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Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis☆

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See Editorial, pages 848–849

***Background/Aims*: A total of 213 patients with compensated cirrhosis, portal hypertension and no varices were included in a trial evaluating beta-blockers in preventing varices. Predictors of the development of hepatocellular carcinoma (HCC), including hepatic venous pressure gradient (HVPG) were analyzed.**

***Methods*: Baseline laboratory tests, ultrasound and HVPG measurements were performed. Patients were followed prospectively every three months until development of varices or variceal bleeding or end of the study in 09/02. The endpoint was HCC development according to standard diagnostic criteria. Univariate and multivariate Cox regression models were developed to identify predictors of HCC.**

***Results*: In a median follow-up of 58 months 26/213 (12.2%) patients developed HCC. Eight patients were transplanted and 28 patients died without HCC. Twenty-one (84%) HCC developed in patients with HCV. On multivariate analysis HVPG (HR 1.18; 95%CI 1.08–1.29), albumin (HR 0.34; 95%CI 0.14–0.83) and viral etiology (HR 4.59; 95%CI 1.51–13.92) were independent predictors of HCC development. ROC curves identified 10 mmHg of HVPG as the best cut-off; those who had an HVPG above this value had a 6-fold increase in the HCC incidence.**

***Conclusions*: Portal hypertension is an independent predictor of HCC development. An HVPG >10 mmHg is associated with a 6-fold increase of HCC risk.**

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***Keywords*: Portal hypertension; End-stage liver disease; Liver cancer; Albumin; Predictive factors; Multivariate analysis**

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Abbreviations: HVPG, hepatic venous pressure gradient; RCT, randomized controlled trial.

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1. Introduction

Patients with cirrhosis are at an increased risk of developing hepatocellular carcinoma (HCC) [1]. HCC is an important cause of death in cirrhosis, particularly in patients with decompensated cirrhosis [2]. In the past, HCC was associated with a dismal prognosis, however, currently there are more therapeutic options, particularly when HCC is diagnosed at earlier stages [3]. This justifies the performance of surveillance programs in patients with cirrhosis, a process that has shown to be related to a survival benefit [3–6].

The success of a screening program depends on the identification of high-risk populations in order to have the highest positive predictive value. Although cirrhosis is the clearest risk factor for HCC in most cases of chronic liver disease, the identification of early predictors of HCC in patients with cirrhosis would allow to further select high-risk patients for screening programs that would then be more cost-effective.

Several predictors of HCC relate to the severity of cirrhosis including parameters indicative of liver insufficiency [7] such as bilirubin, albumin and prothrombin activity and parameters indicative of portal hypertension [1,7,8] such as platelet count and the presence of varices. The role of measurements of portal pressure by the hepatic venous pressure gradient (HVPG), a recognized prognostic factor in compensated cirrhosis [9], has not been investigated as a predictor of the development of HCC.

The aim of this study was to evaluate the role of the HVPG in predicting the development of HCC in a cohort of patients with compensated cirrhosis and portal hypertension but without varices.

2. Patients and methods

This study is a nested cohort study within a randomized controlled trial [10]. Between August 1993 and March 1999, 213 patients with compensated cirrhosis were enrolled in a prospective randomized controlled trial designed to evaluate the efficacy of nonselective beta-blockers in the prevention of the development of gastroesophageal varices. Patients were considered for inclusion if they had cirrhosis and portal hypertension (defined by an HVPG of at least 6 mmHg) without gastroesophageal varices and were between 18 and 75 years of age. The diagnosis of cirrhosis was either biopsy proven or clinically suspected and confirmed by the presence of an HVPG value of 10 mmHg or greater. Exclusion criteria included ascites requiring diuretic treatment, HCC, splenic or portal vein thrombosis, concurrent illnesses expected to decrease life expectancy to less than 1 year, the use of any drug or procedure affecting splanchnic hemodynamics or portal pressure, primary biliary cirrhosis or primary sclerosing cholangitis, contraindication to beta-blocker therapy, pregnancy or alcohol intake during the dose-titration phase. Patients were randomized to receive placebo or timolol, a non-selective beta-blocker. At baseline clinical history, physical exam, blood tests, upper gastrointestinal endoscopy, abdominal ultrasonography and HVPG measurement were performed. Patients were followed at 1 and 3 months after randomization and then every 3 months until the primary end-point of the study (development of small varices observed in two consecutive endoscopies, large varices or variceal hemorrhage), the secondary end-point (death or liver transplantation) or until the end of the study in September 2002. During this time period, 84 patients developed the primary endpoint of the trial and follow-up was discontinued in the setting of the RCT [10].

