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Overall Survival of Hepatocellular Carcinoma Patients with Associated Diabetes Mellitus - A New Possible Prognostic Score

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Abstract

Background: Diabetes Mellitus (DM) and Hepatocellular carcinoma (HCC) are conditions with common pathophysiological correlations. Currently, HCC treatment is based on the Barcelona Clinic Liver Cancer algorithm (BCLC). However, no studies have shown that the association of DM with HCC can influence prognosis. The American and European guidelines for Liver Disease (AASLD and EASL) suggest that intermediate stage (BCLC-B) HCC cases, should be treated with trans-arterial chemoembolization (TACE). However, several centers are still using other treatments (liver transplantation, liver resection, percutaneous radiofrequency ablation, percutaneous ethanol injection, radioembolization, sorafenib, etc). In 2012, Bolondi and colleagues suggested a further stratification of BCLC-B patients in 4 sub-groups (B1-B4).

Aim of the study: The aim of this study was to retrospectively validate the Bolondi stratification for BCLC-B patients and to establish the impact of DM on overall survival (OS).

Methods: We conducted a retrospective multicenter study in HCC intermediate stage patients. The study period was from 2000 up to 2015. The median follow up was 6.4 years, with a cumulative OS of 37% at 5 years.

Results: 276 patients with HCC B2 stage were identified. The OS at 5 years for type of treatment ("Bolondi Model" vs TACE), was better when the Bolondi stratification was used (treated with "Bolondi Model" n= 57 patients, 20.6%; treated with TACE n= 21 patients, 7.6 %; log rang $p<0.001$; Ranyi type test $p<0.001$). Multivariate analysis showed that B2 patients had a better OS compared to all other ($p <0.05$). According to the "Bolondi Model", patients stratified in B3 and B4 stage would have had a better outcome if treated with liver transplantation, TACE or antitumoral therapy with Sorafenib®. Moreover, we noted that the presence of DM in the low risk groups (B1-B2) impacted on outcome, leading to a better OS. Therefore, we created a new mathematical score for OS that assimilates "Bolondi Model"with DM.

Conclusions: Our study validates the "Bolondi Model" and also shows that, if DM is included in the stratification OS improves even further.

Introduction

HCC prognosis depends on tumor stage at diagnosis and the possibility of performing a radical treatment [1]. The BCLC stratifies patients according

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showed a better outcome after one year of follow-up (HR= 0.46, 95CI 0.30-0.69, p<0.001) (Table 5-6). Interestingly, if the OS curves were analysed using the BCLC sub-classification *versus* type of treatment, we found that the B2 group reached a better OS if treated with other therapeutical strategies (Renyi type test, p < 0.05).

Overall survival taking in relation to Bolondi BCLC classification and Diabetes Mellitus.

A better OS for the BCLC-B2 patients with DM (p = 0.021) was seen (Figure 2b). Furthermore, the influence of DM on OS was confirmed by the Cox regression analysis, where patients without DM showed HR = 1.72 (95CI 1.11-2.67; p=0.015). There were no differences in OS according to type of treatment, aetiology of liver disease and HCC type (p value SD).

DM-HCC Score calculation

We defined a score able to define the influence of DM on OS in HCC BCLC-B patients. This score was taking into account the presence or absence of DM and the severity of BCLC-B stage (where B2 was low risk and B3-B4 high risk). The Cox model on B3 showed a lack of proportionality at 3-years. Further, from the analysis of the z-Wald score, we gave weight 1 for B2 and lack of DM, instead we gave weight 2 for B3 until 3-years of follow-up and weight zero for B3 after 3 years of follow-up. The proposed score straties patients in to three groups; low risk (Score 0-1, n=78, 43%), intermediate risk (Score 2, n=85, 47%) and high risk of death (Score 3, n=19, 10%). The 2-OS% was 90% (95CI 81-55%), 68% (95CI 56-77%) and 8% (95CI 1-29%), intermediate and high risk, respectively (p<0.001), as reported in Table 6 and Figure 2c.

