and were carried out in Eastern patients, and in one study B3 and B4 stages were merged because of a similar prognosis [13, 14]. Moreover, the study by Wang et al. included more than 70% of patients with chronic HBV infection and with an unknown proportion of patients with cirrhosis [14]. The only study including a Western population somehow similar to ours was performed by Weinmann et al., who obtained a general behaviour of survival similar to the one seen in our study, especially in B1 and B4 stages, after patients who underwent liver transplantation were excluded from the analysis [15]. Indeed, they too observed a wide survival range, spanning from 28.5 to 5.9 months, thus confirming the marked heterogeneity of intermediate stage HCC patients. However, the lack of survival difference between contiguous sub-stages did not allow this study to support the prognostic quality of the BCLC B sub-classification. Nevertheless, as the authors themselves observed, the lack of discriminatory ability could have been caused by the small number of

patients in some sub-stages since, despite a median survival of B3 patients more than double the one of B4 patients (12.3 *versus* 5.9 months), this difference did not reach the statistical significance [15].

Another interesting finding of our study is that MELD score and platelet count were independent predictors of survival in untreated patients with intermediate HCC. We did not use platelet count to further sub-classify the various BCLC B sub-stages due to its marginal statistical significance. Instead, a sensitive analysis indicated that MELD score was able to provide a finer tuning of prognosis in the BCLC B sub-classification, and in particular in stages B1 and B2. The additional prognostic information was particularly striking in stage B1 patients, where a MELD score cut-off of 11 identified two groups of patients with a survival difference of more than one year (33 *versus* 20 months), while the discriminatory ability of MELD score was less evident (17 *versus* 12 months) and only marginally significant in B2 sub-stage patients. The lack of further prognostic stratification provided by the MELD score in B4 patients, on the contrary, was probably due to the presence in this sub-stage of a large proportion of patients with an HCC beyond the "up-to-seven" *criterion* and with a PS 1, thus with a short-term outcome unlikely to be profoundly influenced by the residual liver function.

This study has some undoubted limitations. Firstly, patients were accrued over a long period of time as this was required in order to reach an adequate sample size for this specific clinical question. In this regard, the period of HCC diagnosis turned out to be a predictor of survival, and this may be related to the improvement in clinical care of patients with cirrhosis in more recent years [27-29]. However, when period of HCC diagnosis was included into multivariate analysis, its prognostic relevance was not significant, thus suggesting that other clinical variables weighed more on prognostic assessment. Secondly, another study limitation may be related to the absence of further sub-categorization of patients with viral etiology of disease, as cirrhotic patients

infected with hepatitis B virus may have a better prognosis as compared to patients infected with hepatitis C virus. Nevertheless, among the 154 patients with viral etiology of cirrhosis alone, only 16 patients had hepatitis B virus infection as a single etiological factor, and therefore this sub-analysis was not clinically meaningful and statistically sound. Thirdly, a subgroup of patients included in this study received tamoxifen. Although some authors may still hypothesize a potential effect of tamoxifen – even a negative one – on the prognosis of patients with HCC, we decided to include taxoxifen-treated patients among the untreated patients in this study on the basis of the results of several studies and of a systematic review showing no effect of tamoxifen on prognosis of HCC patients [18]. Moreover, we have previously shown no effect of tamoxifen on survival in a larger series of untreated HCC patients distributed across all BCLC stages, and also in this study we performed a sensitivity sub-analysis of our cohort showing no survival effect of tamoxifen (Supplementary Figure 1) [24]. Fourthly, it may be objected that absence of treatment due to comorbidities or advanced age may represent a bias of the study and therefore flaw its results, however the fact that the main cause of death (*i.e.*, 78.4%) was represented either by tumor progression of liver-related events (*e.g.*, liver failure, gastrointestinal bleeding) seems to be against this objection. Lastly, we acknowledge that it remains to be established whether the results of this study may be generalizable to treated intermediate stage HCC patients since this was not the aim of our study, although we feel that our results provide a first, substantial step in this direction and provide solid data to compare survival in treated patients in the various intermediate stage sub-stages. In this regard, preliminary results of the ITA.LI.CA group seem to show that the sub-classification of the intermediate stage HCC may have prognostic relevance also in treated patients, although we do acknowledge that our results need to be confirmed in prospectively-enrolled, independent, larger cohorts of untreated intermediate stage HCC patients [30].