The primary endpoint of the present study was the development of HCC. The diagnosis of HCC was established according to well established diagnostic criteria [11]. These was histological confirmation of HCC, typical image suggested by 2 radiological techniques or only in one imaging technique with an alpha-fetoprotein (AFP) greater than 400.

All data regarding development of HCC had been prospectively collected in the RCT by 6-monthly to annual ultrasonography, except in 62 patients who developed the primary endpoint of that trial but had not developed HCC. Retrospective review of charts of these patients was performed in order to have complete follow-up regarding development of HCC until the end of the study (September 2002). Baseline AFP was not part of the data collected at the time of inclusion into the original randomized trial and therefore this information was collected retrospectively for the period of ±6 months from the randomization date. Given that in most centers, negative AFP values were reported as <15 ng/ml, this parameter is reported in this study as a dichotomic variable.

The association between different variables and the development of HCC over time was assessed using univariate Cox analysis. Multivariate analysis with backward stepwise Cox proportional hazards regression analysis was performed with the variables that had attained a p value lower than 0.1 on univariate analysis. In order to avoid the common problems of overfitting and colinearity, several different models were created with variables that were statistically significant in univariate analysis ($p < 0.1$) or that were clinically relevant. The modelling strategy used in this study is based on the reduction in the likelihood ratio (-2LL) of the different models developed and the number of variables in each model. The lower the value of -2LL, the greater amount of variability of the outcome variable is explained by the model; i.e the better the model. The best model is the one with the lowest -2LL and the least number of variables. By using this strategy we could evaluate all the potential variables that may have a role in predicting development of HCC. Colinearity was assessed with the tolerance value, considering excessive colinearity between variables when the tolerance was below 0.1. First order one-way interactions between HVPG and the other variables were assessed by introducing in the model the cross-products between HVPG and the other variables, only interactions that would significantly change the predictive capacity would remain in the model. Assessment of proportional hazards was done by introducing a time-dependent variable and graphically. To evaluate the independent role of HVPG in predicting HCC, explicative multivariate Cox proportional hazards models were developed. ROC curves with HVPG were constructed. Kaplan-Meier curves were constructed and compared with the log rank test. Cox proportional hazards models were also developed in the subgroup with alpha-fetoprotein. Statistical significance was considered with a p value of 0.05 or less. Statistical analysis was done with SPSS package 14.0.

Informed written consent for participation in the RCT was obtained from all patients. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local institutional review board.

3. Results

Baseline data of the patients is shown in Table 1. From the 213 patients who were included in the original trial [10], 26 (12%) patients developed HCC, 8 were transplanted (due to end-stage liver disease without HCC), 28 patients died (neoplasia 5, infections 9, liver failure 10, cardiac events 2, progressive dementia 1, pulmonary vasculitis 1), and the remaining 151 patients were alive at the end of follow-up without HCC or transplant (Fig. 1). The median follow-up was 58 (interquartile range 38–78) months. Median HVPG at baseline was 11 (interquartile range 8–14) mmHg.

Table 1
Baseline characteristics of all patients ($n = 213$) and patients who did ($n = 26$) and did not ($n = 187$) develop HCC during follow-up.

