World Journal of Hepatology

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World J Hepatol 2017 December 28; 9(36): 1322-1331

DOI: 10.4254/wjh.v9.i36.1322

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Reverse time-dependent effect of alphafetoprotein and disease control on survival of patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma

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Institutional review board statement: This is a retrospective study based on the revision of anonymous clinical data; no additional interventional procedures or drug was performed/administered to the study population. Therefore, no institutional review board approval was required.

Informed consent statement: This is a retrospective study based on the revision of anonymous clinical data; no additional interventional procedures or drug was performed/administered to the study population. Therefore, no informed consent was obtained by the patients.

Conflict-of-interest statement: The authors declare no conflict

of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: August 27, 2017
Peer-review started: August 30, 2017
First decision: September 21, 2017
Revised: October 12, 2017
Accepted: November 11, 2017
Article in press: November 12, 2017
Published online: December 28, 2017

Abstract

AIM

To characterize the survival of cirrhotic patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) and to ascertain the factors predicting the achievement of disease control (DC).

METHODS

The cirrhotic patients with BCLC stage C HCC evaluated by the Hepatocatt multidisciplinary group were subjected to the investigation. Demographic, clinical and tumor features, along with the best tumor response and overall survival were recorded.

RESULTS

One hundred and ten BCLC stage C patients were included in the analysis; the median overall survival was 13.4 mo (95%CI: 10.6-17.0). Only alphafetoprotein (AFP) serum level > 200 ng/mL and DC could independently predict survival but in a time dependent manner, the former was significantly associated with increased risk of mortality within the first 6 mo of follow-up (HR = 5.073, 95%CI: 2.159-11.916, P = 0.0002), whereas the latter showed a protective effect against death after one year (HR = 0.110, 95%CI: 0.038-0.314, P < 0.0001). Only patients showing microvascular invasion and/or extrahepatic spread recorded lower chances of achieving DC (OR = 0.263, 95%CI: 0.111-0.622, P = 0.002).

CONCLUSION

The BCLC stage C HCC includes a wide heterogeneous group of cirrhotic patients suitable for potentially curative treatments. The reverse and time dependent effect of AFP serum level and DC on patients' survival confers them as useful predictive tools for treatment management and clinical decisions.

Key words: Hepatocellular carcinoma; Cirrhosis; Barcelona Clinic Liver Cancer stage C; Alphafetoprotein; Disease control; Performance status; Survival

Core tip: Refining the prognosis of Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) is crucial to select patients that can get benefit from and be suitable for locoregional or surgical treatments. This study confirms that high alphafetoprotein serum level and DC are the best predictors of mortality for BCLC C patients, highlighting that the effect of these two variables is reverse and dynamic, in a time dependent manner. Outstandingly, performance status has not been found to be a strong predictor of mortality. According to our results, curative treatments should not be "a priori" excluded in a subset of BCLC stage C patients with favorable prognostic factors.

Ponziani FR, Spinelli I, Rinninella E, Cerrito L, Saviano A, Avolio AW, Basso M, Miele L, Riccardi L, Zocco MA, Annicchiarico BE, Garcovich M, Biolato M, Marrone G, De Gaetano AM, Iezzi R, Giuliante F, Vecchio FM, Agnes S, Addolorato G, Siciliano M, Rapaccini GL, Grieco A, Gasbarrini A, Pompili M. Reverse time-dependent effect of alphafetoprotein and disease control on survival of patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma. *World J Hepatol* 2017; 9(36): 1322-1331 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1322.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1322

INTRODUCTION

Hepatocellular carcinoma (HCC) has been recognized as a major health problem, as it ranks third among the leading causes of death due to cancer and is the sixth most common tumor with a worldwide occurrence[1].

While there are several options available for the treatment of HCC, their choice most likely depends on tumor stage, impairment of normal liver function, patient's performance status (PS) and comorbidities. The most widely accepted staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC), which was based on the patients clinical features along with tumor-related variables and therefore categorized five different stages with progressively worsening prognosis and different treatment options[1,2].

The patients with an advanced HCC belong to the BCLC stage C, which includes tumors with macrovascular invasion, and/or extrahepatic spread

and/or mild cancer-related symptoms, PS 1-2 (Eastern Cooperative Oncology Group), and mild to moderate liver function impairment (Child-Pugh stage A-B). The only therapeutic option recommended for BCLC stage C HCC is the drug sorafenib, a multikinase inhibitor that has been reported to extend the overall survival of patients up to nearly 3 mo[3].

