Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study

Short title: Outcomes of variceal bleeding in patients with HCC.

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Abbreviations:

HCC: Hepatocellular carcinoma
MELD: Model for End-Stage Liver Disease.
BCLC: Barcelona Classification for Liver Cancer

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Abstract

Outcome of variceal bleeding (VB) in patients with hepatocellular carcinoma (HCC) is unknown. We compared outcomes after VB in patients with and without HCC. All patients with HCC and esophageal VB admitted between 2007-2010 were included. Follow up was prolonged until death, transplantation or 06.2011. For each HCC-patient, a patient without HCC matched by age and Child class was selected. 292 patients were included, 146 HCC (BCLC class 0-3 patients, A-25, B-29, C-45, D-41) and 146 without HCC. No differences were observed regarding prior use of prophylaxis, clinical presentation, endoscopic findings, and initial endoscopic treatment. 5-day failure was similar (25% in HCC vs 18% in non-HCC, p=0.257). HCC patients had greater 6-week rebleeding rate (16 vs 7%, respectively, p=0.025) and 6-week mortality (30% vs 15%, p=0.003). Fewer patients with HCC received secondary prophylaxis after bleeding (77% vs 89%, p=0.009) and standard combination therapy was used less frequently (58% vs 70%, p=0.079). Secondary prophylaxis failure was more frequent (50% vs 31%, p=0.001) and survival significantly shorter in patients with HCC (median survival: 5 months Vs greater than 38 months in patients without HCC; p<0.001). Lack of prophylaxis increased rebleeding and mortality. On multivariate analysis Child score, presence of HCC, portal vein thrombosis and lack of secondary prophylaxis were predictors of death. Conclusions: Patients with HCC and variceal bleeding have worse prognosis than patients with variceal bleeding without HCC. Secondary prophylaxis offers survival benefit in HCC patients.

In the last years, there has been an increasing incidence of hepatocellular carcinoma[1] (HCC). The majority of these tumors develop in patients who have liver cirrhosis. The development of HCC has an impact in the natural history of liver disease. In a systematic review of studies that evaluated the natural history of cirrhosis, the presence of HCC was identified as a predictor of death in 66% of the studies in patients with decompensated cirrhosis that included this variable in their analysis [2] . However, an increasing variety of therapeutic options are available for patients with HCC [3]. Many of these options have survival benefit, so it is conceivable that these patients with HCC with longer survival, will have greater chances of developing complications of end-stage liver disease.

Variceal bleeding is one of the complications that characterize decompensated cirrhosis. In the last 30 years there has been a substantial improvement in the survival of patients with variceal bleeding due to the use of vasoactive drugs, the introduction of endoscopic band ligation and the use of antibiotic prophylaxis [4, 5]. Presently, further efforts are targeted at developing individualized therapeutic strategies in order to adjust the approach to the risk the patient has [6, 7].

Several prognostic studies have identified the presence of HCC as a negative prognostic factor in variceal bleeding [5, 8, 9]. However, many studies in the context of variceal bleeding were performed at times when the incidence of HCC was much lower [10, 11]. Furthermore, most observational and experimental studies in the setting of secondary prophylaxis excluded patients with HCC [12-25], while other studies have excluded only patients with advanced HCC [26-28] or HCC outside of the Milan criteria [6, 29]. Therefore it is unclear whether or not secondary prophylaxis is useful in these patients. A recent study in patients admitted due to variceal bleeding demonstrated greater in-hospital mortality in those patients with HCC compared to patients without HCC [9]. However this study was performed on a large database, based on ICD-9 diagnosis, with the limitations these

studies have. Given the lack of information, the management of the acute variceal bleeding episode and then the use of secondary prophylaxis in these patients is most likely very heterogeneous across different centers. This gap in knowledge is becoming increasingly relevant given the rising incidence of HCC, mainly associated to viral cirrhosis, which is expected to peak within the next 10 years [30]. Therefore, the aim of this study was to evaluate the management and long term outcomes, as defined by rebleeding and death, of patients with HCC and esophageal variceal bleeding in comparison to patients without HCC.

PATIENTS AND METHODS

This retrospective observational study was performed in 10 centers in Spain [(Hospital Vall d'Hebron (Barcelona), Hospital Clinic (Barcelona), Hospital Santa Creu i Sant Pau (Barcelona), Hospital del Mar (Barcelona), Hospital Germans Trías i Pujol (Badalona), Hospital Arnau de Vilanova (Lleida), Hospital Puerta de Hierro (Madrid), Hospital Ramón y Cajal (Madrid), Hospital Gregorio Marañón (Madrid), and Hospital Universitario de Canarias (Tenerife)]. Patients meeting the following inclusion criteria were included: 1) Acute variceal bleeding episode due to esophageal varices between January 2007 and December 2010, 2) Liver cirrhosis as diagnosed according to clinical signs, laboratory and imaging tests or by liver biopsy. 3) HCC as diagnosed by current criteria[1], previously known at the time of the variceal bleeding or diagnosed at the time of the bleeding episode. Patients with gastrointestinal bleeding not confirmed by diagnostic upper gastrointestinal endoscopy were not included.

For every patient with esophageal variceal bleeding and HCC, a patient with esophageal variceal bleeding without HCC was included. The patients were paired according to age (+/- 5 years) and Child-Pugh Class (A/B/C).

Follow-up of all patients was prolonged until June 2011. Patients who received liver transplantation during the follow-up were censored at this time point. Data regarding the demographics, the liver disease, the bleeding episode and the follow-up were registered. In the patients with HCC, information regarding the tumoral disease was collected.

