

Prognostic markers in patients with cirrhosis and portal hypertension who have not bled

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Abstract. Prognostic markers of compensated cirrhosis should mainly investigate factors involved with progression to decompensation because death in cirrhosis is related with decompensation. Portal hypertension plays a crucial role in the pathophysiology of most complications of cirrhosis. Accordingly, HVPG monitoring has strong prognostic value. An HVPG ≥ 10 mmHg determines a significantly higher risk of developing decompensation. Esophageal varices also can develop when the HVPG is ≥ 10 mmHg, although an HVPG ≥ 12 mmHg is required for variceal bleeding to occur. Monitoring the changes induced by the treatment of portal hypertension on HVPG, provides strong prognostic information. In compensated cirrhosis hemodynamic response is appropriate when the HVPG decreased to < 10 mmHg or by $> 10\%$ from baseline, because the incidence of complications such as bleeding or ascites significantly decrease when these targets are achieved. Whether serum markers, such as the FibroTest, they, may be valuable to predict decompensation should be established. Transient Elastography is a promising technique that has shown an excellent accuracy to detect severe portal hypertension. However, whether it can adequately determine clinically significant portal hypertension, and risk of developing varices and decompensation, should be established. Magnetic Resonance Elastography is also promising.

Keywords: Compensated cirrhosis, Prognostic markers, hepatic venous pressure gradient, HVPG monitoring

1. Introduction

The natural history of cirrhosis involves an early asymptomatic stage or “compensated”, which over time progresses to a symptomatic or “decompensated” stage, identified by the presence of complications of cirrhosis such as ascites, variceal bleeding or encephalopathy [1]. Furthermore, two distinct stages can be differentiated in the compensated phase of cirrhosis. The first stage is characterized by the absence of esophageal varices and is associated with a mortality of less than 1%, while the second stage is characterized by the presence of varices and is associated with a mortality of 3.4% per year [1].

The course of cirrhosis progressively involves an increase in portal pressure, and worsening of hepatocellular function, which ultimately leads to the development of some of the complications defining the transi-

tion from the compensated to the decompensated phase of the disease [2]. A patient with compensated cirrhosis can have virtually the same survival and causes of death than general population, while a decompensated patient has a median survival of less than 2 years. Patients with compensated cirrhosis die mostly after transition to a decompensated stage, and the annual probability of moving from compensated to decompensated cirrhosis is around 15% of cases [1–3]. In keeping with this, prognostic markers of the compensated stage of cirrhosis should mainly investigate factors involved with progression to decompensation, because death in cirrhosis is clearly related to the development of decompensation. On the other hand, prognostic markers of the decompensated stage should also assess factors determining mortality.

2. Prognostic assessment in pre-primary prophylaxis

Portal hypertension, usually estimated by the hepatic venous pressure gradient or HVPG, plays a crucial role

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in the pathophysiology of most complications associated with cirrhosis [4]. Different studies have demonstrated the prognostic value of HVPG monitoring [5]. It has been shown that the risk of developing varices is significantly higher when the HVPG is ≥ 10 mmHg and that patients with an HVPG ≥ 10 mmHg have a significantly higher probability of developing decompensated cirrhosis [6,7]. The likelihood of decompensation, during a median of 4 years of follow-up, is $< 10\%$ in patients with an HVPG < 10 mmHg and is of 40% in patients with an HVPG ≥ 10 mmHg [7]. In addition to the qualitative value of HVPG (presence or absence of an HVPG ≥ 10 mmHg), the quantitative degree of portal hypertension is also relevant because it has been suggested that for each 1 mmHg increase in HVPG there is an 11% higher risk of clinical decompensation [7].

The assessment of HVPG allows the distinction of two phases with different prognostic implications in compensated cirrhosis. There is an initial phase with moderate portal hypertension indicated by an HVPG > 6 mmHg but < 10 mmHg [6]. In this phase, patients have a very low risk of developing decompensation of cirrhosis. In a subsequent phase, portal hypertension progresses to severe or clinically significant which is defined by an HVPG ≥ 10 mmHg that determines a significantly higher risk of decompensation of cirrhosis [7, 8]. It has been observed that with disease progression, up to 41% of patients who initially had mild portal hypertension (with HVPG < 10 mmHg) develop clinically significant portal hypertension (with HVPG ≥ 10 mmHg) after 24 months of follow up [9].