To conclude, in untreated patients with intermediate stage HCC, further sub-classification on the basis of tumor burden, liver function, and PS have prognostic meaning. Sub-classification of BCLC B patients based on these features identify sub-groups with statistically significant and clinically relevant different prognosis. The survival figures we identified in these untreated patients may be used to compare the potential survival advantage provided by various treatments. Further studies are warranted to assess whether inclusion of the MELD score may provide a finer prognostic tuning and more appropriate treatment allocation.

REFERENCES

1. Davila JA, Morgan RO, Richardson PA, et al. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology 2010; 52: 132-41.

2. Shah SA, Smith JK, Li Y, Ng SC, et al. Underutilization of therapy for hepatocellular carcinoma in the medicare population. Cancer 2011; 117: 1019-26.

3. Giannini EG, Cucchetti A, Erroi V, et al. Surveillance for early diagnosis of hepatocellular carcinoma: how best to do it? World J Gastroenterol 2013; 19: 8808-21.

4. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245-55.

5. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.

6. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-43.

7. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012; 32: 348-59.

8. Piscaglia F, Bolondi L. The intermediate hepatocellular carcinoma stage: Should treatment be expanded? Dig Liver Dis 2010; 42 Suppl 3: S258-63.

9. Leoni S, Piscaglia F, Serio I, et al. Adherence to AASLD guidelines for the treatment of hepatocellular carcinoma in clinical practice: experience of the Bologna Liver Oncology Group. Dig Liver Dis 2014; 46: 549-55.

10. Cucchetti A, Djulbegovic B, Tsalatsanis A, et al. When to perform hepatic resection for intermediate-stage hepatocellular carcinoma. Hepatology 2015; 61: 905-14.

11. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. Liver Int 2015; 35: 1036-47.

12. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006; 44: 723-31.

13. Ha Y, Shim JH, Kim SO, et al. Clinical appraisal of the recently proposed Barcelona Clinic Liver Cancer stage B subclassification by survival analysis. J Gastroenterol Hepatol 2014; 29: 787-93.

14. Wang JH, Kee KM, Lin CY, et al. Validation and modification of a proposed substaging system for patients with intermediate hepatocellular carcinoma. J Gastroenterol Hepatol 2015; 30: 358-63.

15. Weinmann A, Koch S, Sprinzl M, et al. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. Liver Int 2015; 35: 591-600.

16. Yamakado K, Miyayama S, Hirota S, et al. Prognosis of patients with intermediate-stage hepatocellular carcinomas based on the Child-Pugh score: subclassifying the intermediate stage (Barcelona Clinic Liver Cancer stage B). Jpn J Radiol 2014; 32: 644-49.

17. Botta F, Giannini E, Romagnoli P, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated to residual liver function. A European study. Gut 2003; 52: 134-9.

18. Nowak AK, Stockler MR, Chow PK, et al. Use of tamoxifen in advanced-stage hepatocellular carcinoma. A systematic review. Cancer 2005; 103: 1408-14.

19. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33: 464-70.

20. Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding esophageal varices. Br J Surg. 1973; 60: 646-64.

21. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-55.

22. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693-9.

23. MazzaferroV, Llovet JM, Miceli R, et al. Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009; 10: 35-43.

24. Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015; 61: 184-90.

25. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012; 57: 821-9.

26. Trevisani F, Santi V. Prognostication of the outcome of hepatocellular carcinoma: how to rely on science instead of on the art of Nostradamus. Dig Liver Dis 2009; 41: 382-4.

