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Metabolic disorders across hepatocellular carcinoma in Italy.

Short title: *HCC and metabolic disorders.*

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Abbreviations: HCC, hepatocellular carcinoma, HCV, hepatitis C virus, HBV, hepatitis B virus, NAFLD, nonalcoholic fatty liver disease, NASH, nonalcoholic steatohepatitis, MS, metabolic syndrome, ITA.LI.CA, Italian Liver Cancer, BMI, body mass index, TACE, trans-catheter arterial chemoembolization, EASL, European Association for the Study of Liver, AASLD, American Association for the Study of Liver Diseases, BCLC, Barcelona-Clinic Liver Cancer, BSC, best supportive care, AFP, alpha₁-fetoprotein, SD, Standard Deviation, HR, Hazard Ratios

ABSTRACT

Background: Metabolic disorders are well known risk factors for HCC. Conversely, their impact on the natural history of HCC is not established. This study aimed at evaluating the impact of metabolic disorders on clinical features, treatment and survival of HCC patients regardless of its etiology.

Methods: We analyzed the ITA.LI.CA database regarding 839 HCC patients prospectively collected. The following metabolic features were analyzed: BMI, diabetes, arterial hypertension, hypercholesterolemia and hypertriglyceridemia. According to these features, patients were divided into 3 groups: 0-1, 2 and 3-5 metabolic features.

Results: As compared with patients with 0-1 metabolic features, patients with 3-5 features showed lower percentage of HCC diagnosis on surveillance ($p=0.021$), larger tumors ($p=0.038$), better liver function (higher percentage of Child-Pugh class A [$p=0.007$] and MELD <10 [$p=0.003$]), higher percentage of metastasis ($p=0.024$), and lower percentage of portal vein thrombosis ($p=0.010$). The BCLC stage and treatment options were similar among the 3 groups, with the exception of a less frequent access to loco-regional therapies for BCLC stage B patients with 3-5 features ($p=0.012$). Overall survival and survival according to BCLC stage and/or treatment did not significantly differ among the 3 groups. Only using a probabilistic sensitivity analysis, diabetic patients showed a lower survival ($p=0.046$). MELD score, HCC morphology, nodule size, BCLC stage, portal vein thrombosis and metastasis were independent predictors of lead-time adjusted survival.

Conclusions: Our “real world” study suggests that metabolic disorders shapes the clinical presentation of HCC but do not seem to play a major role in setting patient survival.

Abstract Key words: Hepatocellular carcinoma, Metabolic syndrome, Diabetes, Obesity

Key points:

- The causal association between metabolic syndrome and HCC has been largely documented.
- There are well established pathophysiological mechanisms linking obesity, diabetes and HCC.
- Metabolic features shapes the clinical presentation of HCC but do not seem to play a major role in setting patient survival.
- Diabetes seems to reduce only marginally the survival of HCC patients according to a probabilistic sensitivity analysis.

Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing in Europe [1]. Chronic infection with hepatitis C virus (HCV), hepatitis B virus and excessive alcohol consumption are the major risk factors in industrialized countries [2]. However, in concert with the recent epidemic of obesity and metabolic syndrome in developed countries, the incidence and prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) [3,4] have also increased, and today they represent rapidly growing causes of end-stage liver disease and HCC [5-7]. Moreover, regardless of the etiology of liver disease, metabolic disorders, such as obesity and diabetes, contribute to hepatocarcinogenesis [8-10]. Indeed, there are well established pathophysiological mechanisms linking obesity, diabetes and HCC [11,12]. In obese individuals, the relative risk of HCC is higher than that of other cancer [13], and the cumulative incidence of HCC in diabetic patients is three times higher than in non diabetic patients [7]. Both obesity and diabetes are components of the metabolic syndrome (MS) [14,15], characterized by the presence of central obesity, dyslipidemia, diabetes, arterial hypertension [16]. The causal association between MS and HCC has been largely documented [17-20], whereas the impact of different metabolic features (obesity, diabetes mellitus, hypertension, hypertriglyceridemia and hypercholesterolemia) on clinical presentation, natural history, management and prognosis of HCC has been less investigated. We therefore conducted a field-practice study,

reporting the 2009-2014 experience of the Italian Liver Cancer (ITA.LI.CA) group, aimed at evaluating the impact of metabolic disorders on clinical features, treatment and survival of patients with HCC.

Materials and methods

We retrospectively analyzed data of the Italian Liver Cancer (ITA.LI.CA) database. This registry collects data generated by the field-practice of 21 Italian centers spread throughout the Country between January 1987 and December 2014. Patients' data are collected prospectively and updated every 2 years. Data entry is regularly checked for consistency by the group coordinator and when clarification or additional information are deemed necessary, relevant cases are resubmitted to the recruitment center before final inclusion in the database. The ITA.LI.CA database management conforms to the past and the current Italian legislation regarding privacy and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for the study was obtained from the Institutional Review Board of the participating centers. Details on the ITA.LI.CA database management have been already reported [21].