Bleeding was considered from esophageal variceal origin when the emergency endoscopy, performed within 12 hours after admission, showed any of the accepted criteria defining variceal bleeding[31]. Baveno V definition of events associated to the bleeding episode were used: failure to control bleeding, six week rebleeding, six week death and failure of secondary prophylaxis, which includes any significant bleeding due to portal hypertension after day 5 during the complete follow-up, that leads to hospitalization, drop in 3 gr of hemoglobin, blood transfusion or death within six weeks of the rebleeding episode[32]. Previous decompensation was defined by the presence of ascites, hepatic encephalopathy or variceal bleeding.

Statistical Analysis.

Parametric and non parametric variables are described with means (SD) and medians (IQR) respectively. Categorical variables are described with proportions. Chi-square, student T test, Mann-Whitney U test were used according to variable characteristics. Patients who received liver transplantation were censored at the time of the transplant. Kaplan-Meier curves were constructed and compared with log-rank test or Breslow test as appropriate. Multivariate stepwise Cox regression analysis was performed to analyse the independent effect of each variable on survival. The presence of statistical and biological interaction and confusion were analysed by stratified analysis and inclusion of the product term of the interaction. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Ethics committee approval was obtained.

RESULTS

During the study period, a total of 146 patients were admitted because of esophageal variceal bleeding and HCC in the 10 centers (See appendix 1). The patients had a median age of 68 years (IQR 59-74) and were predominantly Child-Pugh class B (A 30, B 76 and C 40) with a median MELD score of 14 (11-17) (table 1). HCC was diagnosed a median of 4 (0-18) months before the variceal bleeding episode. Thirty-seven (25%) patients were diagnosed at the time of the bleeding episode while 109 (75%) patients were diagnosed previously. At the time of the variceal bleeding, among HCC patients BCLC staging was: 0 in 3 patients, A 27 patients, B 28 patients, C 45 patients, D 41 patients. Previous treatments performed in these patients were surgery (3 patients), radiofrequency ablation (14 patients), percutaneous alcoholization (10 patients), TACE (43 patients), radioembolization (1 patient) and sorafenib (17 patients). As planned, 146 patients who were admitted due to variceal bleeding during the same time period without HCC were included with a median age of 67 (56-74) and Child-Pugh class distribution A 30; B 79; C 37 with a median MELD of 14 (10-17) (p=0.691, in comparison with HCC). Expectedly, viral etiology was proportionally more frequent among patients with HCC than in the control patients. Furthermore they had more frequently had previous decompensation than the control group (73% vs 60%, p=0.025). This finding was observed despite the fact that patients were matched by Child-Pugh class and had comparable MELD scores. Finally, HCC patients had more frequently portal vein thrombosis than control patients. Most patients had not had previous variceal bleeding and were eligible for primary prophylaxis (96 in HCC patients, 111 in non HCC patients). From these patients, 44 (43%) patients with HCC had primary prophylaxis compared to 40 (36%) patients without HCC (p=0.186). Similarly, from the patients who were eligible for secondary prophylaxis, no significant differences were observed between patients with HCC 37/44 (84%) vs patients without HCC 30/34 (88%) (p=0.755).

Management and outcomes of variceal bleed.

No differences were observed regarding clinical presentation, endoscopic findings and initial pharmacological and endoscopic treatment (Table 2). Five-day failure was similar (25% and 18% in patients with and without HCC, p=0.257), although more patients with HCC died in this time period (11% vs 4 %, p=0.025). Within the first 6 weeks, HCC patients had greater rebleeding rate (17% vs 7%, respectively, p=0.022) and mortality (30% vs 15%, p=0.003). Significantly fewer HCC patients received secondary prophylaxis after bleeding (83% vs 93%, p=0.015) and, among those who received prophylaxis, standard therapy (combination of drugs and EBL) was used less frequently (59% vs 70%, p=0.098). As expected, patients with greater BCLC stages (C and D) had less frequently secondary prophylaxis (47/71, 66 %), while almost all patients with lower BCLC stages (0, A and B) had secondary prophylaxis (55/57, 96%, p<0.001). Overall, lack of secondary prophylaxis was significantly associated to 6 week rebleeding (25% of those without prophylaxis compared to 9% of patients with prophylaxis, p=0.016) and mortality (59% of those without prophylaxis compared to 8% of patients with prophylaxis, p<0.001). Portal vein thrombosis (none, benign, malignant respectively) was not associated to 5 day failure (20%, 24%, 30%, p=0.385) , although it was associated to 5 day mortality (5%, 0% and 23%, p<0.001) and 6 week rebleeding (8%, 7%, 29%, p=0.001).

Long term outcomes

No significant differences in rebleeding after 6 weeks were observed between patients with and without HCC (19% Vs 17%), p=0.714) (Table 3). However, overall failure of secondary prophylaxis was more frequent in patients with HCC than controls (32% Vs 21%, p=0.05). Expectedly, lack of secondary prophylactic measures was associated with secondary prophylaxis failure (data not shown, p<0.001). Similarly, portal vein thrombosis was associated with secondary prophylaxis failure (None 25%, benign 21%, malignant

35%, <0.001). During follow-up three patients from each group received liver transplant. Most patients without HCC died of decompensated liver disease (40/49), while patients with HCC died of decompensated liver disease (34/109), tumoral disease (7/109), or a combination of both (61/109). Seven patients from each group had non hepatic deaths.

