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Prognostic Role of the Hepatic Venous Pressure Gradient in Cirrhosis

zur Erlangung des akademischen Grades

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Summary

The main pathophysiological mechanisms that lead to the complications of end-stage liver disease are portal hypertension and liver insufficiency. Portal hypertension can be estimated by measuring the hepatic venous pressure gradient. The aim of the present work is to evaluate the role of hepatic venous pressure gradient in the prognosis in cirrhosis. In order to accomplish this task, several studies were performed. The ability of hepatic venous pressure gradient to predict decompensation was evaluated in patients with compensated cirrhosis. In decompensated cirrhosis, the study was focused on the prognostic role of the hepatic venous pressure gradient in the prediction of survival. Taking into account that portal hypertension is a dynamic process, and that changes of its estimation may be more informative than a baseline value, an additional study evaluated this specific issue. Finally the role of hepatic venous pressure gradient in the prediction of the development of hepatocellular carcinoma was evaluated.

As a result of these studies the prognostic role of hepatic venous pressure gradient in prediction of clinical decompensation was demonstrated. In fact, patients without clinically significant portal hypertension were unlikely to present complications of their liver disease in the following years. Furthemore, it was shown that hepatic venous pressure gradient had a role in predicting survival in patients with decompensated liver disease, even when considering the prognostic information that can be derived from MELD score. Despite the fact that cirrhosis and portal hypertension are dynamic processes, the evaluation of the changes between measurements does not offer more information than the baseline measurement. Finally, in patients with compensated cirrhosis, the development of hepatocellular carcinoma was unlikely in patients without clinically significant portal hypertension.

In conclusion, hepatic venous pressure gradient has a role in prediction of relevant events of cirrhosis, especially in compensated cirrhosis. Repeat measurements do not offer more information than a baseline measurement.

INTRODUCTION

1. PORTAL HYPERTENSION. DEFINITION

Cirrhosis is the end stage of chronic liver disease which is defined by the presence of diffuse fibrosis and regeneration nodules in the hepatic tissue. Many different agents which induce chronic injury in the liver can lead to this common end-stage disease.

Clinically cirrhosis can be evidenced by means of two main clinical manifestations besides death. On one hand cirrhosis favors the development of hepatocellular carcinoma, the most frequent primary hepatic tumour. Hepatocellular carcinoma is the sixth most frequent neoplasia worldwide and the third most frequent cause of cancer related death [1]. Its incidence is expected to progressively rise until its peak in approximately 10 years. On the other hand, cirrhosis leads to clinical decompensation, which is characterized by the development of jaundice, variceal bleeding, ascites, and hepatic encephalopathy [2]. These previously mentioned typical complications of end stage liver disease are one of the main causes of morbidity and mortality in advanced liver disease. The most important underlying pathophysiological mechanisms in the development of complications of end stage liver disease are portal hypertension and liver insufficiency.

Portal hypertension is defined by an increase in the portal pressure gradient. The portal pressure gradient is defined by Ohm's law which determines that the portal gradient (ΔP) is related to the blood flow (Q) which circulates through the portal vein and the resistance (R) of the whole portal system to this flow.

$$\Delta P = Q \times R$$

The initial factor in the development of portal hypertension in cirrhosis is the increase in the intrahepatic vascular resistance [3] (Figure 1). The increase in intrahepatic vascular resistance has a structural component and a dynamic component. Structural

changes are associated to the architectural deformation that takes place with continuous inflammation/fibrosis and are theoretically irreversible in nature.

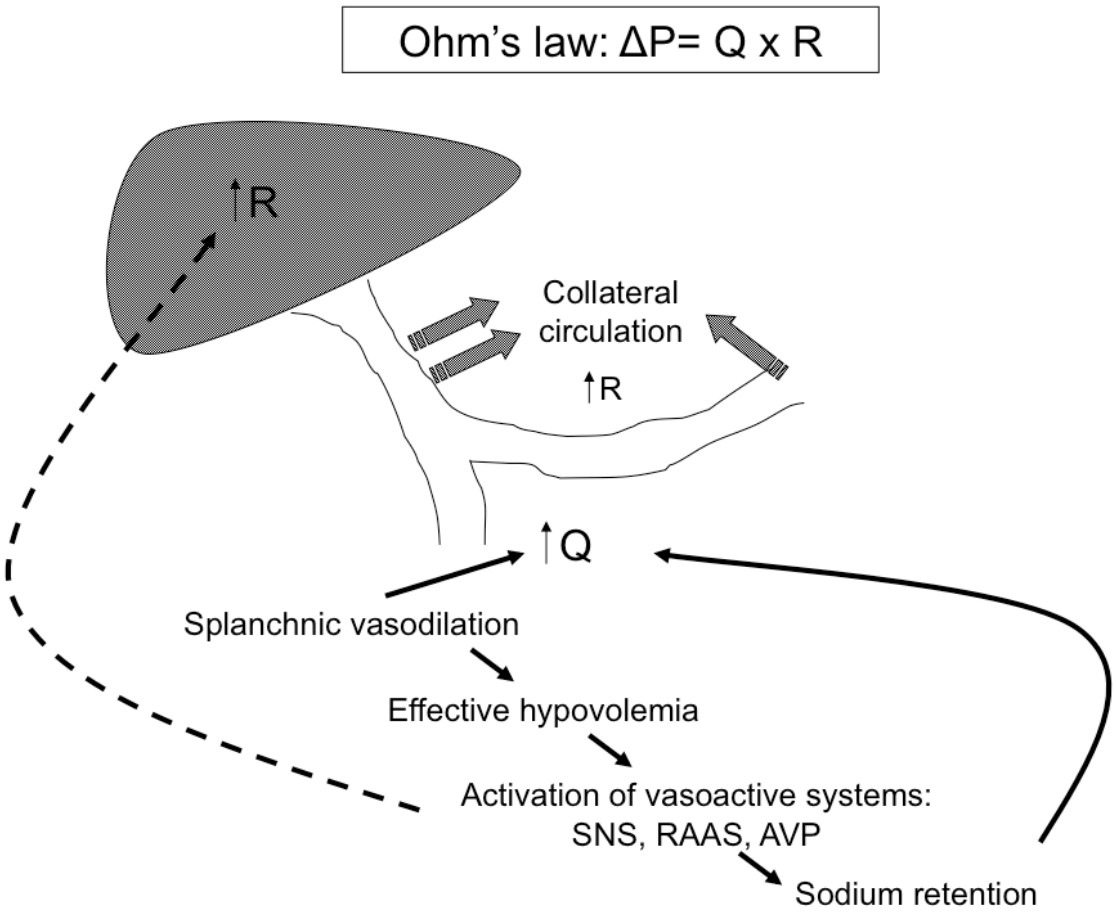


Figure 1 Diagram of the pathophysiology of portal hypertension. The increase in intrahepatic resistance (ΔR) leads to an increase in the pressure in the portal venous system and splanchnic vasodilation which in turn leads to an increase in portal flow and development of collateral circulation. The increase in portal flow (ΔQ) is further aggravated by the effective hypovolemia which favours the liberation of vasoactive mediators which leads to sodium retention and peripheral vasocontriction (including intrahepatic circulation). The development of collateral circulation will lead in turn to an increase in the resistance to portal blood flow.

Besides these structural changes, there are dynamic changes which are due to an imbalance in vasoconstricting and vasodilating mediators in the sinusoids. This imbalance leads to an activation of sinusoidal and extrasinusoidal contractile elements. Although proportionally less relevant, the dynamic component has received great interest given its potentially reversible nature and therefore its susceptibility to pharmacological management. It is important to underline that as the liver disease progresses, with the

development of collateral circulation which characterizes portal hypertension, the global increase in resistance is not only determined by the intrahepatic vascular resistance but also by the resistance that is offered from these collateral vessels.

The second factor that leads to an increase in the portal pressure gradient is the increase in the portal flow. The importance of this factor acquires greater relevance the more advanced the liver disease [4]. This increase in portal flow is due to the development of splanchnic vasodilation which in turn leads to an increase in portal pressure and its perpetuation. Firstly, splanchnic vasodilation is able to produce a great increase in portal flow, that, as shown by Ohm's law, contributes to an increase in portal pressure and in second place, it leads to a decrease in central effective volume, as a greater amount of blood is lodged in the splanchnic vascular bed and a lesser volume in the main vessels of the body. Effective central hypovolemia leads to the activation of diverse endogenous vasoactive systems which include the sympathetic nervous system, the renin-angiotensine and aldosterone axis and finally, the non-osmotic secretion of vasopressin. These endogenous vasoactive systems produce vasoconstriction in several vascular beds including the intrahepatic circulation (by acting on the sinusoidal and extrasinusoidal contractile elements) as well as the activation of sodium retention mechanisms. This leads to the perpetuation of the portal hypertension as the increase in intrahepatic vascular resistance leads to further splanchnic vasodilation and therefore an even greater release of endogenous vasoconstrictors.

2. ESTIMATION OF PORTAL PRESSURE

Taking into account the central role of portal hypertension in the development of advanced end stage liver disease, it is not surprising that different methods to evaluate portal pressure have been developed. These include direct canalization of the umbilical vein, measurement of the intrasplenic pressure, the direct measurement of portal pressure

and the measurement of intrahepatic pressure. However, all these methods are technically difficult and are associated to complications. This has lead to the development of an alternative method which allows the estimation of portal pressure. This procedure is based on the special characteristics of the intrahepatic circulation, so that estimation of the sinusoidal pressure, which corresponds to the portal perfusion pressure, can be performed by measuring the pressure obtained by the occlusion of the immediately distal vascular bed in the hepatic vein.

The hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure and the free hepatic venous pressure[5]. The free hepatic venous pressure should be similar to the pressure in the proximal inferior cava vein (near its entrance in the right atrium).

The estimation of the portal pressure by measuring the wedged hepatic venous pressure (with an end-hole catheter) and its correlation to the direct measurement of portal pressure was described for the first time in the middle of the last century[6]. With the development of HVPG the estimation of the pressure was improved [7, 8] so that this modification allows correction of the wedged hepatic venous pressure according the the pressure in the cava vein. This reflects more precisely the increase in the pressure in the portal venous system in comparison to the systemic circulation. The measurement of HVPG was perfected with the development of the balloon catheter [9, 10] which offers the advantage of allowing the measurement of the free and wedged pressure in the same location, closer to the mouth of the hepatic veins in the inferior vena cava. This lead to relevant improvements in the procedure, firstly it allowed a greater reproducibility of the technique as one can repeat the measurement in the same location and secondly, a wider area of the hepatic parenchyma can be sampled, therefore reducing the possibility of error in the measurement due to a heterogeneous distribution of the lesions in the liver[11].

Presently, HVPG is considered the gold standard in the estimation of portal pressure. Sinusoidal portal hypertension is defined by a HVPG greater than 5 mmHg. Clinically significant portal hypertension is defined by a HVPG greater than 10-12 mmHg. Above this threshold one can observe complications associated to portal hypertension that characterize end-stage liver disease [12-17].

Several attempts have been undertaken to evaluate non invasive methods to estimate hepatic venous pressure gradient. A non-invasive method would offer clear advantages over hepatic venous pressure gradient measurement, if a precise estimation can be obtained. However, up to date, although some methods may identify patients with clinically significant portal hypertension[18-20], no method offers reproducible estimations of hepatic venous pressure measurement.

3. HEPATIC VENOUS PRESSURE GRADIENT MEASUREMENT. THE PROCEDURE.

Measurement of hepatic venous pressure gradient should be done carefully and precisely in order to obtain reliable and reproducible results. Procedure guidelines have been published in an attempt to homogenize the measurement of HVPG and avoid erroneous values due to inappropriate measurement technique [5].

3.1 Hepatic Vein Catheterization Technique

Through an introducer catheter which is normally placed in the right jugular or femoral vein, a multipurpose catheter is used to catheterize one of the main hepatic veins, normally the middle or right hepatic vein. Once the chosen vein is catheterized, a balloon catheter is introduced and positioned approximately 5 cm away from the mouth of the hepatic veins in the cava vein. At this location, with the vein occluded, a small amount of contrast agent is injected in order to confirm complete occlusion of the hepatic vein and to detect the presence of venovenous shunts which would lead to infraestimation of the portal pressure [5, 11]. (Figure 2)

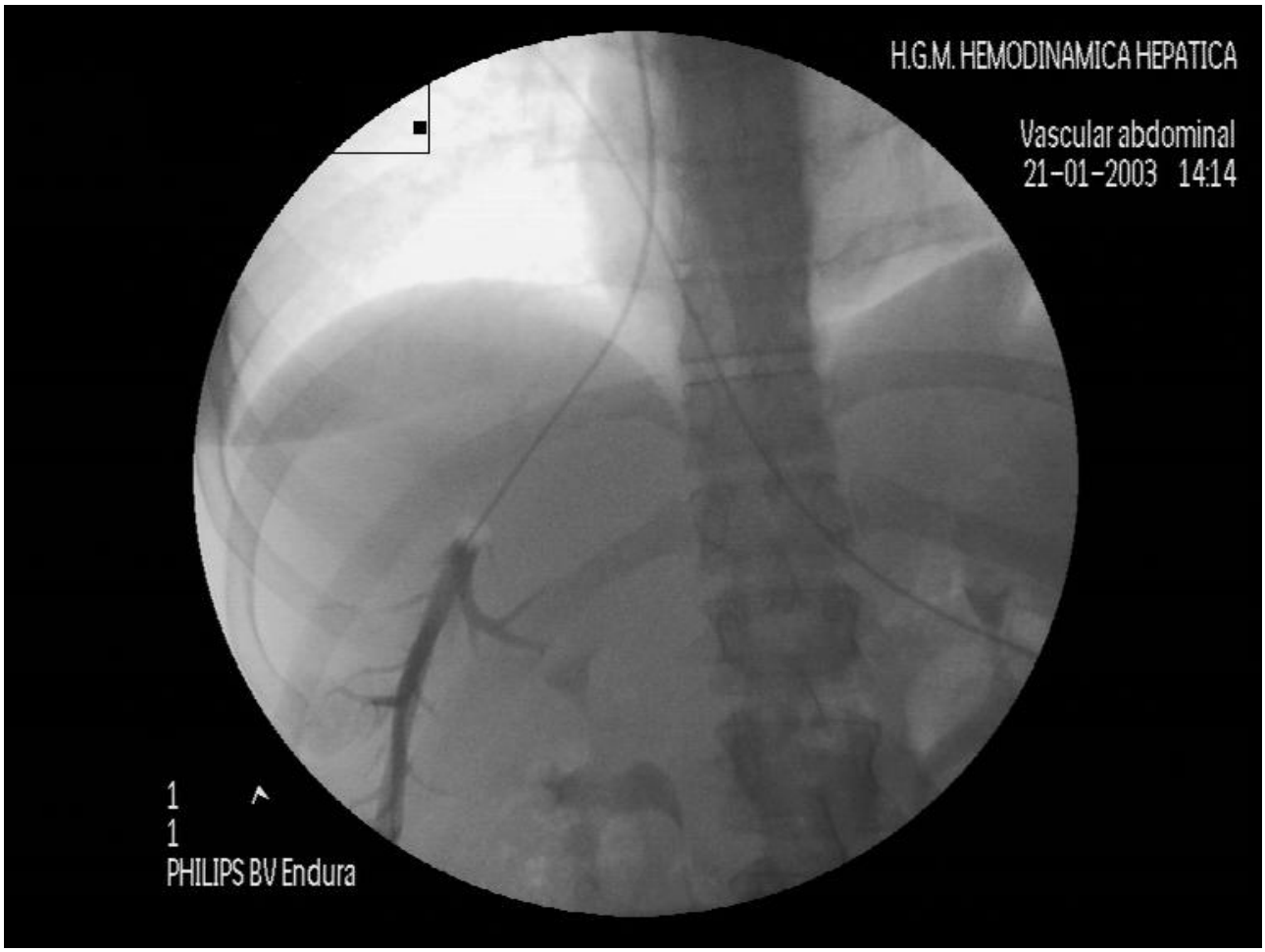


Figure 2. Occlusion of the middle hepatic vein with the balloon catheter

3.2 Pressure Measurement Technique

In order to achieve a correct measurement of the pressure, two basic technical aspects are essential: a) definition of an adequate zero reference value and b) an adequate calibration of the transducer. Therefore, before performing the measurement of the hepatic venous pressure gradient, once must establish the reference point, also known as the zero level, normally located at the level of the right atrium and an adequate callibration of the transducer should be performed for the desired pressure range. Another important aspect is the need for a continuous registry of the pressure which allows a careful reading and measurement.

To achieve a reproducible measurement, at least 3 measurements of the free and the wedged hepatic venous pressure should be done. The measurements should be performed once the registry has stabilized, for at least 1 minute, particularly the wedged pressure. The wedged hepatic venous pressure is the most variable measurement and therefore the one that is the most common cause of errors. If there is more than a 1 mmHg difference in between the different measurements of the wedged hepatic venous pressure, it should be repeated. For the free hepatic venous pressure, the measurement obtained after the wedged pressure should be used preferentially. If there is a difference greater than 1 mmHg between the free hepatic venous pressue and the cava vein, the cava vein pressure should be used. The measurement of cava vein pressure should be done at the level where the hepatic veins drain into the cava vein. The interference of the heart beat could oblige to a more distal measurement, although this should be always above the caudate lobe. The quality of the measurement will be evaluated by its registry (figure 3).

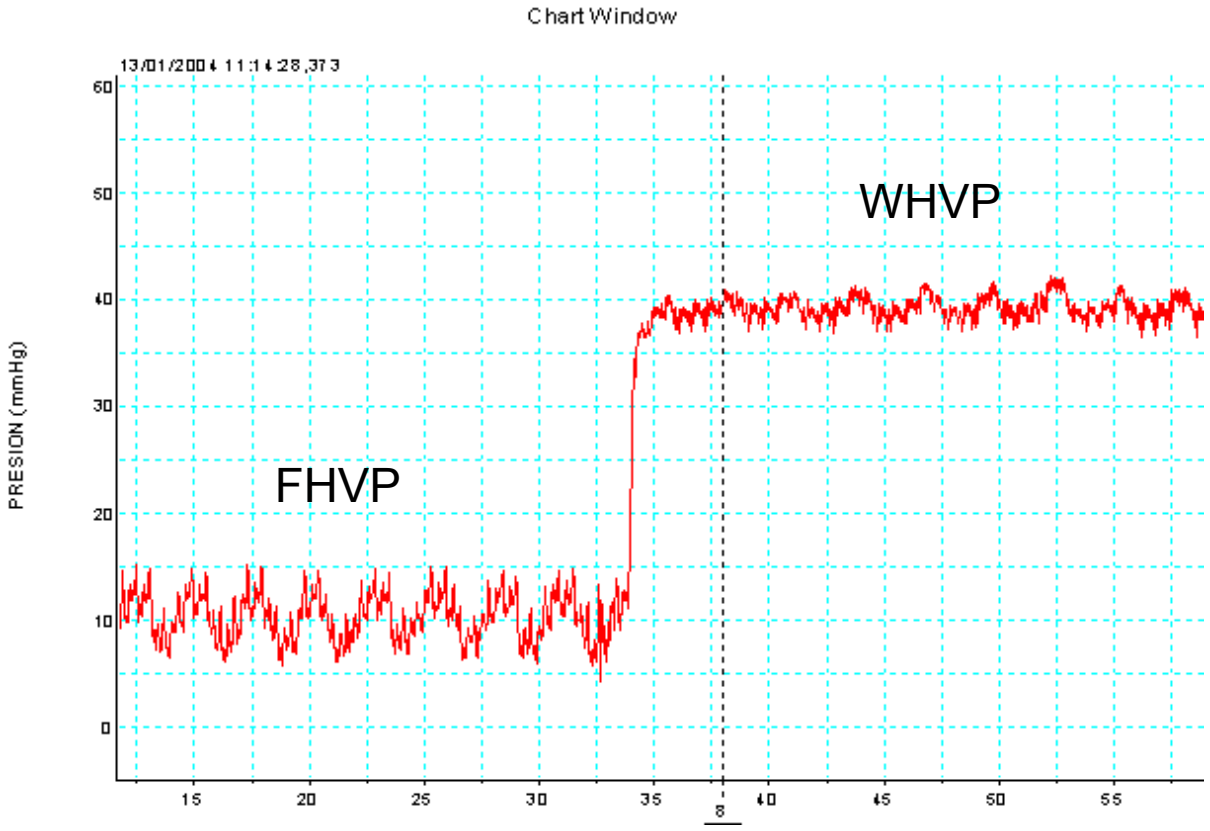


Figure 3. HVPG measurement registration. FHVP: free hepatic venous pressure, WHVP: wedged hepatic venous pressure

3.3 Complications associated to the Procedure

The measurement of HVPG is an invasive procedure which is not completely void of complications. The main complications associated to the technique are neck hematomas following the puncture of the jugular vein and supraventricular heart arrythmias. The former is minimized with the incorporation of ultrasound guidance for internal jugular vein cannulation[21]. Most heart arrythmias revert spontaneously and do not require further intervention.