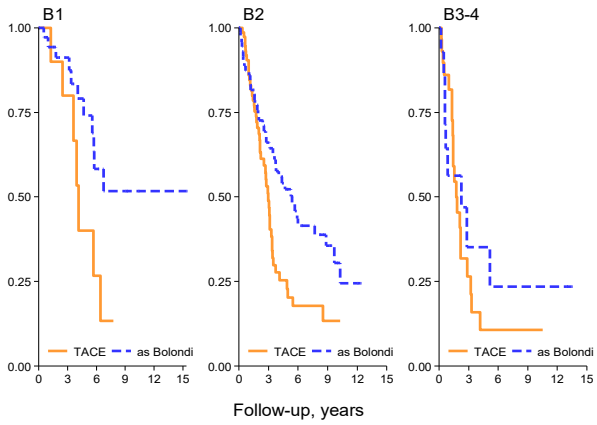

Figure 2a: OS according to BCLC-B subclassification and type of treatment; B1 Bolondi vs B1 TACE (Renyi test; p = 0.043); OS B2 Bolondi vs B2 TACE (Renyi test; p <0.001); OS B3-B4 Bolondi vs B3-B4 TACE (Renyi test; p =0.595) (long rank overall p < 0.001).

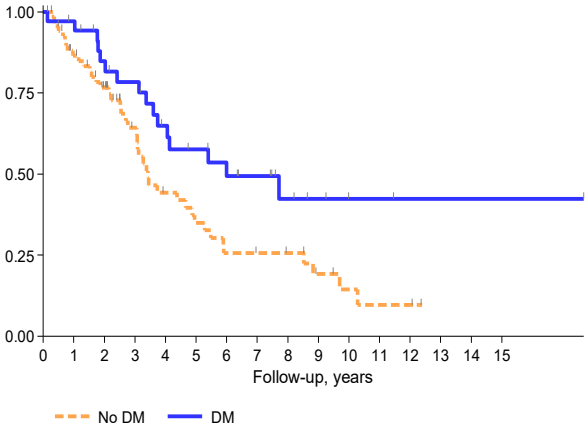

Figure 2b: OS in BCLC-B 2 stratified by DM

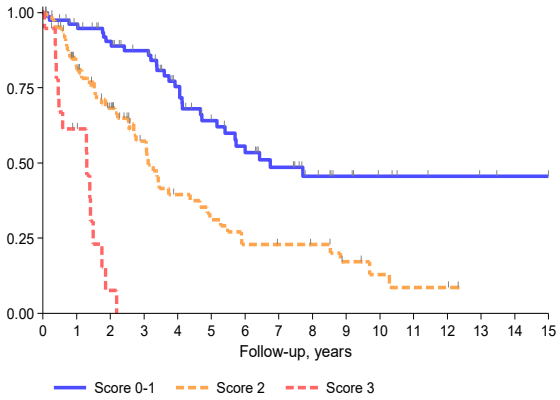

Figure 2 c: Overall survival stratified by the proposed score

Figure 2

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Table 1: Characteristics of the patients of the 3 centers involved in this study (BZ= Bolzano; BG= Bergamo and AUT= Innsbruck) according to type of treatment.

				Total	p value
Variable	BZ (n=101)	BG (n=118)	IBK (n=57)	276	
Median age	69 (IQR 14)	63 (IQR 13)	65 (IQR 14)	67 (IQR 14)	0.425
Gender M	89 (88)	95 (81)	50 (86)	234 (84)	0.277
Child Pugh A	75 (77)	87 (74)	34 (74)	196 (75)	0.02
Child Pugh B	22 (22)	31 (26)	8 (17)	61 (23)	
Child Pugh C	1 (1)	0	4 (9)	5 (2)	
MELD > 9	46 (47)	42 (36)	23 (46)	111 (42)	0.231
Ethiology					**< 0.001**
HCV/HBV	29 (29)	83 (70)	17 (29)	129 (47)	
Alcol	55 (55)	24 (20)	18 (31)	97 (35)	
Other	16 (16)	11 (9)	23 (40)	50 (18)	
Diabete mellitus, yes	31 (31)	32 (39)	-	63 (35)	0.349
Missing value	1				

Table 2: Characteristics of the patients of the 3 centers involved in this study (BZ= Bolzano; BG= Bergamo and AUT= Innsbruck).