Transplant-free survival was significantly shorter in patients with HCC (median survival of 5 months Vs over 38 months in patients without HCC; log rank p<0.001) (figure 1, panel A). This difference was maintained in each Child-Pugh class (log rank p<0.001) (figure 1, panel B-D). Previous decompensation was significantly associated to survival in the overall group, however in patients with HCC, no significant differences were observed according to this variable (figure 2). Survival curves of patients with HCC according to BCLC classification is shown on supplementary figure 1. In order to simplify the statistical analysis and according to these survival curves. Patients were divided in 2 groups of BCLC classification (0, A , B and C, D). Expectedly, patients with BCLC 0, A, B had better survival rates (median survival 17.3 months, IQR 9.6-36.1) than patients with BCLC C and D (1.5 months, IQR 0.3-3.7), and both groups presented a worse outcome than patients without HCC (median survival >60 months), (figure 3).

Given the uneven distribution of well known prognostic markers of rebleeding and death, multivariate analysis was performed to evaluate the adjusted effect of HCC on survival (Table 4A). Even when considering the other variables, HCC and lack of secondary prophylaxis remained independent predictors of death.

Stratified analysis was performed to evaluate specifically the effect of use of secondary prophylaxis in patients according to BCLC. In patients with a BCLC 0, A and B, most patients had secondary prophylaxis. However lack of secondary prophylaxis was associated to death (log rank <0.001) with a median survival of 0.9 months in patients without prophylaxis (2/57, 4 %), compared to 22 months in patients with prophylaxis 55/57, 96 %). Similarly in patients BCLC C and D, and despite their dismal prognosis, lack of

secondary prophylaxis was also associated to death (log rank <0.001)) with a median survival 0.7 months (24/71, 34%), compared to 3 months in patients who had secondary prophylaxis (47/71, 66%) (figure 4).

A second model was performed in order to analyse the predictors of death in the subpopulation of patients with HCC and specifically the impact of the use of secondary prophylaxis taking into account BCLC classification stage. In this multivariate analysis Child-Pugh score, portal vein thrombosis, BCLC classification and use of secondary prophylaxis remained independent predictors of death (Table 4B). When the independent predictors of failure of secondary prophylaxis were evaluated, only BCLC classification [HR 1.78 (95% CI 1.23-2.59)], presence of portal vein thrombosis [benign HR 1.70 (95% CI 0.61-4.74), malignant 4.62 (95%CI 1.96-10.90)] and use of secondary prophylaxis [HR 0.33 (95% CI 0.14-0.75)] were independently associated with the outcome.

Taking into account that the differences in the use of secondary prophylaxis were mainly in the patients with BCLC C and D, further analysis was performed to compare these patients with and without prophylaxis (See Suppl Table 1). Patients who received no prophylaxis had more severe liver disease as shown by greater Child-Pugh score and MELD score, although there were no differences in the severity of the HCC as shown by the proportion of patients with BCLC C or D, portal vein thrombosis or metastasis.

DISCUSSION

In this study, a significantly lower survival rate was observed in patients who had HCC at the time of bleeding than patients who did not have HCC, despite the fact that the patients were matched for Child-Pugh class and age. This issue is of utmost interest as many studies that evaluated the treatment of acute bleeding episode and prophylaxis of rebleeding had excluded patients with HCC[12-25]. Furthermore, given the increasing

incidence of HCC, due to rising hepatitis C virus associated advanced liver disease, which is expected to peak in 2020, HCC and variceal bleeding are an increasingly common clinical problem that clinicians have to deal with. On the other hand, with further improvement in the management of patients with HCC with survival benefit [33-37] , these patients have more probabilities to present with complications of end stage liver disease. A previous study based on ICD-09 diagnostic codes suggested similar results, although due to the design of the study no in depth analysis could be performed [9].

Interestingly patients with HCC were less likely to have secondary prophylaxis than patients without HCC and a trend for a less frequent use of standard secondary prophylaxis with combination of betablockers and endoscopic band ligation in those patients with HCC. The reason why HCC patients were not offered standard therapy is unclear from this study. It is likely that this was due to the assumption by the attending physician that this would not result in a clinical benefit. This is also suggested by the fact that patients with HCC without secondary prophylaxis seemed to have more severe liver disease. However, as lack of secondary prophylaxis was associated to a greater probability of failure and death in models adjusted for severity of liver disease, our results support offering patients with HCC the same treatment after variceal bleeding as it is done for patients without HCC. Although there were no differences in rebleeding rate after 6 weeks when comparing HCC to non-HCC patients, more patients with HCC died in this time period. Indeed, most patients with HCC who died, died of progressive tumoral disease and decompensated liver disease. In addition, when the specific predictors of failure of secondary prophylaxis and death were evaluated in patients with HCC including BCLC classification, the use of secondary prophylaxis had an independent protective effect on the development of rebleeding and death, further suggesting that use of this treatment should be prolonged as long as the clinical condition of the patient allows it.

Despite the fact that the groups were matched by Child-Pugh class and had similar MELD score, patients with HCC had more frequently previous decompensation than patients without HCC. Belonging to the compensated or decompensated phase of the liver disease is of utmost relevance given the well known survival differences between these groups[2]. Indeed, after introduction of MELD score, it had been remarked that different survival rates could be seen in patients with the same MELD score according to the presence or absence of clinical decompensation [38] . In the present study, it should be underlined that from the moment they experience variceal bleeding, all patients are in the decompensated phase. For this reason this variable was not chosen initially as a matching variable. Also, as expected, patients with HCC had more commonly a viral etiology of their liver disease. Viral etiology has been identified as a negative prognostic factor for 5 day failure in acute variceal bleeding [29]. Given the possible confusion that these variables could introduce, they were included in the multivariate analysis. On multivariate analysis both the etiology of liver disease and the presence of previous decompensation were not identified as independent predictors of survival.