	$N = 213$	Did not develop HCC ($n = 187$)	Developed HCC ($n = 26$)
Male (%)	126 (59)	111 (59)	16 (62)
Age	54 (23–75)	53 (23–75)	59 (43–73)
Etiology of cirrhosis (%)			
-Alcoholic	51 (24)	50 (27)	1 (4)
-Nonalcoholic	162 (76)	137 (73)	25 (96)
-HCV	133 (62)	111 (59)	22 (85)
-HBV	9 (4)	9 (5)	0 (0)
-Cryptogenic	10 (5)	8 (4)	2 (8)
-Other	10 (5)	9 (5)	1 (4)
Child-Pugh score	5 (5–8)	5 (5–8)	5 (5–7)
Child-Pugh class (%)			
-A	188 (88)	165 (88)	23 (88)
-B	25 (12)	22 (12)	3 (12)
MELD	8.0 (6.4–16.3)	8.4 (6.4–16.3)	7.6 (6.4–12.4)
Platelets ($\times 10^{-3}$/mm^3)	111 (15–559)	119 (15–559)	83 (29–225)
Total bilirubin (mg/dl)	0.9 (0.2–5.9)	0.9 (0.2–5.9)	1 (0.2–2.2)
INR	1.1 (1–2)	1.1 (1–2)	1.07 (1–2)
Albumin (g/dl)	4.0 (2.1–5.4)	4 (2.1–5.4)	3.7 (3.3–4.4)
Aspartate aminotransferase (IU/l)	73 (16–361)	69 (16–361)	120 (44–288)
Alanine aminotransferase (IU/l)	78 (10–595)	72 (10–595)	113 (57–327)
Serum sodium (mmol/l)	140 (114–148)	140 (131–148)	140 (114–146)
Creatinine (mg/dl)	0.9 (0.2–1.9)	0.9 (0.2–1.9)	0.8 (0.5–1.4)
AFP (% >15) μg/mL)	17% (25/148)	10% (15/148)	7% (10/148)
HVPG (mmHg)	11 (6–25)	11 (6–25)	13 (7–24.5)
HVPG $\geqslant$ 10 mmHg	134 (63)	111 (59)	23 (89)
Follow-up time (months)	58 (0–109)	59 (0–109)	50 (6–92)
Time from diagnosis of cirrhosis (months)[a]	12 (0–395)	12 (0–395)	9 (0–118)
Randomized to timolol	108 (51)	93 (50)	15 (58)

Qualitative variables are expressed in absolute numbers and percentages. Quantitative variables are expressed in medians and ranges. HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, alphafetoprotein; HVPG, hepatic venous pressure gradient.
[a] At inclusion in the RCT.

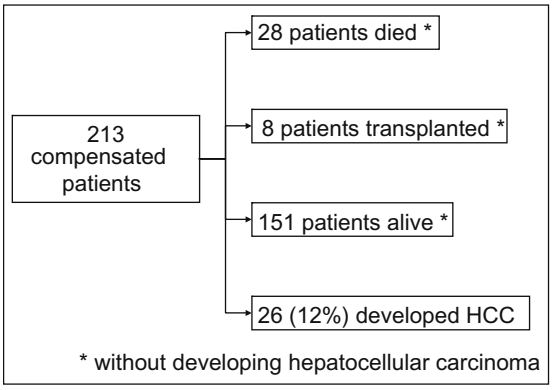

Fig. 1. Evolution of patients during the study.

On univariate analysis (Table 2) patients who developed HCC were older without gender differences, with a significantly higher proportion of patients with a viral-related cirrhosis and, notably, a similar duration of liver disease as estimated from the time from diagnosis of cirrhosis and no differences in Child-Pugh or MELD scores. Patients who developed HCC had significantly higher AST, lower serum albumin and platelet count and a higher HVPG at baseline. No patient had varices as this was a requirement for inclusion in the original study. A subgroup of patients had repeat measurements during follow-up. No differences were observed in the relative change of HVPG between the patients who developed HCC from those who did not develop HCC (data not shown).

On multivariate analysis only baseline HVPG, albumin and viral etiology remained independent predictors of the development of HCC during follow-up (Table 3). This model had the lowest likelihood ratio with the least number of variables.

In order to evaluate the effect (if any) of AFP levels in HCC prediction, a multivariate model developed in the subset of patients who had baseline AFP results ($n = 148$) of whom 19 (13%) developed HCC. Despite overfitting, HVPG (HR: 1.25; 95%CI: 1.12–1.4), an AFP > 15 ng/mL (HR: 4.49; 95%CI: 1.72–11.72) and viral etiology (HR: 6.05; 95%CI: 1.22–30.06) remained independent predictors of the development of HCC in this subgroup, with HVPG remaining one of the strongest predictors.