For the purpose of this study, we analyzed the data of 1950 cirrhotic HCC patients, consecutively examined and managed during 5 years, from January 2009 to December 2014, in order to analyze the updated managing of HCC and to avoid any interference related to the use of the new direct acting antivirals (DAAs) for HCV treatment. Of them, 839 meet the selection criterion, i.e. the availability of all data for a metabolic evaluation.

No difference was detected in 1111 excluded patients (compared to 839 patients) in terms of age, gender, BMI, Diabetes, Child-Pugh Class, BCLC stage, alpha-fetoprotein (AFP) levels and performed treatments by means of Univariate Statistical Analysis.

Liver disease was considered hepatitis virus C (HCV) or hepatitis virus B (HBV)-related if patients carried anti-HCV antibodies or HBV surface antigen (HBsAg), respectively. Liver disease etiology was considered alcoholic if men consumed > 40g and female > 30g per day of alcohol for > 10 years,

and no other causes of liver damage were found. Patients were classified as having NAFLD if all other known etiologies of liver disease could be ruled out and if consistent present or past histological or ultra-sonographic features of fatty liver and alcohol intake < 30g/ day were present.

Demographic characteristics, liver function tests, HCC features, body mass index (BMI), presence of comorbidities, diabetes mellitus (fasting plasma glucose > 125mg/dl or antidiabetic therapy), hypertension (blood pressure > 140/90mmHg or anti-hypertensive therapy), hypertriglyceridemia (triglycerides > 150mg/dl) and hypercholesterolemia (cholesterol > 200mg/dl) were collected. No data about treatment for diabetes, hypertension or hyperlipidemia was available.

The diagnosis of HCC was based on the European Association for the Study of Liver (EASL) [22] or American Association for the Study of Liver Diseases (AASLD) [23] guidelines for HCC management.

Treatment options were considered according to the Barcelona-Clinic Liver Cancer (BCLC) staging system and their update when possible [24-25]. After 2011, the patient management followed the recommendations released by the Italian Association for the Study of the Liver (AISF) [26]. In each center, treatment decisions were taken by a multidisciplinary team, and were influenced by several factors, including comorbidities, specific contraindications for each procedure, local transplant criteria and patient's opinion. In particular, liver transplantation was also evaluated in the setting of a down-staging protocol [27] or a program using expanded selection criteria [28]. Patients were defined suitable for surgical resection according to the following criteria: single nodule or few contiguous nodules in the presence of a preserved liver function (Child-Pugh class A, MELD score ≤ 10); no evidence of portal vein infiltration or thrombosis, no evidence of extrahepatic metastasis, no general contraindications to surgery. Patients were defined suitable for local ablation (radiofrequency ablation, laser thermal ablation, percutaneous ethanol injection, cryoablation) in case of non-resectable nodules ≤ 4 cm in size and with no more than 4 lesions. Trans-catheter arterial chemoembolization (TACE) was indicated in paucifocal HCC not treatable with local ablation or multifocal HCC, involving less than 40% of the liver volume, Child-Pugh A-B, no portal vein

infiltration or thrombosis, no extrahepatic metastasis, no severe associated diseases, no general contraindications to TACE. Systemic therapy with sorafenib was indicated in advanced HCC, Child-Pugh A, adequate hematologic, hepatic and renal function, no severe associated diseases, no contraindications to sorafenib. Best supportive care (BSC) or different treatment options were considered in patients not amenable to (or refusing) the above mentioned treatments.

As a diagnosis of MS was not possible to make according to the data reported in the ITA.LI.CA. database, the presence of the following 5 different metabolic features was analyzed: BMI \geq 25, diabetes, hypertension, hypercholesterolemia and hypertriglyceridemia. According to the number of metabolic features, the patients were divided into 3 groups:

- **Group 1:** 0-1 metabolic features;
- **Group 2:** 2 metabolic features;
- **Group 3:** 3-5 metabolic features.

The section about the statistical analysis methodology is reported as supplementary methodology.

Results

Relationship among tumor burden, liver function and metabolic features

Baseline demographics, clinical and laboratory characteristics of patients are summarized in Table 1.

The majority of patients were males (654/839-78%), and median age was 69 years (IQR 62-75 years).