Given the higher number of heterogeneous and complex cases encountered in the field-practice, the BCLC classification is often not exhaustive, and the increasing number of new therapeutic options and their combinations makes difficult to strictly adhere to BCLC suggestions. This has been largely demonstrated in other categories of patients such as those belonging to the BCLC stage B group, who had not been subjected to transarterial chemoembolization (TACE), the treatment recommended by the BCLC algorithm, in more than one third of cases[4-6].

The BCLC stage C HCC encompasses a wide spectrum of tumors and patients' with different characteristics that may get benefit from and be suitable for locoregional or surgical treatments[7-9]. Nonetheless, in this stage too, the universal administration of sorafenib to the patients following the BCLC algorithm may sometimes be arguable and other therapeutic options could be explored according to patient's individual conditions.

The current study is principally aimed at characterizing the prognosis of cirrhotic patients with BCLC stage C HCC as assessed by a multidisciplinary team in an Italian tertiary care center. In addition to this, the other objective is the identification of the factors predicting the achievement of disease control (DC).

MATERIALS AND METHODS

The present study was performed at the Agostino Gemelli University Hospital, Rome, Italy. The prospective database of the Hepatocatt multidisciplinary group, containing clinical, tumor and outcome data of all liver cancer subjects evaluated in the seven years at our Institute was reviewed, and the cohort of cirrhotic patients with BCLC stage C HCC were selected as the prime object of the investigation.

The following criteria were adopted for the selection of patients: PS grade $\leqslant$ 2; Child-Pugh class A or B; tumor macrovascular invasion (mainly portal vein and/or hepatic veins and/or inferior vena cava); and/or extrahepatic spread. The HCC was diagnosed by multiphasic contrast-enhanced computed tomography (CT), gadolinium-enhanced magnetic resonance imaging (MRI) and/or by ultrasound-guided biopsy, as per the guidelines of European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[1,2]. Based on the liver function and patients' characteristics, the modalities of HCC treatment were decided by the Hepatocatt multidisciplinary board, comprising of hepatologists, hepatobiliary and transplant surgeons, oncologists, radiologists, and pathologists. The imaging criteria (CT and/or MRI) for assessing the tumor response established by mRECIST were followed[10]. For individual patient, the treatment outcome was documented; DC was achieved in those patients who acquired a stable disease (SD), partial response (PR) or complete response (CR) as the best treatment outcome.

The patients' survival was the measure of success as primary outcome. The follow-up time was defined as the number of months from the entry in the BCLC stage C till their death or last visit. The factors that could predict the achievement of DC were also investigated as secondary endpoint.

Statistical analysis

Statistical analysis was performed using non-parametric tests due to the non normal distribution of data. The continuous variables were expressed as median and range, while the categorical variables as frequencies and percentages.

Pre-treatment variables [Child-Pugh score, PS, number and maximum size of HCC lesions, presence of macrovascular invasion or extrahepatic spread, alphafetoprotein (AFP) serum level, NIACE score value[11], and diabetes] and post-treatment variables (the number of treatments received after entry in the BCLC stage C and the achievement of DC) were considered as prognostic factors of patients' survival. The univariate analysis of survival estimates was performed using the Kaplan-Meier curve and the *log-rank* test was applied to check the differences between the groups. The variables with a $P < 0.100$ were included in the Cox proportional hazard regression model for the multivariate survival analysis, adjusting for gender and age.

The assumption of proportionality was confirmed by plotting the scaled Schoenfeld residuals over the time [log hazard ratio (beta) over time] and by performing a non-proportionality test (Pearson correlation test) for the overall model and for each covariate of the model. Interaction terms were subsequently introduced in the analysis for that factors that varied significantly over time. Fisher's exact test and binomial logistic regression were performed to identify the predictors of DC among pre- and post-treatment variables.

Statistical analysis was carried out using the R statistics program version 3.1.2. All statistical tests were two-sided and differences were considered significant at $P < 0.05$.

RESULTS

A total of 1030 records of liver cancer patients evaluated between May 2008 and May 2015 were reviewed, of which, 146 non-HCC liver tumors and 774 HCC in BCLC stage other than C (0, A, B or D) were disqualified from the study. Therefore, finally, 110 patients classified as BCLC stage C were included in the investigation. Clinical data and tumor characteristics of the study population are given in Table 1.