4. PREDICTIVE FACTORS IN THE NATURAL HISTORY OF CIRRHOSIS

Many studies have evaluated the predictive factors in the natural history of liver disease, regarding the development of clinically relevant events in the course of the disease and mortality.

In the sixties, Child and Turcotte developed a classification to evaluate the surgical risk of patients who had had variceal hemorrhage previous to shunt surgery [22]. Empirically, 5 variables were included in the classification: ascites, hepatic encephalopathy, nutritional status, albumin and bilirubin. This classification allowed to separate patients in 3 degrees of liver failure: A, B and C, from the best to the worse prognosis respectively. At the beginning of the seventies, Pugh proposed a modification of this classification in which nutritional status was substituted with prothrombin time and each variable was divided in 3 categories with 1 to 3 points in each category [23]. This allowed to score the severity of the patients between 5 and 15 points so that patients with the lowest score had the best prognosis (Table 1). Although the initial development of this score was empirical, it is a useful prognostic tool which has stood the test of time and is still widely used nowadays.

For a long time Child Pugh score had been used as the main criteria to distribute organs in liver transplant programs. However, in recent years, the limitations of Child-Pugh score have been underlined: the use of subjective parameters, arbitrary categorization of numerical variables, the presence of a ceiling effect and the narrow severity range.

Particularly this latter limitation lead to the fact that the decisive factor in organ distribution was the waiting time on the list, so that patients were included very early on the liver transplant waiting list in order to gain time. This lead to an unfair distribution of organs, so that the need for a new scoring system was identified, one which would overcome these limitations.

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (gr/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Ascites	absent	responsive to diuretics	non-responsive
Hepatic Encephalopathy	absent	I-II	III-IV

Table 1. Child-Pugh Score. Each variable is assigned 1 to 3 points. The overall score ranges from 5-15. Patients with lower scores have milder disease. Child-Pugh class is divided according to the points: A: 5-6; B: 7-9; C:11-15. Hepatic encephalopathy grading is according to the West-Haven criteria.

The MELD score was initially developed to estimate the 3 month death risk after the placement of transjugular intrahepatic portosystemic shunt [24] (Figure 4). This new scoring system was considered as a potentially adequate tool to distribute the organs to patients on the liver transplant waiting list as it overcame the previously stated limitation (ceiling effect, limited categories, narrow range). For this reason the discriminity ability of this score was used in increasingly heterogeneous groups of patients with liver disease [25]. This lead to a modification of the initial scoring system in which etiology of liver disease was included in order to avoid favoring or discriminating patients on the liver transplant waiting list according to the etiology of the disease. After this modification of the scoring system, no significant differences in the discriminant ability were observed.

MELD score = 0.957 Ln(Cr) + 0.378 Ln(Bi) + 1.12 Ln(INR) + 0.643

Figure 4. MELD score calculation. Cr: Creatinine (mg/dl), Bi: bilirubin (mg/dl). The minimum value of each variable is 1. Values under one will be rounded to 1. The maximum value of Cr is 4 mg/dl

Since 2002, the UNOS (United Network for Organ Sharing), adopted the MELD score for organ distribution in the USA and it has been applied in the Eurotransplant zone since 2006. However, the generalization of its use has shown that MELD score also has its disadvantages. One of the most important limitations is that only variables associated to hepatic failure (bilirubin, INR) and circulatory dysfunction (creatinine) are included and it does not include any variable associated to portal hypertension. Paradoxically, it had been observed that different patients with the same MELD score had significantly different survival according to the presence or absence of previous episodes of portal hypertensive associated complications [26]. However, and despite these limitations, the discriminative ability of MELD, that is its ability to order patients according to its risk of death, is satisfactory. This fact allows a more just and equitative distribution of organs with a reduction of mortality on the waiting list, although the post-transplant benefits remain unclear [27-33].

A land-mark systematic review evaluated predictors of mortality in cirrhosis [2]. In this study, Child-Pugh score, or the variables that compose this score were the most frequently identified mortality risk factors in the literature. When the survival predictors were evaluated separately in compensated and decompensated patients, variables associated to portal hypertension were most frequently identified in compensated patients while in decompensated patients, the most frequently identified variables were the ones associated to renal failure or hepatocellular carcinoma. Although few studies had evaluated the role of HVPG, this variable was identified as a predictor of death in two thirds of the studies that evaluated it.

In this systematic review the authors underlined the well known fact that in cirrhosis there are 2 clinical phases: the compensated and decompensated phase [2]. Being in one

phase or another is clinically relevant since the risk of death is much greater in the decompensated phase. It was also emphasized that compensated patients will ultimately decompensate before dying from liver disease. On the other hand, as long as one stays in the compensated phase the 5 year survival is 85%. Therefore, models that evaluate the risk of death linearly are inadequate as they do not consider adequately the two chronological frames previously described. Therefore, the authors concluded that specific prognostic models should be developed for every phase of the disease with different relevant end-points: decompensation in the compensated patients and death in patients who are decompensated. In this review a staging system was proposed which divided patients into 4 groups, 2 groups of compensated patients according to the presence or absence of varices and two groups of decompensated patients according to the presence and absence of ascites and variceal hemorrhage (Table 2). Although this staging system still needs further refinement [34], it is easily applicable and provides a useful tool for every day clinical practice.

	Varices	Ascites	Bleeding
Stage 1	-	-	-
Stage 2	+	-	-
Stage 3	+/-	+	-
Stage 4	+	+	+

Table 2. Clinical stages of cirrhosis (according to D'Amico et al)

5. EVALUATION OF THE PROGNOSTIC VALUE OF HEPATIC VENOUS PRESSURE GRADIENT.

The studies that have evaluated the relationship between HVPG and the different complications of cirrhosis can be classified according to their design. Some studies have a

transversal design in which the variable of interest and the event are studied at the same moment. However, this study design does not allow the study of the temporal relationship between the predictive factor and the event of interest, which is necessary to establish causality. Longitudinal studies involve a follow up on the patients and therefore the temporal relationship between the predictive factor and the event of interest can be studied. These studies can be prospective or retrospective.

5.1 Transversal Studies

The relationship between HVPG and the presence or absence of varices in patients with cirrhosis has been evaluated in numerous studies. In general, these studies observed that patients with varices had a greater HVPG than patients without varices[13, 15, 35-37]. Therefore, its accepted that a threshold value of 10-12 mmHg of HVPG is required for the development of varices in patients with cirrhosis[13, 14, 38]. Similarly, esophageal variceal bleeding requires an HVPG above the 12 mmHg threshold[13, 15-17]. Similarly, greater values of HVPG have been observed in patients with ascites compared to patients without ascites[17, 36] and even a greater HVPG value was observed in patients with SBP in comparison with patients with non infected ascites [39].

However, due to their transversal design, these studies are not adequate to establish a predictive relationship between HVPG and different portal hypertensive related complications.

5.2 Longitudinal Studies

Follow-up studies, either prospective or retrospective, are the most adequate to evaluate the use of HVPG in the prediction of complications associated to portal hypertension and death. These studies have evaluated both the prognostic use of a single measurement and repeat measurements of HVPG.

-Use of HVPG for the Prediction of Varices

The role of HVPG in the prediction of the development of varices has been specifically evaluated in a randomized placebo controlled trial [40]. The main aim of the study was to evaluate the use of non cardioselective betablockers in the prevention of development of varices in patients with cirrhosis and portal hypertension without varices at the time of inclusion. As a secondary aim, the study evaluated whether the changes of HVPG could predict the development of varices, variceal bleeding or both. Rather unexpectedly, the incidence of the endpoints were similar in both groups. Despite these unfortunate results, the authors showed a close relationship between the changes in HVPG and the incidence of the outcome variable, independently from the treatment assignment to drug or placebo. In this sense, the patients who achieved at least a 10% reduction in HVPG had a lower incidence in varices and variceal bleeding. On the other hand, patients who had a similar increase in HVPG had an increase in these events.

-Use of HVPG in Variceal Bleeding

Variceal bleeding is an important cause of morbidity and mortality in advanced liver disease. Therefore, it is not surprising that it is in this context in which the prognostic role of HVPG has been most thoroughly studied. The role of HPVG has been evaluated for the prediction of development of variceal bleed as well as its use in the prediction of the natural history of the patient who has had a variceal bleed, both during the acute episode and the latter course.

-Prediction of the Development of Variceal Bleeding.

Several prospective studies have shown that patients with greater HVPG have greater risk of bleeding from varices during follow-up[37, 41]. However, other studies have not been able to confirm these results[17, 42].

The first favorable study is a secondary analysis of a randomised placebo controlled clinical trial that evaluated the administration of testosterone to 58 males with recently

diagnosed alcoholic cirrhosis [37]. The aim of this study was to evaluate the ability of HVPG, measured with a straight catheter, to predict the development of variceal bleeding or death. Secondly, the progostic role of HVPG was analyzed taking into account other clinical, endoscopical, functional prognostic variable in the multivariable analysis. Fifty-eight patients with alcoholic cirrhosis were included with a median baseline HVPG of 14 mmHg (range 3-26 mmHg). Thirty percent of patients had varices at baseline and 16 % had had a previous episode of variceal bleeding. During the follow up (median time 31 months, range 2 - 51 months), 12 patients (21%) had at least one episode of variceal bleeding. On multivariate analysis, the independent predictive factors of variceal bleeding were HVPG, big varices at endoscopy, previous bleeding from varices and the indocyanin green clearance.

A second study [41] included 129 patients with cirrhosis and esophageal varices without prophylactic treatment. The aim was to evaluate the role of HVPG, hepatic plasmatic flow and indocyanin green clearance in the prediction of variceal bleeding and death and secondarily whether or not these variables provided more information than the Child-Pugh score or the size of varices. The patients had predominantly alcoholic cirrhosis with a basal HVPG of 20.2 mmHg (interquartillic range 18.2-22.8 mmHg). Initially, all included patients had known esophageal varices for at least one year. Patients who were receiving any primary or secondary prophylaxis were excluded, although previous variceal bleeding was not an exclusion criteria per se. During the study (median follow up 45 months) approximately one third of the patients had a portal hypertensive related bleeding episode. As in the previous study, the independent predictors of upper gastrointestinal bleed were the presence of big varices, previous variceal bleeding, an HVPG value over 16 mmHg and high Child-Pugh score. This allowed the development of a prognostic index based on these 4 variables. The role of HVPG (included as a categorical variable) in this

index was just as important as the role of previous variceal bleeding or high Child-Pugh score, so that HVPG could not be substituted by other less invasive variables.

Nevertheless, two studies observed no relationship between baseline HVPG and development of variceal bleeding during follow-up. The first is a prospective study [17] in which 30 patients with alcoholic cirrhosis and esophageal varices without previous history of portal hypertensive related bleeding episodes were included. No patient had received prophylactic treatment previous to study inclusion or during the study, although patients were informed regarding the convenience to maintain alcoholic abstinence. HVPG measurement was repeated on a yearly basis. Mean baseline HVPG was 19.1 mmHg (SEM 0.7 mmHg). Patients were followed up for a mean of 42 months (SEM 5 months). During this time period, 10 patients had a portal hypertensive related bleeding episode (8 had variceal bleeding and 2 patients bled from portal hypertensive gastropathy). Patients who did not bleed had a significant reduction of HVPG while a slight non significant increase in HVPG was observed in those patients who bled during follow up. On multivariate analysis, alcohol abstinence, the first repeat HVPG measurement and age were the best independent predictors of portal hypertensive bleeding during follow-up. This apparently contradictory result in comparison to the previous studies may be due to the influence of the alcohol abstinence which perhaps covered up the prognostic information that could be derived from the baseline hemodynamic study. This study, however, highlights the prognostic relevance of changes of HVPG.

The other retrospective study in which no relationship was observed between baseline HVPG and variceal bleeding was designed to evaluate the prognostic role of HVPG to predict further episodes of variceal bleeding and mortality in a group of patients with cirrhosis of different etiologies with previous variceal bleeding [42]. The baseline hemodynamic study was performed a median of 11 days (range 0-372 days) after the baseline hemorrhage. The median follow up time was of 566 days (range 10-2555 days).

The independent predictors of variceal rebleeding were previous endoscopic treatment and prothrombin time. HVPG, however, was not associated to rebleeding. This contradictory result has several plausible explanations. Firstly the study population was very heterogenous, secondly the simultaneous administration of betablockers in the setting of prophylaxis, which has well known beneficial effects could lead to some confusion [43, 44] , and lastly the baseline measurement of HVPG was done at a variable time interval (up until 372 days) after the bleeding episode, which added further heterogeneity and could have limited the prognostic ability of the measurement.

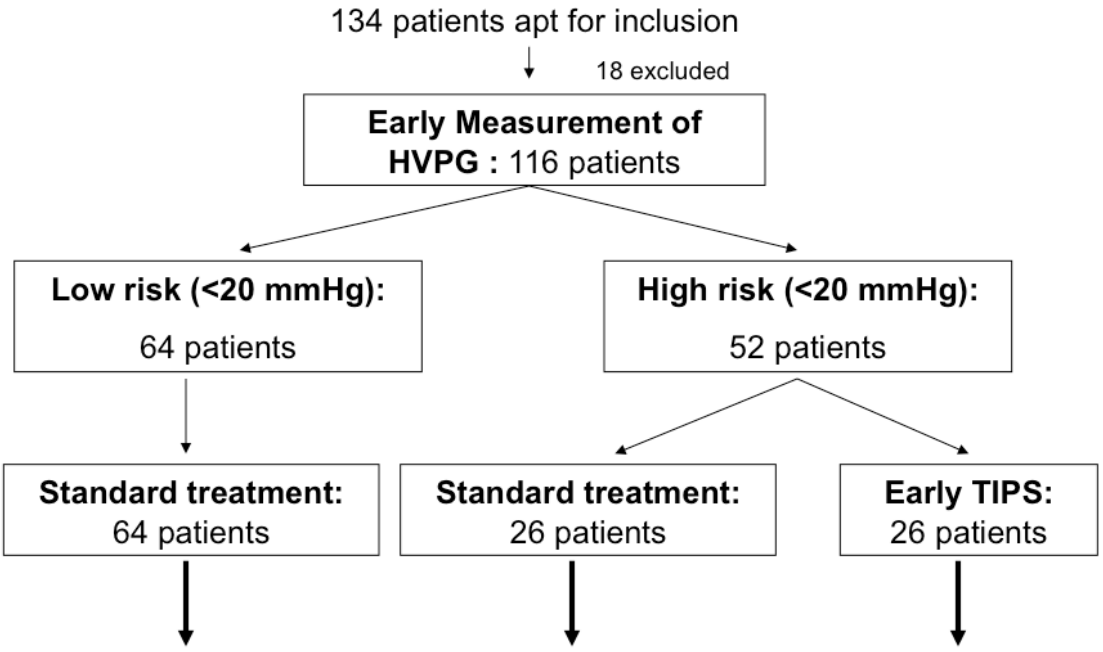
-Prediction of the natural history of variceal bleeding

The possible role of the early measurement of HVPG in the prediction of the outcomes of variceal bleeding has also been evaluated [45]. In a first study, 65 patients with cirrhosis and variceal bleeding who received HVPG measurement in the first 48 hours after admission were included. Initial therapy was done with sclerotherapy (43 patients) or somatostatin (22 patients). From the 65 patients, 23 patients had an adverse outcome as defined by the Baveno criteria, with lack of initial control of the bleeding (7 patients), or early rebleeding (16 patients). Patients with adverse outcome had greater need of transjugular intrahepatic portosystemic shunt, emergency derivative surgery, longer stay in the ICU, longer hospital stay and greater number of red blood cells packs. However, no differences in survival were observed between both groups of patients.

Interestingly, patients who had an adverse outcome had a significantly higher HVPG at baseline than those who had an adequate control of the bleeding episode. On multivariate analysis, only HVPG was identified as an independent predictor of the outcome of the bleeding episode. Indeed, a cut-off value of 20 mmHg identified two different groups with different outcomes. Patients with an HVPG above 20 mmHg had a worse outcome (lack of initial control and early rebleeding), greater ICU stay, greater hospital stay and greater transfusional needs as well as greater mortality at 3,6, and 12

months. Although patients with HVPG greater than 20 mmHg had greater Child-Pugh score, the latter could not discriminate satisfactorily the course of the bleeding episode.

This study lead to the development of a randomised controlled trial [46], aimed at evaluating prospectively whether an individualised treatment strategy according to risk of failure as predicted by early HVPG measurement could improve outcomes in esophageal variceal bleeding (Figure 5). All patients were initially treated with sclerotherapy according to the current standard at the time of the design of the trial. High risk patients, as defined by an HVPG above 20 mmHg (52 patients) were randomized to receive a) standard therapy with betablockers (26 patients), or endoscopical band ligation in those patients in whom betablockers were contraindicated (3 patients) or not intolerated (1 patient), or b) early transjugular intrahepatic portosystemic shunt (26 patients). Patients were followed up for a year. The main result of the study was that patients with high risk of failure who received early TIPS had less episodes of rebleeding and lower mortality than those patients who were randomized to standard treatment (betablockers or endoscopic band ligation). On the other hand, patients with high risk who were randomized to standard therapy had greater risk of treatment failure, (due to lack of control of the bleeding episode or early rebleeding) than those patients who had an HVPG under this threshold.



Treatment failure	8 (12%)	13 (50%)	3 (12%)
6-week mortality	3 (4%)	10 (40%)	5 (20%)
1 year mortality	11 (16%)	17 (67%)	8 (31%)

Figure 5. Summary of the study of Monescillo et al [46], in which HVPG is used to taking clinical decisions in the context of variceal bleeding.

However, when these studies were performed, the standard treatment of variceal bleeding was based on endoscopic treatment or vasoactive therapy which is not the present day standard of care, which involves combined pharmacological and endoscopic therapy [47]. Recently, the prognostic role of HVPG in variceal bleeding was reevaluated with the current standard of care in which endoscopic and pharmacological therapy should be combined [48]. In this study, a multivariate analysis was performed with a hierarchical introduction of variables to evaluate the role of HVPG in the prediction of a non-favorable bleeding outcome as defined by uncontrolled bleeding, early rebleeding or death within 5 days. In this study, the presence of HVPG >= 20 mmHg, non alcoholic etiology and arterial blood pressure under 100 mmHg were identified as the independent predictors of an unfavorable outcome.

Therefore, the results of these studies indicate clearly the prognostic role of HVPG in the prediction of the outcomes of esophageal variceal bleeding.

-Repeat Measurements in the Context of Primary and Secondary Prophylaxis

Several studies have focused on the prognostic ability of changes of HVPG to predict clinical events in advanced liver disease. This has been mainly studied in the context of primary and secondary prophylaxis of variceal bleeding [49-58]. In this scenario, changes of HVPG have been associated to the risk of rebleeding and death. Traditionally it has been considered that a reduction of HVPG under the 12 mmHg threshold confers almost complete protection from the risk of rebleeding and also a reduction of 20% from the baseline value leads to a considerable reduction in the risk of rebleeding. However, the clinical relevance of these thresholds has been questioned in other studies [54]. In order to clarify this issue two meta-analysis [43, 44] evaluated the global effect of the reduction of HVPG on the risk of bleeding. Both meta-analysis concluded that a reduction of HVPG under the 12 mmHg threshold or at least 20% from baseline significantly reduces the risk of rebleeding. Furthermore, both meta-analysis identified that the time between the measurement was of critical relevance as the predictive value of HVPG was less the greater the time interval between the two measurements.

Despite this data which underlines the prognostic relevance of HVPG measurement in the setting of variceal bleeding, few studies have evaluated the use of an HVPG directed strategy in clinical practice [50, 59, 60]. The first pilot study [50] that evaluated the use of primary or secondary prophylaxis directed by HVPG measurement included thirty-four patients, of whom 20 patients had never had variceal bleeding. All patients had baseline HVPG measurement, after which a fixed dose of long acting propranolol was given. After a median of 4 days (range 1-60), a second hemodynamic study was performed. All patients who had hemodynamic response according to the standard definition were maintained on the betablocker. In patients who did not obtain a hemodynamic response, additional

treatment was started with vasodilators. Then, a third hemodynamic study was done to evaluate the response in patients who did not achieve response in the second hemodynamic study. Similarly, patients who achieved response were maintained on the treatment with vasodilators and betablockers. On the other hand, patients who did not obtain hemodynamic response went on to have endoscopic banding ligation only in the setting of secondary prophylaxis while patients in primary prophylaxis had no further treatment. From the 34 patients, 20 patients had hemodynamic response with propranolol (7 of them with combined pharmacological treatment). Patients were followed up for a median time of 24 months (range 1-96 months) and during this time period 11 patients had portal hypertensive related bleeding (figure 6). Bleeding episodes were more frequent in the context of secondary prophylaxis (9 patients) and in those patients who did not achieve hemodynamic response (9 patients). The authors concluded that the use of the hemodynamic response criteria had prognostic value and that the use of HVPG measurement could allow an individualized prophylactic treatment in which the expected benefit with the least risk could be obtained.

