

Cirrhosis and portal hypertension: The importance of risk stratification, the role of hepatic venous pressure gradient measurement

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for any stage of risk. Experts recommend to move toward a pathophysiological classification of cirrhosis that considers both structural and functional changes. The hepatic venous pressure gradient HVPG, is the reference gold standard to estimate the severity of portal hypertension in cirrhosis. It correlates with both structural and functional changes that occur in cirrhosis and carries valuable prognostic information to stratify the mortality risk. This article provides a general overview of the pathophysiology and natural course of cirrhosis and portal hypertension. We propose a simplified classification of cirrhosis based on low, intermediate and high mortality stage. The prognostic information provided by HVPG is presented according to each stage. A comparison with prognostic models based on clinical and endoscopic variables is discussed in order to evidence the additional contribute given by HVPG on top of other clinical and instrumental variables widely used in clinical practice.

Key words: Cirrhosis; Portal hypertension; Hepatic venous pressure gradient; Variceal bleeding; Prognosis

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Core tip: Recently a pathophysiological classification of cirrhosis has been strongly encouraged. Hepatic venous pressure gradient (HVPG) measurement is the most reliable tool to estimate the severity of portal hypertension in cirrhosis but several methodological concerns have limited its use in clinical practice. The article summarizes the results published about the prognostic value of HVPG and originally offers a critical revision of the information provided by this hemodynamic parameter on top of the most widely used models based on non-hemodynamic parameters.

Abstract

Portal hypertension is the main prognostic factor in cirrhosis. The recent emergence of potent antiviral drugs and new algorithm of treatment for the management of complications due to portal hypertension have sensibly changed our perception of cirrhosis that can be now considered as a multistage liver disease whose mortality risk can be reduced by a tailored approach

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INTRODUCTION

Advanced chronic hepatitis, whatever the etiology, accounts for the development of regenerative nodules surrounded by fibrotic septa that are the histological hallmark of liver cirrhosis^[1]. These architectural changes are associated with a relevant increase of intra-hepatic resistance to portal blood flow and, as a consequence, an increase of portal pressure^[2]. In particular, a portal pressure gradient (the difference between the portal pressure and the inferior cava vein pressure) greater than 5 mmHg defines the condition of portal hypertension^[3]. The hepatic venous pressure gradient (HVPG) (the difference between wedged and free hepatic venous pressure measurement) accurately reflects the portal pressure gradient in the most common causes of cirrhosis^[4,5].

No specific symptoms are associated with chronic hepatitis, even in the early phases of cirrhosis, up to the development of clinical significant portal hypertension (CSPH, HVPG ≥ 10 mmHg)^[6]. Ascites and gastroesophageal varices are the most frequent manifestations of CSPH. Other complications as variceal bleeding (VB), spontaneous bacterial peritonitis (SBP), and infections other than SBP, hepato-renal syndrome (HRS) and hepatic encephalopathy (HE) parallel the severity of portal hypertension and substantially worsen the prognosis. As a consequence, cirrhosis should no longer be considered "*per se*" an end-stage liver disease, but a multi-stage disease with different outcomes according to the mortality risk^[7]. By contrast hepatocellular carcinoma (HCC) can occur at any stage of liver disease although the severity of portal hypertension influences the therapeutic options^[8].

In the last years, the development of very effective antiviral drugs and new therapeutic strategies to prevent or manage acute complications of portal hypertension have changed our general perception of cirrhosis^[9]. At present, cirrhosis should be regarded as a disease whose mortality risk can be significantly reduced by a specific tailored approach for any stage of risk^[7].

This article is focused on the clinical implications of cirrhosis as a multistage liver disease with low, intermediate and high mortality risk (Table 1) and discusses the use of HVPG measurement as a surrogate indicator of clinical outcome for any stage.