Table 1 Clinical and tumor characteristics of patients included in the study

Variable	Overall (110)
Age (yr)	67.5 (41-80)
Gender	
Male	91 (82.7)
Female	19 (17.3)
Etiology of liver disease	
Viral (HBV/HCV/HBV and HCV)	70 (63.6)
Alcohol	17 (15.5)
NASH/NAFLD	14 (12.7)
Viral and alcohol	9 (8.2)
PS	
0	33 (30)
1	64 (58.2)
2	13 (11.8)
Diabetes	
No	87 (79.1)
Yes	23 (20.9)
Child-Pugh score	
A	82 (74.5)
B	28 (25.5)
N nodules	
Single	35 (31.8)
2-3	20 (18.2)
> 3 or infiltrating	55 (50)
Maximum size	
⩽ 5 cm	56 (50.9)
> 5 cm	54 (49.1)
Macrovascular invasion	
No	60 (54.5)
Yes	50 (45.5)
Extrahepatic spread	
No	91 (82.7)
Yes	19 (17.3)
Macrovascular invasion and/or extrahepatic spread	
No	49 (44.5)
Yes	61 (55.5)
NIACE	
⩽ 3	84 (76.4)
> 3	26 (23.6)
AFP	
⩽ 200 ng/mL	74 (67.3)
> 200 ng/mL	36 (32.7)
Treatment before BCLC C diagnosis	
No	53 (48.2)
Yes	57 (51.8)
Type of treatment before BCLC C diagnosis (one or more per patient)	
TACE	35
Surgical resection	20
RFA	18
Sorafenib	13
PEI	11
TACE + RFA	8
TARE	4
DSM-TACE	1
Number of treatments after BCLC C diagnosis	
None	22 (20)
Single	32 (29.1)
Multiple	56 (50.9)
Type of treatment after BCLC C diagnosis (one or more per patient)	
Sorafenib	53
TACE	25
TARE	18
Second line systemic agent	15
PEI	12
DSM-TACE	5
LT	3
RFA	1
Best tumor response	
CR	10 (9.1)
PR	21 (19.1)
SD	12 (10.9)
PD	67 (60.9)
DC	
No	67 (60.9)
Yes	43 (39.1)

Continuous variables are reported as median value and range, categorical variables as frequencies and percentage. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholic Steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; PS: Performance status; AFP: Alphafetoprotein; DC: Disease control; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; DSM-TACE: Degradable starch microspheres transarterial chemoembolization; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; LT: Liver transplant; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; DC: Disease control.

Primary endpoint: Patients' survival

Out of 110 BCLC stage C patients included in the investigation, only 32 received a single treatment and 56 more than once, whereas 22 of them received only best supportive care due to the inadequate liver function. Sorafenib was the most common choice of treatment, followed by TACE, TARE, and second-line systemic agents in patients who were either intolerant to sorafenib or sorafenib failed for them (Table 1). In selected cases, PEI or RFA in combination with other treatments and DSM-TACE were also performed; three PS 1 patients without macrovascular invasion or extrahepatic spread and with tumors complying the Milan criteria after effective downstaging (when needed) underwent liver transplant (LT). The best-succeeded response was CR in 9.1% of cases, PR in 19.1%, SD in 10.9%, and PD in 60.9% of cases; overall, 43 (39.1%) patients obtained DC.

After a median follow-up of 22.9 mo (95%CI: 17.3-38.1), the cumulative median survival of the overall population was 13.4 mo (95%CI: 10.6-17.0, Figure 1). A total of 66 patients died and the most prevailing cause of death was attributed to tumor progression (50/66; 75.7%), followed by liver function failure (13/66; 19.7%), while in the remaining 3 patients, the death was caused by sepsis, post LT complications and bone fracture.