All the enrolled patients had cirrhosis. Viral etiology accounted for the majority (58%) of cases, followed by metabolic etiology (23%) and alcoholic etiology (19%). BMI was \geq 25 and $<$ 30 (overweight) in 467 patients (56%) and \geq 30 (obesity) in 105 (13%). Moreover, 343 (41%) patients were diabetic, 393 (48%) had arterial hypertension and 171 (23%) hypercholesterolemia and/or hypertriglyceridemia.

HCC developed in a setting of well-compensated liver cirrhosis (Child-Pugh class A) in 66% of cases and it was detected during a surveillance program in 430 patients (51%). According to BCLC staging system, 44% of patients were included in early or very-early stages, 18% in the intermediate stage, 30% in the advanced stage, and 8% in the terminal stage. Regarding HCC morphology, 403 patients had a single nodule (50%), 337 a multinodular (41%), 51 an infiltrating (6%) and 25 patients a massive (>10cm)(3%) tumor. The mean size of the main nodule was 3 cm (range 2-5). Metastasis and neoplastic portal vein thrombosis were present in 6% and 18% of cases, respectively.

Table 2 reports the characteristics of the 3 metabolic groups of patients.

Overall, the groups of patients significantly differed for several clinical features, according to the Kruskal-Wallis analysis (Table 2). As compared with Group 1 (reference group), patients with ≥ 3 metabolic disorders (outcome B) had higher prevalence of metabolic etiology (41% vs 9%, $p < 0.001$), better liver function (Child-Pugh A, 72% vs 60%, $p = 0.007$, and MELD < 10 , 70% vs 59%, $p = 0.003$), higher percentage of metastasis (9% vs 5%, $p = 0.024$), lower percentage of HCC diagnosis on surveillance (46% vs 55%, $p = 0.021$), larger tumors (3 cm vs 2.7 cm, $p = 0.038$), lower percentage of portal vein thrombosis (14% vs 22%, $p = 0.010$), higher platelet count (137000/ml vs 109000/ml, $p < 0.001$), and lower AFP levels (8 ng/ml vs 17 ng/ml, $p = 0.004$). Differently, as compared with Group 1, patients with 2 metabolic disorders (outcome A) significantly differ for the following features: age, Child-Pugh class, MELD score, AFP levels, size of the largest nodule, and presence of portal vein thrombosis and metastasis. Finally, the comparison of Group 2 with Group 3 (outcome C) did not show significant differences except for the presence of metastasis (Table 2). Despite these differences, the distribution of BCLC stages did not differ among the metabolic groups, due to the high heterogeneity of patients included in each stage of this classification.

In order to scrutinize the role played by metabolic disorders on the access to treatment options, a sub-analysis by BCLC stage was performed (Table 3). The only significant difference was found in BCLC stage B, where patients with ≥ 3 metabolic features had a less frequent access to loco-regional therapies and TACE as compared to Group 1 (47% vs 62%, $p = 0.012$). This imbalance was associated

with a tendency toward a more frequent access to surgery (23% vs 15%), although the difference did not reach the statistical significance.

Survival analysis

Over a median follow-up of 26 months (IQR 11-42months), 369 (44%) patients died: 165 (48%) in Group 1, 84 (43%) in Group 2 and 120 (41%) in Group 3.

The causes of death did not differ among groups ($p=0.081$) and were: cancer progression (45% in Group 1, 38% in Group 2 and 49% in Group 3, $p=0.290$), hepatic failure (22%, 17% and 19%, respectively, $p=0.538$), hemorrhage (3%, 5% and 0%, $p=0.036$), infection (1%, 1% and 3%, $p=0.450$), renal failure (1%, 3% and 1%, $p=0.155$), other causes (28%, 36% and 28%, $p=0.403$).

In the whole population, the 75th centile OS was 14 ± 1.2 months. After lead-time adjustment, the 75th centile OS decreased to 13 ± 1.1 months. Survival rates at 1, 3 and 5 years were $76 \pm 1.5\%$, $54 \pm 1.9\%$ and $49 \pm 2.0\%$, respectively. After lead-time adjustment, these figures slightly decreased to $75 \pm 1.5\%$, $52 \pm 1.9\%$ and $49 \pm 2.0\%$, respectively.

The 75th centile OS did not significantly differ among the 3 groups, both before lead-time adjustment (8 ± 1.7 for Group 1; 13 ± 2.6 for Group 2; 16 ± 1.5 for Group 3; $p=0.075$) and after lead-time adjustment (8 ± 1.5 for Group 1; 12 ± 2.4 for Group 2; 15 ± 1.5 for Group 3; $p=0.075$). Survival rates at 1, 3 and 5 years in the 3 groups did not significantly differ also after lead-time adjustment (Figure 1).

The 75th centile OS according to BCLC stage did not significantly differ among the 3 groups, both before and after lead-time adjustment (Suppl. Figure 1).