THE PATHOPHYSIOLOGY OF CIRRHOSIS (SHORT OVERVIEW)

Portal hypertension is the main driving factor in the

natural history of cirrhosis^[10]. In the earliest stages of the disease, portal pressure is determined by the increase of liver resistance to portal blood flow caused by histological changes of the liver, like fibrosis and nodules^[6-11]. On top of these histological features, there is an over-activation of contractile elements at the portal and sinusoidal level (e.g., hepatic stellate cells, hepatic myofibroblasts, vascular smooth muscle cells) that weakens the ability of the liver to accommodate the vascular tone to portal blood flow^[12]. Along with the progression of the disease, extrahepatic vascular changes occur^[13]. Indeed, arterial vasodilation and neo-angiogenesis at the splanchnic circulation creates a condition of "effective hypovolemia" featured by a discrepancy between the relatively low blood volume flowing into the great central vessels and the increased vascular filling capacity. Effective hypovolemia is the trigger of a hyperkinetic syndrome that causes portal venous blood flow increase^[2]. Hallmarks of the hyperkinetic syndrome are a high cardiac output and a low peripheral vascular resistance. Along with these changes, an activation of neuro-humoral vasoactive systems occurs that, finally, causes hydro-electrolyte retention by the kidney^[14]. The final consequence is a major increase of blood volume flowing through the splanchnic circulation. The inability of the liver to accommodate sinusoidal resistance to this high blood flow fosters a further increase of portal pressure that determines fluid escape into the peritoneal cavity (ascites) and induces the development of collateral vessels (varices). In the latest stages of cirrhosis, the extreme consequences of vasodilation and hydro-electrolyte imbalance are type-2 hepato-renal syndrome (HSR-2) and/or hyponatremia^[15,16]. Recently, a reduction of cardiac output, and the consequent reversal of the hyperdynamic syndrome into a (relative) hypodynamic circulatory state has been shown to trigger type-1 HRS^[17]. Given the importance of splanchnic vasodilation in the genesis of effective hypovolemia and the hyperdynamic circulation, and the consequent further increase of portal pressure, any superimposed condition able to further reduce the vascular tone and/or the cardiac function is, potentially, life-threatening, as it could irreversibly impair organ perfusion. This may occur either in the presence of SBP (or, potentially, other infections), or in the case of large volume paracentesis without adequate volume expansion with albumin (post-paracentesis circulatory dysfunction)^[18-22]. All in all, along with the development of severe portal hypertension, the control of vascular homeostasis and organ perfusion becomes frail and this is among the main pathogenic mechanisms underlying the high mortality rate of acute on chronic liver failure^[23]. The occurrence of hepato-cellular insufficiency is another important pathogenic mechanism clinically manifested in advanced stages of cirrhosis. We know that portal pressure reduction can ameliorate liver function^[24]. Further emergent factors such as cytokine release^[25], the prothrombotic imbalance described in cirrhosis^[26],

Table 1 Natural history of cirrhosis

Stages of cirrhosis Mortality risk at 1 yr			
	Low ≤ 1%	Intermediate 1%-20%	High > 20%
Clinical features	Asymptomatic no varices	Varices/ascites or both	Bleeding/re-bleeding SBP Refractory ascites HRS/AKI Infection other than SBP
HVPG of risk	10 mmHg		
Main outcome to prevent	Decompensation and/or HCC and/or varices	Decompensation and/or HCC mortality	HCC and/or mortality
Main pathophysiologic factor	Intrahepatic structural and hemodynamic changes Portal pressure	Extrahepatic hemodynamic changes Portal pressure	Hepatocellular dysfunction Portal pressure Cytokine release Peripheral perfusion Coagulopathy? Other?

Each category of risk is presented with the clinical features, the hepatic venous pressure gradient value, the main outcome to prevent, the main pathophysiologic factor related with that category of risk. SBP: Spontaneous bacterial peritonitis; HRS: Hepato-renal syndrome; AKI: Acute kidney injury; HCC: Hepatocellular carcinoma; ACLF: Acute on chronic liver failure; HVPG: Hepatic venous pressure gradient.

the increased levels of von Willebrand factor^[27,28] and the intra- and extrahepatic changes induced by bacterial derived byproducts^[29-31] could, in our opinion, play a relevant role in determining the outcome of advanced cirrhosis.

PROGNOSTIC INDICATORS IN CLINICAL PRACTICE: ADVANTAGES AND LIMITATIONS

The appearance of any among ascites, variceal bleeding, hepatic encephalopathy, hepato-renal syndrome, spontaneous bacterial infection or jaundice heralds the passage from compensated to decompensated cirrhosis^[32,33]. This distinction is commonly used to establish two conditions with different prognosis, however it has both advantages and drawbacks. It is easy to use in clinical practice and appears rationale, as several studies have consistently demonstrated that such events are associated with a relevant mortality rate and worsen the prognosis. However, major drawbacks rely on considering at similar risk episodes of decompensation of diverse severity (e.g., the first appearance of ascites responsive to diuretics or spontaneous bacterial peritonitis, that is an infective complication of ascites), or including in the same prognostic group complications strictly related with the degree of portal hypertension and complications due to hepato-cellular insufficiency (such as jaundice).