27. Talwalkar JA, Kamath PS. Influence of recent advances in medical management on clinical outcomes of cirrhosis. Mayo Clin Proc 2005; 80: 1501-8.

28. Ripoll C, Genescà J, Araujo IK, et al. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study. Hepatology 2013; 58: 2079-88.

29. Giannini EG, Trevisani F. Improving survival of cirrhosis patients with hepatocellular carcinoma through application of standard of care. Hepatology 2014; 60: 1446-7.

30. Piscaglia F, Pecorelli A, Venerandi L, et al. Clinical validation of a sub-staging proposal of patients with intermeidate HCC (BCLC B). J Hepatol 2013; 58: S48-S49.

Guarantor of the article: Edoardo G. Giannini.

Specific author contributions: Edoardo G. Giannini: design of the work, acquisition, analysis and interpretation of data, drafting the work.

Alessandro Moscatelli, Gaia Pellegatta: acquisition of data, revising the work critically for important intellectual content.

Alessandro Vitale: analysis and interpretation of data, revising the work critically for important intellectual content.

Fabio Farinati, Francesca Ciccarese, Fabio Piscaglia, Gian Lodovico Rapaccini, Maria Di Marco, Eugenio Caturelli, Marco Zoli, Franco Borzio, Giuseppe Cabibbo, Martina Felder, Rodolfo Sacco, Filomena Morisco, Gabriele Missale, Francesco Giuseppe Foschi, Antonio Gasbarrini, Gianluca Svegliati Baroni, Roberto Virdone, Alberto Masotto: acquisition and interpretation of data, revising the work critically for important intellectual content.

Franco Trevisani: design of the work, acquisition and interpretation of data, revising the work critically for important intellectual content.

All the authors approved the final version of the submitted work.

Financial support: None.

Potential competing interests: None.

Note: Preliminary results of this study have been accepted for presentation at the Annual Meeting of the American Association for the Study of Liver Disease (The Liver Meeting® 2015) that will be held in San Francisco, CA, November 13-17, 2015.

LEGEND TO FIGURES

Figure 1.

Kaplan-Meier survival curves of untreated patients with hepatocellular carcinoma subdivided according to the sub-classification of the intermediate stage hepatocellular carcinoma (blue line, BCLC B1; red line, BCLC B2; green line, BCLC B3; yellow line, BCLC B4).

Figure 2.

Kaplan-Meier survival curves in contiguous stages of the BCLC B sub-classification of patients with intermediate stage hepatocellular carcinoma [A: thick line = BCLC B1, dotted line = BCLC B2; B: thick line = BCLC B2, dotted line = BCLC B3; C: thick line = BCLC B3, dotted line = BCLC B4].

Supplementary Figure 1.

Kaplan-Meier survival curves of study patients with hepatocellular carcinoma subdivided according to receipt of best supportive care alone (dashed line) or tamoxifen (solid line).

Table 1. Proposed sub-classification of the intermediate (BCLC B) stage hepatocellular carcinoma patients.

BCLC sub-stage	**B1**	**B2**	**B3**	**B4**
Child-Pugh score	5-6-7	5-6	7	8-9
Beyond Milan and within up-to-seven	In	Out	Out	Any
ECOG performance status (tumor-related)	0	0	0	0-1
Portal vein thrombosis	No	No	No	No

BCLC, Barcelona Cancer Liver Clinic; ECOG, Eastern Cooperative Oncology Group.

Table 2. Main demographic, biochemical, and clinical characteristics of the study population subdivided according to the proposed sub-classification of the intermediate stage hepatocellular carcinoma.