Portal vein thrombosis was also distributed unevenly between patients with HCC and control patients. This variable was significantly associated with outcomes of variceal bleeding and survival. Previous studies have associated the presence of portal vein thrombosis with negative outcomes in variceal bleeding[39]. Interestingly, the prognostic information derived from the presence of portal vein thrombosis was independent from the BCLC classification.

Among patients with HCC, survival was mainly influenced by disease stage, best described by the BCLC classification. So patients in class C and D had a much greater likelihood of dying within 6 months (79%) compared to class 0, A and B (14%) Nevertheless, lack of secondary prophylaxis was an independent predictor of death taking into account BCLC classification. Therefore use of secondary prophylaxis in these

patients, even in those with the most advanced tumoral disease (BCLC C and D), had survival advantages. Logically, patients with less advanced tumors are the ones who have the most to benefit from the use of secondary prophylaxis. Physicians taking care of patients with advanced HCC after a variceal bleeding episode should individualize therapies according to clinical practice, common sense and patient needs. Some may judge that the survival benefit in these BCLC C and D patients who received secondary prophylaxis is not clinically relevant (average 3 months) and that more interventional therapies (banding ligation) should be avoided taking into account the possible adverse effects.. Nevertheless, this survival benefit is similar to the survival benefit offered with sorafenib treatment in BCLC C patients, which also has side effects, which may impact quality of life. The present study showing a global survival effect of prophylaxis patients with advanced HCC, provides further evidence to indicate prophylaxis in this subgroup of patients as long as their clinical condition allows to do so.

There are several setbacks to the study. Some patients with very advanced HCC and upper gastrointestinal bleeding were not included in the study as no endoscopy was performed. This could lead to some bias in the results, as it is probable that these patients who were not included would be the ones who would be most likely to die. However, the decision to exclude these patients from the study was based on several reasons. Firstly, although suspected, the cause of the bleeding was not proven as endoscopy was not performed. It is well established that about one third of upper gastrointestinal bleeding episodes in patients with cirrhosis are due to other causes rather than esophageal varices[40, 41]. Secondly, most likely the patients who would not receive endoscopy would probably be the sickest ones and therefore with the most dismal outcome. Therefore inclusion of these patients in the analysis might further enhance the differences in the outcomes of variceal bleeding in patients with and without HCC. Furthermore, and although it seems that patients with HCC without secondary prophylaxis were more sick

than the ones who received secondary prophylaxis,which may have influenced the physicians opinion, it could be that there are other factors that influenced this decision that are not included in the analysis. Unfortunately, the study design does not allow analysis of the impact of sorafenib treatment on variceal bleeding. It has been establshed both in animal and human studies that sorafenib has a portal hypotensive effect, perhaps through an inhibition of angiogenesis[42, 43]. Therefore, there could be an impact of the administration of this drug on the outcomes. In the present study, sorafenib was administered exclusively to patients with advanced HCC, therefore it is logical to speculate that lack of sorafenib could further worsen the outcome of these patients, who already have a dismal prognosis. Another limitation of the study is the uneven distribution of the etiologies among patients with and without HCC. Although on multivariate analysis viral disease was not identified as an independent predictor of death (and therefore non-viral disease, which was mainly alcohol, was not identified as a predictor of survival), it could be that non-HCC patients with alcoholic liver disease ceased alcohol consumption after the variceal bleed and therefore had a better outcome. Finally, the design of this study does not allow evaluation of the impact of variceal bleeding in the natural history of HCC.

In conclusion patients with HCC with variceal bleed have worse outcomes than patients without HCC. These differences are only partially explained by differences in secondary prophylaxis measures, as in patients with variceal hemorrhage and HCC. Use of secondary prophylaxis has survival benefit in patients with HCC irrespective of BCLC stage.

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Figure legends:

Figure 1: Survival curves of patients after variceal bleeding with hepatocellular carcinoma (dotted line) compared to patients without hepatocellular carcinoma (continuous line) (Panel A) and according to Child-Pugh class. Panel B: Child-Pugh class A, Panel C: Child-Pugh class B, Panel D: Child-Pugh class C. Log rank test p< 0.001

Figure 2: Survival curves of patients after variceal bleeding according to the presence (dotted line) or absence (continuous line) of prior clinical decompensation (Panel A). Log rank test p< 0.001. Subanalysis in patients with hepatocellular carcinoma according to the presence (dotted line) or absence (continuous line) of prior clinical decompensation (Panel B) Log rank test p=0.231.

Figure 3: Survival curves of patients after variceal bleeding with hepatocellular carcinoma according to BCLC stage (0, A, B: short dotted line; C,D: long dotted line) compared to patients without hepatocellular carcinoma (continuous line). Breslow test p < 0.001

Figure 4: Survival curves of patients after variceal bleeding with hepatocellular carcinoma BCLC C and D according to presence (continuous line) or absence (dotted line) of secondary prophylaxis. Log rank p< 0.001

Supplementary Figure 1: Survival curves of patients after variceal bleeding with hepatocellular carcinoma according to BCLC stage (curves identified on the graph) compared to patients without hepatocellular carcinoma (continuous line). Breslow test p< 0.001