ROC curves identified a HVPG value of 10 mmHg as the cut-off with the greatest sensitivity and specificity. The clinical relevance of this cut-off has been demonstrated previously [9]. Patients with an HVPG equal to

Table 2
Univariate Cox analysis.

Variable	Regression coefficient	DS	Hazard Ratio	95%CI	*p* Value
Age (years)	0.037	0.019	1.04	0.99–1.08	0.055
Male Gender (yes/no)[a]	−0.09	0.403	0.91	0.41–2.02	0.823
Viral etiology (yes/no)[a]	−0.995	0.545	2.71	0.93–7.87	0.068
Child-Pugh score	0.279	0.245	1.32	0.82–2.14	0.255
MELD	−0.02	0.103	0.98	0.8–1.2	0.845
Bilirubin (mg/dl)	0.113	0.231	1.12	0.71–1.76	0.641
INR	1.12	1.316	3.31	0.23–40.46	0.395
Albumin (g/dl)	−1.185	0.394	0.31	0.14–0.66	0.003
HVPG (mmHg)	0.132	0.037	1.14	1.06–1.23	<0.001
Platelets ($\times 10^{-3}$/mm^3)	−0.014	0.005	0.99	0.98–1	0.006
AST (IU/l)	0.006	0.002	1.01	1.00–1.01	0.001
ALT (IU/l)	0.002	0.001	1.00	1–1.01	0.08
AFP $\geqslant$ 15 ng/ml (yes/no)[a] ($n = 148$)	1.747	0.411	5.74	2.56–12.84	<0.001

Quantification of the effect is expressed as the regression coefficient and standard deviation as well as the hazard ratio (HR) and 95%CI. All continuous variables were introduced in the univariate model as such. MELD, model of end-stage liver disease; HVPG, hepatic venous pressure gradient.

[a] Reference values: Gender (male: yes/no): no; viral etiology (yes/no): no; AFP $\geqslant$ 15 ng/ml (yes/no): no.

Table 3
Modeling strategy (26 events).

Variables introduced	Final model	Regression coefficient (SD)	HR (95%CI)	*p* Value	−2LL	Chi square/df/p
HVPG, AST, age, albumin, viral yes/no	HVPG	0.168 (0.045)	1.18 (1.08–1.29)	<0.001	217.42	26.823
	Albumin	−1.072 (0.452)	0.34 (0.14–0.83)	0.018		/3
	Viral yes/no	1.523 (0.567)	4.59 (1.51–13.92)	0.007		/<0.001
HVPG, albumin, age, AST	HVPG,	0.120 (0.043)	1.13 (1.04–1.23)	0.005	221.177	26.913
	Albumin	−1.037 (0.448)	0.35 (0.15–0.85)	0.02		/3
	AST	0.005 (0.002)	1.01 (1.00–1.01)	0.007		/<0.001
HVPG, albumin, AST	HVPG,	0.120 (0.043)	1.13 (1.04–1.23)	0.005	221.177	26.913
	Albumin	−1.037 (0.448)	0.35 (0.15–0.85)	0.02		/3
	AST	0.005 (0.002)	1.01 (1.00–1.01)	0.007		/<0.001
HVPG, AST, viral yes/no	HVPG	0.187 (0.043)	1.21 (1.11–1.31)	<0.001	222.797	20.951
	Viral yes/no	1.653 (0.592)	5.22 (1.64–16.66)	0.005		/2 /<0.001
HVPG, albumin, viral yes/no	HVPG	0.168 (0.045)	1.18 (1.08–1.29)	<0.001	217.42	26.823
	Albumin	−1.072 (0.452)	0.34 (0.14–0.83)	0.018		/3
	Viral yes/no	1.523 (0.567)	4.59 (1.51–13.92)	0.007		/<0.001

No one way interactions were observed. Assumption of proportional hazards was confirmed. All variables were introduced as continuous variables. HR, Hazard ratio; -2LL, Likelihood ratio (amount of variability of the outcome explained by the model; the closer to 0 and with the fewest amount of variables, the better the model adjusts to explain the outcome). HVPG, hepatic venous pressure gradient; AST, aspartate aminotransferase; viral, viral etiology of cirrhosis.

or greater than 10 mmHg had a 6-fold increase in the incidence rate of HCC (Univariate HR 6.1; 95%CI 1.8–20.1) (Fig. 2).