Furthermore, using a probabilistic sensitivity analysis approach, we evaluated the impact of five main metabolic features on survival: diabetes, obesity, arterial hypertension, hypercholesterolemia and hypertriglyceridemia. This analysis showed that diabetes marginally reduced the OS ($p=0.046$), while obesity, hypercholesterolemia, arterial hypertension and hypertriglyceridemia did not have a significant impact on prognosis ($p=0.269$, $p=0.802$, $p=0.602$, $p=0.643$ respectively).

Univariate and multivariate analysis

In the whole population, at univariate analysis MELD score, BCLC stage, HCC morphology, nodule size, portal vein thrombosis, metastasis and diagnosis outside surveillance, but not male sex, age, etiology and presence of metabolic RFs were associated with the lead-time adjusted OS (Table 4, section 1).

Therefore, we launched 3 multivariate models, including separately BCLC stage or portal vein thrombosis or metastasis (the last two being component of BCLC staging system). Variables independently associated with the lead-time adjusted OS in all the three models were: MELD score > 10, HCC morphology and nodule size. In addition, BCLC stage B-C, portal vein thrombosis or metastasis independently predicted the lead-time adjusted OS in the pertinent model (Table 4, section 1).

The same statistical procedures were repeated in the 3 metabolic groups. In Group 1, at univariate analysis MELD score > 10, BCLC stage B-C, HCC morphology, nodule size, portal vein thrombosis, metastasis and diagnosis outside surveillance were associated with the lead-time adjusted OS, while the multivariate models selected as independent prognostic factors MELD score > 10 and HCC morphology in all the three models, and BCLC stage B-C or portal vein thrombosis in model 1 and model 2, respectively (Table 4, section 2).

In Group 2, at univariate analysis, MELD score > 10, BCLC stage B-C, HCC morphology, nodule size, portal vein thrombosis, and diagnosis outside surveillance were associated with the lead-time adjusted OS, while only BCLC stage B-C and nodule size in model 1, and portal vein thrombosis in model 2 were independently associated with the lead-time adjusted OS at the multivariate models (Table 4, section 3).

In Group 3, at univariate analysis MELD score > 10, BCLC stage B-C, HCC morphology, nodule size, presence of portal vein thrombosis and of metastasis were associated with the lead-time adjusted OS, while the multivariate models selected as independent predictors the HCC morphology in all the

three models and the BCLC class B-C and portal vein thrombosis and metastasis in each pertinent model (Table 4, section 4).

Discussion

Features of the metabolic syndrome, such as diabetes and obesity, have been associated with both increased risk of cancer development and cancer-related mortality regarding both gastrointestinal (colorectal, esophagus, stomach, and pancreas) and extra-intestinal (kidney and breast) malignancies [29-30]. The increased oncologic risk would be due to a number of molecular mechanisms (insulin resistance, chronic inflammation, reduced apoptosis, and imbalance of gut microbiota) that initiate and fuel carcinogenesis. In recent years, several studies have shown a strong correlation also between metabolic features and the development of HCC. In particular, the presence of diabetes would increase the incidence and aggressiveness of HCC [12,14]. However, studies describing the impact of metabolic disorders on clinical presentation, management and survival of patients with HCC are lacking.

Our study showed that, at the time of HCC diagnosis, cirrhotic patients with ≥ 3 disorders had a more preserved liver function than those with no or one metabolic risk factors, suggesting that, in metabolic patients, HCC develops at an earlier stage of underlying liver disease. This information is in line with the data reported in literature, showing that in NAFLD patients HCC frequently occurs before the appearance of liver cirrhosis [18,31]. Moreover, we found that these patients more frequently presents with an advanced stage of tumor, as documented by the larger nodule size and the higher frequency of metastasis, even if with a lower frequency of portal vein thrombosis. This dismal oncologic presentation can be fundamentally attributed to the lower use of surveillance as compared to viral patients. However, it might also reflect a “reinforced” carcinogenesis and faster neoplastic progression related to hyperinsulinemia, lipotoxicity, oxidative stress and imbalance in the relative proportion of pro-inflammatory/anti-inflammatory cytokines [31-33].

We also observed no differences in the access to therapies by the presence of metabolic disorders with the exception of BCLC B stage, where patients with several metabolic disorders less frequently underwent ablative/trans-arterial treatments and a slightly greater access to surgical therapies in comparison to those without metabolic problems. This shift toward surgical procedures, and principally to hepatic resection, is probably related to the better liver function and the larger size of the tumor we found in these patients. Since there is no similar data in the literature, larger and dedicated studies are required to confirm that metabolic comorbidities prompt a treatment shift toward surgery in HCC patients.