Table 1. Baseline characteristics

	Non HCC patients n=146	HCC patients n=146	p value
Male	101 (69%)	116 /79%)	0.060
Age (yrs)	67 (56-74)	68 (59-74)	0.778
Etiology			<0.001
Alcohol	62 (42%)	37 (25%)	
Alcohol + HCV	15 (10%)	20 (14%)	
HCV	43 (29%)	71(49%)	
HBV	6 (4%)	11 (8%)	
Others	20 (14%)	7 (5%)	
HIV infection	4 (3%)	9 (6%)	0.165
Child-Pugh Class			0.797
A	30 (21%)	30 (21%)	
B	79 (54%)	76 (52%)	
C	37 (25%)	40 (27%)	
MELD	14(10-17)	14(11-17)	0.691
Previous decompensation			
Total	88 (60%)	107 (73%)	0.025
Variceal bleeding	31 (21%)	43 (29%)	0.139
Ascites	78 (53%)	95 (65%)	0.057
Hepatic Encephalop.	19 (13%)	22 (16%)	0.737
Bilirubin (mg/dL)	1.6 (1.1-2.4)	1.5 (1-3.0)	0.985
INR	1.4 (1.3-1.7)	1.4 (1.3-1.6)	0.155
Albumin (g/dL	2.8 (2.4-3.3)	2.9 (2.5-3.3)	0.431
Creatinine (mg/dL)	0.9 (0.7-1.2)	1.0 (0.8-1.3)	0.025
Previous Primary Prophylaxis*	40/112 (36%)	44/102 (43%)	0.186
Previous Secondary Prophylaxis*	30/34 (88%)	37/44(84%)	0.755
Time from HCC diagnosis (months)	-	4 (0-18)	-
BCLC 0/A/B/C/D	-	3/27/28/45/41	-
Portal vein thrombosis			<0.001
None	137 (94%)	78 (53%)	
Benign	9 (6%)	20 (14%)	
Malignant	0	48 (33%)	

Variables are presented in proportion or medians (IQR). Denominator of the proportions is the number of patients in the group unless otherwise stated. Chi-square and Mann-Whitney U tests were used as appropriate. Proportions of primary and secondary prophylaxis are calculated according to the number of eligible patients.

Abbreviations: HCC: Hepatocellular carcinoma, HCV: Hepatitis C virus, HBV: Hepatitis B virus, HIV: human immunodeficiency virus, MELD: Model for End

stage Liver Disease, Hepatic Encephalop: Hepatic Encephalopathy. BCLC: Barcelona Clínic Liver Cancer Classification

Table 2. Characteristics of Variceal Bleeding and Outcomes (according to Baveno)

	Non HCC patients n=146	HCC patients n=146	p value
Shock at presentation	43 (29%)	32 (22%)	0.141
Infection	15/145 (10%)	21 (14%)	0.295
Size of varices			0.795
Small	10 (7%)	11 (8%)	
Large	136 (93%)	133 (92%)	
Bleeding signs at endoscopy			0.764
None	75 (51%)	75/141 (53%)	
Nipple	38 (26%)	35/141 (25%)	
Oozing	16 (11%)	19/141 (13%)	
Jet	17 (12%)	12/141 (9%)	
Initial endoscopic treatment			0.215
None	9 (6%)	18 (12%)	
Sclerotherapy	22 (15%)	20 (14%)	
EBL	114 (78%)	105 (72%)	
Glue	1 (1%)	3 (2%)	
Initial pharmacological therapy			0.946
None	1 (1%)	2 (1%)	
SMT (6 mg/24h)	93 (64%)	93 (64%)	
SMT (12 mg/24h)	50 (34%)	48 (33%)	
Terlipressin	2 (1%)	2 (1%)	
Antibiotic prophylaxis			0.860
None	3/142 (2%)	5/140 (4%)	
Ceph. 3rd Gen	112/142 (79%)	111/140 (79%)	
Quinolones	27/142 (19%)	24/140 (17%)	
Balloon tamponade	2 (1%)	3 (2%)	0.652
Initial control of bleeding	129/135 (96%)	131 (90%)	0.271
5 day failure	27 (18%)	37 (25%)	0.257
5 day death	6 (4%)	16 (11%)	0.044
6 week rebleeding*	10/140 (7%)	22/130(17%)	0.023
6 week death	22 (15%)	44 (30%)	0.003

Variables are presented in proportions. The denominator of the proportions is the number of patients in the group in whom the information was available or applicable* unless otherwise stated. Small varices are Grade I, large varices are > Grade I varices. Chi-square tests were applied.

Abbreviations: HCC: Hepatocellular carcinoma, EBL: Endoscopic band ligation, SMT: somatostatin, Ceph 3rd Gen: 3rd generation cephalosporins

Tabla 3. Long-term outcomes

	Non HCC patients n=140	HCC patients n=130	p value
Follow up (months)	11.6 (2.7-24.9)	3.3 (0.6-13.4)	<0.001
Rebleeding (> 6w)*	19/112 (17%)	18/94 (19%)	0.718
Failure of secondary prophylaxis	29 (21%)	41 (32%)	0.05
Liver Transplantation	3 (2%)	3 (2%)	0.675
Death	49 (35%)	109 (84%)	<0.001
Transplant-free survival (months)	>38 (6.4-not calculable)	5.0 (0.8-17.3)	<0.001

Patients who died within the first 5 days are excluded. Variables are presented in proportion or medians (IQR). The denominator of the proportions is the number of patients in the group unless otherwise stated. Chi-square, Mann-Whitney U and log-rank tests were used as appropriate. * Proportions are calculated according to the number of eligible patients, that is the patients who were still alive 6 weeks after the original bleeding episode.