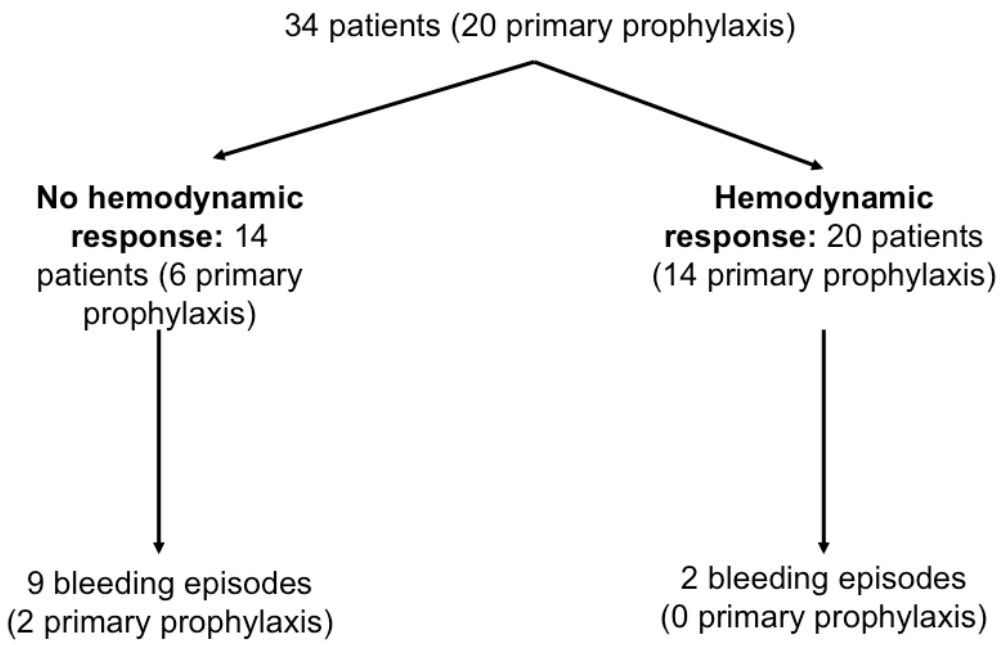


Figure 6. Summary of the study of Bureau et al [50], which evaluates the use of HVPG to take clinical decisions in the context of primary and secondary prophylaxis.

In a second pilot study[59], a baseline hemodynamic study was performed 5 days after the bleeding episode. All patients received nadolol and nitrates and the hemodynamic study was repeated 5-7 days after achieving the maximum doses. In this study, three different response groups were established. Firstly the complete responders, in whom a reduction of HVPG below 12 mmHg or a 20% reduction from baseline was achieved. Secondly the patients who achieved a partial response with an HVPG reduction between 10-20%. These patients were then included in a endoscopic ligation program. Finally those patients who had a less than 10% reduction of HVPG and were classified as non responders in whom a transjugular intrahepatic shunt was performed (figure 7). Patients were then followed up during a median time period of 22 months. The endpoint variable was secondary prophylaxis failure defined by the presence of clinically significant rebleeding as

defined by the Baveno IV consensus. From the 50 patients included, 8 patients did not have a hemodynamic study because of rebleeding (6 patients) or because of progressive hepatic failure (2 patients). From the 42 patients left, 24 (57%), 10 (24%), and 8 (19%) were responders, partial non responders and non-responders respectively. No differences were observed in the proportion of rebleeding (12%, 20% and 0% in complete, partial and non-responders, respectively) nor in mortality (12%, 0% and 12% respectively) between the 3 groups. The results of the study suggest that adapting the therapeutic strategy according to the hemodynamic results allows minimization of the risk of rebleeding and death, however this information should be interpreted cautiously, since this pilot study has a complex design and few patients.

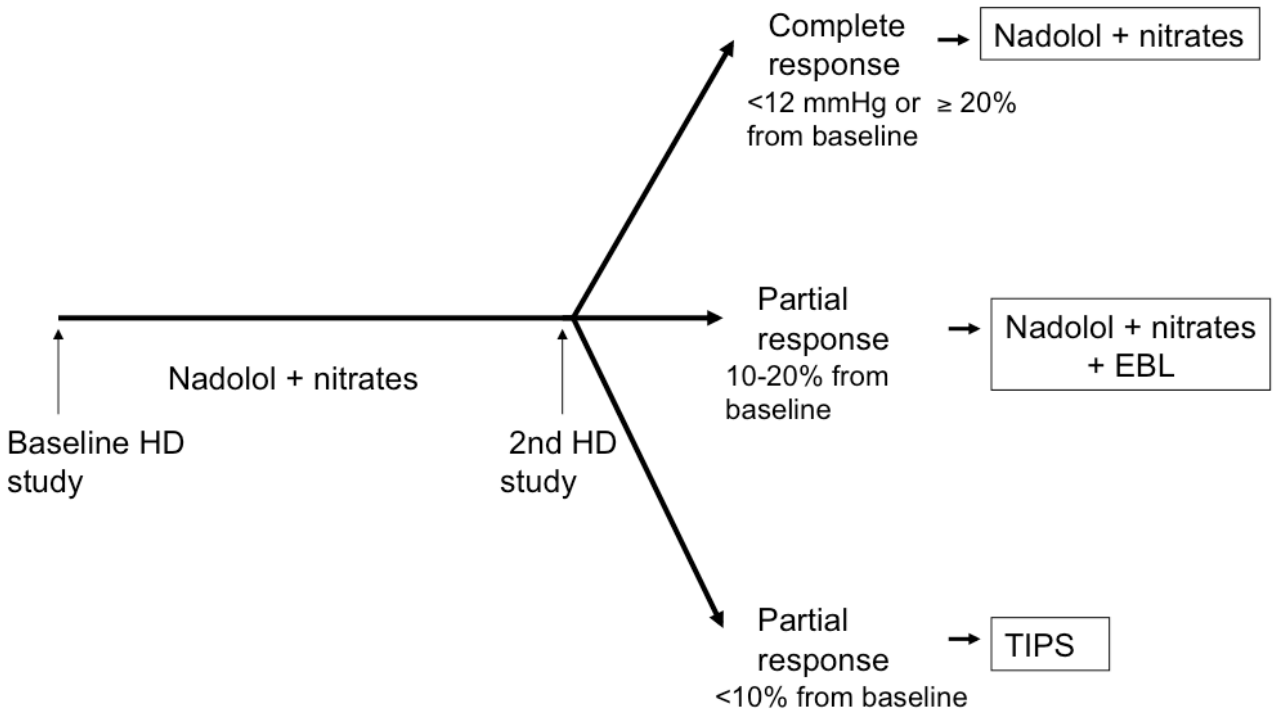


Figure 7. Diagram of the study from González et al [59]. HD: Hemodynamic study, EBL: Endoscopic band ligation, TIPS: Transjugular intrahepatic portosystemic shunt.

The most recently published study which evaluates the use of HVPG to guide prophylaxis from variceal bleeding was done in the setting of primary prophylaxis [60]. Patients had an initial HVPG measurement and were then given betablockers. Once the appropriate dose had been achieved hemodynamic measurement was repeated. Non-responders according to the traditional standards were then given nitrates. Finally hemodynamic measurement was repeated and patients were followed up for 2 years. By using HVPG to direct the prophylactic therapy of the patients, the proportion of patients who achieved a hemodynamic response increased from 38 to 48%. Achieving a hemodynamic response was one of the independent predictive factors for the development of a first variceal bleeding.

-Use of HVPG in Other Complications associated to Portal Hypertension

Advanced liver disease is characterized by the development of hepatic failure and complications associated to portal hypertension. In comparison to variceal bleeding, the relationship between HVPG and other complications associated to portal hypertension (ascites, spontaneous bacterial peritonitis, hepatorenal syndrome) have not been as thoroughly studied. Generally, these are observational studies that compare the incidence of other complications in patients who receive prophylactic betablocker therapy according to their hemodynamic response.

The development of de novo ascites or worsening of previous ascites, -defined by the need to increase the dose of diuretics or the need for large volume paracentesis- is reduced significantly in the long term follow-up in patients with hemodynamic response in the context of secondary prophylaxis [49, 58]. In compensated patients with clinically significant portal hypertension, achievement of hemodynamic response in the setting of primary prophylaxis is associated to a reduction in the incidence of ascites and associated complications[61]. In fact, hemodynamic non-response was the best predictor of ascites during follow-up on multivariate analysis[61].

The hemodynamic response to betablockers also reduces the incidence of spontaneous bacterial peritonitis both in primary and secondary prophylaxis [49, 56, 58]. Interestingly, one study observed a greater HVPG at admission in those patients who were admitted with spontaneous bacterial peritonitis who later went on to develop renal failure during the follow up[62]. Furthermore, patients who had hemodynamic response had a significantly lower probability of developing hepatorenal syndrome [49, 58].

The relationship between hepatic encephalopathy and HVPG is not as evident due to the fact that one of the main pathogenic factors that determine the development of hepatic encephalopathy is the presence of portalsystemic shunts. The presence of the portalsystemic shunts is associated to portal hypertension, however HVPG measurement does not allow an exact quantification of their flow [63]. Although the information is scarce, it seems that the hemodynamic response in the context of secondary prophylaxis is associated to a lower incidence of hepatic encephalopathy [49, 58].

-Use of HVPG in the Prediction of Hepatocellular Carcinoma

The other main clinical event of liver cirrhosis, besides the development of liver decompensation, is the development of hepatocellular carcinoma (HCC)[2]. HCC can take place in the compensated or decompensated phase of the disease and is an event which has a negative impact on the outcome of the liver disease. Several studies have found an association between indirect markers of portal hypertension such as platelet count and the presence of varices with the development of HCC [64-66]. Previous to the publication of the articles that conform this habilitation there was no data regarding the prognostic information derived from the presence of clinically significant portal hypertension as estimated by the HVPG measurement in the prediction of hepatocellular carcinoma.

-Use of HVPG in Survival Prediction

The role of HVPG as a predictor of mortality has been evaluated in different studies, as this was not the only aim of the studies, some of these studies have already been

referred to partially. Therefore, in this section, only the results of the study that pertain specifically to the role of HVPG as a predictor of death will be commented.

The first study is a secondary analysis of randomised controlled trial in patients with recently diagnosed alcoholic cirrhosis [37]. The aim of the study was to evaluate the prognostic role of HVPG, measured with a straight catheter, to predict the development of upper gastrointestinal bleeding or death and secondly to evaluate the prognostic role of HVPG taking into account other clinical and endoscopical prognostic variables. Fifty-eight patients with alcoholic cirrhosis were included with a baseline HVPG of 14 mmHg (range 3- 26 mmHg). The median follow-up time was 31 months (range 2-51 months). During this time period 17 patients died, 15 patients due to their hepatic disease and 2 due to non hepatic causes. On univariate analysis, Child-Turcotte C class, the presence of big varices, baseline HVPG and indocyanin green clearance were predictors of death. On multivariate analysis, the presence of big varices and HVPG (introduced as a continuous variable) were maintained as independent predictors of death.

Merkel and collaborators included 129 patients with cirrhosis and esophageal varices without bleeding prophylaxis[41]. The aim of the study was to evaluate HVPG, hepatic plasma flow, and indocyanin green clearance in the prediction of variceal bleeding and death and whether or not these variables offered further information to the information already derived from Child-Pugh class or the size of varices. The patients had predominantly alcoholic cirrhosis with a median basal HVPG of 20.2 mmHg (IQR 18.2-22.8 mmHg). During the median follow up of 45 months, 54 patients died, 47 related to liver disease. Multivariate analysis identified Child-Pugh score, HVPG (> 16 mmHg), indocyanin green clearance, introduced as a dichotomical variable, and previous variceal bleed, as the best independent variables to predict death.

Another study evaluated the prognostic value of repeat measurements in a group of patients with alcoholic cirrhosis with esophageal varices without previous variceal bleed[17].

Hemodynamic studies were repeated on a yearly basis. Median baseline HVPG was 19.1 mmHg (SEM 0.7 mmHg). Median follow-up was 42 months (SEM 5 months). During this time period, 17 patients died. Interestingly, there were no significant differences in the baseline HVPG between the patients who died during the follow-up and the patients who survived. However, a decrease of HVPG was observed in patients who survived (mean reduction (19.2% (SEM 4.9%)), while those who died had an increase in HVPG although the latter was not statistically significant. On multivariate analysis HVPG in the first follow-up hemodynamic study and the size of varices at baseline and at the first follow up were the independent predictors of mortality.

Patch and the collaborators evaluated the prognostic role of HVPG in the prediction of variceal bleeding and death in a group of patients with cirrhosis of different etiologies [42]. A hemodynamic study was performed after a median time of 11 days after the baseline hemorrhage and then patients were followed up for a median of 566 days (range 10-2555 days). During this time period 33 patients died and only one patient died due to a non-hepatic death. On multivariate analysis, HVPG, prolonged previous endoscopic prophylactic treatment, ascites, bilirubin and prothrombin time were identified as independent death predictors. Patients with an HVPG value over 16 mmHg had a significantly greater risk of death than patients with an HVPG value under this threshold.

Moitinho and collaborators evaluated the prognostic role of early HVPG in the context of bleeding varices [45]. In this study, a hemodynamic study was performed in the first 48 hours in 65 patients with cirrhosis and upper gastrointestinal bleeding. Both HVPG measurement as well as Child-Pugh score were identified as independent predictors of death at one year. Furthermore, a threshold value of HVPG of 20 mmHg could discriminate between patients who would have treatment failure (as defined by lack of initial control or early rebleeding) and death.

The presence of clinically significant portal hypertension was associated to survival in patients with compensated cirrhosis in a large cohort of patients with predominantly alcoholic cirrhosis[34]. The main aims of the study were to evaluate the survival of patients according to the previously proposed stage classification[2], and then to evaluate the prognostic value of HVPG in each one of these stages. The fact that HVPG was included as a dichotomic variable may explain the fact that it was only predictive of survival in compensated patients, while it had no prognostic value in decompensated patients. These latter patients, by definition, had complications of end-stage liver disease which require the presence of clinically significant portal hypertension. Furthermore, HVPG has been associated to in-hospital mortality in patients with acute alcoholic hepatitis[67].

A more recent study evaluated the use of HVPG and ultrasound to predict death in a population of patients with predominantly compensated cirrhosis [68]. In this study HVPG remained an independent predictor of first decompensation and death. Ultrasonographic findings lacked predictive value regarding these events, although it allowed identification of patients who were more likely to have greater values of HVPG and therefore greater risk of these events.

Lastly, in the context of variceal bleeding prophylaxis it has been observed that changes in HVPG observed with repeat measurement could predict mortality, so that patients who have hemodynamic response as defined by a decrease below 12 mmHg or 20% from baseline, had significantly lower probability of death than patients who did not achieve this threshold [43, 44, 49, 58] .

A summary of the findings of the studies that evaluated the prognostic information derived from HVPG is provided on Table 3.

	End-point
Single measurement	-presence of varices [12-14,34-37] -development of varices [39] -variceal bleeding [12,14-16] -prognosis of variceal bleeding [44-47] -presence of ascites [16,35] -presence of SBP [38] -death during follow-up [33,36,40-44,48,57,66,67] -in-hospital mortality in acute alcoholic hepatitis [66]
Repeat Measurements	-development of varices [39] development of variceal bleeding [42,43, 48-59] -development of ascites [48,57,60] -development of SBP [48,55,57] -development of hepatorenal syndrome [48,57] -development of hepatic encephalopathy [48, 57] -death during follow-up [42,43,48,57]

Table 3. Summary of end-points in the natural history of cirrhosis associated to HVPG.

HYPOTHESIS AND AIMS

In the natural history of liver disease there are 3 relevant endpoints: decompensation, hepatocellular carcinoma and death. Traditionally, prognostic factors in the evaluation of cirrhosis have been applied independently of the stage of the disease. However in the recent years, there has been a relevant change in the concept of the natural history of cirrhosis. So that two clearly defined phases of the disease are identified: compensated and decompensated cirrhosis, the latter of which is characterized by the development of typical complications of end stage liver disease. Distinguishing between these two phases of cirrhosis is clinically relevant, as it has been demonstrated that once the patient develops complications of liver disease the patient's prognosis worsens. On the other hand, death of patients with cirrhosis is mostly preceded by the development of decompensation. Therefore, the main prognostic aim in compensated patients is to predict decompensation while in decompensated patients the main prognostic aim is to predict death. Finally, the development of hepatocellular carcinoma can occur both in the compensated and decompensated phase and can accelerate the natural history of the disease. For this reason, evaluation of potential prognostic factors and prognostic models should be adjusted to the phase of the disease.

Portal hypertension has a central role in the pathophysiology of liver disease, so that a clear relationship between the degree of portal pressure as estimated by HVPG and the development of complications and survival in patients with compensated and decompensated disease has been established. Furthermore indirect data suggests that there could be an association between portal pressure and the development of hepatocellular carcinoma.

However, the relationship between the degree of portal hypertension and the development of clinical decompensation defined by the development of variceal bleeding, ascites, and hepatic encephalopathy in patients with compensated cirrhosis is unclear.

This question is relevant as practically all compensated patients will have decompensation of their liver disease before death.

Secondly, although there is more data regarding the relationship between the degree of portal hypertension and death in decompensated patients than compensated patients, there is no relevant information that has evaluated the contribution of HVPG taking into account the prognostic information that can be derived from MELD score, to predict survival in patients with cirrhosis. Its important to underline that although MELD score has been demonstrated to be useful in cirrhosis, it does not include any variable associated to portal hypertension, so that it would be expected that inclusion of HVPG as an estimation of portal pressure would improve the prognosis provided by MELD score.

Thirdly, indirect data suggest that there could be an association between portal hypertension and development of hepatocellular carcinoma, however no study has specifically evaluated this aspect.

Finally, it is well established that the estimation of portal pressure by means of HVPG is a dynamic measurement and that reductions of HVPG with the administration of betablockers lead to an improvement in the outcome of patients. One study has shown that increases in HVPG lead to a greater incidence of varices[40]. However no study has evaluated the prognostic value of changes of HVPG to predict clinically relevant outcomes such as decompensation and death.

In this context, the hypothesis of the studies that conform this habilitation is that portal pressure has independent prognostic relevance in cirrhosis, both in the compensated and decompensated phase of the disease as well as in the development of hepatocellular carcinoma. In the compensated phase, portal pressure could contribute to identify patients with the greatest risk to develop clinical decompensation taking into account its central pathophysiological role in their development. On the other hand, in decompensated disease, portal pressure contributes to the identification of patients with

the greatest risk of death. Its logical to consider that the prognostic relevance of portal hypertension in each phase will be different, and probably will be greater in the compensated phase while in the decompensated phase other factors gain more importance in determinating survival such as liver failure and circulatory dysfunction. Furthermore, portal pressure could also contribute to identify the patients with the greatest risk of development of hepatocellular carcinoma. On the other hand, taking into account the dynamic properties of HVPG, perhaps more information may be derived from repeat measurements in the prediction of relevant events in patients with cirrhosis, rather than just the presence or absence of a decrease in its value beyond a certain threshold.

The aims of this study were:

1) To evaluate the possible contribution of the measurement of portal pressure as estimated by HVPG as a predictor of decompensation in patients with compensated cirrhosis.
2) To evaluate the possible contribution of the measurement of portal pressure as estimated by HVPG as a predictor of mortality in patients with decompensated cirrhosis.
3) To evaluate the prognostic value of changes of HVPG in predicting clinically relevant outcomes (decompensation in compensated cirrhosis and death in decompensated cirrhosis).
4) To evaluate the possible contribution of the measurement of portal pressure as estimated by HVPG as a predictor of hepatocellular carcinoma in patients with compensated cirrhosis.

ARTICLES

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GASTROENTEROLOGY 2007;133:481–488

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Hepatic Venous Pressure Gradient Predicts Clinical Decompensation in Patients With Compensated Cirrhosis

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See Roberts SK et al on page 932 in the August 2007 issue of CGH.

Background & Aims: **Our aim was to identify predictors of clinical decompensation (defined as the development of ascites, variceal hemorrhage [VH], or hepatic encephalopathy [HE]) in patients with compensated cirrhosis and with portal hypertension as determined by the hepatic venous pressure gradient (HVPG).** ***Methods:*** **We analyzed 213 patients with compensated cirrhosis and portal hypertension but without varices included in a trial evaluating the use of β-blockers in preventing varices. All had baseline laboratory tests and HVPG. Patients were followed prospectively every 3 months until development of varices or VH or end of study. To have complete information, until study termination, about clinical decompensation, medical record review was done. Patients who underwent liver transplantation without decompensation were censored at transplantation. Cox regression models were developed to identify predictors of clinical decompensation. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic capacity of HVPG.** ***Results:*** **Median follow-up time of 51.1 months. Sixty-two (29%) of 213 patients developed decompensation: 46 (21.6%) ascites, 6 (3%) VH, 17 (8%) HE. Ten patients received a transplant and 12 died without clinical decompensation. Median HVPG at baseline was 11 mm Hg (range, 6–25 mm Hg). On multivariate analysis, 3 predictors of decompensation were identified: HVPG (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.05–1.17), model of end-stage liver disease (MELD) (HR, 1.15; 95% CI, 1.03–1.29), and albumin (HR, 0.37; 95% CI, 0.22–0.62). Diagnostic capacity of HVPG was greater than for MELD or Child–Pugh score.** ***Conclusions:*** **HVPG, MELD, and albumin independently predict clinical decompensation in patients with compensated cirrhosis. Patients with an HVPG <10 mm Hg have a 90% probability of not developing clinical decompensation in a median follow-up of 4 years.**

A recent systematic review of predictors of death in cirrhosis confirmed the different survival rates between patients with compensated and decompensated cirrhosis and underscored that these are two distinct stages of cirrhosis with different predictors of survival.[1] In fact, in patients with compensated cirrhosis, death does not occur until patients develop complications that characterize the decompensated phase of the disease, that is, ascites, variceal hemorrhage (VH), and encephalopathy. Therefore, it was suggested that in patients with compensated disease prediction of decompensation was more relevant than prediction of survival.