The survival rates of our patients at 1, 3 and 5 years was $75\% \pm 1.5$, $52\% \pm 1.9$ and $49\% \pm 2.0$, respectively. These data are comparable with those already reported in literature in Italy and worldwide [1, 34, 35]. The survival analysis showed no impact of metabolic features even after lead time adjustment. The absence of impact on survival was confirmed also when survival analysis was made according to BCLC stage. This finding could be explained by the fact that the adverse impact on survival of metabolic disorders was counterbalanced by the occurrence of HCC at an earlier stage of underlying liver disease with respect to patients without or with an incomplete metabolic syndrome.

In addition, the study allowed us to perform a cross-sectional evaluation of the impact of the five main metabolic features (diabetes, obesity, arterial hypertension, hypercholesterolemia and hypertriglyceridemia) on survival with a probabilistic sensitivity analysis approach. This analysis showed that only diabetes marginally reduces the overall survival of HCC patients. Our result supports and extends to Western HCC patients - managed in an updated way - the findings of quite old studies usually based on small surgical cohorts of Asiatic patients, reporting an adverse impact of diabetes on the outcome of patients with cirrhosis and HCC [36-40]. Nevertheless, despite these evidences and the well know pathogenic role of diabetes on cardiac, renal, and neurologic diseases, other studies report a better prognosis of patients with HCC and diabetes as compared to non-diabetic patients [8, 41]. This surprising and difficult to understand discrepancy probably relies on the effect of selection biases and confounding factors on results. Therefore, future studies on this topic should take

into account, for instance, insulin and hypoglycemic drugs (in particular metformin that seems to have strong antineoplastic effects [42, 43]) as factors potentially capable to influence results.

Finally, the multivariate analysis selected BCLC stage as the only factor related to OS in Group 1 and 2, whereas, in Group 3, the prognosis was dictated by HCC morphology, portal vein thrombosis and presence of metastasis. Taken together, these results indicate that metabolic disorders *per se* do not play a crucial role in survival, despite their effects on clinical picture of HCC, as recently reported by Labenz et al. in the subgroup of HCC patients treated with sorafenib [44].

This study presents some limitations. First, this is a retrospective and multicenter study and therefore it may suffer of unintended biases (for example, treatment choice influenced by different local facilities or conviction of the HCC team leader). Second, the incomplete clinical and laboratory information, for about 60% of our initial population, limit the complete transferability of our results to the whole patient population. However, it should be pointed out that enrolled and excluded patients did not differ for main clinical characteristics, as resulted comparing the two groups by means of univariate statistical analysis. Third, a selection bias may derive from the fact that ITA.LI.CA centers include hospital and academic centers in which surveillance programs are well applied and, for this reason, only a 30% of our patients had an advanced HCC. In particular, a high adherence rate to current recommendations for surveillance of at high risk patients likely favored, in terms of cancer presentation and survival, cirrhotic patients (particular the viral ones) rather than non-cirrhotic metabolic patients (who do not represent a group to be surveyed). However, we tried to minimize this unavoidable bias by the adjustment of survival for the lead-time and by assessing survival in each BCLC stage.

In conclusions our study, conducted on a large series of cirrhotic patients with HCC managed in the “real world” of clinical practice, documented that: a) HCC cirrhotic patients with metabolic disorders show a worse neoplastic picture, but this does not impact on survival probably because of a more preserved liver function; b) diabetes marginally reduces survival of HCC cirrhotic patients.

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Figure Legends

Figure 1. Lead-time adjusted overall survival in the 3 analyzed groups.

Supplementary Figure 1. Lead-time adjusted overall survival in the 3 analyzed groups according to BCLC stage.

TABLES

Table 1. Demographic, clinical and laboratory characteristics of HCC population.

Patients n.	839	
	n	%
Age, years (median, IQR)	69 (62-75)	
Female/Male	185/654	22/78
BMI \geq 25	467	56
Smoke	289	41
Etiology		
Viral	486	58
NAFLD	190	23
Alcoholic	159	19
Child-Pugh Class		
A	523	66
B	227	29
C	43	5
MELD \leq 10	540	65
BCLC class		
0-A	354	44
B	147	18
C	241	30
D	68	8
Laboratory tests		
AFP (median, IQR)	12 (5-91)	
Creatinine (median, IQR)	0,9 (0,72-1,04)	
Sodium (median, IQR)	139 (137-141)	
Platelets (median, IQR)	123 (84-175)	
HCC morphology		
Single nodule	914	51
Multinodular	703	39
Infiltrating	114	6
Massive (> 10 cm)	59	3
Size of largest nodule, cm (mean, range)	3 (2-5)	
Portal vein thrombosis	144	18
Metastasis	47	6
Diagnosis on surveillance	430	51