Abbreviations: HCC: Hepatocellular carcinoma, 6w: 6 weeks

Table 4A. Uni- and Multivariate Cox analysis of predictors of death

Variable	Univariate HR (95% CI)	Adjusted HR (95% CI)
HCC	3.35 (2.38-4.71)	5.45 (2.69-11.05)
MELD	1.11 (1.08-1.14)	-
Previous decompensation	1.99 (1.38-2.86)	-
Lack of Secondary prophylaxis	6.67 (4.54-10.00)	6.67 (4.16-11.11)
Etiology*	2.09 (1.49-2.92)	-
Child-Pugh class -A (reference) -B -C	 - 1.48 (0.94-2.32) 3.30 (2.04-5.32)	 -
Child-Pugh score	1.23 (1.14-1.33)	1.28 (1.15-1.42)
Portal vein thrombosis -none (reference) -benign -malignant	 - 0.99 (0.55-1.76) 5.68 (3.62-8.92)	 - 1.41 (0.75-2.62) 3.29 (2.03-5.33)
Sex	1.07 (0.75-1.54)	-
Age	1.01 (0.99-1.02)	-
Bilirubin	1.08 (1.03-1.13)	-
Albumin	1.01 (0.99-1.03)	-
INR	2.22 (1.49-3.30)	-
Creatinine	1.33 (1.21-1.46)	-
Standard prophylaxis	0.83 (0.56-1.24)	-

Multivariate stepwise Cox regression analysis to evaluate the independent predictors of death (n=142). Etiology was recoded in two categories (non viral, which was the reference category, and viral disease). Variables initially included in the multivariate analysis: age, HCC, MELD, previous decompensation, secondary prophylaxis, etiology, portal vein thrombosis and Child Pugh Score. Variables included in MELD score were not included in the multivariate analysis to avoid colinearity. Child-Pugh class was not included due to the fact that this was a matching variable.

Table 4B. Multivariate predictors of death among HCC patients.

Variable	95% CI
BCLC Classification	4.04 (2.24-7.27)
Lack of secondary prophylaxis	4.00 (2.27-6.67)
Child-Pugh Score	1.29(1.15-1.44)
Portal vein thrombosis **-none (reference)** **-benign** **-malignant**	 - 0.90 (0.42-1.96) 2.16 (1.27-3.68)

Multivariate stepwise Cox regression analysis to evaluate the independent predictors of death (n=99). Variables initially included in the multivariate

analysis: BCLC (classified in two categories: 0.A, B and C, D), previous decompensation, secondary prophylaxis, etiology, Child-Pugh score and portal vein thrombosis.

Appendix 1: Patient distribution according to centers.

Center	Number of Patients (HCC/nonHCC)
Canarias	6/6
LLeida	9/9
Clínic	32/32
Sta Creu St. Pau	17/17
Vall D'Hebron	17/17
Ramon y Cajal	14/14
Gregorio Marañón	26/26
Germans Trias i Pujol	7/7
Hospital del Mar	12/12
Puerta de Hierro	6/6

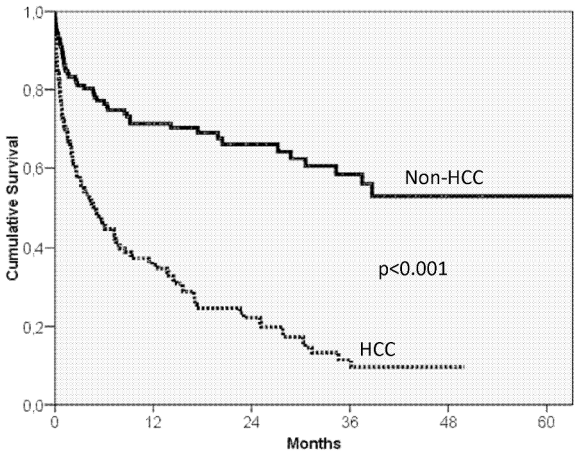
Suplementary Table 1. Comparison of BCLC C and D with and without secondary Prophylaxis

	Patients without Prophylaxis (n=24)	Patients with secondary Prophylaxis (n=47)	p-value
Male	20 (83)	39 (83)	1
Age (yrs)	74 (60-77)	65 (59-73)	0.038
Child-Pugh score	9 (7-10)	8 (7-9)	0.052
MELD	16 (15-22)	13(10-17)	0.001
BCLC **C** **D**	 13 (54) 11 (46)	 28 (60) 19 (40)	0.800
Time of diagnosis (months)	7 (0-24)	4 (0-22)	0.743
Follow-up (months)	0.6 (0.3-1.7)	2.6 (1.1-5.0)	<0.001
Etiology Alcohol Virus	 7 (29) 17 (71)	 11 (23) 36 (77)	0.774
Previous Ascites	19 (79)	26 (55)	0.041
Previous Hepatic Encephalopathy	7 (29)	6 (13)	0.088
Previous Variceal Bleeding	6 (25)	15 (32)	0.376
Previous Decompensation	19 (79)	32 (68)	0.244
Portal Vein Thrombosis No Benign Malignant	 13 (54) 2 (8) 9 (38)	 14 (30) 8 (17) 25 (53)	0.085
Metastases	3 (13)	4 (9)	0.676
Bilirubin (mg/dL)	2.2 (1.4-3.5)	1.3 (1-2.2)	0.035
INR	1.45 (1.29-1.72)	1.33 (1.24-1.50)	0.215
Albumin (gr/dL)	3.0 (2.4-3.6)	2.9 (2.5-3.3)	0.626
Creatinin (mg/dL)	1.3 (0.9 -2.0)	0.9 (0.7-1.3)	0.002
Bleeding at endoscopy	13 (54)	19 (40)	0.237
Hypovolemic shock	4 (17)	7 (15)	1
Balloon	0	0	

Tamponade			
Infection	4 (17)	9 (19)	1
Rebleeding <6 weeks	8 (33)	10(21)	0.260
Mortality <6 weeks	18 (75)	8 (17)	<0.001
Failure of secondary prophylaxis	20 (83)	15 (32)	<0.001
Rebleeding >6 weeks	2(8)	7 (15)	0.708
Mortality at 3 months	21 (88)	19 (40)	<0.001
Mortality at 6 months	23 (96)	30 (64)	0.003
Mortality at 1 year	23 (96)	35 (74)	0.641
Mortality at end of follow-up	24 (100)	38 (81)	0.024