Because most of the complications that characterize decompensation are related to portal hypertension, it would follow that portal pressure would be predictive of decompensation. It is well known that a threshold value of hepatic venous pressure gradient (HVPG) is required for the development of varices and variceal bleeding.[2] Furthermore, a reduction in HVPG after pharmacologic

Abbreviations used in this paper: CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; MELD, model of end-stage liver disease; RCT, randomized controlled trial; ROC, receiver operating characteristic; VH, variceal hemorrhage.

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therapy was identified as a negative predictor of VH and spontaneous bacterial peritonitis.[3–5] However, the role of baseline levels of HVPG in prediction of decompensation in early cirrhosis has not been evaluated.

Therefore, the aim of this study was to evaluate the predictors of clinical decompensation in a homogenous cohort of compensated patients with cirrhosis and portal hypertension without varices and, second, to evaluate the independent role of portal pressure (as determined by HVPG) in predicting clinical decompensation.

Materials and Methods

This study is a nested cohort study within a randomized controlled trial (RCT).[6] Between August 1993 and March 1999, patients with compensated cirrhosis were enrolled in a prospective RCT designed to evaluate the efficacy of nonselective β-blockers in preventing the development of gastroesophageal varices. Patients were considered for inclusion if they had cirrhosis and portal hypertension (defined by an HVPG of ≥6 mm Hg) without gastroesophageal varices and were between the age of 18 and 75 years. The diagnosis of cirrhosis was either biopsy proven or clinically suspected and confirmed by the presence of an HVPG value of ≥10 mm Hg. Exclusion criteria included ascites requiring diuretic treatment, hepatocellular carcinoma, splenic or portal vein thrombosis, concurrent illnesses expected to decrease life expectancy to <1 year, the use of any drug or procedure affecting splanchnic hemodynamics or portal pressure, primary biliary cirrhosis or primary sclerosing cholangitis, contraindication to β-blocker therapy, pregnancy, or alcohol intake during the dose-titration phase. From the 780 patients screened for varices in the RCT, 490 (63%) did not have any. From these patients 277 (57%) were excluded and 213 (43%) patients were finally included in the RCT. The reasons for exclusion are described in the previously published paper.[6] Patients were randomly assigned to receive placebo or timolol, a nonselective β-blocker. At baseline clinical history, physical examination, blood tests, upper gastrointestinal endoscopy, abdominal ultrasonography, and HVPG measurement were performed. Patients were followed at 1 and 3 months after random assignment and then every 3 months until the primary end point of the study (development of small varices observed in 2 consecutive endoscopies, large varices, or VH), 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 end point of the trial, and follow-up was discontinued in the setting of the RCT.[6]

The primary end point of the present study was the development of clinical decompensation defined by the presence of ascites, encephalopathy, or VH. Ascites was defined by the presence of signs and symptoms suggestive of ascites on physical examination and confirmed on ultrasonography. The presence of free intraperitoneal fluid on ultrasonography not detectable on physical examination or the sole presence of peripheral edema was not considered an end point. HE was defined by the presence of temporospatial disorientation, asterixis, or both in the absence of other possible causes. The presence of subclinical encephalopathy was not investigated. Variceal bleeding was defined according to the Baveno IV criteria.[7] Patients who received liver transplants because of hepatocellular carcinoma without clinical decompensation previous to the surgery were censored at the time of transplantation. All data about clinical decompensation had been prospectively collected in the RCT, except in 62 patients who developed the primary end point of that trial but had not developed clinical decompensation. Retrospective review of charts of these patients was performed to have complete follow-up about clinical decompensation until the end of the study (September 2002).

Comparisons between patients with and without decompensation were first performed by 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 <.1 on univariate analysis. To avoid the common problems of overfitting and colinearity, several different models were created with variables that were statistically significant in univariate analysis ($P < .1$) 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. The lower the value of −2LL, the greater amount of variability of the outcome variable is explained by the model, that is, the better the model. By using this strategy we could evaluate all the potential variables that may have a role in predicting clinical decompensation. Colinearity was assessed with the tolerance value, considering excessive colinearity between variables when the tolerance was <0.1. First order two-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 portal pressure (as determined by HVPG) in predicting clinical decompensation, Cox proportional hazards model was developed. Receiver operating characteristic (ROC) curves were constructed with Child–Pugh score, model of end-stage liver disease (MELD), albumin, and HVPG as predictors of clinical decompensation. The area under each

Table 1. Baseline Characteristics of All Patients and Patients Who Remained Compensated or Developed Decompensation During Follow-Up

	All patients (N = 213)	Remained compensated (n = 151)	Developed decompensation (n = 62)
Men, n (%)	126 (59)	86 (57)	40 (64)
Age (*y*), median (interquartile range)	54 (46–63)	54 (45–62)	56 (48–64)
Cause of cirrhosis			
Alcoholic, n (%)	51 (24)	36 (24)	15 (24)
Nonalcoholic, n (%)	162 (76)	115 (76)	47 (76)
HCV, n (%)	134 (62)	95 (63)	38 (61)
HBV, n (%)	8 (4)	8 (5)	2 (3)
Cryptogenic, n (%)	10 (5)	4 (3)	6 (10)
Other, n (%)	10 (5)	8 (5)	0 (0)
Child–Pugh score, median (interquartile range)	5 (5–5)	5 (5–5)	5 (5–6)
Child–Pugh class			
A, n (%)	188 (88)	137 (91)	51 (82)
B, n (%)	25 (12)	14 (9)	11 (18)
MELD, median (interquartile range)	8.0 (7.0–10.0)	7.9 (6.8–9.5)	9.0 (7.5–11.1)
Platelets ($\times 10^{-3}/mm^3$), median (interquartile range)	111 (74–149)	120 (84–150)	88 (66–138)
Total bilirubin (*mg/dL*), median (interquartile range)	0.9 (0.7–.4)	0.9 (0.6–1.2)	1.3 (0.8–1.7)
INR, median (interquartile range)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.3)
Albumin	4.0 (3.6–4.3)	4.1 (3.7–4.3)	3.8 (3.4–4.1)
Aspartate aminotransferase (*U/L*), median (interquartile range)	73 (48–115)	69 (48–109)	84 (48–130)
Alanine aminotransferase (*U/L*), median (interquartile range)	78 (41–132)	73 (45–117)	88 (40–141)
Serum sodium (*mmol/L*), median (interquartile range)	140 (139–142)	140 (139–142)	141 (139–142)
Creatinine (*mg/dL*), median (interquartile range)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.0)
HVPG (*mm Hg*), median (interquartile range)	11 (8–14)	10 (7.5–13.5)	13 (11–16)
HVPG ≥10 mm Hg, n (%)	134 (63)	80 (53)	54 (87)
HVPG responders (n = 147)			
No, n (%)	81 (55)	57 (50)	24 (71)
Yes, n (%)	66 (45)	56 (50)	10 (29)
Hepatocellular carcinoma, n (%)	19 (9)	12 (8)	7 (11)
Follow-up time (*mo*), median (interquartile range)	51 (33–77)	62 (43–81)	31 (16–57)
Randomly assigned to timolol, n (%)	108 (51)	72 (48)	36 (58)

NOTE. HVPG responders are those in whom HVPG decreased >10% at 12 months.
HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model of end-stage liver disease; INR, International Normalized Ratio; HVPG, hepatic venous pressure gradient.

of the curves (*c* statistic) was estimated. A threshold value of HVPG that distinguished 2 populations with different incidence of clinical decompensation was identified. Kaplan–Meier curves of the 2 populations were constructed and compared with the log-rank test.

Finally, a secondary analysis was performed in the subgroup of patients who had a second hemodynamic study 1 year after inclusion in the RCT. Patients were considered "responders" (independent of whether the patients were taking β-blockers or placebo) if they had a 10% decrease in HVPG from baseline. This cutoff was identified as a predictor of primary end points in the original RCT.[6] The independent role of hemodynamic response, aside from baseline HVPG, was evaluated with Cox proportional hazards regression analysis.

Statistical significance was considered with a *P* value of ≤.05. Statistical analysis was done with SPSS package 12.0 (SPSS Inc, Chicago, IL). Approval from the local institutional review board was obtained.

Results

Baseline data of the patients is shown in Table 1. From the 213 patients who were included in the original trial,[6] 62 patients developed clinical decompensation, 12 received a transplant (because of hepatocellular carcinoma), 10 patients died (4 of extrahepatic neoplasia, 4 of bacterial infection, 1 of sudden death, and 1 of mediastinitis after aortic valve replacement surgery) in both cases without having developed previous clinical decompensation, and, finally, 129 patients were alive at the end of follow-up (Figure 1). The median follow-up was 51.1 months (interquartile range, 33–77 months). A significantly greater proportion of patients from the group that had developed the original RCT end point (small varices in 2 consecutive endoscopies, large esophageal varices, or VH) developed clinical decompensation (35/84; 42%) compared with those who did not reach the end point (27/129; 21%) ($P = .002$). Most patients presented with ascites

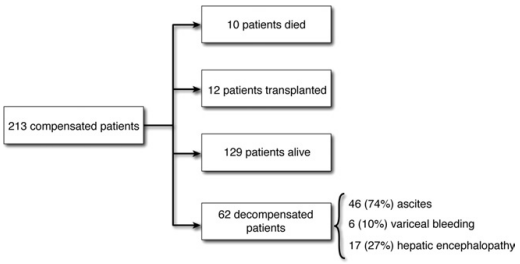

Figure 1. Flow chart showing the outcome of patients included in the study. Patients who died or received a liver transplant did so without developing cirrhosis decompensation.

as their first episode of clinical decompensation (46 patients, 74%) either alone (40 patients) or in combination with other types of clinical decompensation (3 VH, 3 HE). Only 6 patients presented with VH as first clinical decompensation (10%) (2 alone, 3 in combination with ascites, and 1 with HE). Finally 17 patients (27%) had HE during the follow-up, in 13 cases as the only complication (21%) and in the rest of the cases in combination with other types of decompensation (see above). Median HVPG at baseline was 11 mm Hg (interquartile range, 8–14 mm Hg).

As shown in Table 2, on univariate analysis, HVPG, MELD, Child–Pugh score, and its biochemical components, aspartate aminotransferase and platelet count, were significantly more altered in patients who developed decompensation compared with patients who remained compensated. Both groups had a similar proportion of alcoholic liver disease, and a similar proportion of patients randomly assigned to the treatment group (β-blocker or placebo) in the original study.

When all variables significant on univariate analysis were entered in a multivariable model, HVPG (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.05–1.17), MELD [HR, 1.15; 95% CI, 1.03–1.29, and albumin HR, 0.37; 95% CI, 0.22–0.62] remained independent predictors of clinical decompensation (Table 3). No 2-way interactions between HVPG and the other variables were detected.

Different models were developed to avoid colinearity and overfitting (Table 3). The final model (HVPG, MELD, albumin) was chosen according to the reduction in the likelihood ratio. In all models HVPG remained an independent predictor of clinical decompensation. Of interest, the robustness of the quantification of the effect of HVPG on clinical decompensation was emphasized by the similar value of HR obtained in the different models.

ROC curves were constructed to identify the diagnostic capacity of HVPG, MELD, and Child–Pugh score. HVPG had a greater discriminative ability (*c* statistic, 0.71; 95% CI, 0.64–0.78) compared with albumin (*c* statistic, 0.66; 95% CI, 0.58–0.74), MELD (*c* statistic, 0.64; 95% CI, 0.55–0.72), and Child score (*c* statistic, 0.61; 95% CI, 0.52–0.7) (Figure 2).

To identify a threshold value of HVPG to separate different risk populations, it was a priori considered that it would be preferable to identify patients who would not develop decompensation. With this consideration, the threshold HVPG value of 10 mm Hg identified 2 different risk populations for development of clinical decompensation with a 90% negative predictive value. Therefore, compensated patients with a HVPG value $<$10 mm Hg had a 90% chance of not having any clinical decompensation in a median follow-up of 4 years. Kaplan–Meier curves were constructed in patients with an HVPG $\leq$10 mm Hg and $\geq$10 mm Hg [unadjusted HR, 5.7; 95% CI, 2.7–12; $P < .001$] (Figure 3). No patient with an HVPG $<$10 mm Hg developed clinical decompensation during the first 20 months of follow-up. Evaluation of the other 2 variables that had an independent predictive role on multivariable analysis showed that the best cutoff values of both MELD (MELD score = 10; unadjusted HR, 2.3; 95% CI, 1.4–3.9; $P = .001$) and albumin (4 g/dL; unadjusted HR, 2; 95% CI, 1.2–3.3; $P = .007$) had a negative predictive value of 78% and 77%, respectively, lower than that shown for the HVPG (Figure 3).

During follow-up 154 patients had repeat HVPG measurements done 1 year after random assignment. From these patients, 7 had developed clinical decom-

Table 2. Univariate Cox Analysis

	Hazard ratio	95% CI	*P* value
Men	1.271	0.755–2.14	.367
Age	1.011	0.988–1.035	.344
Alcohol cause	1.344	0.751–2.405	.32
Child–Pugh score	1.751	1.341–2.286	$<$ .001
Child–Pugh class	2.748	1.423–5.308	.003
MELD	1.245	1.117–1.387	$<$ .001
Platelets ($\times 10^{-3}/mm^3$)	0.992	0.987–0.998	.008
Total bilirubin (*mg/dL*)	1.447	1.174–1.782	.001
INR	14.26	3.14–64.77	.001
Albumin	0.285	0.175–0.464	$<$ .001
Aspartate aminotransferase (*U/L*)	1.003	1–1.006	.064
Alanine aminotransferase (*U/L*)	1.001	0.998–1.003	.524
Serum sodium (*mmol/L*)	1.011	0.936–1.09	.787
Creatinine (*mg/dL*)	0.598	0.19–1.886	.381
HVPG (*mm Hg*)	1.132	1.079–1.187	$<$ .001
HVPG $\geq$10 mm Hg	3.95	2.286–6.827	$<$ .001
12-mo response	0.571	0.272–1.199	.139
Randomly assigned to timolol	1.371	0.827–2.272	.221

NOTE. All continuous variables were introduced in the univariate model as quantification of the effect.
CI, confidence interval; MELD, model of end-stage liver disease; INR, International Normalized Ratio; HVPG, hepatic venous pressure gradient.

Table 3. Modelling Strategy Used to Avoid Colinearity and Overfitting (62 Events)

Variables introduced	Final model	HR	95% CI	*P* value	−2LL
HVPG, age, AST, MELD, albumin, platelets, timolol, or placebo	HVPG	1.105	1.046–1.169	.001	531.72
	MELD	1.153	1.032–1.288	.014	
	Albumin	0.368	0.217–0.624	< .0001	
HVPG, age, AST, albumin, INR, total bilirubin, timolol, or placebo	HVPG	1.105	1.046–1.167	.001	534.162
	INR	5.339	1.076–26.486	.05	
	Albumin	0.347	0.205–0.589	< .0001	
HVPG, age, creatinine, AST, CPS, timolol, or placebo	HVPG	1.116	1.061–1.174	< .0001	557.48
	CPS	1.761	1–1.1007	< .0001	
	AST	1.004	1.324–2.342	.052	
HVPG, bilirubin, INR, albumin, AST, MELD, CPS	HVPG	1.105	1.046–1.169	.001	531.72
	MELD	1.153	1.032–1.288	.014	
	Albumin	0.368	0.217–0.624	< .0001	
Albumin, platelets, bilirubin, INR, AST, MELD, CPS, creatinine	Albumin	0.354	0.205–0.612	< .0001	535.58
	Platelets	0.995	0.99–1.001	.08	
	AST	1.004	1–1.007	.035	
	MELD	1.184	1.057–1.327	.004	

NOTE. No one-way interactions were observed. Assumption of proportional hazards was confirmed. All variables were introduced as continuous variables.

HR, hazard ratio; CI, confidence interval; −2LL, likelihood ratio (amount of variability of the outcome explained by the model; the closer to 0, the better the model adjusts to explain the outcome); HVPG, hepatic venous pressure gradient; AST, aspartate aminotransferase; MELD, model of end-stage liver disease; INR, International Normalized Ratio; CPS, Child–Pugh score.

pensation before the second HVPG measurement and were therefore not included in further analysis. Patients were then classified in "responders" (HVPG decrease of ≥10% from baseline) or "nonresponders." This subgroup of patients had similar characteristics to the original cohort, except for a longer follow-up (63 vs 51 months, $P < .0001$) (Table 1). When included in the multivariate model with the previously identified variables (baseline HVPG, MELD, albumin), baseline HVPG (HR, 1.15; 95% CI, 1.08–1.23), nonresponders at 12 months (HR, 2.6; 95% CI, 1.1–5.6), and albumin (HR, 0.42; 95% CI, 0.18–0.91) were independent predictors of clinical decompensation. No 2-way interactions were detected. Although patients who were nonresponders had a significantly greater HVPG at baseline (12 mm Hg vs 10.5 mm Hg, $P = .045$), no colinearity between these variables was detected.

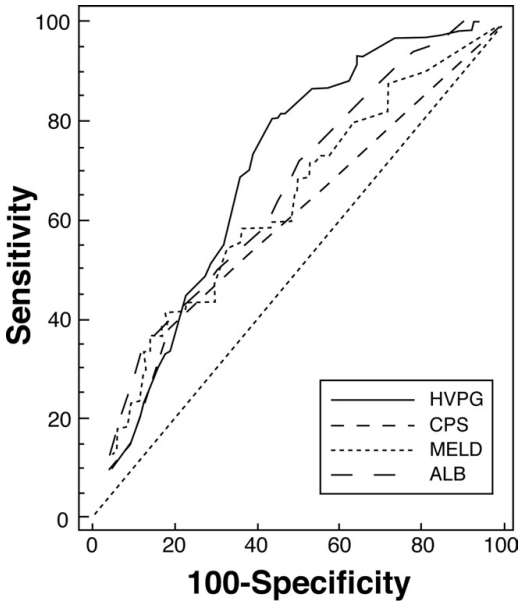

Figure 2. ROC curves for cirrhosis decompensation for the main prognostic factors: HVPG, hepatic venous pressure gradient (*c* statistic, 0.71; 95% CI, 0.64–0.78); albumin, serum albumin (*c* statistic, 0.66; 95% CI, 0.58–0.74); MELD, model for end-stage liver disease score (*c* statistic, 0.64; 95% CI, 0.55–0.72); CPS, Child–Pugh score (*c* statistic, 0.61; 95% CI, 0.52–0.71).

Discussion

The natural history of chronic liver disease involves the progression to cirrhosis, first compensated, then to decompensated cirrhosis and ultimately to death. Identification of predictors of decompensation among compensated patients is warranted, because death in cirrhosis is clearly related to the development of decompensation.[1] Even in the compensated phase, 2 stages with different survival rates have been identified: stage 1 without varices and stage 2 with varices.[1]

This large prospective cohort study looked specifically at a homogenous group of compensated patients with portal hypertension but without varices (stage 1). In this same group of patients, we had previously shown that an HVPG >10 mm Hg was the strongest predictor of the development of varices, which is not considered a decompensating event. In this study our aim was to identify predictors of clinical decompensation (ascites, VH, or

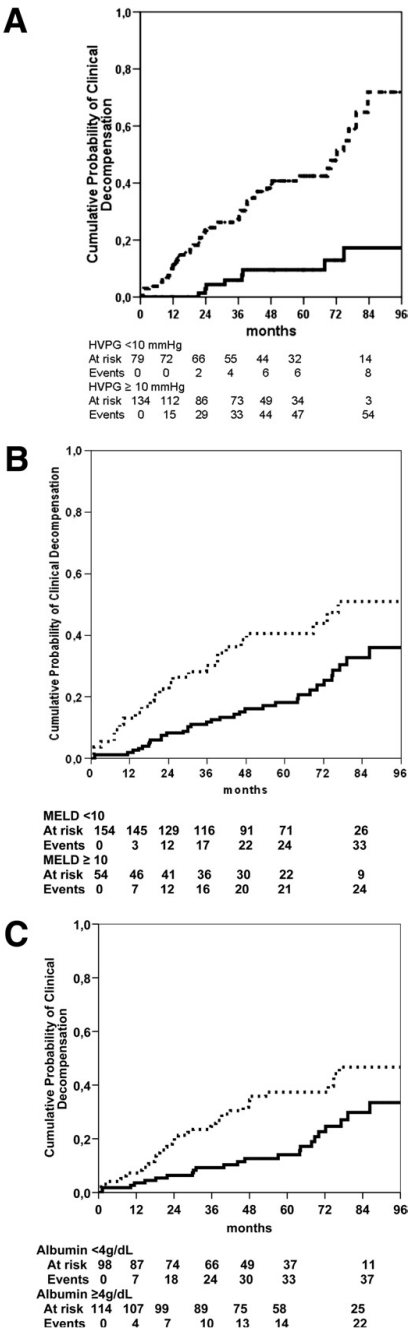

Figure 3. Kaplan–Meier survival curves according to the best cutoff level for (*A*) HVPG, hepatic venous pressure gradient (best cutoff level is 10 mm Hg); (*B*) MELD, model for end-stage liver disease (best cutoff score is 10); and (*C*) serum albumin (best cutoff level is 4 mg/dL). Discontinuous line represents HVPG ≥10 mm Hg, MELD ≥10, albumin <4 g/dL in (*A*), (*B*) and (*C*) respectively.

encephalopathy), and we found that, in a median follow-up of 51.1 months, decompensation occurred in 62 of 213 patients (29%). This relatively high rate of decompensation is most probably related because all patients had portal hypertension (ie, an HVPG of ≥6 mm Hg) at baseline. The predictors of clinical decompensation identified in this study (HVPG, albumin, and MELD) are well-known predictors of survival in decompensated patients[1,8] and are related to the severity of portal hypertension and liver insufficiency. Similar results were shown in a recent study in compensated patients with hepatitis C virus (both stage 1 and stage 2) that identified the presence of esophageal varices and bilirubin as the only independent predictors of clinical decompensation.[9]

HVPG was the most robust predictor of clinical decompensation because it remained an independent predictor across different models. The hazard ratio (ie, the quantification of the effect of HVPG on decompensation prediction) was also similar among the different tested models.