Table 2. Characteristics of the 3 groups of HCC patients

Variables	Group 1	Group 2	Group 3	<i>p</i> values			
	0-1 features (n. 347)	2 features (n. 197)	3-5 features (n. 295)	Overall	Outcome A	Outcome B	Outcome C
Age, years (median, IQR)	68 (57-75)	70 (63-76)	69 (64-75)	0,023	0,017	0,029	0,605
BMI (median, IQR)	24 (21-25)	26 (24-29)	28 (26-31)	<0,001			
≥ 25, n (%)	73 (21)	127 (64)	267 (92)				
Female/Male, n (%)	81/266 (23/77)	43/154 (22/78)	61/234 (21/79)	0,717	0,685	0,417	0,760
Smoke, n (%)	105 (37)	65 (38)	119 (46)	0,082	0,773	0,033	0,118
Etiology, n (%)				<0,001			
Viral	254 (73)	115 (59)	117 (40)				
NAFLD	30 (9)	39 (20)	121 (41)				
Alcoholic	61 (18)	42 (21)	56 (19)				
Child-Pugh Class, n (%)				0,008	0,044	0,007	0,130
A	200 (60)	129 (68)	194 (72)				
B	110 (33)	56 (29)	61 (23)				
C	24 (7)	5 (3)	14 (5)				
MELD ≤ 10, n (%)	204 (59)	131 (66)	205 (70)	0,011	0,076	0,003	0,417
BCLC class, n (%)							

A	137 (40)	89 (46)	128 (47)	0,208	0,120	0,452	0,201
B	61 (18)	43 (22)	43 (16)				
C	111 (33)	51 (26)	79 (29)				
D	32 (9)	11 (6)	25 (9)				
Laboratory tests (median, IQR)							
AFP	17 (6-144)	9,9 (4-51)	8 (4-78)	0,003	0,005	0,004	0,810
Creatinine	0,85 (0,7-1)	0,9 (0,74-1,04)	0,9 (0,75-1,1)	0,026	0,177	0,007	0,312
Sodium	139 (136-141)	139 (137-141)	140 (137-141)	0,084	0,053	0,075	0,879
Platelets	109 (72-161)	129 (85-178)	137 (95-188)	<0,001	0,007	<0,001	0,099
HCC morphology, n (%)							
Single nodule	157 (46)	96 (50)	150 (54)	0,248	0,303	0,137	0,591
Multinodular	153 (44)	76 (39)	108 (39)				
Infiltrating	26 (8)	12 (6)	13 (5)				
Massive	8 (2)	9 (5)	8 (3)				
Size of largest nodule, cm (median, IQR)							
	2,7 (1,8-4,7)	3 (2-5)	3 (2-5)	0,096	0,151	0,038	0,733
Portal vein thrombosis, n (%)							
	76 (22)	28 (15)	40 (14)	0,015	0,035	0,010	0,879
Metastases, n (%)							
	15 (5)	7 (4)	25 (9)	0,020	0,653	0,024	0,024
Diagnosis on surveillance, n (%)							
	190 (55)	105 (54)	135 (46)	0,056	0,736	0,021	0,097

Table 3. Treatment options according to BCLC stage.

	All	Group 1 <i>0-1 features</i>	Group 2 <i>2 features</i>	Group 3 <i>3-5 features</i>	OUTCOME A <i>(p value)</i>	OUTCOME B <i>(p value)</i>	OUTCOME C <i>(p value)</i>
	n %	n %	n %	n %			
Treatment options for BCLC 0/A (n. 354)							
<i>BSC</i>	52 15	21 16	10 11	21 17	ns	ns	ns
<i>Sorafenib</i>	7 2	2 1	3 3	2 2	ns	ns	ns
<i>LRT & TACE</i>	239 67	92 67	65 73	82 64	ns	ns	ns
<i>Surgery and LT</i>	60 17	22 16	13 15	25 20	ns	ns	ns
Treatment options for BCLC B (n. 147)							

<i>BSC</i>	21 15	10 17	4 10	7 17	ns	ns	ns
<i>Sorafenib</i>	14 9	5 8	7 16	2 5	ns	ns	ns
<i>LRT & TACE</i>	83 56	38 62	25 58	20 47	ns	0.012	ns
<i>Surgery and LT</i>	27 18	9 15	8 19	10 23	ns	ns	ns
Treatment options for BCLC C (n. 241)							
<i>BSC</i>	99 43	44 42	24 50	31 39	ns	ns	ns
<i>Sorafenib</i>	41 17	21 19	6 12	14 18	ns	ns	ns
<i>LRT & TACE</i>	74 31	35 32	14 27	25 32	ns	ns	ns
<i>Surgery and LT</i>	16 7	6 5	1 2	9 11	ns	ns	ns