Some of these limitations were overcome by the Child-Pugh classification that distinguishes between compensated (Child-Pugh class A) and decompensated patients and subgroups the latter category of patients in intermediate (Child-Pugh class B) or high degree of liver dysfunction (Child-Pugh class C). However, some of the parameters of Child-Pugh classification are subjective and influenced by therapy, thus decreasing

the accuracy of the classification^[34]. Moreover, the categorization of continuous laboratory parameters, characteristic of this classification system, reduces the discriminative power of the model. A further, important inadequacy of the Child-Pugh classification is that it does not take into account the renal function, whose impairment is associated with a high mortality rate in patients with liver cirrhosis. The more recently introduced MELD score, firstly devised to predict the outcome of patients undergoing transjugular intra-hepatic porto-systemic shunt (TIPS)^[35], but currently used in daily practice to prioritize patients for liver transplantation, is certainly more objective and reproducible^[34].

All these systems are widely used in clinical practice. They simplify the work-up of physicians to define the degree of liver dysfunction and prognosis of patients by using the most common clinical and laboratory findings and are, for that, very easy-to-use.

However, these models ignore the problems related with the presence or not of endoscopic signs of portal hypertension, whose detection indicate the use of pharmacologic and/or endoscopic therapy to manage the bleeding risk. Indeed, according to international guidelines, all patients diagnosed with cirrhosis should be screened for the presence of gastro-esophageal varices every 2-3 years^[10]. The presence of varices and a history of previous bleeding define different clinical scenarios, each associated with a specific mortality risk: prevention of varices development and first bleeding episode (pre-primary and primary prophylaxis) in compensated patients; treatment of acute variceal bleeding and prevention of recurrent bleeding (secondary prophylaxis) in decompensated patients. In this respect, a further discrimination of patients at high risk of bleeding and bleeding related mortality has been encouraged since a good pre-selection of patients may determine better results on survival by using more

aggressive strategies of treatment^[36].

In recent years, the availability of non-invasive tools to diagnose cirrhosis, together with the development of potent antiviral drugs able to reduce fibrosis, has significantly increased the proportion of patients with chronic liver disease diagnosed in the asymptomatic stage of cirrhosis with the ultimate result that the surveillance schedule for the presence of varices should be revised in order to reduce the number of unnecessary endoscopies performed in daily clinical practice^[37]. Another clinical outcome that sensibly influences the outcome of patients with cirrhosis is the possibility of predicting the response to pharmacologic therapy to prevent variceal bleeding/rebleeding. Unfortunately, the low intra- and inter-observer reproducibility of the endoscopic features does not allow recommending the use of this technique systematically^[38].

In summary, the natural history of cirrhosis is strongly dependent on portal hypertension related complications. The use of several clinical and/or instrumental signs, in particular, upper gastro-intestinal endoscopy, characterizes the work-up of physicians to predict and manage the risk of portal hypertension related complications in several stages of risk mainly based on varices, ascites and bleeding^[39]. However, recently, a pathophysiological classification of cirrhosis has been evoked to promote a system that better reflects the dynamic state of cirrhosis and provides a useful tool to predict outcomes and individualize therapy^[7].

THE ADDITIONAL PROGNOSTIC INFORMATION PROVIDED BY HVPG

Given the importance of portal hypertension in the natural history of patients with cirrhosis, it would be expected that HVPG measurement hold prognostic information in this setting. Theoretically, the use of HVPG as a prognostic tool has several advantages: (1) it is an objective and continuous variable; (2) it changes in presence of specific therapeutic interventions and/or an improvement of liver function^[40-42]; and (3) it has been widely studied in cross sectional-, longitudinal-studies, randomized controlled trials and metanalysis to consider it as one of the most reliable surrogate markers of clinical outcome in Hepatology^[43]. However, there are several disadvantages limiting its use^[3,44,45]: (1) the costs associated with the methodology; (2) the need of trained physicians to get a reliable measurement; and (3) the relatively invasiveness of the methodology. Since its introduction, evidence has been accumulated that HVPG correlates with the degree of liver dysfunction^[46-49]. Due for that, it has been recommended to test the prognostic value of the HVPG in the context of multivariable analysis in order to quantify the additional prognostic information provided on top of that achieving by common clinical and instrumental parameters.