At univariate analysis, AFP serum level > 200 ng/mL, tumor size > 5 cm, the presence of macrovascular invasion, the presence of macrovascular invasion and/or extrahepatic spread as pre-treatment factors and the absence of DC as post-treatment factor were considered to be correlated with a worse outcome (Table 2). However, at the multivariate Cox regression, only AFP serum level > 200 ng/mL and DC were independent predictors of mortality (HR = 2.194, 95%CI: 1.249-3.855, P = 0.006 and HR = 0.190, 95%CI: 0.098-0.367, P < 0.0001, respectively). In particular, the effect of these two variables was reverse in a time dependent

Table 2 Univariate (Kaplan-Meier) and multivariate (Cox proportional hazard regression) survival analysis of patients with Barcelona Clinic Liver Cancer C hepatocellular carcinoma according to clinical and tumor variables

Variable	Univariate analysis		Multivariate analysis	
	Survival time (mo)	*P* value	Hazard ratio (95%CI)	*P* value
Age				
< 65 yr	13.9	0.903	-	-
⩾ 65 yr	13.8			
Gender				
Male	13	0.900	-	-
Female	14.2			
PS				
0	10.3	0.128	-	-
1/2	13.9			
Diabetes				
No	13	0.813	-	-
Yes	13.8			
Child-Pugh score				
A	13.4	0.957	-	-
B	12.8			
N nodules				
Single	13.8	0.776	-	-
2-3	13.4			
Multinodular/infiltrating	13			
Tumor size				
⩽ 5 cm	13.9	0.022[1]	1	0.275
> 5 cm	9.9		1.357 (0.784-2.349)	
Macrovascular invasion				
No	15.8	0.014[1]	1	0.866
Yes	9.5		1.095 (0.379-3.162)	
Extrahepatic spread				
No	11.2	0.274	-	-
Yes	6.7			
Macrovascular invasion and/or extrahepatic spread				
No	13.8	0.008[1]	1	0.429
Yes	6.3		1.547 (0.523-4.571)	
AFP				
⩽ 200 ng/mL	15.8	0.0002[1]	1	0.006[1]
> 200 ng/mL	6.3		2.194 (1.249-3.855)	
DC				
No	7.6	< 0.0001[1]	1	< 0.0001[1]
Yes	15.8		0.190 (0.098-0.367)	
NIACE score				
⩽ 3	13.8	0.515	-	-
> 3	6.7			

[1]Statistically significant results. PS: Performance status; AFP: Alpha-fetoprotein; DC: Disease control.

manner, as depicted by plotting the log hazard ratios (beta) over time (Figure 2). In the first 6 mo of follow-up, serum AFP > 200 ng/mL was directly associated with lower chances of survival, but the effect declined subsequently. Conversely, the favorable prognostic impact of DC curtailed in the early-intermediate period and became noticeable after 1 year of follow-up.

A term of interaction of these two covariates with time was then introduced in the Cox model and hazard

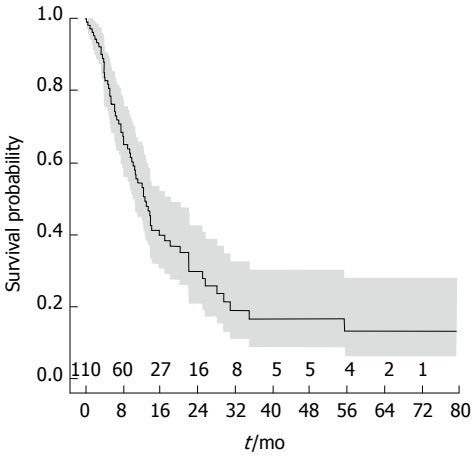

Figure 1 Cumulative survival of the overall cirrhotic patients with Barcelona Clinic Liver Cancer C stage hepatocellular carcinoma included in the study. The solid line shows the overall survival and the dotted lines the 95%CIs.

ratios were reported by each time interval (⩽ 6 mo, 7-12 mo, > 12 mo; Table 3). The AFP serum level > 200 ng/mL was significantly associated with higher risk of mortality within the first 6 mo of patients' entry into the BCLC stage C (⩽ 6 mo, HR = 5.073, 95%CI: 2.159-11.916, *P* = 0.0002). Conversely, DC exercised a significant protective effect in long-term phase (> 12 mo, HR = 0.110, 95%CI: 0.038-0.314, *P* < 0.0001).

There were also identified 5 patients who had unexpectedly longer survival (above the 95th percentile; median 63.3 mo). The characteristics of those subjects have been described in Table 4; outstandingly, in most of the cases (3/5) PS 1-2 was the major cause for categorizing them in BCLC stage C. Pre-treatment AFP serum level was ⩽ 200 ng/mL in all these patients; and two of them showed tumor macrovascular invasion without any extrahepatic spread. In one case Sorafenib, and in another TARE was prescribed; whereas, in the remaining three patients, curative treatments (LT), DSM-TACE or second-line systemic therapies were administered. Remarkably, DC was achieved in all these long-term survivors.