Variables are presented in proportion or medians (IQR). Chi-square and Mann-Whitney U tests were used as appropriate.
Abbreviations: HCC: Hepatocellular carcinoma, MELD: Model for End stage Liver Disease, BCLC: Barcelona Clínic Liver Cancer Classification

Figure 1 A



No HCC					
At risk	146	72	37	27	7
Events	0	39	43	47	49
HCC					
At risk	145	39	19	6	2
Events	0	87	100	108	109

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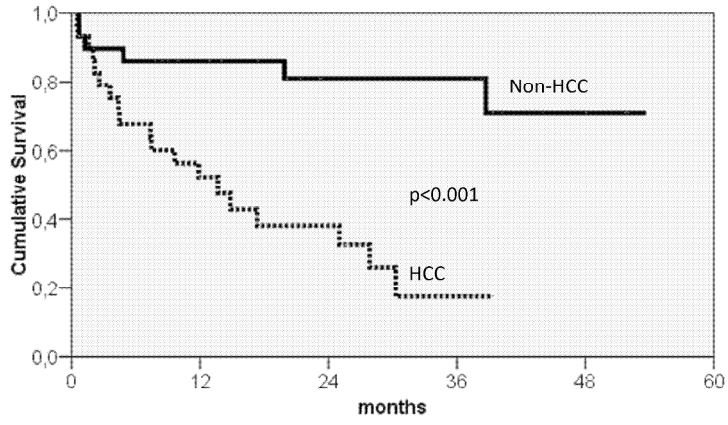
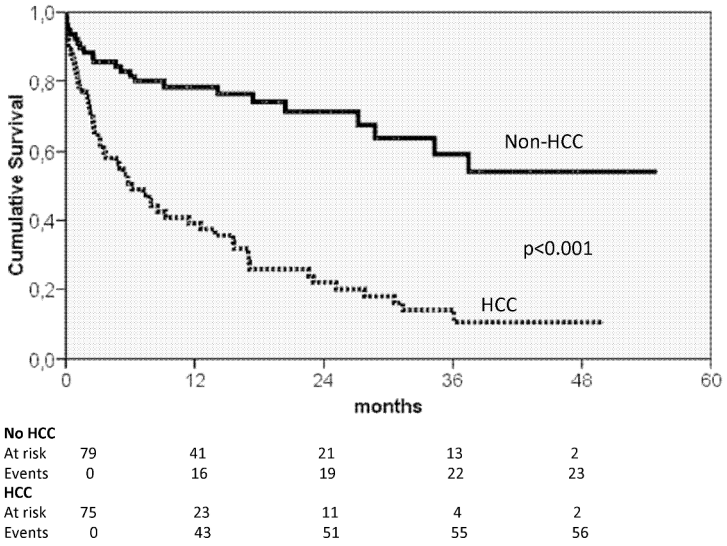
Figure 1 B



No HCC					
At risk	30	20	13	11	4
Events	0	4	5	5	6
HCC					
At risk	30	12	7	2	-
Events	0	13	16	19	-

297x209mm (300 x 300 DPI)

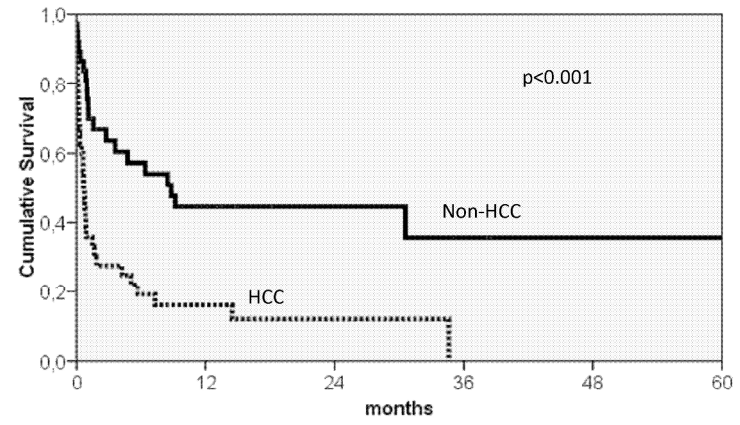
Figure 1 C



No HCC					
At risk	79	41	21	13	2
Events	0	16	19	22	23
HCC					
At risk	75	23	11	4	2
Events	0	43	51	55	56

297x209mm (300 x 300 DPI)

Figure 1 D

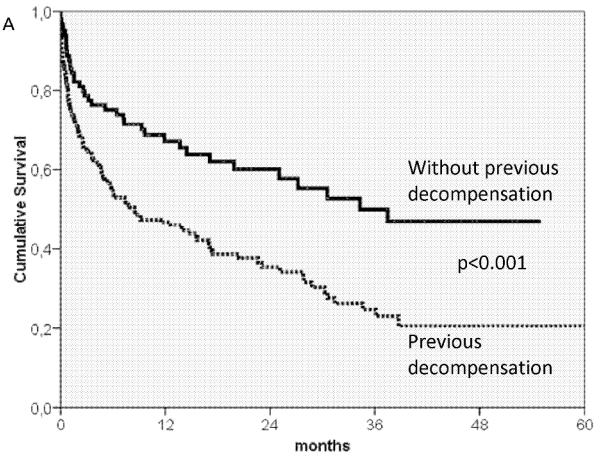


No HCC					
At risk	37	11	5	3	1
Events	0	19	19	20	20
HCC					
At risk	40	3	1	-	-
Events	0	33	33	-	-

297x209mm (300 x 300 DPI)