Furthermore, according to the HVPG, 2 different risk populations could be distinguished so that patients with an HVPG value <10 mm Hg have a 90% chance of not developing clinical decompensation. This further supports the clinical applicability of HVPG measurement because it enables the identification of patients who are unlikely to develop clinical decompensation during the following years. Importantly, in predicting decompensation, it is not only the qualitative value of HVPG that is important (presence or absence of an HVPG ≥10 mm Hg), but it is also the quantitative degree of portal hypertension that is relevant because, according to our model, the HVPG has a hazard ratio of 1.11, implying that for each 1 mm Hg increase in HVPG there is an 11% higher risk of clinical decompensation. In this way, a patient with a baseline HVPG of 15 mm Hg has 55% higher chance of developing decompensation compared with a patient with an HVPG of 10 mm Hg, at equivalent MELD and albumin values.

We also provide further evidence on the independent role of a decrease in HVPG in the prediction of clinical decompensation. This effect is independent of baseline HVPG. Previous studies had evaluated the role of a reduction in HVPG in predicting clinical decompensation in patients undergoing primary[4,10] or secondary prophylaxis.[3,5] Similar to our results, these studies have shown that being an HVPG nonresponder is independently associated with a greater incidence of portal hypertension–related complications and death.[3,5,11] The definition of response in our study (decrease of ≥10%) differs from the traditional criteria (ie, a reduction of >20% from baseline or <12 mm Hg).[7] However, these criteria were obtained in patients with more severe portal hypertension (large varices with or without VH), whereas our patients had portal hypertension but had not yet developed varices. In fact, several studies have already suggested that, in more

compensated patients, a 10% to 11% threshold is the best cutoff in predicting development of varices or VH[6] or spontaneous bacterial peritonitis or bacteraemia.[4]

According to the literature, the Child–Pugh score should have been a better predictor in compensated patients and MELD a better predictor in decompensated patients.[1] However, in the present study, MELD, and not Child–Pugh score, is an independent predictor of clinical decompensation in compensated patients. This is probably because the MELD score is composed of laboratory markers that can reflect subtle abnormalities of the liver function. However, one of the setbacks of the MELD score is that it does not include any variable associated to portal hypertensive syndrome.[12,13] A previous study has evaluated the role of HVPG and MELD score in survival prediction in a population of predominantly decompensated patients with cirrhosis.[8] In that population group HVPG was independently associated to mortality, although it did not improve the discriminative ability of MELD score. Interestingly, in our study in compensated patients, HVPG gains a predominant role with a greater discriminative ability in the prediction of decompensation, which will ultimately determine survival. This is probably because, in compensated patients, the distribution range of the MELD score is much narrower than in decompensated patients, whereas the HVPG, by virtue of a wider distribution range, provides the most information to predict decompensation.

One limitation of our study is that it constitutes a subanalysis of another study designed for another aim. However, in the original RCT,[6] data on VH (primary end point) and other decompensating events (secondary end points) were collected prospectively with an a priori definition of each complication so that data collection about complications of cirrhosis was uniform across study centers. Only the 62 patients (29%) who developed varices (and had not developed decompensation) were not followed prospectively until the development of decompensation. The charts of those patients were the only ones that were reviewed retrospectively. Although this review may have introduced some bias, we consider that it is highly unlikely that the development of relevant clinical end points such as ascites, VH, or encephalopathy, requiring specific management, would have been missed and not recorded in the clinical chart, particularly because most of the patients remained under the care of specialists at the same study centers. In fact, we chose not to include jaundice, a complication that has been traditionally considered a decompensating event, in our definition of decompensation. We considered that it would be more difficult to reliably investigate this indicator retrospectively and also because jaundice is often due to an acute-on-chronic illness and thereby would not constitute a "permanent" decompensation. Furthermore, and as expected given a more advanced stage of the disease,[1] patients who developed varices in the original RCT (ie, progression from stage 1 to stage 2) had a higher rate of clinical decompensation than patients who did not develop varices.

Another possible limitation is related to the study population. The study population was composed of compensated patients with portal hypertension without varices on upper gastrointestinal endoscopy. Therefore, the results can be applied only to this population. Whether the results may be applied to other groups of compensated patients (ie, with varices) remains to be determined. Moreover, cross-validation of the model in a subset of patients of this sample was not done, in order to not reduce the size of the sample and therefore the robustness of the estimates. Further studies will be required to test the model in other datasets and to evaluate more heterogeneous populations (eg, patients with compensated cirrhosis with varices or patients with compensated cirrhosis without varices) with or without portal hypertension.

In conclusion, the results of this large study suggest that in compensated patients with portal hypertension but without varices, HVPG, MELD, and albumin are independent predictors of the development of clinical decompensation which marks a threshold beyond which survival prognosis changes considerably. HVPG is the most robust predictor of clinical decompensation in patients with compensated cirrhosis and portal hypertension without varices.

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This study is based on the rationale that patients in the compensated and decompensated phase of liver disease have different relevant clinical outcomes and very likely different predictors of these outcomes. As portal hypertension is one of the main pathophysiological mechanisms that leads to the development of complications that characterize the decompensated phase of liver cirrhosis, our hypothesis was that portal pressure, as estimated by the hepatic venous pressure gradient, would be a relevant predictor of the transition from the compensated to the decompensated phase of the disease.

Aims: Our aim was first to identify predictors of clinical decompensation (defined as the development of ascites, variceal hemorrhage [VH], or hepatic encephalopathy [HE]) in patients with compensated cirrhosis and with portal hypertension as determined by the hepatic venous pressure gradient (HVPG) and then to evaluate the independent role of portal pressure (as determined by HVPG) in predicting clinical decompensation.

Methods: We analyzed 213 patients with compensated cirrhosis and portal hypertension but without varices included in a randomized controlled trial evaluating the use of beta-blockers in preventing varices. All patients had baseline laboratory tests and HVPG. Patients were followed prospectively every 3 months until the development of varices or variceal hemorrhage or the end of the original study in September 2002. To have complete information regarding clinical decompensation until study termination, medical record review was done. Patients who underwent liver transplantation without decompensation were censored at transplantation. Cox regression models were developed to identify predictors of clinical decompensation. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic capacity of HVPG.

Results: The median follow-up time was 51.1 months. During this time period sixty-two (29%) of 213 patients developed decompensation. Most patients presented with ascites as

their first episode of clinical decompensation (46 patients, 74%) either alone (40 patients) or in combination with other types of clinical decompensation. Only 6 patients presented with VH as first clinical decompensation (10%). Finally 17 patients (27%) had HE during the follow-up. Some patients presented more than one type of clinical decompensation at once. During the follow-up 10 patients received a liver transplant due to hepatocellular carcinoma and 12 patients died without any clinical decompensation. Median HVPG at baseline was 11 mm Hg (range, 6–25 mm Hg). On univariate analysis, patients who developed decompensation during follow-up were sicker at baseline as shown by greater HVPG, Child-Pugh Score and MELD. On multivariate analysis, 3 predictors of decompensation were identified: HVPG (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.05–1.17), model of end-stage liver disease (MELD) (HR, 1.15; 95% CI, 1.03–1.29), and albumin (HR, 0.37; 95% CI, 0.22–0.62). Comparison of ROC curves showed a greater diagnostic capacity of HVPG, in comparison to albumin, MELD and Child–Pugh score. Cut-off thresholds of HVPG, MELD and albumin were determined. An HVPG of 10 mmHg had a 90% negative predictive value, meaning that patients who had compensated cirrhosis with an HVPG below this threshold were unlikely to develop decompensation during a 4 year follow up.

Conclusions: HVPG, MELD, and albumin independently predict clinical decompensation in patients with compensated cirrhosis. Patients with an HVPG <10 mm Hg have a 90% probability of not developing clinical decompensation in a median follow-up of 4 years.

Influence of Hepatic Venous Pressure Gradient on the Prediction of Survival of Patients With Cirrhosis in the MELD Era

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Measurements of portal pressure, usually obtained via the hepatic venous pressure gradient (HVPG) may be a prognostic marker in cirrhosis. The aim of this study was to evaluate the impact of HVPG on survival in patients with cirrhosis in addition to the Model for End-Stage Liver Disease (MELD) score. We also examined whether inclusion of HVPG in a model with MELD variables improves its prognostic ability. Retrospective analyses of all patients who had HVPG measurements between January 1998 and December 2002 were considered. Proportional hazards Cox models were developed. Prognostic calibrative and discriminative ability of the model was evaluated. In this period, 693 patients had a hepatic hemodynamic study, and 393 patients were included. Survival was significantly worse in those patients with greater HVPG value (univariate HR, 1.05; 95% CI, 1.02-1.08; $P = .001$). HVPG remained as an independent variable in a model adjusted by MELD, ascites, encephalopathy, and age (multivariate HR, 1.03; 95% CI, 1.00-1.06; $P = .05$) so that each 1-mmHg increase in HVPG had a 3% increase in death risk. In addition, HVPG as well as MELD score variables and age, significantly contributes to the calibrative predictive capacity of the prognostic model; however, discriminative ability improved only slightly (overall C statistic [95% CI]; MELD score variables: 0.71 [0.62-0.80], MELD score variables, age, and HVPG 0.76: [0.69-0.83]). In conclusion, HVPG has an independent effect on survival in addition to the MELD score. Although inclusion of HVPG and age in a survival predicting model would improve the calibrative ability of MELD, its discriminative ability is not significantly improved. (HEPATOLOGY 2005;42:793-801.)

The Model for End-Stage Liver Disease (MELD) score, initially developed for survival prediction of patients undergoing the transjugular intrahepatic portal systemic shunt (TIPS) procedure,[1] has been subsequently validated in an increasingly heterogeneous population of patients with cirrhosis as a very good tool to rank patients according to their short-term risk of death.[2-5]

In the initial validation of the MELD score, individual complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal bleeding, and encephalopathy) were added to the model, producing only minimal improvement in its discriminative ability.[2] However, each individual portal hypertension–related complication is only one aspect of the underlying pathophysiological mechanism, the portal hypertensive syndrome. Re-evaluation of the role of portal hypertension indexes in such predictive scores has been suggested, as portal hypertension has been described as the third parameter most frequently found to be a significant predictor of survival in cirrhosis.[6] Interestingly, after dividing patients in categories according to MELD score, 1-year mortality within each category was higher among patients with portal hypertension–related complications.[7]

Abbreviations: MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portal systemic shunt; HVPG, hepatic venous pressure gradient; FHVP, free hepatic venous pressure; WHVP, wedged hepatic venous pressure.

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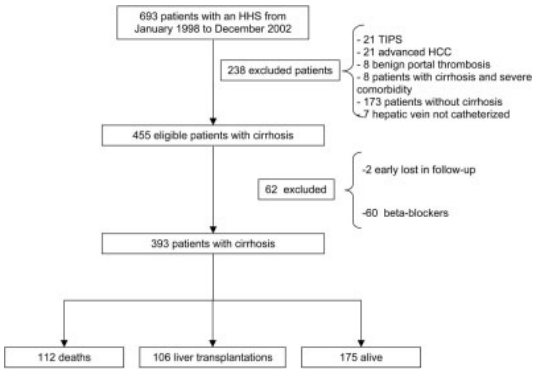

Fig. 1. Flow chart of patients. HHS, hepatic hemodynamic study; TIPS, transjugular intrahepatic portal systemic shunt; HCC, hepatocellular carcinoma.

Although many indicators exist for the portal hypertensive syndrome, the most direct and accessible evaluation is done via the hepatic venous pressure gradient (HVPG), which has been validated as a measurement of portal pressure in cirrhosis.[8] The prognostic value of HVPG has been demonstrated in different settings associated with chronic liver disease.[8-14] Particularly, it has been shown to have prognostic value for survival in variceal bleeding prophylaxis and in acute variceal bleeding.[10-12,14] Additionally, individual manifestations of portal hypertension have been associated with survival in many studies.[7,15-20] Therefore, the first aim of our study was to evaluate the impact of HVPG on survival in patients with cirrhosis, taking into account the MELD score. We hypothesized that HVPG as an estimation of portal pressure would improve the predictive ability of the MELD score. Second, HVPG was included in a model with the MELD score variables to evaluate its prognostic calibrative and discriminative ability.

Patients and Methods

Study Population and Variable Description. A retrospective single-center cohort study was designed. All patients who underwent a hepatic hemodynamic study from January 1998 to December 2002 were recruited. The final population was composed of 393 patients with cirrhosis (Fig. 1). Patients were excluded due to previous TIPS placement (n = 21), advanced hepatocellular carcinoma (n = 21) according to the published criteria,[21] benign portal thrombosis (8 patients), severe extrahepatic comorbidity (n = 8), patients without cirrhosis (n = 173), and inability to catheterize hepatic veins (n = 7). Patients receiving beta-blocker therapy in whom this treatment was not discontinued at least 72 hours before hepatic hemodynamic study were excluded (n = 60). Follow-up continued until December 2003, so a minimum follow-up of 1 year was achieved.

Clinical variables regarding demographic data, cause of liver disease, indication of hepatic hemodynamic study, and the date of surgery in the case of liver transplantation recipients were collected. Variables used to calculate Child-Turcotte-Pugh score also were registered. Responsiveness to treatment was used to grade ascites (none/controlled with diuretic therapy/uncontrolled with diuretic therapy) and encephalopathy (none/easily controlled/difficultly controlled).

Biochemical variables to determine MELD score (creatinine, bilirubin, International Normalized Ratio [INR]) were collected. The closest possible determination was used with a maximum of 1-week difference between the hemodynamic evaluation and the blood test. Special care was taken particularly in critical patients to obtain the data from a blood test done the same day of the hemodynamic measurement.

Because of recent reports[22-24] emphasizing the role of serum sodium in survival prediction, we collected the data of serum sodium in a subgroup of patients (from June 2000 to December 2002) whose laboratory data were accessible.

Hepatic Hemodynamic Study. After an overnight fast, a vascular introducer sheath (Medikit Co. Ltd., Tokyo, Japan) was placed into the right internal jugular or femoral vein according to Seldinger's technique. Afterward, a 7-F balloon catheter (Cordis SA, Miami, FL) was placed into the right hepatic vein for the assessment of free and wedged hepatic venous pressures (FHVP and WHVP) as previously described.[25] The wedged position was confirmed by the absence of reflux after injection of 2 mL contrast medium, and FHVP was measured with the tip of the catheter less than 5 cm into the hepatic vein. The zero pressure level in the calibrated transducer was set in the mid-axillary line. The HVPG, which closely reflects the degree of portal hypertension in both, alcohol-induced or viral cirrhosis,[26,27] was calculated as WHVP minus FHVP. The normal value of HVPG ranges from 1 to 5 mmHg in our laboratory. All hemodynamic measurements were recorded and performed at least in duplicate.

Statistical Analysis. To evaluate the impact of HVPG on survival, a univariate Cox model was developed initially. Thereafter, a multivariate Cox model was developed to evaluate the effect of HVPG on survival, taking into account other possible survival-influencing variables: MELD score, ascites, encephalopathy, and age. One-way interactions between HVPG and the other co-

variates were tested. Assessment of proportional hazards was performed by including a time-dependent variable as appropriate. MELD score was introduced as a categorical variable as previously defined.[28] To precisely evaluate the impact of HVPG on survival, it was introduced as a continuous variable so that its hazard ratio represents the increase in the risk of death per 1-mmHg increase in HVPG.

Due to the inconvenience and possible bias introduced into the model by using subjective and retrospectively re-collected variables such as ascites and encephalopathy and as HVPG level is closely related to the presence of ascites, a second model was constructed with only MELD, age, and HVPG.

As Child-Turcotte-Pugh classification has been considered as a classical prognostic tool, the possible contribution of HVPG and age to the survival prediction of Child-Turcotte-Pugh was assessed by multivariate proportional hazards Cox regression model.

To evaluate the possible contribution of HVPG to the predictive ability of MELD score, a different modelling strategy was taken to develop a survival predictive model which includes individual MELD variables, HVPG, and age. Two aspects of predictive models were evaluated: calibrative and discriminative ability.[3,29] The former refers to the ability to predict survival in an individual patient, and the latter is the ability to rank patients according to their death risk, which is the mainstay for MELD score.[3] In this study, calibrative ability was assessed by comparing observed and estimated survival rates of the patients divided into 4 groups by categorizing the prognostic index into quartiles. The prognostic index was calculated in each patient by $\Sigma b_i x_i$; where b_i represents the coefficient of each variable in the Cox model and x_i represents the value of the variable in each individual.[30] Mean values of each variable in each prognostic index category were calculated; then estimation of survival rate based on the Cox model was performed for these mean values. Observed survival rates for each prognostic index category were calculated according to the Kaplan-Meier method. To assess discriminative ability, we applied the recently described overall C index,[29] which has been developed to measure discrimination in survival analysis instead of using the classical c statistic that quantifies the discriminative ability in the context of logistic regression, which evaluates a dichotomous outcome at a particular time point. This allows comparison of overall survival data instead of only using the information at a certain time point. This test is similar to the c statistic except that instead of evaluating concordance between observed and predicted probabilities, evaluation of concordance between observed and predicted time periods between two individuals is done. For instance, if the predicted time for individual A is greater than that for individual B and the observed time for individual A is greater than that for individual B, this pair is considered as concordant.

Because the use of individual MELD score variables with coefficients based on our own population could increase the predictive ability of these variables over that of MELD score itself in this sample, and might downgrade the predictive ability of HVPG on top of MELD, another model with original MELD score, age, and HVPG was developed. For all calculations, transplant recipients were censored at the time of liver transplantation.

Conventional Cox modeling assumes that censorship is done in a randomized fashion; however, censorship because of liver transplantation is not independent of the course of the disease. Nevertheless, liver transplantation is a clinically significant outcome, because when a patient undergoes a transplant, it is because life expectancy without this procedure is very short. Conversely, we could not consider these patients as deaths at the time of liver transplantation because we cannot have absolute certainty about whether and when the death would take place. In this case, a Cox competing risk model for survival analysis can be applied. In this model, one defines more than one event as possible outcomes, so that no relevant information is lost.[31]

To evaluate the possible influence of HVPG, taking into account serum sodium and MELD, Kaplan-Meier survival curves were constructed in three different previously defined MELD categories: below 15, between 15 and 24, over 24. This division had been previously reported because of its approximate coincidence with former UNOS status.[28] Patients were classified according to the presence of none, one, or both risk factors, which were serum sodium below 130 mEq/L[24] and HVPG above 20 mmHg. This level of HVPG was chosen for this particular analysis because it was the mean level of HVPG of the study sample.

Statistical significance was considered with a *P* value of .05 or less. Statistical analysis was done with SPSS version 12.0 (SPSS Inc., Chicago, IL) and R version 2.1.0. Approval of the local institutional review board was obtained.

Results

Baseline data of the patients are shown in Table 1. A total of 108 patients received liver transplant, and 112 patients died during follow-up.