Low risk cirrhosis

With the term of low risk cirrhosis we defined the condition of asymptomatic cirrhosis without neither gastroesophageal varices nor other gastro-intestinal signs of portal hypertension with a mortality rate at one year less than 1%. In this context the main clinical outcome to be predicted is the appearance of the first decompensation, that, often, is the appearance of ascites, but another clinical outcome to predict is the development of varices at risk of bleeding. At this stage, HVPG significantly reflects structural and functional changes occurring in the liver^[6,11]. However, above the threshold of 10 mmHg, the high correlation of HVPG with intrahepatic changes is blunted^[50] and the degree of portal pressure is determined by the concomitant activation of extrahepatic hemodynamic and humoral changes that foster a state of hyperdynamic circulation^[13]. A large longitudinal study including patients with compensated cirrhosis without varices demonstrated that patients with a HVPG < 10 mmHg carry a negligible risk of developing varices and a very low risk of decompensation where a HVPG \geq 10 mmHg is associated with 28% rate of varices development and 20% of first decompensation at two years^[51,52]. This demonstrates that patients with asymptomatic cirrhosis, classically defined as compensated and/or Child-Pugh class A, are a heterogeneous population at different risk of becoming symptomatic. However, opportunely designed studies are warranted to translate this prognostic information into the decision making process. Interesting, from the same cohort of patients, it was also demonstrated that HVPG \geq 10 mmHg is associated with a 6-fold increase of HCC risk^[53]. In this context, 10 mmHg was, again, the threshold able to identify the candidates to liver resection at risk of decompensation. Such valuable prognostic information allows considering HVPG as the strongest surrogate marker of clinical outcome to guide the decision making in this setting.

Intermediate risk cirrhosis

The diagnosis of varices, with or without ascites, or ascites alone is the hallmark of CSPH. The need at this step is to predict the risk of portal hypertension related complications (*e.g.*, bleeding, SBP, refractory ascites, *etc.*), and the hemodynamic response to non-selective beta-blockers (NSBBs), the mainstay of pharmacologic treatment to reduce portal pressure. We know that esophageal varices, whatever the diameter, are at risk of bleeding for HVPG \geq 12 mmHg^[54,55]. Moreover a second hemodynamic study that demonstrates the achievement of a HVPG below this value or a reduction \geq 20% of the basal value is highly specific of a good clinical response to NSBBs treatment^[3]. At this stage, a reduction of HVPG also correlates with a reduced risk of SBP or bacteremia^[42]. Importantly, the prognostic contribution provided by HVPG appears to be independent by the degree of liver insufficiency and the

bleeding risk assessed by endoscopy markers of risk such as variceal diameter and the presence of red wale markers of risk (North Italian Endoscopic Club)^[56], thus suggesting that the degree of portal hypertension is the main determinant of prognosis, and its reduction should be the principal aim at this stage of the disease^[41,42]. One limitation of monitoring response to NSBBs treatment by HVPG is that two measurements are needed. This doubles the costs, but also the invasive procedures for the patients. Moreover, not all patients classified as non-responders to NSBBs will bleed in the follow-up, while some patients can bleed before the second HVPG measurement^[57]. To overcome these limitations, a single HVPG measurement by testing the acute hemodynamic response to intra-venous propranolol has been proposed and proved to correlate with the chronic response to NSBBs. Moreover, such single measurement seemed to be able to predict the prognosis of candidates to NSBBs treatment more accurately than the HVPG response to NSBBs requiring two hemodynamic sessions^[58,59]. Further clinical studies to confirm the role of acute HVPG response to propranolol in the decision making are waited.

High risk cirrhosis

This stage includes all patients experiencing a first or further episode of decompensation at high mortality risk such as VB, refractory ascites, SBP, HRS, hyponatremia and HE. Recently, a metanalysis^[60] showed that any kind of bacterial infection is dramatically associated with a 67% mortality rate at one year, even though patients overcome the infection. The role of a prognostic marker, at this stage, is to help in identifying, among patients with decompensation, those at the highest mortality risk in order to implement more aggressive therapeutic strategies.