Treatment options for BCLC D (n. 68)							
<i>BSC</i>	45 69	22 71	10 91	13 57	ns	ns	ns
<i>Sorafenib</i>	4 6	2 6	0 0	2 8	ns	ns	ns
<i>LRT & TACE</i>	11 16	4 12	1 9	6 24	ns	ns	ns
<i>Surgery and LT</i>	1 2	1 3	0 0	0 0	ns	ns	ns

BSC, best supportive care; *LRT*, loco-regional therapy (ablation); *TACE*, transcatheter arterial chemoembolization, *LT*, liver transplantation, *ns*, not significant

Outcome A, comparing Group 1 and Group 2;

Outcome B, comparing Group 1 and Group 3;

Outcome C, comparing Group 2 and the Group 3.

Table 4. Univariate and multivariate Cox proportional hazard regression analysis of factor affecting the lead-time adjusted survival.

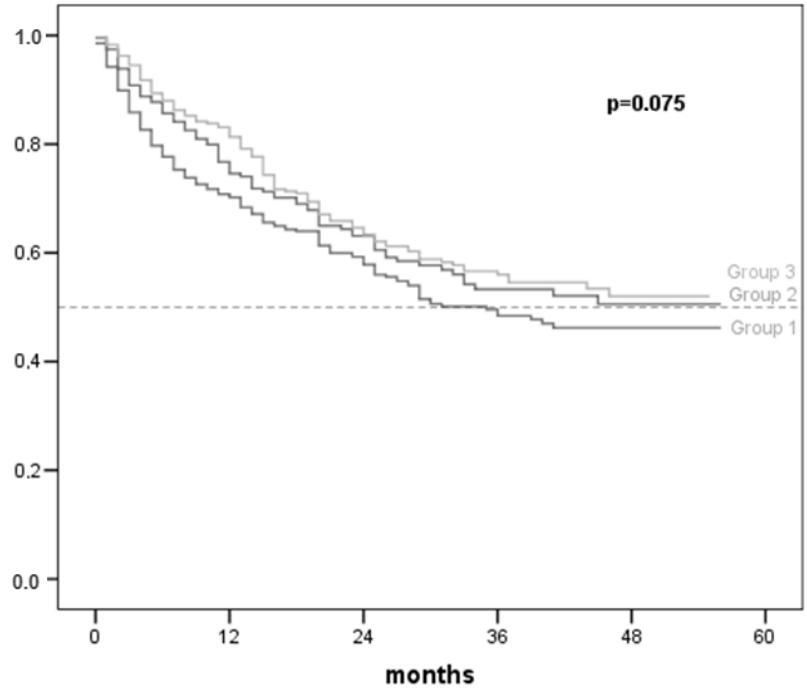
UNIVARIATE COX REGRESSION					MULTIVARIATE COX REGRESSION													
Section 1					All patients (n=839)													
	p value	HR	95% CI		Model 1				Model 2				Model 3					
					p value	R	95% CI		p value	HR	95% CI		p value	HR	95% CI			
Male sex	0,107	-	-	-														
Age	0,192	-	-	-														
Etiology	0,591	-	-	-														
Presence of metabolic RF	0,075	-	-	-														
MELD score >10	6,8E-08	1,76	1,43	2,17	4,1E-04	1,477	1,19	1,83	5,0E-06	1,64	1,32	2,03	1,4E-06	1,73	1,38	2,16	2,16	
Multinodular or infiltrating HCC	6,9E-12	2,12	1,71	2,64	2,5E-05	1,635	1,30	2,05	2,9E-05	1,63	1,29	2,06	1,1E-05	1,70	1,34	2,16	2,16	
Size of the largest nodule	2,2E-08	1,07	1,05	1,10	0,014	1,045	1,00	1,08	0,014	1,04	1,00	1,08	0,022	1,04	1,00	1,08	1,08	
Diagnosis outside surveillance	2,4E-06	1,64	1,33	2,01	0,069	1,232	0,98	1,54	0,120	1,19	0,95	1,50	0,027	1,31	1,03	1,66	1,66	
BCLC class B-C	3,7E-23	2,87	2,33	3,53	5,9E-13	2,271	1,81	2,83										
Presence of portal vein thrombosis	2,5E-26	3,50	2,77	4,41					3,9E-14	2,60	2,03	3,34						
Presence of metastasis	1,0E-08	2,83	1,98	4,05									4,2E-04	1,99	1,35	2,92	2,92	