Variable						**P value**
Centers		BZ	BG	AUT	Total	
All Therapies	TACE	47(47)	48(41)	28(49)	123(45)	
	OLT	5(5)	4(3)	12(21)	21(8)	
	RF/PEI	9(9)	27(23)	10(18)	46(17)	
	Liver resection	16(16)	26(22)	5(9)	48(17)	
	Sorafenib	6(6)	1(1)	1(2)	8(3)	
	No therapy	17(17)	12(10)	1(2)	30(11)	
TACE versus other						0.02
	TACE	47(47)	48(41)	28(49)	123(45)	
	Other	37(37)	58(58)	28(49)	123(45)	
	No therapy	17(17)	12(12)	1(2)	30(11)	
Type of treatment						0.067
	Curative	30(36)	57(54)	27(48)	87(46)	
	Palliative	53(64)	49(46)	29(52)	102(54)	
BCLC-B						0.937
	1	19	22	12	53	
	2	61	69	29	159	
	3	12	16	10	58	
	4	9	11	6	26	

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Table 3: Most important characteristics of the patients of the three centers according to the Bolondi et al sub-classification (B1-B4).

		n (%)	5-yrs OS%	p value
Age	<70	162(59)	41	0.165
	>70	114(41)	32	
Gender	M	233(84)	38	0.291
	F	43(16)	33	
BCLC	1	95(35)	47	**<0.001**
	2	130(48)	37	
	3-4	48(18)	16	
MELD	<10	152(58)	41	0.06
	>10	110(42)	33	
Child Pugh	A	196(75)	40	**0.011**
	B-C	66(25)	30	
Diabetes	No	119 (65)	39	0.054
	Yes	63 (35)	52	
Aethiology	HCV/HBV	129(47)	38	0.652
	Alcol	96(35)	33	
	Other	50(18)	44	
Treatment	TACE	123 (45)	21	<0.001
	Bolondi	123 (45)	56	
	No treatment	30 (10)	8	

Table 4: Multiple Cox regression in overall survival. Treatment adjusted by age at diagnosis and BCLC staging. FU: time – varying coefficient, follow-up which change the proportionality of hazard ST (age): standardized age (mean=67, SD 10: increase of in HR for increase of 1 standard deviation in age = 10 years).

			HR	95 CI	P
STD age		Continuous	1.14	0.97-1.35	0.114
BCLC		1	1		
		2	1.64	1.01-2.64	0.044
		3-4	3.28	1.89-5.67	<0.001
Treatment		TACE	1		
	*FU < 1 yr	Bolondi	1.35	0.67-2.72	0.399
	FU > 1 yr	Bolondi	0.34	0.15-0.75	0.008
	*FU < 1 yr	No treat	5.85	2.87-11.9	< 0.001
	FU > 1 yr	No treat	1.24	0.59-2.62	0.566

Table 5: Overall survival: treatment effect adjusted by age at diagnosis. FU: time – varying coefficient, follow-up which change the proportionality of hazard; ST (age): standardized age (mean=67, SD 10: increase of in HR for increase of 1 standard deviation in age = 10 years)

	Follow Up (FU)	Treatment	HR (95CI)	P
		TACE	1	-
	FU < 1 yr	Bolondi	1.13 (0.56-2.26)	0.738
	FU > 1 yr	Bolondi	0.39 (0.26-0.58)	< 0.001
	FU < 1 yr	No	7.01 (3.48-14.1)	< 0.001
	FU > 1 yr	No	1.13 (0.54-2.39)	0.738
STD age			1.11 (0.95-1.30)	0.172

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Table 6: Cox proportional hazard model and proposed "DM-HCC score".

Cox PH model	HR (95IC)	Wald z score (weight)	p
B1	1		
B2	2.07 (1.11-3.87)	2.29 (1)	0.022
B3 < 3yr FU	10.2 (4.74-21.8)	5.96 (2)	<0.001
B3 > 3yr FU	0.80 (0.18-3.62)	-0.30 (0)	0.765
No DM	1.72 (1.11-2.67)	2.44 (1)	0.015
Score	**N (%)**	**2-yr OS%**	**HR (95IC)**
Low (0-1)	78 (43)	90	1
Intermediate (2)	85 (47)	68	2.73 (1.73-4.30)
High (3)	19 (10)	8	14.9 (7.32-30.5)
High vs Intermediate			5.47 (2.86-10.5)