The univariate Cox model showed that HVPG had a significant influence on survival (univariate HR, 1.05

Table 1. Baseline Characteristics of All Patients (n = 393) and Patients With Serum Sodium Data (n = 180)

	All Patients (n = 393)	Patients With Serum Sodium Data (n = 180)
Male/female, n (%)	300/93 (76.3/23.7)	137/43 (76.1/23.9)
Age, yrs	54 (11.56)	54.43 (11.49)
Cause of cirrhosis, n (%)		
OH	172 (43.8)	90 (50)
HVC	142 (36.1)	55 (29.4)
HVB	35 (8.9)	15 (8.4)
Metabolic	6 (1.5)	3 (1.7)
Cholestasis	22 (5.6)	8 (4.4)
Unknown	16 (4.1)	9 (5)
Ascites, n (%)		
No previous ascites	158 (40.2)	75 (41.7)
Responsive to diuretics	204 (51.9)	91 (50.6)
Not responsive to diuretics	31 (7.9)	14 (7.8)
Hepatic encephalopathy, n (%)		
No previous HE	305 (77.6)	141 (78.3)
Responsive to treatment	70 (17.8)	34 (18.9)
Not responsive to treatment	18 (4.6)	5 (2.8)
Presence of varices, n (%)		
No varices	52 (13.2)	25 (14)
Small varices	96 (24.4)	46 (25.7)
Large varices	177 (45)	70 (38.9)
Unknown	68 (17.3)	39 (21.8)
Previous variceal bleeding, n (%)	101 (25.7)	42 (23.3)
Previous clinical decompensation, n (%)	316 (80)	144 (80)
Bilirubin (mg/dL)	2 (0.3–37.3)	2.1 (0.3–37.3)
Creatinine (mg/dL)	0.98 (0.41)	0.9 (0.5–4.49)
INR	1.6 (0.59)	1.43 (0.91–5.13)
Albumin (g/dL)	3.06 (0.67)	2.98 (0.68)
Serum Na (mEq/mL)	–	134 (5.1)
HVPG*	19.65 (6.43)	19.18 (7.21)
HVPG <12 mmHg (%)	36 (9.2)	21 (11.7)
Beta-blocker treatment during follow-up, n (%)	96 (24.4)	47 (26.3)
MELD score	13.87 (6.4–44.59)	13.41 (6.4–44.6)
<15, n (%)	220 (56.2)	100 (55.6)
15–24, n (%)	132 (33.6)	58 (32.2)
>24, n (%)	41 (10.3)	22 (12.2)
Child-Turcotte-Pugh, n (%)		
A	113 (28.8)	47 (26.1)
B	174 (44.3)	77 (42.8)
C	106 (27)	56 (31.1)
Indication of hemodynamic study, n (%)		
Transjugular liver biopsy	116 (29.5)	56 (31.1)
Evaluation before liver transplant	115 (29.3)	56 (31.1)
Hepatocellular carcinoma	36 (9.2)	19 (11)
Acute variceal bleeding	73 (18.6)	41 (22.8)
Before beta-blocker therapy	45 (11.4)	2 (1)
Other indications	8 (2.1)	6 (3)
Follow-up time (mos)	19.33 (0.03–72.7)	15.88 (0.03–43)
Liver transplantation, n (%)	108 (27.5)	39 (21.6)
Death, n (%)	112 (28.5)	50 (27.8)

NOTE. Qualitative variables are expressed as absolute values and proportions. Continuous variables are expressed as mean (SD) or median (range) as appropriate.
*HVPG range, 3–50 mmHg.

[95% CI, 1.02-1.08]; $P = .001$); therefore, patients had a 5% increase in death risk with each 1-mmHg rise of HVPG.

The effect of HVPG on survival was maintained when the model was adjusted for other known predictors of survival, including MELD score (multivariate HR, 1.03 [95% CI, 1-1.06] $P = .05$) (Table 2). This implies that each 1-mmHg increase of HVPG produces a 3% increase in death risk so that a patient with 15 mmHg has a 30% increase in death risk compared with a patient with an HVPG value of 5 mmHg. No one-way interactions between HVPG and the other variables were observed. In the model evaluating the role of HVPG on survival with only MELD and age, HVPG also remained as an inde-

Table 2. Cox Proportional Hazards Models

Model and Variables	Hazard Ratio	95% CI	P
Model 1			
HVPG*	1.03	1.00–1.06	.05
MELD†			<.001
<15	1		
15–24	1.47	0.90–2.40	
>24	5.06	2.70–9.60	
Ascites†			.019
None	1		
Responsive	1.21	0.75–1.95	
Nonresponsive	2.72	1.36–5.46	
Encephalopathy†			.009
None	1		
Easily treated	1.14	0.67–1.94	
Difficulty treated	3.49	1.64–7.43	
Age*	1.05	1.03–1.07	<.001
Model 2			
HVPG*	1.04	1.01–1.07	.011
Age*	1.05	1.03–1.07	<.001
MELD score†			<.001
<15	1		
15–24	1.79	1.14–2.81	
>24	7.50	4.39–12.84	

NOTE. No one-way interactions were observed. Abbreviations: HR, hazard ratio; HVPG, hepatic venous pressure gradient.

*HVPG and age were introduced as a continuous variable.

†MELD less than 15, absence of ascites, and absence of encephalopathy were considered the reference category.

pendent predictor of survival (multivariate HR, 1.04 [95% CI, 1.01-1.07]; $P = .011$) (Table 2).

The multivariate Cox model introducing Child-Pugh classification, as well as HVPG and age, also demonstrated an independent predictive role for HVPG. (multivariate HR, 1.05 [95% CI, 1.02-1.08]; $P = .002$) (Table 3).

Because of recently published data emphasizing the role of serum sodium in survival, the role of HVPG taking into consideration the MELD score and serum sodium was evaluated in the previously mentioned subgroup of patients. Baseline characteristics of these patients can be seen in Table 1. A considerably lower survival rate was observed when both risk factors were present compared with those who had only one or none ($P < .001$) (Fig. 2).

When a Cox proportional hazards model was constructed with the variables that conform MELD score, age, and HVPG, no variable could be withdrawn without significantly changing the predictive capacity of the model (Table 4). Therefore, HVPG had a significant role in predicting survival rate as well as the variables that conform MELD score and age.

When the calibrative ability of a model including MELD score variables, age, and HVPG was assessed, a fairly good match between observed and estimated survival rates was observed (Fig. 3). This suggests that the use of HVPG and age may improve the MELD estimation of survival rate for a particular patient.

Conversely, the addition of HVPG and age did not improve the discriminative ability of the MELD score. A similar value of overall C statistic was observed in the models that included only MELD variables, MELD variables and age, and lastly MELD variables, age, and HVPG. Nevertheless, a trend toward a greater overall C in the model that incorporated HVPG was seen (Table 5). When the calculations were repeated using MELD with its original coefficients instead of the MELD variables with coefficients adjusted to our sample, similar results were observed so that only a trend toward a greater overall C was observed when HVPG was incorporated into the model (Table 5).

Competing risks model confirmed the influence of HVPG on survival. In this case, hazard ratio expresses the risk of developing one or the other endpoint (death or liver transplantation) so that each mmHg increase in HVPG had a 2% increase in the risk of death or undergoing liver transplantation (Table 6).

Discussion

This large retrospective cohort study was designed to evaluate the prognostic influence of portal pressure measurement on survival of patients with cirrhosis. The first aim of our study was to evaluate the possible influence of HVPG in survival, taking into account MELD score because it is one of the most widely used prognostic tools. Interestingly, a multivariate Cox model showed that the HVPG value independently influences survival, in addition to the MELD score. One of the major concerns regarding the statistical management of a variable is to define the cutoff values for the modeling process. Although the use of HVPG as a continuous variable may allow more precise modeling and therefore was used in the current study, one may speculate that there may not be a linear relationship between HVPG and survival. In this study, other mathematical relationships between HVPG and survival were explored without better estimation of

Table 3. Cox Proportional Hazards Model

Variables	HR	95% CI	P
HVPG*	1.05	1.02–1.08	.001
Child-Turcotte-Pugh classification†			<.001
A	1		
B	1.15	0.69–1.92	
C	4.25	2.57–7.04	
Age*	1.05	1.03–1.07	<.001

*HVPG and age were introduced as a continuous variable.

†Grade A of Child-Turcotte-Pugh classification was considered as the reference category.

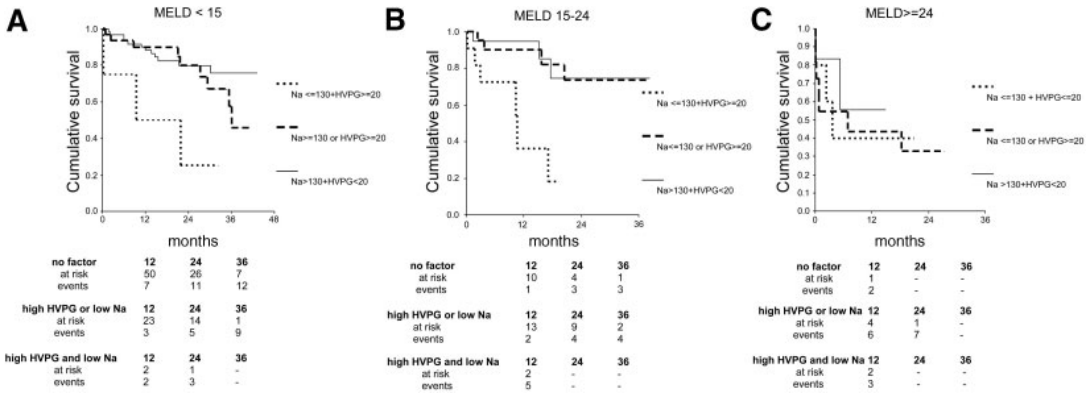

Fig. 2. Survival curves within each MELD strata of patients with normal serum Na and HVPG below 20, low serum Na or high HVPG, and both low serum sodium and high HVPG. Breslow test = 16.01; $P < .001$.

survival prediction. However, the existence of threshold values of HVPG that determine two different outcomes in different clinical settings is well known.[8-11,13,14,32,33]

The influence of HVPG on survival is not surprising from a pathophysiological point of view, because it had already been indirectly suggested by previous studies.[7] In fact, HVPG has been considered as a relevant factor in most complications of advanced liver disease.[8-14] Conversely, a growing body of evidence underlines the importance of hyponatremia in survival prediction.[22-24] Even when considering hyponatremia in the available population, we observed that HVPG still had a significant role in survival. In addition, we observed a particularly ominous prognosis in those patients who had both hyponatremia and an HVPG value greater than 20 mmHg, although these data should be cautiously interpreted because of the small number of patients in this analysis. These findings are clearly related to the previously described influence of other manifestations of portal hypertension complications such as the presence of hepatorenal syndrome, which have been recognized as predictors of survival, in addition to MELD score,[34] emphasizing the relationship between survival and portal hypertensive manifestations. Initially, portal hypertensive manifestations were included in the model because they are recognized factors that influence survival. However, in this study, retrospective evaluation of subjective variables such as ascites and encephalopathy is difficult, and information withdrawn from ascites may be, at least partially, redundant to the information provided by HVPG. For these reasons, a model without these variables was constructed, reinforcing the prognostic influence of HVPG. Interestingly, HVPG had an independent predictive value when considering Child-Pugh classification and age as covariates, and although this result was expected, because most of the variables included in Child-Pugh classification were included in the first model, the contribution of HVPG to this classical prognostic index reinforces the role of HVPG in survival prediction. Prospective evaluation of the influence of portal hypertensive-related complications as well as HVPG in survival of patients with advanced liver disease is, therefore, warranted.

The second aim of our study was to evaluate whether portal pressure measurements significantly improve the

Table 4. Cox Proportional Hazards Model

Variable	HR	95% CI	P
LnBi	1.43	1.09–1.87	.01
LnCr	14.94	7.23–30.89	<.001
LnINR	3.89	1.78–8.51	<.001
Age*	1.05	1.03–1.07	<.001
HVPG*	1.03	1.0–1.06	.043

NOTE. A predictive model was developed with MELD score variables, with coefficients estimated from the study population as well as age and HVPG.

*Age and HVPG were introduced as a continuous variable.

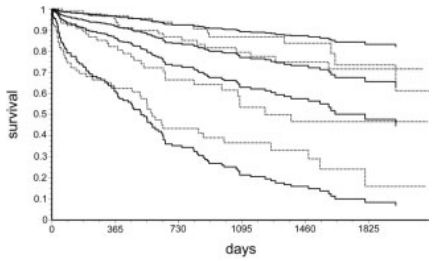

Fig. 3. Evaluation of calibrative ability of the model, including MELD variables, age, and HVPG. Observed (continuous line) and estimated (dotted line) survival rates of the patients divided into 4 groups according to their prognostic index (see Patients and Methods).

Table 5. Overall C-Statistic for Each Cox Predictive Model

Variables in the Model	Overall C-Statistic	95% CI
LnBi, LnCr, LnINR	0.71	0.62-0.80
LnBi, LnCr, LnINR, age	0.76	0.68-0.83
LnBi, LnCr, LnINR, age, HVPG	0.76	0.69-0.84
MELD	0.70	0.62-0.79
MELD, age	0.76	0.68-0.83
MELD, age, HVPG	0.76	0.68-0.84

NOTE. No significant difference in discriminative ability was observed by adding age or HVPG to MELD score variables. When calculations were repeated with original MELD, similar results were observed.

predictive ability of MELD score. A considerable amount of confusion has been created when regarding the predictive ability of MELD score, it has been determined as a good tool to rank patients according to their death risk for organ allocation, but this is not the same faculty as determining the survival rate for an individual patient, which is defined by the calibrative ability.[3,7] In the Cox regression model we constructed, all variables contributed significantly to the calibrative ability, allowing us to predict survival time more correctly. However, the model was obtained with all of the possible observations collected from patients from only one center. Therefore, further confirmation of our results should be done in other representative cohorts of patients from different institutions to evaluate the validity of this predictive model.

The second important characteristic of a predictive model is its discriminative ability. In this case, the aim of the model is not to predict the most exact time period but to have the patients properly ordered. The discriminative ability of MELD score for the prediction of 90-day mortality obtained from estimations of c statistics from a logistic regression model has been clearly established.[2] However, the use of information provided from survival analysis is much more attractive[29] than logistic regression, which only evaluates a dichotomous outcome at a determined moment. This approach means that all incomplete observations or possible outcomes beyond this time are not taken into consideration for the analysis. Conversely, survival analysis contemplates possible incomplete observations so no possible information is lost; this allows a much more thorough use of the available data. For this reason, we used for discriminative ability analysis the overall C statistic,[29] with a previously proven validity.[35] When this approach was used, a trend toward improvement of the discriminative ability when adding HVPG and age to the variables of MELD score was observed, suggesting that these two variables could be included. Even though from a statistical viewpoint, inclusion of variables with their own coefficients provides a more accurate estimation of survival, this might overestimate the predictive ability of MELD score variables and may downgrade the predictive ability of HVPG. However, when the calculations were repeated with the original MELD score, similar results concerning the predictive ability of HVPG were obtained.

Another interesting issue when considering survival in end-stage liver cirrhosis is the possibility that more than one possible outcome could be relevant, which is clearly the case when considering liver transplantation. In addition, one of the assumptions of the extensively used Cox regression model is that right censoring occurs randomly. However, this is not the case when considering censoring for patients who received liver transplantation. For this reason, we developed a competing risk model in which each failure mechanism (*i.e.,* death or liver transplantation) proceeds independently from the other and therefore allows a more accurate extraction of information from the set of patients. Interestingly, when the competing risk model was applied, HVPG remained as an important predictor of survival or need of liver transplantation.

Several limitations to our study should be analyzed. Initially, the retrospective nature could be considered a drawback; however, the careful procedure used for HVPG measurement and for the recollection of biochemical variables limits the possibility of bias. Moreover, the study population represents the total number of patients who received hemodynamic measurements during the study period, a procedure commonly used in our institution for evaluation of patients with end-stage liver disease.

Two clinical contexts exist in cirrhosis, with clearly different prognoses.[36] Once a patient passes from a compensated to decompensated state, predicted survival rate is shortened. In our study population, 81% of patients had a previous history of clinical decompensation, so the results of this study suggest that HVPG is important for survival rate prediction in decompensated disease; however, this aspect should be confirmed in further studies.

An important drawback for the use of HVPG for survival rate prediction is the fact that this measurement is not done as easily as a biochemical determination, with

Table 6. Results of Cox Proportional Hazards Model, Applying a Competing Risk Model Strategy (Multistate Model Stratified by Relevant Outcomes)

Variable	HR	95% CI
Age*	1.02	1.01-1.03
LnCr	8.51	5.1-14.2
LnINR	1.64	0.881-3.06
LnBi	1.53	1.25-1.87
HVPG*	1.02	1.00-1.04

*Age and HPVG were introduced as a continuous variable.

two consequences. First, HVPG is not an easily accessible technique in many centers, and second, it is more difficult to do repeat determinations of HVPG.

Another interesting potential limitation is that HPVG is a dynamic parameter that changes after pharmacological therapy or after alcoholic abstinence, with clearly defined benefits on survival.[10,14,18] For this reason, patients receiving beta-blocker therapy at the moment of the hemodynamic measurements were excluded from the analysis because baseline portal pressure cannot be determined. Sensitivity analysis was done, excluding patients who had acute alcoholic hepatitis in whom HVPG values are greater than in other conditions[37] without significant differences (HVPG HR, 1.06; 95% CI, 1.02-1.09; $P = .02$). Finally, we evaluated the effect of a reduction of HVPG of 20% or to a value below the 12-mmHg threshold in those patients who had a second hemodynamic study. From the 75 patients who had a second hemodynamic study, almost one third (24 patients) had obtained this relevant hemodynamic objective. However, this is only 6% of the total sample, so it is unlikely that this data could influence our model. In fact, a sensitivity analysis excluding these patients did not change the estimation of the effect of HVPG (HR, 1.04; 95% CI, 1.01-1.07; $P = .005$).

In conclusion, the results of this large study suggest that HVPG has independent influence on survival in a model adjusted for MELD, age, ascites, and encephalopathy. Conversely, when evaluating its contribution in a predictive model, addition of HVPG and age improve the calibrative ability, allowing better prediction of survival for an individual patient. However, when including HVPG in model with MELD variables, the discriminative ability is only slightly improved. Further studies are needed to validate and confirm these results.

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MELD score has been used to allocate organs since 2002 in the USA as it offers several advantages over Child-Pugh score such as objectivity and the lack of a ceiling effect. However it was initially developed to predict mortality after TIPS placement. In this model, no variable associated to portal hypertension is included. However portal hypertension is the underlying pathophysiological mechanism behind complications of liver disease and can be estimated by the measurement of the hepatic venous pressure gradient. Inclusion of the hepatic venous pressure gradient in the MELD score may offer advantages as it would include portal hypertension in the model, without losing the advantages of MELD score (objectivity, no ceiling effect).

Aims: The aim of this study was to evaluate the impact of HVPG on survival in patients with cirrhosis in addition to the Model for End- Stage Liver Disease (MELD) score. We also examined whether inclusion of HVPG in a model with MELD variables improves its prognostic ability, that is the discriminative (ability to order according to risk) and callibrative (ability to predict for an individual patient) capacity.

Methods: Retrospective analyses of all patients who had HVPG measurements between January 1998 and December 2002 were considered. Proportional hazards Cox models were developed. Prognostic discriminative ability was evaluated with the c-statistic. The calibrative ability was assessed by comparing observed and estimated survival rates of the patients divided into 4 groups by categorizing a prognostic index into quartiles.

Results: In this period, 693 patients had a hepatic hemodynamic study, and 393 fulfilled the inclusion and exclusion criteria. Most patients (80%) had previous clinical decompensation. During the follow-up a total of 108 patients received liver transplant, and 112 patients died. Survival was significantly worse in those patients with greater HVPG value (univariate HR, 1.05; 95% CI, 1.02-1.08; P<0.001). HVPG remained as an

independent variable in a model adjusted by MELD, ascites, encephalopathy, and age (multivariate HR, 1.03; 95% CI, 1.00-1.06; P< 0.05). In addition, HVPG as well as MELD score variables and age, significantly contributes to the calibrative predictive capacity of the prognostic model; however, discriminative ability improved only slightly with the addition of HVPG to MELD score (overall C statistic [95% CI]; MELD score variables: 0.71 [0.62-0.80], MELD score variables, age, and HVPG 0.76: [0.69-0.83]).

Conclusions: HVPG has an independent effect on survival when taking into account the MELD score. Although inclusion of HVPG and age in a survival predicting model would improve the calibrative ability of MELD, its discriminative ability is not significantly improved.

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ORIGINAL ARTICLE

Comparison of MELD, HVPG, and their changes to predict clinically relevant endpoints in cirrhosis

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Abstract

Aim. Identification of predictors in the natural history of cirrhosis is based on determinations at a fixed time point. However, changes of these predictors may offer more information. To evaluate the predictive value of Model for End Stage Liver Disease (MELD) and hepatic venous pressure gradient (HVPG) and their changes in cirrhosis. ***Methods.*** Patients with repeat HVPG measurements between January 2000 and December 2008 were considered for inclusion. Patients were followed until decompensation/death or July 2009. Multivariate Cox regression was used to analyze the predictive value of a single measurement of MELD and HVPG, and changes between measurements. Compensated and decompensated patients were analyzed separately. ***Results.*** One hundred and seventeen patients were included (51 compensated, 66 decompensated). Median time between measurements and follow-up was 13 (2–24) and 11 (6–38) months in compensated and 8 (1–16) and 10 (3–21) months in decompensated patients, respectively. Fifteen compensated patients developed decompensation while twelve decompensated patients died. On multivariate analysis, MELD (HR 1.12 (95% CI 1–1.24)) and HVPG (HR 1.16 (95% CI 1.04–1.29)) were independent predictors of decompensation in compensated, while MELD (HR 1.18 (95% CI 1.09–1.27)) was the only predictor of death in the decompensated. ***Conclusion.*** Single and repeat measurements of MELD and HVPG are associated to outcomes in cirrhosis. Use of repeat measurements does not seem to add further information.