		BCLC B sub-stages			
		B1 (n=65)	**B2 (n=105)**	**B3 (n=22)**	**B4 (n=77)**
Gender	male	47 (85.5)	83 (79.0)	19 (86.4)	55 (71.4)
Age	years	67 (44-92)	69 (43-89)	67 (24-82)	69 (40-95)
Etiology	virus	49 (75.4)	70 (66.7)	15 (68.2)	57 (74.0)
	alcohol	12 (18.5)	20 (19.0)	5 (22.7)	17 (22.1)
	others	4 (6.1)	15 (14.3)	2 (9.1)	3 (3.9)
Albumin	g/dL	3.6 (2.7-4.9)	3.6 (2.8-5.0)	3.4 (2.6-4.5)	3.0 (2.1-4.2)
Bilirubin	mg/dL	1.1 (0.6-2.2)	1.2 (0.3-2.9)	2.1 (0.4-14.0)	2.5 (0.3-12.2)
Creatinine	mg/dL	1.0 (0.6-6.1)	1.0 (0.6-2.6)	1.0 (0.7-2.3)	1.0 (0.5-1.8)
INR		1.28 (0.93-2.28)	1.21 (0.91-2.0)	1.33 (1.11-2.22)	1.43 (1.0-2.56)
Platelet count	$x10^9/L$	126 (45-270)	130 (26-557)	121 (36-345)	103 (37-400)
Esophageal varices	present	37 (56.9)	47 (44.8)	14 (63.6)	66 (85.7)
Child-Pugh score	5	33 (50.8)	62 (59.0)		
	6	24 (36.9)	43 (41.0)		
	7	8 (12.3)		22 (100)	
	8				46 (59.7)
	9				31 (40.3)
MELD	score	11 (6-32)	10 (6-16)	14 (8-19)	15 (8-22)
Alpha-fetoprotein	ng/mL	52 (6-45,000)	68 (6-36,000)	54 (6-18,141)	318 (6-72,918)
Up-to-7 criteria	out		105 (100)	22 (100)	59 (76.6)
ECOG PS	1				65 (84.4)

Data are shown as median and range or absolute value and percentage. Virus category includes patients with viral hepatitis alone and patients with viral hepatitis and alcohol. BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; MELD, Model for End-stage Liver Disease; PS, Performance Status.

Table 3. Results of the univariate analysis for survival in the study cohort.

Parameter	Unit	n	Survival (months)	Hazard Ratio (95% CI)	*P*
Gender	male vs female	204/65	13 vs 13	0.924 (0.645-1.308)	0.636
Age	<65 vs ≥65 years	98/171	12 vs 13	0.917 (0.662-1.253)	0.567
Etiology	non-viral vs viral	78/191	13 vs 13	1.166 (0.842-1.668)	0.330
Year of HCC diagnosis	’87-’00 vs ’01-‘12	145/124	11 vs 17	1.657 (1.239-2.296)	0.0009
Platelet count	<127vs ≥127x10^9/L	143/126	12 vs 15	1.312 (0.982-1.807)	0.065
MELD score	≤11 vs >11	137/132	19 vs 8	0.395 (0.215-0.426)	<0.0001
Alpha-fetoprotein	≤10 vs >10	64/205	13 vs 13	0.850 (0.598-1.190)	0.332
Alpha-fetoprotein	≤400 vs >400	160/109	14 vs 12	0.769 (0.532-1.028)	0.073
Esophageal varices	Absent vs present	105/164	16 vs 11	0.584 (0.417-0.774)	0.0003

HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease.

Table 4. Survival in the various intermediate stage hepatocellular carcinoma sub-stages subdivided according to Model for End-stage Liver Disease score.

	MELD score ≤11		MELD score >11		
Sub-stage	**n**	**Survival (months)**	**n**	**Survival (months)**	***P***
BCLC B1	41	33	20	20	0.003
BCLC B2	80	17	25	12	0.047
BCLC B3	5	6	17	9	0.848
BCLC B4	11	5	66	5	0.250

BCLC, Barcelona Clinic Liver Cancer; MELD, Model for End-stage Liver Disease.