In several studies HVPG disclosed an independent predictive value on mortality in decompensated patients^[39]. Ripoll *et al.*^[61] in a series of 393 patients, mostly with previous decompensation, showed that the HVPG, independently by MELD, had an overall effect of 3% increase of mortality for each 1 mmHg of HVPG increase. Unfortunately, the addition of the HVPG to the MELD score augmented very little the discriminative power of the MELD score alone to rank the mortality risk of decompensated patients. Then, although portal hypertension can further increase at this advanced stage of cirrhosis, hepato-cellular dysfunction, and, probably, other factors related to acute on chronic liver failure, like inflammatory cytokine release or the impairment of cardiac function and peripheral organ perfusion, probably play a major prognostic role in this clinical setting.

Another important aspect is that the relationship between HVPG and the risk of death could be non-linear. This can be evidenced by considering dichotomization of the HVPG value. In this respect, several studies found an increased mortality risk in patients with HVPG beyond the threshold of 16 mmHg^[48,62-64]. The biological rationale behind this finding is intriguing but still unclear. The

threshold of 16 mmHg would allow an early detection of patients at high mortality risk, and is a promising threshold to be tested in the clinical decision process.

Acute variceal bleeding is the complication of advanced cirrhosis with the highest mortality reduction achieved in the last decades, from 40%-50% to 10%-20%^[65]. In acute variceal bleeding, an HVPG ≥ 20 mmHg identifies patients at high risk of early rebleeding and bleeding related mortality^[66]. Recently, two randomized trials have shown that the reduction of portal pressure achieved by an early TIPS (within 72 h from bleeding) significantly decreases the mortality rate of "high risk patients"^[67,68] (those with a HVPG ≥ 20 mmHg or patient in Child-Pugh class C or in class B who have persistent bleeding at endoscopy). The positive effect on survival achieved by TIPS in patients at high risk of mortality during acute variceal bleeding confirms the importance of the degree of portal pressure in this clinical setting.

Beyond HVPG measurement: Liver/spleen stiffness

Several clinical studies have tried to demonstrate that portal pressure can be indirectly estimated by also non-invasive techniques, in particular, measurement of liver stiffness and, more recently, splenic stiffness by transient elastography^[69,70]. Moreover, several attempts have been made in order to test the ability of these parameters (alone or in combination with other clinical variables) to predict the presence of varices, the risk of decompensation, the presence of CSPH in order to facilitate the sub-classification of cirrhosis by a non-invasive methodology^[71,72].

Liver stiffness is mainly determined by fibrosis that plays a determinant role in the pathogenesis of portal hypertension in the earliest stages of cirrhosis. Due for that, it shows a good correlation with HVPG only before extrahepatic hemodynamic changes determine the increase of portal pressure over the threshold of CSPH. The accuracy of this parameter to detect CSPH is high, good for the detection of varices, however the cut-offs proposed to predict these clinical conditions differs from one study to another^[69]. In our opinion this sensibly reduces the possibility of introducing liver stiffness measurement in the clinical decision process neither allows to detecting the response to pharmacological reduction of portal pressure. Theoretically, splenic stiffness would be a better candidate for the non-invasive assessment of portal pressure since spleen congestion and fibrosis are both effects related with portal pressure increase^[73]. At now the most interesting results have been achieved in hepatitis c virus positive cirrhotic patients. In this clinical subset splenic stiffness has been showed promising results for the non-invasive assessment of portal hypertension, the detection of varices, the prediction of the first decompensation^[74,75].

CONCLUSION

The introduction of potent antiviral drugs and the definition of new algorithms of treatments to prevent

and manage complications due to portal hypertension has revealed that cirrhosis is a multi-stage disease featured by different survival risks. The HVPG measurement is, at present, the most reliable tool for clinicians to predict the clinical outcome and dictate the decision making in several complications. HVPG is particularly promising in low risk cirrhosis for any complication related to portal hypertension and for HCC screening and management. HVPG is a useful tool to predict the response to NSBBs in primary and secondary prevention of variceal bleeding, respectively, in intermediate and high risk cirrhosis. The occurrence of critical complications of portal hypertension and the increasing hepato-cellular insufficiency in this stage of high mortality risk apparently reduce the prognostic contribution of HVPG measurement. Probably, at this clinical stage, other clinical variables may substitute HVPG with a good level of accuracy.

Liver/spleen stiffness are new non-invasive emerging tools to, potentially, estimate the degree of portal hypertension. They might resemble in several aspects the HVPG measurement with the additional advantage of a higher tolerability and reduced costs. However, further studies are needed before a non-invasive "portal sphygmomanometer" can substitute the prognostic information provided by HVPG in cirrhosis.

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