Key Words: *death, decompensation, repeat measurements*

Introduction

Relevance of distinguishing between the compensated and the decompensated phases in the natural history of cirrhosis has been underlined. Patients in the compensated phase have a good prognosis in the long term while decompensated patients (previous history of variceal bleeding, ascites, hepatic encephalopathy or jaundice) have a poor prognosis in the medium term [1]. As most compensated patients develop decompensation before death, it has been suggested that the clinically relevant endpoint to predict in compensated patients is decompensation, while in decompensated patients the clinically relevant endpoint is death.

Many studies have identified predictors of decompensation and/or death in compensated or decompensated cirrhosis [1]. Most studies focus on a fixed baseline determination and then follow patients. Fewer studies have evaluated the predictive value of changes of these variables, which offers a more dynamic view of the disease. Some of the most important prognostic variables in cirrhosis are hepatic venous pressure gradient (HVPG) and Model for End Stage Liver Disease (MELD) score.

Single measurements of HVPG offer prognostic information regarding the incidence of varices [2,3], bleeding [3], decompensation [4], and death [5]. Repeat measurements of HVPG have also shown to have prognostic relevance. Patients who have a

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reduction of HVPG evaluated dichotomically (presence of a reduction of HVPG below 12 mmHg or at least 20% from baseline) are protected from bleeding and death during follow-up [6,7]. The prognostic information derived from increases of HVPG, defined again dichotomically (increase of at least 10%), has been evaluated in one study showing an association with an increase incidence of varices [2]. However, no study has been specifically aimed at evaluating the prognostic information that can be derived from overall quantitative changes of HVPG, nor whether the information derived from changes of HVPG offers more information than what is already offered by a single measurement.

MELD score has been used since 2002 in the US to classify patients on the liver transplant (LT) waiting list [8]. Afterward, several studies that studied the prognostic information that can be derived from changes in MELD score in LT recipients [9,10] and cirrhotic patients [11–13] have led to controversial results. Although all studies suggest that changes in MELD are predictive of death, there is controversy regarding whether or not changes of MELD offer more information than a single measurement.

Therefore, the aim of the study was to evaluate the ability of MELD, HVPG, and changes of these variables to predict clinically relevant endpoints in compensated and decompensated cirrhosis. Specifically, we evaluated whether or not repeat measurements add significant information to single measurements.

Methods

This is a retrospective, single-center observational study. All patients who underwent repeat HVPG measurement in a tertiary health-care center from January 2000 to December 2008 were considered for inclusion. Patients without cirrhosis, LT recipients or transjugular intrahepatic portosystemic shunt (TIPS) patients, non-sinusoidal portal hypertension, cholestatic liver diseases, hepatocellular carcinoma beyond Milan criteria, and severe comorbidities were excluded (see Figure 1). The final study population was composed of all patients with cirrhosis who had repeat HVPG measurements without any exclusion criteria. Indications for hemodynamic study include transjugular liver biopsy, evaluation of changes of HVPG to drug therapy, evaluation of HVPG in the context of hepatocellular carcinoma treatment, and routine LT candidate evaluation. Repeat measurements were performed in the context of evaluation of HVPG response to drug therapy or in the context of the patient management according to the natural history of the disease.

Demographic data, etiology of liver disease, previous decompensation (variceal bleeding, ascites, and hepatic encephalopathy), and HIV infection were recorded. Presence of varices, treatment with beta blockers, alcohol consumption, antiviral therapy, and hepatocellular carcinoma as well as ascites and encephalopathy at the time of the first and second hemodynamic studies were registered. Laboratory data including red blood cell, platelets, and white blood cell counts, AST, ALT, serum sodium, and the necessary variables to calculate MELD and Child-Pugh score were compiled.

Hepatic hemodynamic study

After an overnight fast, a vascular introducer sheath *(Medikit Co Ltd. Tokyo, Japan)* was placed into the right internal jugular or femoral vein according to Seldinger's technique. Afterward, a 7 F balloon catheter *(Cordis SA, Miami, Florida)* was placed into the right hepatic vein for the assessment of free and wedged hepatic venous pressures (FHVP and WHVP) as previously described [14]. The wedged position was confirmed by the absence of reflux after injection of 2 ml of contrast medium, and FHVP was measured with the tip of the catheter less than 5 cm into the hepatic vein. The zero-pressure level in the calibrated transducer was set in the mid-axillary line. The HVPG is an estimation of portal pressure in cirrhosis and is calculated as WHVP minus FHVP. The normal value of HVPG ranges from 1 to 5 mmHg in our laboratory. All hemodynamic measurements were recorded and performed at least in duplicate.

Follow-up

Patients were divided into compensated and decompensated patients according to the presence of decompensation at the time of the first hemodynamic study. Development of decompensation between the first and the second hemodynamic study was recorded. These patients were excluded from further analysis. For the purpose of this study, the baseline moment from which the patients were followed was the moment of the second hemodynamic study. Compensated patients were followed up until decompensation, TIPS placement, liver transplantation, and/or death. Decompensated patients were followed up until TIPS placement, liver transplantation, and/or death. Development of hepatocellular carcinoma during follow-up was also registered [15]. For this study, the relevant endpoint for compensated patients was the development of decompensation. If any other endpoint (LT, TIPS placement, or death) was reached without previous decompensation, the patient was censored at that time. The relevant endpoint for decompensated

patients was death. Similarly, if any of the other endpoints (LT or TIPS placement) were reached before death, patients were censored at the time of reaching these other endpoints. Patients were followed up until July 2009.

Statistical analysis

Data were processed in *SPSS* version 15.0. Data are expressed as percentages or medians (interquartillic range, IQR). The changes between measurements were calculated: second HVPG or MELD minus first HVPG or MELD respectively. In this sense, patients who had an increase in these variables had positive values, while those who had a decrease had negative values. Univariate Cox regression was used to analyze the predictive value of a single measurement of MELD, HVPG, Child–Pugh, albumin, creatinine, INR, bilirubin, and sodium at basal moment and relative changes between measurements. Multivariate stepwise Cox regression analysis was used in order to evaluate the independent predictive information obtained from MELD, HVPG, and the changes of these variables. In order to overcome the common problem of overfitting, several models including different combinations of the four variables were constructed maintaining at least five events per variable included. ROC curves were constructed in order to evaluate the discriminative ability of baseline HVPG and MELD and changes in HVPG and MELD (MedCalc statistical software (version 11.3)). Cutoff points were calculated taking into account an a priori assumption that a false negative (predicting that the patient would not die or would not decompensate and being wrong) was more costly than a false positive (predicting that a patient would die or would decompensate and then being wrong). Compensated and decompensated patients were analyzed separately. Taking into account that beta-blocker therapy and the time between the two hemodynamic studies could influence the results, separate analysis taking into account these variables was performed. STROBE guidelines for reporting observational studies were followed [16]. Approval by the local IRB was obtained. The study was performed in accordance with the guidelines of the Helsinki Declaration.

Results

During the study period, 414 patients had repeat HVPG measurements. From these 414 patients, finally 117 patients were included (Figure 1). Most of the excluded patients with repeat HVPG measurements were LT patients or patients without cirrhosis ($n = 142$). From the 117 included patients, 51 patients were in the compensated phase and 66 patients were in the decompensated phase of the disease. Baseline characteristics of these patients are described in Table I. Compensated patients who developed decompensation before a second hemodynamic study were excluded as changes in the parameters could be more a consequence of the natural history of the disease than a predictor of relevant events (Figure 1, $n = 48$). Expected differences between compensated and decompensated patients were observed regarding liver function. Furthermore, there was a higher proportion of compensated patients with hepatocellular carcinoma. The median time between measurements was 13 (2–24)

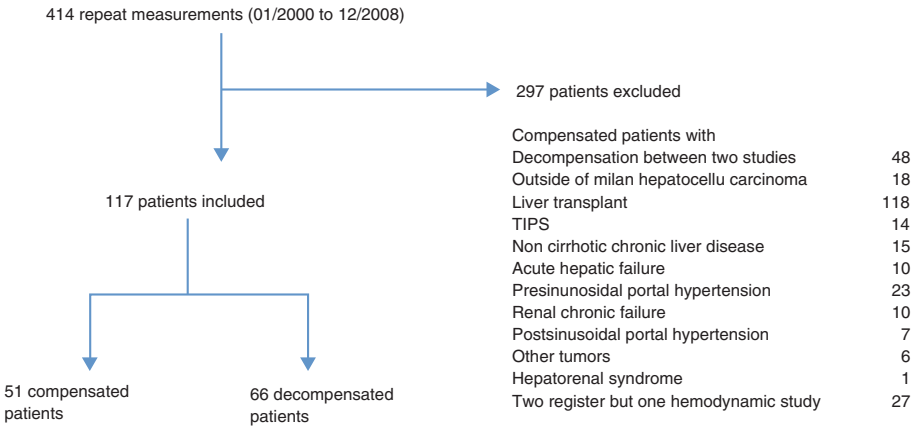

Figure 1. Flow chart of patients with repeat measurements included in the study.

Table I. Baseline characteristics of all patients.

	All patients (N = 117)	Compensated patients (N = 51)	Decompensated patients (N = 66)	p Value
Age	50 (8)	48 (9)	52 (7)	0.097
Male sex (%)	92 (79)	42 (82)	50 (76)	0.496
Etiology of liver disease (%)				0.035
Alcohol	35 (30)	12 (24)	23 (35)	
HCV	66 (56)	35 (69)	31 (47)	
HBV	7 (6)	2 (4)	5 (8)	
Others	9 (8)	2 (4)	7 (11)	
HIV infection (%)	8 (7)	3 (6)	5 (6)	1.0
Previous decompensation n (%)				
Ascites	50 (76)	NA	50 (76)	NA
Hepatic encephalopathy	9 (14)		9 (14)	
Variceal bleeding	32 (48)		32 (48)	
Presence of varices (%)	56 (48)	12 (24)	44 (67)	< 0.001
Presence of hepatocellular carcinoma (%)	21 (18)	15 (29)	6 (9)	< 0.010
Beta blockers n/N (%)*	69/107 (63)	24/48 (50)	45/62 (73)	0.018
HVPG (mmHg)	17 (7)	14 (5.5)	19 (6.5)	< 0.001
Delta HVPG				
Absolute (mmHg)	−1 (−4–(+2))	−1 (−4–(+2))	−2 (−4–(+2))	0.878
Relative (%)	−7.5 (−23–(+12.5))	−7 (−28–(10))	−7.5 (−21.5–(13.5))	0.672
MELD	13 (7)	9 (8–11)	12 (9–18)	0.002
Delta MELD				
Absolute	−0.5 (−2–(+1))	−0.5 (−2.5–(0.5))	0 (−1.5–(2))	0.112
Relative (%)	−4 (−17–(+14.5))	−6 (−20–(5.5))	0 (−13.5–(15.5))	0.129
Bilirubin (mg/dL)	1.6 (0.9–2.8)	1.4 (0.8–2.2)	1.3 (1.8–3.6)	< 0.029
Creatinine (mg/dL)	0.8 (0.7–1)	0.8 (0.7–0.9)	0.8 (0.7–1)	0.307
INR (IU)	1.19 (1.08–1.43)	1.10 (1.01–1.23)	1.28 (1.13–1.61)	< 0.001
albumin (g/dL)	3.6 (0.7)	3.9 (0.5)	3.4 (0.7)	< 0.001
GOT (IU/L)	54 (35–87)	55 (31–99)	54 (37–82)	0.868
GPT (IU/L)	40 (27–76)	50 (27–92)	33 (27–52)	0.045
Serum sodium (mmol/L)	137 (5)	138 (4)	136 (5)	0.042
Time between measurements (days)	327 (54–671)	396 (87–726)	255 (51–478)	0.264

Baseline characteristics of patients included in the study. Parametric variables are expressed as means (standard deviation) and non-parametric variables are expressed as medians (interquartillic range). Categorical variables are presented as absolute values (percentage). Delta HVPG and delta MELD are the changes between baseline and the previous measurement. They are calculated by subtracting the baseline from the previous, so that increases are positive and decreases are negative. As expected, significant differences between compensated and decompensated patients were observed.
*7 patients had missing data regarding beta-blocker therapy.
HVPG = hepatic venous pressure gradient; MELD = Model for End Stage Liver Disease.

months in compensated and 8 (1–16) months in the decompensated patients (Table I).

Patients were followed up for a median of 11 (6–38) and 10 (3–21) months in compensated and decompensated patients respectively. During the follow-up, 15 compensated patients developed their first decompensation (11 ascites, 6 variceal bleeds, 6 hepatic encephalopathies), while 12 decompensated patients died.

On univariate analysis, MELD and HVPG and the changes of these variables were associated with the endpoint in each group (Table II). On multivariate analysis, MELD (HR 1.12 (95% CI 1–1.24)) and HVPG (HR 1.16 (95% CI 1.04–1.29)) were independent predictors of decompensation in compensated, while MELD (HR 1.18 (95% CI 1.09–1.27)) was the only predictor of death in the decompensated patients. Interestingly, the changes in MELD and HVPG were not identified as independent predictors on multivariate analysis.

In order to further evaluate the discriminative ability of MELD, HVPG, and the changes of these variables, ROC curves were calculated and compared. In compensated patients, HVPG was the variable with the greatest discriminative ability to identify patients who would decompensate during follow-up (c-statistic (95% CI) 0.792 (0.655–0.893)). However, in decompensated patients, MELD score had the greatest area under the curve (c-statistic (95% CI) 0.679 (0.549–0.792)). Although the small sample size precluded withdrawing statistically significant results between groups regarding all variables, it is

Table II. Univariate and multivariate Cox regression analysis.

	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Predictors of decompensation (in compensated patients)				
HVPG	1.18	1.07–1.3	1.16	1.04–1.29
MELD	1.18	1.08–1.3	1.12	1–1.24
Delta HVPG	1.07	0.95–1.2	-	-
Delta MELD	0.92	0.81–1.05	-	-
Predictors of death (in decompensated patients)				
HVPG	1.10	1.05–1.16	-	-
MELD	1.14	1.1–1.2	1.18	1.09–1.27
Delta HVPG	1.11	1.04–1.18	-	-
Delta MELD	1.11	1.03–1.21	-	-

Univariate and multivariate Cox regression analysis. Delta HVPG and delta MELD are the changes between baseline and the previous measurement. They are calculated by subtracting the baseline from the previous, so that increases are positive and decreases are negative. HVPG = hepatic venous pressure gradient; MELD = Model for End Stage Liver Disease.

to be noted that in compensated patients, the area under the curve was significantly greater for single HVPG compared with change in HVPG (c-statistic (95% CI) 0.600 (0.448–0.738)) to predict decompensation ($p = 0.027$).

Cutoffs of HVPG and MELD were searched in order to identify the best predictor of decompensation and/or death during follow-up. Among compensated and similarly to previously published data, 10 mmHg had over a 90% negative predictive value (94%, (95% CI 70–100)), meaning that patients with HVPG values below this value were highly unlikely to decompensate in this study with a median follow-up of 11 months. Similarly, a cutoff of 10 points of MELD was identified as the best with a high positive (53% (95% CI 30–76%)) and negative predictive value (87% (95% CI 70–96%)). In decompensated, both higher values of HVPG (16.5 mmHg, PPV 23% (95% CI 12–37); NPV 94% (95% CI 73–100)) and MELD (12, PPV 33% (95% CI 17–53); NPV 94% (95% CI 80–99)) were identified.

Relative changes of HVPG were divided into three groups according to the presence of a reduction greater than 10%, an increase greater than 10%, or not one or the other (no change). Among the compensated patients, there was a nonsignificant trend to a greater incidence of decompensation in those patients who had an increase greater than 10% than those without this increase (decompensation among ≥10% increase: 6/13, ≥10% reduction: 5/22, no change 4/15). In a similar fashion, in decompensated patients, a nonsignificant trend to a greater proportion of death was observed in those patients with a ≥10% increase (5/19) or no change (3/16) than those who had a ≥10% reduction (4/31).

Evaluation as to whether the timing between measurements influenced the results was done. In order to evaluate this aspect, a sensitivity analysis in patients in whom there was no delay between the first and the second study (<120 days; $n = 39$) was performed. In this analysis, similar results were observed, in the sense that in compensated patients single HVPG (HR 1.31 (1.04–1.65)) and the changes in HVPG (HR 1.12 (0.97–1.3)) had prognostic significance while in decompensated patients only the changes in MELD were significant (HR 1.3 (0.96–2.1)). Unfortunately, the small sample size precluded further multivariate analysis.

Sixty-three percent of patients (66/110, 7 patients had no information) were using beta blockers at the time of the second hemodynamic study. The characteristics of these patients are shown in Table III. From these patients, 41 patients had initiated beta-blocker therapy between the first and the second hemodynamic study. Patients who had initiated beta blockers had a greater, although nonsignificant, probability of having a reduction of HVPG of at least 10% (54 vs. 42%). The initiation of beta blockers between the first and second study was not associated with the development of the endpoint.

Discussion

The prognostic information derived from baseline and repeat measurements of HVPG and MELD was evaluated, particularly whether repeat measurements could provide more information to predict relevant events than baseline values. Our data confirm previous data regarding the prognostic value of changes in HVPG, single HVPG measurement, changes in MELD, and single MELD measurement [1,4–7,9,17]. Furthermore, as previous studies have

Table III. Characteristics of patients with beta-blocker therapy.

	All patients (n = 110)	Compensated patients (n = 48)	Decompensated patients (n = 62)
Beta-blocker therapy (%)	69 (63%)	24 (50)	45 (73)
Dose (mg/d)*	100 (70–150)	120 (80–160)	80 (60–140)
HVPG (mmHg)	18 (15.5–21.5)	16.5 (13–19)	18.5 (16.5–21.5)
Delta HVPG			
Absolute (mmHg)	−2.5 (−5–(2))	−1.5 (−5-(+0.5))	−3 (−5–(2.5))
Relative (%)	−9.5 (−23–(13.5))	−7.5 (−29.5–(+3))	−11.5 (-23–(+14))
MELD	11 (8–15.5)	10 (8–13)	12 (8.5–17)
Delta MELD			
Absolute	−0.5 (−1.5–(1))	−0.5 (−2–(0))	0 (−1.5–(2))
Relative (%)	−4 (−16.5–(14.5))	−6.5 (−17–(2.5))	−1 (−12.5–(17.5))
Patients who started beta-blocker therapy between the two HD studies (%)	41 (59)	18 (75)	23 (51)
HVPG in patients who started between the two HD studies (mmHg)	17.5 (14–21)	17 (13–19)	18 (15.5–21.5)
Delta HVPG in patient who started BB between the two HD studies			
Absolute	−2.5 (−5–(+1.5))	−2 (−5-(0))	−3 (−5–(3.5))
Relative	−12.5 (−23–(+8.5))	−10 (−22-(0))	−14.5 (−23–(15))

BB = beta blocker; HD = hemodynamic; HVPG = hepatic venous pressure gradient; MELD = Model for End Stage Liver Disease.

suggested, HVPG plays a predominant role in the prediction of decompensation in compensated patients, while in decompensated patients MELD acquires greater relevance [1,4,5]. Finally, it is interesting to underline that the estimated HR for HVPG in the prediction of clinical decompensation is similar to the previously reported in compensated patients [4] remarking the consistency of the results.

However, although changes in HVPG and MELD were predictive of clinically relevant outcomes on univariate analysis, on multivariate analysis these variables were not independently associated to the outcome. Therefore, the change did not seem to add further information to the information provided by the single measurement in predicting the outcome.

Previous studies have evaluated whether the changes in MELD (delta MELD) could improve survival prediction in patients on the LT waiting list. Although an initial study suggested that there could be some benefit of delta MELD over a single measurement of MELD [9], another study [10] showed that other aspects could influence these previous findings, such as the time period between the moment in which the change was detected and death. If the time period was short, these changes were not predictive of, but part of, the death process itself. Interestingly, when the cases with deaths that took place shortly (i.e., within 2 weeks) after the blood sample extraction were not considered, the advantages offered by the delta MELD were no longer observed [10].

Reduction of HVPG secondary to pharmacological treatment leads to a decrease in the incidence of variceal bleed and death [6,7]. A threshold value of reduction of HVPG has been identified. Patients who achieve a reduction of HVPG under 12 mmHg or a 20% reduction from baseline have almost complete protection from the development of bleeding during follow-up. A recent study has suggested that perhaps a 10% reduction of HVPG secondary to pharmacological therapy could be enough to confer protection regarding first bleed in the setting of primary prophylaxis [18]. These studies have several aspects in common. Firstly, a threshold value of HVPG decrease was identified, and the variable was categorized. Secondly, the independent effect of the changes of HVPG in the prediction of relevant outcome was not evaluated taking into account the baseline value of HVPG in most studies. The only study that evaluated both variables in a multivariate analysis observed that baseline HVPG and hemodynamic response according to the traditional definition were independent predictors of clinical decompensation during follow-up in the subset of compensated patients with portal hypertension although without varices at baseline who had a second HVPG, 1 year after the baseline measurement [4].