Discussion

Despite, new promising treatments (e.g. Sorafenib©) being more widely available, HCC outcome remains poor. For these reasons, a fine-tuning of current clinical management is needed. Reviews of evidence-based staging systems in many national and international centres have suggested that, HCC patients stratified as BCLC B should be treated outside current guidelines. Bolondi *et al* suggested that staging the patients in a more tailored manner, might improve HCC outcome [8]. However, so far this hypothesis has never been fully confirmed. Piscaglia F *et al*, looked at OS of Child Pugh B patients in BCLC B stage. However, these authors did not clarify the Bolondi hypothesis. Conversely, our study takes into consideration a large cohort of BCLC B patients only. Furthermore, this cohort was sufficiently strong to verify the Bolondi *et al* hypothesis, that if by changing patients-stratification (and therefore the associated treatment), OS improves. The OS analysis for type of treatment (Bolondi *et al* stratification *versus* TACE as suggested by EASL and AASLD guidelines) showed that OS was statistically significantly better when Bolondi *et al* stratification was used. We believe that the main reason for this finding is that BCLC B patients undergo a more aggressive approach, such as liver resection and liver transplantation. This allows BCLC-B patients to avoid uneffective treatment and their toxicities (e.g. TACE) and allowing those patients to receive more efficacious therapies. This finding is further supported by our univariate analysis, which showed that the strongest parameters influencing OS are Child Pugh score ($p<0.05$) and the BCLC B1-B4 stage ($p<0.01$), exactly what is contemplated within the Bolondi *et al* stratification. The finding that a follow up of 1 year is needed in order to detect a statistical significant difference of OS, supports our study. In fact, by applying the Bolondi *et al* sub-stratification, we practically propose a better "tailored therapy". This allows delivering treatment-toxicity only where is needed. Key data and OS results between each center were overlapping. This finding indirectly validates our patients' cohort. The pitfalls of our study are the retrospective nature and the fact that data were collected in 3 different centers. For example, it was not possible to evaluate the impact of the liver transplantation *per se* on outcome.

An unexpected finding of our study is the role of DM in the outcome of HCC patients. The association between DM and HCC is well known. The clinical link between these two diseases has been the subject of investigation for over a century, and DM has been established as a risk factor for HCC. Metformin, a first-line oral anti-diabetic, was first proposed as a candidate anti-cancer agent in 2005 in a cohort study in Scotland. Several subsequent large cohort studies and randomized controlled trials have not demonstrated significant efficacy for metformin in suppressing HCC incidence and mortality in diabetic patients. The search for biological links between cancer and diabetes has revealed intracellular pathways that are shared by cancer and diabetes. The signal transduction mechanisms by which metformin suppresses carcinogenesis in cell lines or xenograft tissues and improves chemo-resistance in cancer stem cells have also been elucidated. According to some authors, DM is associated with higher incidence and poorer prognosis of HCC but the influence of DM on patient survival in different HCC stages is unknown (Su YW abstract). Some authors demonstrated that DM is correlated with intrahepatic HCC recurrence after surgery.

In conclusion greater attention should be paid to manage patients with HCC and DM to better understand the influence of DM in OS of DM patients and the role of antidiabetic therapy on HCC development **[16]**. The Kaplan Meier OS curves obtained with the BCLC stratification showed a better OS for the BCLC-B2 patients with DM on treatment ($p= 0.05$). This suggests that patients with a lower degree of HCC (such as those in stage BCLC 1-2) have a better OS if they also have DM comorbidity on treatment. This finding has never been reported before. Previous studies have already

shown that a controlled hyperglycemia might positively impact on cancerogenesis **[22]**. Interestingly, in our study, DM does not impact positively on OS in patients on BCLC stages 3-4. In fact, those patients have a more advanced disease and therefore a larger HCC tumoral-mass and therefore the positive effect played by DM and DM-treatment may be negligible in these cases. Based on these findings we suggest a new HCC score system to better help clinicians in the management of HCC patients. We have called this new score the *MEGA HCC score*, derived from the name of the first author. This score needs to be validated in prospective external database.

Conclusion

Approximatively one -third of BCLC-B patients can benefit from treatment with TACE in the presence of compensated cirrhosis (Child–Pugh status A or B). Our study confirms the validity of the Bolondi stratification, which allows a more "tailored therapy" and a better OS. A review of the official guidelines and the definition of new treatment models are needed for HCC BCLC-B patients, as OS may change significantly.

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