Secondary endpoint: DC

The examination of factors associated with DC was the second landmark of the study (Table 5). The patients who achieved DC (43/110; 39.1%) were illustrated by small-size tumors (> 5 cm: 13/43, 30.2% *vs* 41/67, 61.2%; *P* = 0.002), a lower frequency of macrovascular invasion (11/43, 25.6% *vs* 39/67, 58.2%; *P* = 0.0009), extrahepatic spread (3/43, 7% *vs* 16/67, 23.9%; *P* = 0.036) and of macrovascular invasion and/or extrahepatic spread (14/43, 32.6% *vs* 47/67, 70.1%; *P* = 0.0001), lower AFP serum level (> 200 ng/mL: 8/43, 18.6% *vs* 28/67, 41.8%; *P* = 0.013) and more frequently received at least one treatment (39/43, 90.7% *vs* 49/67, 73.1%; *P* = 0.029). However, only the presence of macrovascular

Table 3 Multivariate Cox regression model including alpha-fetoprotein and disease control as time dependent covariates

Variable	Multivariate analysis	
	Hazard ratio (95%CI)	*P* value
Macrovascular invasion		
No	1	0.917
Yes	1.066 (0.412-2.762)	
Macrovascular invasion and/or extrahepatic spread		
No	1	0.366
Yes	1.552 (0.584-4.124)	
Tumor size		
⩽ 5 cm	1	0.266
> 5 cm	1.369 (0.786-2.382)	
AFP (> 200 ng/mL *vs* ⩽ 200 ng/mL)		
< 6 mo	5.073 (2.159-11.916)	0.0002[1]
7-12 mo	0.948 (0.275-3.267)	0.932
> 12 mo	1.698 (0.620-4.648)	0.303
DC (Yes *vs* No)		
< 6 mo	0.220 (0.075-0.650)	0.096
7-12 mo	0.463 (0.181-1.189)	0.109
> 12 mo	0.110 (0.038-0.314)	< 0.0001[1]

For all other variables single hazard ratios were reported. [1]Statistically significant results. AFP: Alphafetoprotein; DC: Disease control.

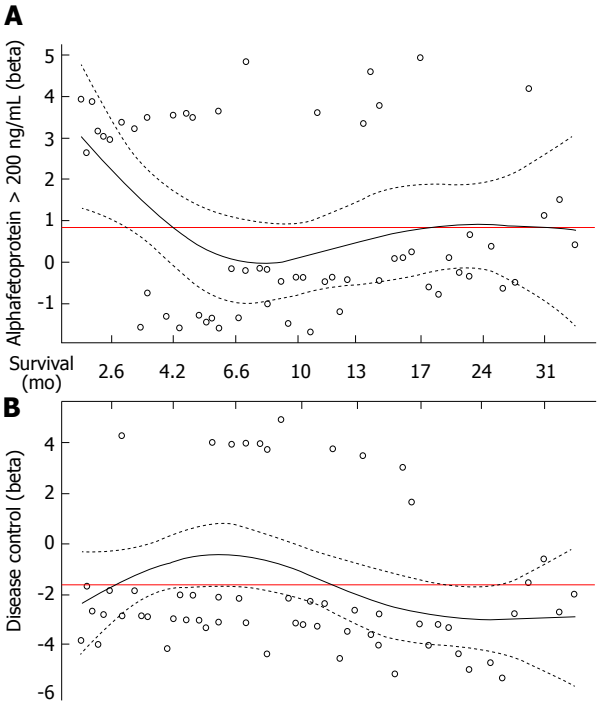

Figure 2 Plot of the scaled Schoenfeld residuals over time for alpha-fetoprotein serum level > 200 ng/mL (A) and disease control (B). The solid line shows the log of hazard ratio (beta) as a function of survival time with the 95%CI (dotted lines). The average beta value obtained at the Cox model without any time-adjustment is also reported (solid red line).

invasion and/or extrahepatic spread was independently associated with reduced likelihoods of achieving DC (OR 0.263, 95%CI: 0.111-0.622, *P* = 0.002). It is important to mention that among the 61 patients who showed macrovascular invasion and/or metastases, 44 (72.1%) received treatment and this proportion was significantly lower than that of patients showing intrahepatic disease without vascular involvement (44/49, 89.8%, *P* = 0.029).