Section 2					Group 1, 0-1 metabolic features (n=347)												
	p value	HR	95% CI		Model 1				Model 2				Model 3				
					p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		
Male sex	0,772	-	-	-													
Age	0,196	-	-	-													
Etiology	0,926	-	-	-													
MELD score >10	6,9E-05	1,86	1,37	2,52	0,003	1,633	1,17	2,26	1,8E-04	1,84	1,33	2,53	7,3E-05	1,97	1,41	2,76	
Multinodular or infiltrating HCC	1,2E-06	2,26	1,62	3,15	0,005	1,658	1,16	2,35	0,002	1,74	1,21	2,48	0,002	1,80	1,25	2,59	
Size of the largest nodule	1,4E-04	1,08	1,04	1,13	0,070	1,047	0,99	1,10	0,052	1,04	1,00	1,10	0,051	1,05	1,00	1,10	
Diagnosis outside surveillance	1,4E-04	1,81	1,33	2,46	0,050	1,383	1,00	1,91	0,042	1,40	1,01	1,94	0,030	1,46	1,03	2,07	
BCLC class B-C	1,1E-11	2,96	2,16	4,05	1,2E-06	2,302	1,64	3,22									
Presence of portal vein thrombosis	4,0E-11	3,05	2,19	4,24					5,4E-06	2,25	1,58	3,20					
Presence of metastasis	8,5E-03	2,37	1,24	4,51									0,080	1,81	0,93	3,52	
UNIVARIATE COX REGRESSION					MULTIVARIATE COX REGRESSION										MULTIVARIATE COX		

REGRESSION

					REGRESSION									
Section 3					Group 2, 2 metabolic features (n=197)									
	p value	HR	95% CI		Model 1				Model 2					
					p value	HR	95% CI		p value	HR	95% CI			
Male sex	0,535	-	-	-										
Age	0,752	-	-	-										
Etiology	0,786	-	-	-										
MELD score >10	0,018	1,69	1,09	2,62	0,329	1,263	0,79	2,02	0,090	1,48	0,94	2,35		
Multinodular or infiltrating HCC	7,4E-03	1,83	1,17	2,86	0,174	1,391	0,86	2,23	0,267	1,31	0,81	2,11		
Size of the largest nodule	1,5E-05	1,13	1,07	1,19	0,018	1,082	1,01	1,15	0,052	1,07	0,99	1,14		
Diagnosis outside surveillance	0,007	1,81	1,17	2,78	0,415	1,226	0,75	2,00	0,658	1,12	0,67	1,84		
BCLC class B-C	7,3E-06	2,70	1,75	4,18	0,004	2,035	1,25	3,30						
Presence of portal vein thrombosis	4,4E-06	3,33	1,99	5,56					0,007	2,25	1,25	4,06		
Presence of metastasis	0,317	-	-	-										
Section 4					Group 3, 3-5 metabolic features (n=295)									
	p	HR	95% CI		Model 1				Model 2				Model 3	

	value				p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI	
Male sex	0,055	-	-	-												
Age	0,775	-	-	-												
Etiology	0,383	-	-	-												
MELD score >10	0,018	1,57	1,08	2,29	0,147	0,747	0,50 1,10		0,047	1,49	1,00	2,21	0,011	1,68	1,12	2,53
		5	3	0			3 8			1	5	0		8	5	3
Multinodular or infiltrating HCC	1,2E-04	2,08	1,43	3,03	0,007	0,579	0,38 0,86		0,007	1,73	1,16	2,58	0,014	1,69	1,11	2,58
		7	5	6			9 2			4	1	9		7	4	6
Size of the largest nodule	0,034	1,05	1,00	1,10	0,426	1,029	0,95 1,10		0,319	1,03	0,96	1,11	0,718	1,01	0,94	1,09
		2	4	2			9 5			9	4	9		4	1	3
Diagnosis outside surveillance	0,053	-	-	-	0,690	1,089	0,71 1,65		0,991	1,00	0,65	1,53	0,743	1,07	0,69	1,68
							6 5			3	4	7		7	0	1
BCLC class B-C	5,6E-08	2,79	1,92	4,04	1,9E-05	2,349	1,58 3,47									
		0	7	0			8 4									
Presence of portal vein thrombosis	3,2E-11	4,17	2,73	6,37					3,3E-07	3,31	2,09	5,25				
		8	9	2						6	3	5				
Presence of metastasis	2,6E-09	4,49	2,74	7,37									8,8E-06	3,65	2,06	6,47
		7	2	5										5	4	3



	0	0-12	12-24	24-36	36-48	48-60
patients at risk	834	819	568	352	164	42
Group1	346	340	218	138	59	13
Group2	196	192	133	84	42	13
Group3	292	287	217	130	63	16