4. Discussion

This study shows that portal hypertension is a predictor of development of HCC in a large cohort of patients with cirrhosis without varices. Importantly, this association is independent from the degree of liver dysfunction and the duration of liver disease. It should be emphasized that one of the strengths of the design of the study is that the group of patients included is at a very well-defined and homogeneous stage, specifically patients with cirrhosis with portal hypertension but who had not yet developed varices or ascites, what has recently been designated as "stage 1" of cirrhosis [2].

Many studies have found an association between indirect markers of portal hypertension such as platelet count [7,8,12] and presence of varices [8] and development of HCC. However this is the first study that associates the development of HCC to a quantitative measure of portal hypertension. Of the previously identified predictors of HCC in cirrhosis, we confirm that albumin, a marker of the severity of cirrhosis, was also

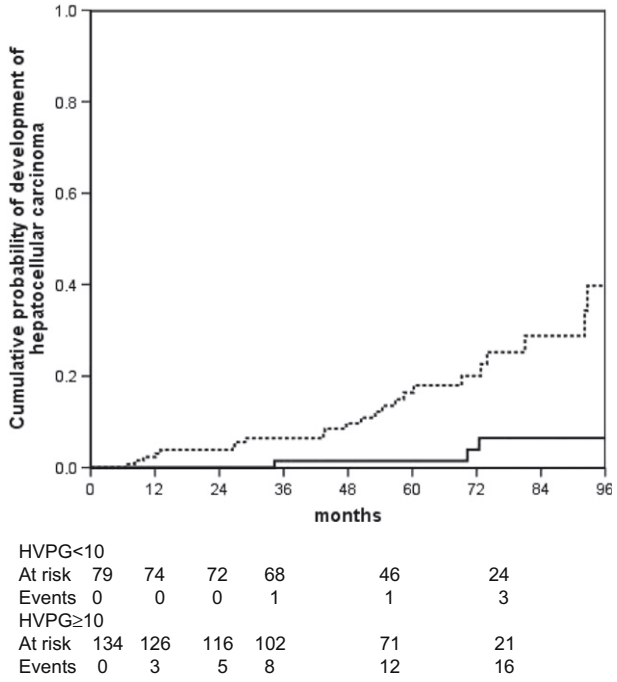

Fig. 2. Incidence of HCC according to a 10 mmHg cutoff of HVPG. KM Curves with all patients including HBV according to HVPG ⩾ 10 (dotted line) or <10 (continuous).

an independent predictor of HCC. It has been suggested that the predictive value of parameters of portal hypertension or liver insufficiency reflect a more advanced stage due to a longer duration of cirrhosis [7], however, we were able to demonstrate that HVPG and albumin were independent of duration of disease as this was the same in both patients who developed and did not develop HCC. These findings suggest that patients with more severe disease, as shown by greater HVPG and lower albumin, have greater risk of developing HCC. These variables are independent predictors of the development of HCC in this homogenous group of compensated cirrhosis. Possibly, the role of HVPG may be more evident in this otherwise very homogenous group, as other indicators of severity of liver disease were fairly constant. However, it should be underlined that in this same group of patients HVPG, albumin and MELD (that indicates disease severity) were found to be predictive of clinical decompensation. A finding that deserves further evaluation is the predictive value of baseline AFP values. AFP has been deemed an inadequate *screening* test for the presence of HCC and is useful in its diagnosis when a liver mass is present but its role in the prediction of the development of HCC is unclear.