DISCUSSION

The BCLC staging system is the most widely used approach for the therapeutic and prognostic classification of cirrhotic patients with HCC. While exploring the implementation of biomarker research in clinical practice to stratify tumors based on their biological aggressiveness[11], several sub-classifications of the BCLC stages consistent with prognostic factors and new scores have been proposed to improve the predictive power of this algorithm[12-14]. A more detailed stratification system based on the life expectancy may avoid offering treatments having a poor impact on patients' prognosis and often impairing the quality of life. These considerations are extremely important with regard to the selection of patients for the clinical trials of first or second line novel systemic agents.

The present study was aimed at investigating the predictors of survival in cirrhotic patients with BCLC stage C HCC and at assessing their effect in a time dependent manner. At the preliminary survival analysis, AFP serum level > 200 ng/mL and DC were found to be independent predictors of mortality (HR = 2.194, *P* = 0.006 and HR = 0.190, *P* < 0.0001, respectively).

Hence, the first finding of our report confirms high AFP serum level as a negative predictive marker in patients with advanced HCC and its impact on survival irrespective of the tumor stage at the time of diagnosis[15-20]. Furthermore, although this category of patients is classified as "advanced stage", we demonstrated a promising impact of the response to treatment, as shown by DC, on prognosis. Based on these findings, curative and locoregional treatments should not be "a priori" excluded in a subset of BCLC stage C patients with favorable predictive factors. As reported previously, surgical resection and LT can extend patients' survival in the BCLC stage C also[4-6,8,9,21], which supports the need of a novel method of prediction more customized to the specific patient. The identification of 5 long-term survivors (median 63.3 mo), where 3 were included in this stage only at impaired PS (1 or 2) in absence of vascular invasion or extrahepatic tumor spread, confirms the heterogeneity of patients included in the BCLC stage C and the benefits they got in terms of DC. In four patients, locoregional treatments were feasible and two of them were subjected to LT successfully. As already reported[22], the provision based on PS used in the BCLC algorithm is questionable. Furthermore, PS scores are subjective measures with high inter-observer variability, and it is often difficult to correctly evaluate tumor-related symptoms in patients already presenting compromised general conditions. In the current study, PS has not been found to be an independent predictor of survival, and this supports the hypothesis that alone it cannot be considered as an

Table 4 Characteristics of the 5 patients with long-survival (median 63.3 mo)

PT	Gender	Age	Etiology	PS	Child-Pugh	AFP > 200 ng/mL	No. of nodules	Maximum size	Macrovascular invasion	Extrahepatic spread	Diabetes	Pre-BCLC C treatments	Post-BCLC C treatments	Best response	DC	Survival (mo)	Status
PT3	M	65	HBV	1	A	No	Infiltrating	Infiltrating	Yes	No	No	None	Sorafenib	CR	Yes	79.4	Alive
PT10	M	73	HCV	1	A	No	> 3	18	No	No	No	TACE, resection, sorafenib	Second line systemic agent, DSM-TACE (2)	SD	Yes	63.3	Alive
PT27	M	58	HBV	2	B	No	2	19	No	No	No	RFA, TACE	LT	CR	Yes	67.1	Alive
PT53	M	63	Alcohol	1	B	No	> 3	50	No	No	No	None	TACE (4), TACE + RFA (1), LT	CR	Yes	58.9	AliVe
PT54	M	65	HCV	0	A	No	Single	40	Yes	No	Yes	None	TARE (2)	SD	Yes	38.1	Alive

HBV: Hepatitis B virus; HCV: Hepatitis C virus; PS: Performance status; BCLC: Barcelona Clinic Liver Cancer; AFP: Alphafetoprotein; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; DSM-TACE: Degradable starch microspheres transarterial chemoembolization; LT: Liver transplant; TARE: Transarterial radioembolization; CR: Complete response; SD: Stable disease; DC: Disease control.

exclusion criterion for curative treatments. Outstandingly, the majority of the patients (88.2%) in our series showed a PS 0 or 1, and therefore, only a small subgroup of patients (11.7%) fell in PS 2 class, and that may have influenced the overall survival insignificantly. However, the non-homogeneity of PS stages among BCLC C patients may be attributed to the sequential enrollment of the subjects included in the analysis rather than a selection-bias, and gives a better understanding of what happens in the real field practice.