Figure 2

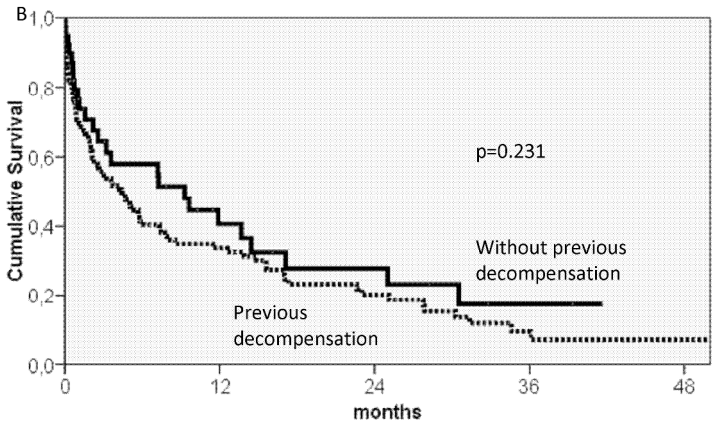
A



No previous decompensation					
At risk	97	42	25	16	2
Events	0	28	33	37	38
Previous decompensation					
At risk	194	67	29	14	5
Events	0	97	110	118	120

297x209mm (300 x 300 DPI)

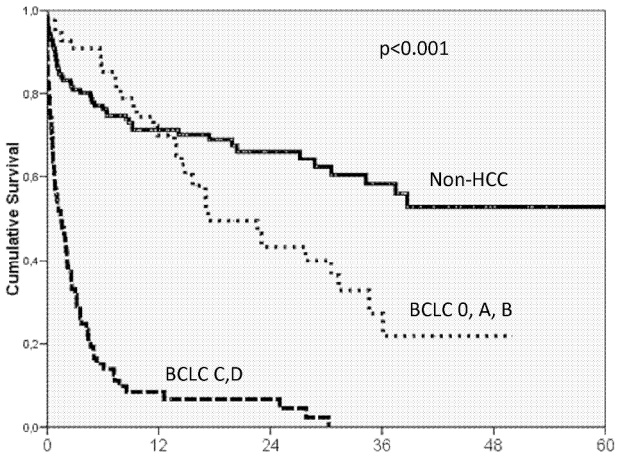
Figure 2



No previous decompensation				
At risk	39	10	6	3
Events	0	20	23	25
Previous decompensation				
At risk	106	29	13	4
Events	0	67	77	83

297x209mm (300 x 300 DPI)

Figure 3



No HCC					
At risk	146	72	37	27	7
Events	0	39	43	47	49
HCC BCLC 0, A, B					
At risk	58	30	14	5	1
Events	0	15	25	29	30
HCC BCLC C, D					
At risk	86	5	3	-	-
Events	0	72	74	-	-

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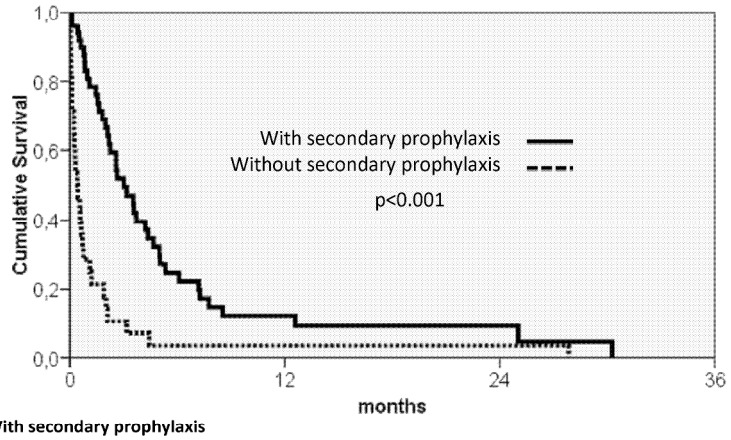
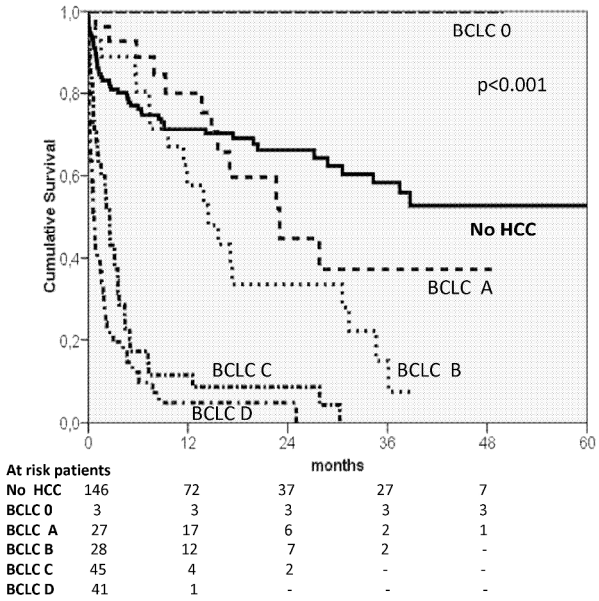
Figure 4



With secondary prophylaxis				
At risk	47	4	2	-
Events	0	37	38	40
Without secondary prophylaxis				
At risk	24	1	1	-
Events	0	27	27	28

297x209mm (300 x 300 DPI)

Supplementary Figure 1



At risk patients					
No HCC	146	72	37	27	7
BCLC 0	3	3	3	3	3
BCLC A	27	17	6	2	1
BCLC B	28	12	7	2	-
BCLC C	45	4	2	-	-
BCLC D	41	1	-	-	-

297x209mm (300 x 300 DPI)