Current clinical guidelines recommend periodic screening imaging techniques in patients with cirrhosis [3]. The identification of a subpopulation of patients with cirrhosis at a greater risk of developing HCC would make the screening process more efficient and cost-effective. In fact, it has recently been established that for surveillance to be cost-effective, it should be offered, when the risk of developing HCC is 1.5% per year or greater [3]. Our patients with an HVPG > 10 mmHg had an HCC incidence of 2.1% per year and, more importantly, patients with cirrhosis and an HVPG < 10 mmHg had an incidence of only 0.35% per year, far below the recommended screening level, suggesting that screening would not be cost-effective in this low-risk population. Further research of the most cost-effective approach to identify this subgroup of patients with greater risk of HCC is needed. It is well established that patients with viral disease have a greater risk of developing HCC [1,13].We also identified viral etiology as an independent risk factor for the development of HCC. Furthermore patients with HBV chronic liver disease are at a high risk of developing HCC even prior to the development of cirrhosis. Only 9 of our patients had HBV cirrhosis and excluding them from analyses did not change the incidence of HCC at each of the two HVPG levels. However, this was probably linked to viral etiology, since when both AST and viral etiology were entered the model selected viral etiology, but not AST.

The pathophysiological explanation as to why patients with higher portal pressure are more prone to develop HCC remains unknown. An elevated HVPG, especially in early stages of cirrhosis (portal hypertension) reflects the degree of fibrogenesis and of structural abnormalities, which leads to altered sinusoidal perfusion. The best known changes are capillarization of sinusoids, formation of fibrous septa and intrahepatic shunts. Recently, these changes have been linked with a process of neoangiogenesis [14]. Interestingly it is well known that HCC vasculature depends on the arterial bed and whether or not neoangiogenesis preceeds the development of HCC has recently been a matter of debate [15–17].

A potential limitation of the current study is that although the data was prospectively collected in the context of a randomized controlled trial, the present study is retrospective and therefore, our findings require prospective validation. Furthermore, the results may be applied to the study population from which the sample for the randomized controlled trial was derived. This is an asset regarding the robustness of the results, although the generalizability to patients that would not have been included in the original randomized controlled trial may be limited. Whether the predictive role of HVPG withstands in a group of more heterogenous patients with greater variation of other indicators of severity of liver disease remains to be determined.

In conclusion, baseline HVPG, albumin and viral etiology are independent predictors of the development of hepatocellular carcinoma in a homogenous group of patients with compensated cirrhosis without varices. The role of portal hypertension seems to be independent

from the degree of liver dysfunction and the duration of the disease. If results are validated prospectively, a greater portal hypertension in patients with compensated cirrhosis would identify a subgroup of patients who would most benefit from close HCC surveillance.

References

[1] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127 (5 Suppl 1):S35–S50.

[2] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–231.

[3] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

[4] Sherman M. Alphafetoprotein: an obituary. J Hepatol 2001;34:603–605.

[5] Bruix J, Llovet JM. HCC surveillance: who is the target population? Hepatology 2003;37:507–509.

[6] Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417–422.

[7] Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003;37:520–527.

[8] Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, et al. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut 2000;47:131–136.

[9] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–488.

[10] Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254–2261.

[11] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430.

[12] Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology 2006;43:1303–1310.

[13] Solà R, Alvarez M, Ballesté B, Montoliu S, Rivera M, Miguel M, et al. Probability of liver cancer and survival in HCV-related or alcoholic-decompensated cirrhosis. A study of 377 patients. Liver Int 2006;26:62–72.

[14] Lee JS, Semela D, Iredale J, Shah VH. Sinusoidal remodeling and angiogenesis: a new function for the liver-specific pericyte? Hepatology 2007;45:817–825.

[15] Dalgleish AG, O'Byrne K. Inflammation and cancer: the role of the immune response and angiogenesis. Cancer Treat Res 2006;130:1–38.

[16] Mazzanti R, Messerini L, Monsacchi L, Buzzelli G, Zignego AL, Foschi M, et al. Chronic viral hepatitis induced by hepatitis C but not hepatitis B virus infection correlates with increased liver angiogenesis. Hepatology 1997;25:229–234.

[17] Salcedo X, Medina J, Sanz-Cameno P, Garcia-Buey L, Martin-Vilchez S, Borque MJ, et al. The potential of angiogenesis soluble markers in chronic hepatitis C. Hepatology 2005;42:696–701.