The novel finding surfaced out from our study is the dynamic influence of AFP serum level and DC on survival period (Figure 2). In particular, the log curve of the hazard ratio for AFP serum level > 200 ng/mL elevated at high beta points implying a direct correlation with mortality, but declined steadily over time. This was more evident during the early follow-up (within 6 mo), which reached the zero point and then increased slightly afterwards, and finally became constant in the later stage. The DC beta value showed an inverse tendency, being constantly negative and increasing towards the zero point at about 6 mo of follow-up; however, it decreased significantly after the first year. At the Cox regression model including time-dependent coefficients, the most noticeable prognostic effect of AFP appeared in the early follow-up period, with 83.5% probability of mortality during the first 6 mo of follow-up of patients with AFP serum level > 200 ng/mL compared to those with a lower value (HR 5.073, 95%CI: 2.159-11.916, $P = 0.0002$). On the other hand, the DC was found to be defensive against death, as evident especially in the long-term follow-up (> 12 mo, HR 0.110, $P < 0.0001$). This type of dynamic behavior of prognostic factors has not been documented earlier during the establishment of HCC, while for other malignancies, such as breast, lung, and colorectal cancer, it has already been described. Time-dependent analysis has allowed to model patients' survival more precisely, considering the dynamic behavior of mortality risk factors and pointing out the reverse effect of AFP serum level and DC on prognosis temporally. Our findings, therefore, emphasize that tumor biological aggressiveness remains the most important short time prognostic indicator whereas in the long term, the achievement of DC is very decisive to ameliorate patients' survival expectancy. This further supports the efforts towards improving the therapy management and also implementing the treatment options in the BCLC algorithm for stage C patients. Nevertheless, since high AFP serum level is associated with an increased risk of early mortality, the trials assaying new systemic agents or second line therapies should be very careful in selecting the patients, and consequences should be evaluated optimally based on the stratification of the biological aggressiveness.

The second milestone of our study was to identify predictive factors of DC. The presence of macrovascular invasion and/or extrahepatic spread was found to be independently associated with a reduced likelihood of achieving DC (OR = 0.263, $P = 0.002$). The negative effect of tumor diffusion outside the liver or into the bloodstream on patients' prognosis is well known, as thoroughly discussed in previous reports[23-25], and this could be indirectly due to the inadequacy of the currently available treatments to control an aggressive disease in an effective and systemic manner. Nevertheless, in our study the 61 patients showing macrovascular invasion and/or extrahepatic spread received treatment with a lower frequency as compared to those with non-invasive tumors (44/61, 72.1% *vs* 44/49, 89.8%, $P = 0.029$). Due to the extensive tumor burden, in this subgroup of patients supportive care was taken more often and this may also be the reason for the reduced DC rates to some extent.

Table 5 Univariate (Fisher's exact test) and multivariate (binomial logistic regression) analysis of factors associated with the achievement of disease control in patients with Barcelona Clinic Liver Cancer C hepatocellular carcinoma

Variable	DC (43)	No DC (67)	Univariate analysis	Multivariate analysis	
			P value	Odds ratio (95%CI)	*P* value
Age					
< 65 yr	15	27	0.229	-	
⩾ 65 yr	28	40			
Gender					
Male	35	56	0.471	-	
Female	8	11			
PS					
0	37	60	0.06	-	
1/2	6	7			
Diabetes					
No	34	53	0.653	-	
Yes	9	14			
Child-Pugh score					
A	31	51	0.524	-	
B	12	16			
N nodules					
Single	13	22	0.078		
2-3	11	9		-	
Multinodular/infiltrating	19	36			
Tumor size					
⩽ 5 cm	30	26	0.006[1]	1	0.298
> 5 cm	13	41		0.617 (0.236-1.610)	
Macrovascular invasion					
No	32	28	0.0003[1]	-	-
Yes	11	39			
Extrahepatic spread					
No	40	51	0.02[1]	-	-
Yes	3	16			
Macrovascular invasion and/or extrahepatic spread					
No	29	20	< 0.0001[1]	1	0.002[1]
Yes	14	47		0.263 (0.111-0.622)	
AFP					
⩽ 200 ng/mL	35	39	0.008[1]	1	0.179
> 200 ng/mL	8	28		0.461 (0.169-1.258)	
NIACE score					
⩽ 3	34	50	0.502	-	
> 3	9	17			
Treatment after BCLC C diagnosis					
No	4	18	0.04[1]	1	0.270
Yes	39	49		0.531 (0.147-1.917)	

[1]Statistically significant results. PS: Performance status; AFP: Alpha-fetoprotein; DC: Disease control.