In the present study, the changes of HVPG and MELD were introduced in the models as continuous variables in an attempt to evaluate whether increases of these variables could be of prognostic value. Due to the fact that nonsignificant variations of the variables, particularly HVPG, could influence the results, the variables were categorized into three groups: those patients with no change, those with an increase, and those with a decrease. In this context, a trend toward a

greater incidence of decompensation in the compensated patients and death in the decompensated patients was observed among those patients with increases of HVPG. This is in agreement with a previous report of an increased incidence of varices in compensated patients with portal hypertension at baseline with at least a 10% increase in HVPG [2].

The study has several limitations. Firstly, data have been collected retrospectively. All patients who had at least two hemodynamic measurements were included. Possibly there could be a selection bias due to the simple fact that there were clinical reasons why the patients underwent the hemodynamic studies. In fact, there is a greater proportion of hepatocellular carcinoma among patients with compensated disease, although all cases of hepatocellular carcinoma were within the Milan criteria. However, analysis of the indications of the hemodynamic studies revealed that these were not only performed due to worsening disease (data not shown). In the same way, although it is possible to quantify the number of compensated patients who achieve the endpoint before the second hemodynamic study and to analyze their baseline characteristics, it is impossible to quantify the number of decompensated patients who died between a first hemodynamic and a hypothetical second hemodynamic study. Another possible source of bias is the time between the hemodynamic studies. Recent meta-analysis [6] that analyzed the prognostic value of the traditionally defined hemodynamic response showed that the controversial results that one study threw on this topic was most likely due to the long time period between the measurements and therefore they recommended that in order to withdraw relevant information from HVPG in the setting of prophylaxis with beta blockers, one must do the repeat measurement within a short period of time, preferably as soon as beta blockers are titrated. On the other hand, other studies with yearly repeat measurements observed that even despite the long time period between repeat measurements, these had prognostic significance both in the prediction of the development of varices [2] and in decompensation [4]. Lastly, the lack of association between beta-blocker therapy and the clinical outcomes of interest is another setback. The study was not aimed to evaluate the impact of the use of beta blockers on clinical outcomes, but the impact of changes of objective variables (HVPG and MELD), which are confidently retrievable in a retrospective analysis. Furthermore, a recent study has suggested that the beneficial impact may be lost over time, especially when there is continuous worsening of liver function [19]. This, together with the small size, may explain the only weak association between reduction of HVPG and beta-blocker therapy.

In conclusion, both single measurements of MELD and HVPG and the changes observed over time of these values have prognostic information for predicting relevant events in compensated and decompensated cirrhosis. However, the quantitative change of HVPG and MELD does not seem to offer further information than what is offered by a single measurement.

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Summary Scand J Gastroenterol 2012; 47: 204–211

Identification of predictors in the natural history of cirrhosis is based on determinations at a fixed time point, so that a single determination is considered to predictive of clinically relevant outcomes in patients with liver cirrhosis. However, repeat measurements may offer more information as the changes of these parameters offer a more dynamic view of the course of the disease. In fact it is well established in the setting of variceal bleeding prophylaxis that patients who achieve a reduction of hepatic venous pressure gradient of 20% , have a reduction in the incidence of variceal bleeding during follow-up. Similarly, several studies have suggested that repeat measurements of MELD score could be better than a single measurement in survival prediction, although other studies have demonstrated contradictory results.

Aims: The aim of this study was to evaluate the predictive value of Model for End Stage Liver Disease (MELD) and hepatic venous pressure gradient (HVPG) and their changes to predict relevant outcomes in cirrhosis, that is clinical decompensation in compensated patients and death in decompensated cirrhosis. Specifically, we evaluated whether or not repeat measurements add significant information to single measurements.

Methods: Patients with repeat HVPG measurements between January 2000 and December 2008 were considered for inclusion. Patients were followed until decompensation/death or July 2009. Multivariate Cox regression was used to analyze the predictive value of a single measurement of MELD and HVPG, and changes between measurements. Compensated and decompensated patients were analyzed separately.

Results*:* From 414 patients with repeat measurements, 117 patients were included (51 compensated, 66 decompensated). Median time between measurements and follow-up was 13 (2–24) and 11 (6–38) months in compensated and 8 (1–16) and 10 (3–21) months in decompensated patients, respectively. Fifteen compensated patients developed decompensation while twelve decompensated patients died. On univariate analysis, MELD

and HVPG and the changes of these variables were associated with the endpoint in each group. On multivariate analysis, MELD (HR 1.12 (95% CI 1–1.24)) and HVPG (HR 1.16 (95% CI 1.04–1.29)) were independent predictors of decompensation in compensated, while MELD (HR 1.18 (95% CI 1.09–1.27)) was the only predictor of death in the decompensated. Interestingly, the changes in MELD and HVPG were not identified as independent predictors on multivariate analysis. ROC curves were calculated in order to evaluate the discriminative ability of the different variables. In compensated patients, HVPG was the variable with the greatest discriminative ability to identify patients who would decompensate during follow-up (c-statistic (95% CI) 0.792 (0.655–0.893)). However, in decompensated patients, MELD score had the greatest area under the curve (c-statistic (95% CI) 0.679 (0.549–0.792)).

Conclusion: Single and repeat measurements of MELD and HVPG are associated to clinically relevant outcomes in compensated and decompensated cirrhosis. Use of repeat measurements does not seem to add further information to the baseline data.

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

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***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.

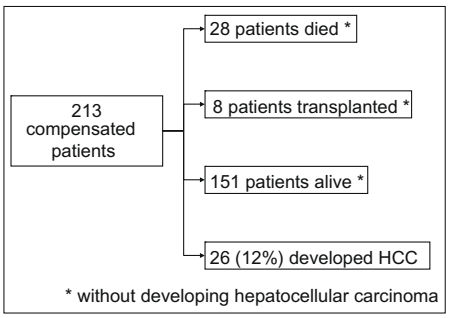

Fig. 1. Evolution of patients during the study.

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

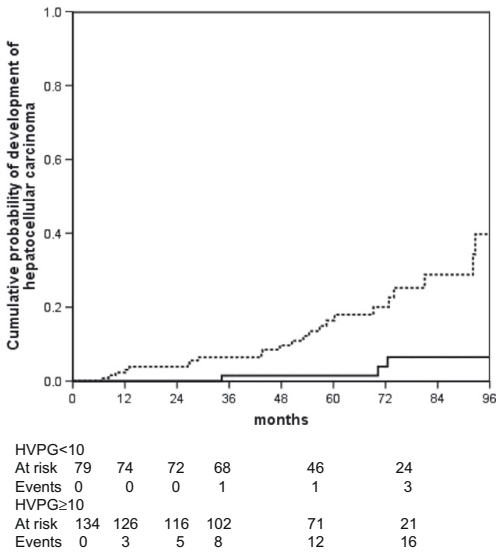

Fig. 2. Incidence of HCC according to a 10 mmHg cutoff of HVPG. KM Curves with all patients including HBV according to HVPG ⩾ 10 (dotted line) or <10 (continuous).

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.

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Summary: Journal of Hepatology 2009; 50: 923-8.

Hepatocellular carcinoma is an important cause of death in cirrhosis. Nowadays there are many effective treatment options so that early detection of the tumours is of utmost importance. Although cirrhosis is a risk factor for HCC per se, the use of predictive factors would allow the identification of a high risk group who would most benefit from screening programs. Several predictors of HCC relate to the severity of cirrhosis including parameters indicative of liver insufficiency, however the role of portal hypertension as estimated by the measurement of the hepatic venous pressure gradient has never been evaluated.

Aims: 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.

Methods: This study is a nested cohort study within a randomized controlled trial designed to evaluate the use of betablockers in patients with compensated cirrhosis. We analyzed 213 patients with compensated cirrhosis and portal hypertension but without varices. All patients had baseline laboratory tests and HVPG. Patients were followed prospectively every 3 months with blood tests and ultrasound until the development of varices or variceal hemorrhage or the end of the original study in September 2002. The endpoint of the present study was HCC development according to standard diagnostic criteria. To have complete information regarding hepatocellular carcinoma until study termination, medical record review was done. Patients who underwent liver transplantation without HCC were censored at transplantation. Univariate and multivariate Cox regression models were developed to identify predictors of HCC. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic capacity of HVPG.

Results: In a median follow-up of 58 months, 26 (12.2%) patients developed HCC. Eight patients were transplanted and 28 patients died without HCC. On univariate analysis patients who developed HCC were older, with a significantly higher proportion with viral related liver disease (84%), higher ASAT and HVPG and lower serum albumin and platelet count. The estimation of the duration of the liver disease was similar between both groups. There were no differences in MELD score nor Child-Pugh score. 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. A sub analysis was performed in the group in whom alpha-fetoprotein was measured. In this subgroup HVPG remained an independent predictor of HCC. ROC curves identified 10 mmHg of HVPG as the best cutoff; 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.

DISCUSSION

There are two phases in cirrhosis with a markedly different prognosis [2]. The first one is the compensated phase and is characterized by the lack of clinical decompensation. In this phase the liver maintains relatively well conserved synthetic and depurative function. On the other hand, and although there may be portal hypertension and even asymptomatic varices in this phase, manifestations associated to portal hypertension are not observed. Patients have a good prognosis as long as they remain in this phase with a survival estimate of 85% at 5 years [2]. The decompensated phase is characterized by the onset of variceal bleeding, ascites, hepatic encephalopathy and/or jaundice. The prognosis of patients in the decompensated phase is much worse, approximately 50% and 25% survival rate at 1 and 5 years [2]. The development of decompensation can be secondary to an acute event, which leads to further lesion of hepatic parenchyma and which may be potentially reversible. Although this situation remains still unclearly defined, it is known as acute on chronic liver failure. The prognostic meaning of this acute on chronic liver failure in compensated patients is not well established. On the other hand decompensation can be produced as a consequence of the natural history without detecting a clear precipitating event.

Hepatocellular carcinoma is another event that may take place in the natural history of liver disease. The development of hepatocellular carcinoma can occur both in the compensated and decompensated phase of the liver disease and accelerates the natural history of the disease towards decompensation and/or death [2, 73, 74].

The studies that conform this habilitation, are aimed at evaluating the prognostic role of portal hypertension, estimated by HVPG, in the whole spectrum of cirrhosis. The first study evaluated the predictive value of portal hypertension in the compensated phase, specifically the role of HVPG in the prediction of decompensation in a homogenous

population of patients with compensated cirrhosis. HVPG was identified as an independent predictor of clinical decompensation (besides MELD and albumin) as defined by the presence of variceal bleeding, hepatic encephalopathy and ascites. In this study HVPG was the most robust variable in the prediction of clinical decompensation, on top of MELD score. The clinical relevance of this study lies in the identification of a subgroup of patients who are at risk for progressive liver disease with decompensation and then death, and therefore permits narrowing the group of patients who are the most likely to obtain benefit from future prophylactic measures [75].

The second study evaluated the role of HVPG in the prediction of mortality in a group of patients with predominantly decompensated disease. In this study, it was observed that HVPG had a role in explaining survival in this population on top of MELD score and age. Its important to underline that HVPG was an independent predictor, so that the contribution of this variable in explaining death could not be substituted by the other variables. Similarly, including HVPG would improve the calibrative ability of a model that included the variables that form part of the MELD score, so that one could obtain a more precise estimation of the survival of a specific patient if HVPG was included in the prognostic model. On the other hand, adding HVPG did not improve the discriminative ability of the MELD score variables, that is the ability of a model to order the patients of the study population according to their risk of death.

The third study evaluated the prognostic role of changes of HVPG in comparison to baseline measurements to predict relevant outcomes in both compensated and decompensated cirrhosis. This study is based on the fact that portal hypertension is a dynamic process which is continuously changing along the natural history of liver disease. Therefore, it was speculated that perhaps repeated estimations of portal pressure by means of the hepatic venous pressure gradient could offer a more correct view of the natural course of the disease. In this study, both the baseline measurements of MELD and

HVPG and the changes of these variables were evaluated as predictors of relevant events in cirrhosis. Interestingly the changes of the variables were introduced as continuous variables (that is the difference between the two measurements). This contrasts with previous studies [49, 56, 58] in which the increase or reduction of HVPG was introduced as a categorical variable according to the achievement or not of a certain threshold of change. According to the strategy in the current study, and although the changes of HVPG were predictive of the events on univariate analysis, when included in multivariate analysis, the extra information offered by the repeat measurement did not improve sufficiently the information already provided by baseline HVPG to predict decompensation in patients with compensated cirrhosis. In decompensated cirrhosis, MELD score was the only predictor of death. It is remarkable that the hazard ratio of HVPG in the prediction of decompensation is similar to the previous study, despite the fact that the study was performed in another country with a different study sample. The consistency of the results further supports the prognostic role of HVPG in patients with compensated cirrhosis.

The comparative analysis of these studies allows to suggest that HVPG has greater prognostic relevance in the compensated phase of the disease while in the decompensated phase of the disease MELD score seems more relevant for the prediction of relevant events. A possible explanation for this finding could be that portal hypertension develops earlier on in the natural history of cirrhosis than liver insufficiency. Indeed bilirubin and INR, two of the three variables that conform MELD score, reflect the synthetic and depurative function of the liver, and the last variable, creatinine, is an indirect marker of circulatory dysfunction which is an event that takes place later on in the natural history of cirrhosis[76] . In the compensated phase the range of HVPG is much wider, while the variability of MELD score is narrow. Therefore, HVPG is the variable which allows to establish a greater difference, a greater discrimination between patients. However in advanced phases, MELD score has a greater range of variability while most patients in this

phase of the disease have clinically significant portal hypertension and therefore there is less variability of HVPG. Due to its greater variability, MELD is the variable that seems to be the most relevant in establishing prognostic differences between patients.

The prognostic role of MELD in compensated patients is also interesting, taking into account that this score was developed to predict survival in decompensated patients, particularly to predict survival after TIPS placement[24]. Furthermore, one of the three variables (Creatinine) that conform MELD score reflects circulatory dysfunction that is not present in compensated cirrhosis. A possible explanation for these finding is that perhaps the incorporation of blood values in the calculation of this score with no previous categorization allows a greater influence from small variations of these variables.

The last study evaluated the prognostic role of portal hypertension as estimated by hepatic venous pressure gradient in the prediction of hepatocellular carcinoma. Interestingly, HVPG, viral etiology and albumin were independent predictors of the development of hepatocellular carcinoma during follow-up of this homogenous group of compensated patients. This finding is supported by another study published at the same time in which baseline HVPG above 15 mmHg was predictive of development of hepatocellular carcinoma during follow-up in decompensated cirrhosis[77]. The first explanation that arises for this particular finding would be that patients with greater HVPG would have more advanced liver disease and therefore be at risk for this complication. However, this was a very homogenous group of patients and there were no differences in the MELD score of the patients who developed hepatocellular carcinoma during follow-up compared to the ones who did not. A second, more speculative explanation of this finding could be perhaps that portal hypertension has a putative role in the development of hepatocellular carcinoma. In fact, with greater portal hypertension, there is greater sinusoidal hypoxia[78]. This hypoxia is a great drive for arterial vasodilation through the buffer response and angiogenesis which is necessary for carcinogenesis[78]. In fact, this

explanation could also be supported by a case control study which observed greater incidence of hepatocellular carcinoma in patients who received TIPS compared to age and Child-Pugh matched controls [79]. TIPS, despite resolving portal hypertension, also leads to this sinusoidal hypoxemia and arterial vasodilation.

Taking into account the available information with HVPG, different experts in hepatology have claimed for a greater application of HVPG measurement in clinical practice [80-83] . In the last years, an increase in its present and future applications has been observed.

In all fields of medicine there are surrogate markers, that is, variables that are used as targets, for which a clear relationship with a variable (surrogate marker) and a clinically relevant event has been established. These are used in order to facilitate research, particularly when the development of the clinically relevant event requires a follow-up which would be unfeasible for clinical trials. For example in the field of cardiology, it is usual to use the reduction of arterial pressure with a hypotensive drug as a therapeutic aim as it has been demonstrated that reduction of arterial pressure has an impact on the incidence of cardiovascular disease.

On top of the prognostic information that HVPG measurement provides, the presence of changes in its values is one of the few markers used in hepatology that can be considered as a validated surrogate marker [84]. In order to be a surrogate marker, a variable must demonstrate, besides a strong correlation between the marker and the clinical event, that repeated improvements in the surrogate marker with therapeutic interventions are associated with an improvement in the clinical result of interest [85]. HVPG has demonstrated to fulfill these first two criteria with changes in HVPG and pharmacological treatment with betablockers regarding the prevention of gastrointestinal bleeding due to portal hypertension. The last criteria to establish a marker as a surrogate marker is to confirm that improvements of the surrogate marker lead to improvements of

the clinical result of interest independently of the method used to produce an improvement in the surrogate marker, that is with drugs from other families. Recently, different studies have suggested that other compounds have an effect on HVPG, however these studies are exclusively hemodynamic studies without any clinical outcomes and therefore confirmation that they also reduce the incidence of variceal bleeding, remains to be demonstrated[86-91].

The general application of the hemodynamic response to monitorize the response to prophylactic treatment has the clear inconvenience that it requires 2 hemodynamic studies. In the recent years, 2 studies have been published regarding the use of acute changes of HVPG after an intravenous bolus of propranolol as an alternative target for prophylaxis strategy [92, 93].

These studies suggest two ideas, firstly that the acute response to propanolol could allow discriminating those patients who will obtain hemodynamic response with the chronic administration after the chronic administration of propranolol with the advantage that a second hemodynamic study could be avoided. Secondly, both studies show that perhaps a smaller reduction of HVPG after the acute administration of propranolol could identify those patients with lower risk of bleeding. Indeed, the initial study that proposed a 20% reduction of HVPG, no difference in bleeding recurrence in patients who had a 10-20% reduction compared to the patients who had no reduction of HVPG was observed. However, since then, indirect data has suggested that a lower reduction of HVPG could be relevant in evaluating other clinical aspects, such as the development of varices [40], the influence in other complications associated to portal hypertension [56] or regarding acute response to intravenous propranolol [92, 93].

Furthermore there are other clinical scenarios, different to bleeding varices in which HVPG could provide valuable information. Possibly the use of repeat measurements of HVPG could also have a role in the evaluation of the severity of post transplant HCV

recurrence[94]. It has also been suggested that HVPG could indirectly reflect histological changes [95] and could overcome the sampling error inherent to liver biopsy, as it collects information from a wider area of liver parenchyma.

In the setting of HCC, HVPG measurement could help the clinician identify patients with cirrhosis who should undergo screening of hepatocellular carcinoma, as the incidence of hepatocellular carcinoma in this subgroup is superior to the threshold that is established as cost-effective for inclusion in a screening program[73]. This is particularly relevant taking into account that the transition from advanced fibrosis to cirrhosis, and therefore the moment at which a patient should start a screening program according to the current guidelines, is sometimes difficult to identify, while the presence of clinically significant portal hypertension can be easily measured [5].

Finally measurement of HVPG could allow further distinction between different degrees of severity of cirrhosis. Traditionally cirrhosis has been considered as a final stage of histological lesion. Once it has been reached it is believed that it is an irreversible state in which one does not await further microscopical changes and one can only observe a progressive worsening of synthetic and depurative liver function and the development of complications associated to portal hypertension. However, recently, it has been proposed that there are different degrees of histological severity within cirrhosis [96-98]. A relationship between specific histological parameters and HVPG has been observed. Interestingly, it was observed that the presence of small nodules and wider fibrous septae was correlated to the presence of clinically significant portal hypertension and that a quantitative evaluation of fibrosis correlated with HVPG. This allowed a sub-classification of cirrhosis according to these parameters. Therefore, use of HVPG could allow to establish different degrees of severity in cirrhosis.

5. CONCLUSIONS

1. In patients with compensated cirrhosis and portal hypertension, without varices, the hepatic venous pressure gradient has an independent role in the prediction of clinical decompensation besides MELD score and albumin.
2. The hepatic venous pressure gradient has an independent role in survival prediction of patients with decompensated cirrhosis in a model adjusted by age, MELD score, presence of ascites and hepatic encephalopathy.
3. Addition of hepatic venous pressure gradient and age to the variables that compose MELD score improve the calibrative ability, and therefore the survival prediction, of an individual patient with decompensated cirrhosis. However, adding hepatic venous pressure gradient and age to the variables that compose MELD score, does not improve the ability to rank patients according to their risk of death.
4. Change in hepatic venous pressure gradient has a role in the prognosis of patients with compensated and decompensated cirrhosis, however it has no independent prognostic value when taking into account baseline value.
5. Hepatic venous pressure gradient has an independent role in prediction of the development of hepatocellular carcinoma in a model adjusted by MELD and albumin. This can allow identification which patients should be included in screening programs.

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