Recently, the NIACE score has been proposed as a useful tool for the prognostic sub-staging of BCLC stage C patients, as well as for the management of treatment and for the selection of patients in clinical trials[14]. Probably, the different biological characters of tumors encompassed in our investigation could have negatively affected the prognostic ability of the NIACE score. Indeed, only 14% of the patients in the NIACE study cohort had previously undergone a treatment for HCC, as compared to 51.8% of the patients in our series, and the prevalence of alcohol related liver disease was higher than in our series of patients (30% *vs* 15.5%).

A possible limitation of this study could be its retrospective nature, although this was partially overcome by the rigorous and prospective collection of clinical records by the multidisciplinary group. Despite of having limited the number of records included in the analysis, the inclusion of patients treated only at our Center has reduced biasness related to diverse modalities of treatment or imaging interpretation by radiologists at different Centers.

The liver function did not appear to have a significant impact on patients' prognosis in our analysis; probably, a high tumor-related mortality has overcome the impact of hepatic impairment on survival. However, this cannot be absolutely confirmed, as the number of patients with conserved liver function largely exceeded that of patients with more severe liver impairment (74.5% Child A *vs* 25.5% Child B class).

In conclusion, our data confirm that the BCLC stage C comprises a huge heterogeneous group of cirrhotic patients suitable for locoregional and potentially curative treatments. This is the first report highlighting the reverse

and time-dependent effect of AFP serum level and DC as prognostic factors in cirrhotic patients with advanced stage HCC. In the patients with pre-treatment AFP serum level > 200 ng/mL the risk of early death increases up to 80%, while the achievement of post-treatment DC, which is less likely in the presence of macrovascular invasion and/or extrahepatic tumor spread, suggests higher chances of long-term survival. The combination of these predictive factors may be helpful in the sophistication of patients' prognosis, thereby being valuable in the selection of patients suitable for clinical trials and in designing the therapeutic strategy.

ARTICLE HIGHLIGHTS

Research background

Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) includes a heterogeneous group of patients with different clinical and tumor characteristics and survival expectancy, for whom sorafenib is the only recommended treatment option. The present study investigates the outcome of BCLC C patients who underwent different locoregional, surgical or systemic treatments.

Research motivation

To better stratify the prognosis of patients with BCLC C stage HCC.

Research objectives

To characterize the prognosis of cirrhotic patients with BCLC stage C HCC as assessed by a multidisciplinary team in an Italian tertiary care center and to identify those factors predicting the achievement of disease control (DC).

Research methods

The prospective database of the Hepatocatt multidisciplinary group, containing clinical, tumor and outcome data of all liver cancer subjects evaluated in the seven years at our Institute was reviewed.

Research results

The study confirms that the BCLC stage C comprises a huge heterogeneous group of cirrhotic patients suitable for locoregional and potentially curative treatments. Moreover, this is the first report highlighting the reverse and time-dependent effect of alphafetoprotein (AFP) serum level and DC as prognostic factors in cirrhotic patients with advanced stage HCC.

Research conclusions

The novel finding surfaced out from our study is the dynamic influence of AFP serum level and DC on survival period. In particular, the AFP serum level > 200 ng/mL was significantly associated with higher risk of mortality within the first 6 mo of patients' entry into the BCLC stage C; conversely, DC exercised a significant protective effect in long-term phase. Our report also highlight that the presence of macrovascular invasion and/or extrahepatic spread is independently associated with a reduced likelihood of achieving DC. Based on these findings, curative and locoregional treatments should not be "a priori" excluded in a subset of BCLC stage C patients. Indeed, predictive factors may be helpful in the sophistication of patients' prognosis, thereby being valuable in the selection of patients suitable for clinical trials and in designing the therapeutic strategy.

Research perspectives

Given the higher number of heterogeneous and complex cases encountered in the field-practice, the BCLC classification is often not exhaustive, and the increasing number of new therapeutic options and their combinations makes difficult to strictly adhere to BCLC suggestions. New algorithms for the stratification of patients' prognosis are needed to improve clinical practice.

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P- Reviewer: Makisalo H, Zhao HT **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

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