Esophageal varices can develop when the HVPG is ≥ 10 mmHg [8]. However, an HVPG ≥ 12 mmHg is usually required for variceal bleeding to occur, and it has been demonstrated that the reduction of HVPG below this threshold value virtually abolishes the risk of bleeding [10].

Monitoring the changes induced by the treatment of portal hypertension on HVPG, provides strong prognostic information [5,11]. A relevant number of studies, mainly dealing with patients treated to prevent variceal rebleeding, have shown that the hemodynamic response is appropriate when the HVPG decreased to < 12 mmHg or $> 20\%$ from to baseline [8,12, 13]. Patients who achieve these targets have a bleeding risk significantly reduced to below $10\text{--}15\%$ [14]. Hemodynamic response is also associated with a lower incidence of other complications of portal hypertension such as ascites, spontaneous bacterial peritonitis and hepatorenal syndrome, and with increased sur-

vival [15–17]. However, recent studies suggest that the diagnostic accuracy of hemodynamic monitoring can be improved, mainly in compensated cirrhosis [14,18]. Although the negative predictive value of this technique is very high (around 90%), positive predictive value is modest, especially in primary prophylaxis [19]. In primary prophylaxis the majority of patients (up to 60%) do not have an HVPG reduction $\geq 20\%$ from baseline with β -blockers, but despite it variceal bleeding occurs in few patients (around 15%) [8,20,21]. A recent study shows that, in this setting, a cut-off reduction $> 10\%$ in HVPG can improve the diagnostic accuracy achieved using the cut-off of 20% decrease to define response, substantially increasing specificity [22]. In that study, by using the 10% target, the proportion of nonresponders decreased markedly, from 66% to 36% , and a notable increase in the rate of first bleeding among nonresponders was also observed, from 27% to 46% , thus improving the positive predictive value [22]. These results clearly suggest a relevant improvement in the diagnostic accuracy of HVPG monitoring in primary prophylaxis using the 10% target to define response.

In addition to the prognostic value for bleeding, monitoring of changes on HVPG also provides relevant prognostic information on the probability of developing ascites in patients with compensated cirrhosis at high risk of decompensation as indicated by a baseline HVPG > 10 mmHg [7]. A recent study showed that once clinically significant portal hypertension has been reached, it is still possible to reduce the probability of developing ascites by achieving a decrease in HVPG $\geq 10\%$ from baseline [23]. This represents a relevant issue because ascites is the most frequent complication of cirrhosis and is often the first decompensation to appear. On the other hand, that study showed that when such a reduction in HVPG was not achieved, ascites developed in the majority of patients (up to 90%) [23]. Several studies have already suggested that, even in earlier stages of cirrhosis with compensated disease and moderate portal hypertension with HVPG > 6 mmHg and absence of varices, a 10% threshold may be the best cutoff to predict the development of clinical decompensation [6,7].

Recent studies have also shown that the evaluation of acute response to administration of intravenous beta-blockers in a single hemodynamic study, can accurately predict the long-term outcome [22,24]. As compared to nonresponders, acute responders had a lower probability of a first bleeding, a lower risk of developing ascites during the follow-up and better survival [22]. This is a particularly important issue because assessing response

in a single hemodynamic study, not only eliminates the need for a second invasive procedure, but also allows an immediate rescue therapy for nonresponders. It is possible that these factors will improve the diagnostic yield of hemodynamic monitoring and its applicability in clinical practice.

In addition to HVPG monitoring, different predictors of clinical decompensation related with the severity of portal hypertension and liver insufficiency have been identified. A recent study in compensated patients with hepatitis C virus (both stage 1 and stage 2), identified the presence of esophageal varices and bilirubin as the only independent predictors of clinical decompensation [25]. Child–Pugh score and MELD score have been predictors in compensated patients in some studies [25,26]. In another study, in compensated patients with cirrhosis of different etiologies and portal hypertension, but without varices, HVPG, MELD, and albumin were independent predictors of the development of clinical decompensation [7]. However, HVPG had a predominant predictive role and was the most robust predictor of clinical decompensation, with a greater discriminative ability in the prediction of decompensation, which will ultimately determine survival.

Because disease-related complications of cirrhosis are mediated by the development and progression of hepatic fibrosis, a variety of serum markers have been developed for identifying patients who are at risk for clinically significant hepatic fibrosis. The practical advantages of serum fibrosis markers include their non-invasiveness, potential for widespread availability, and reproducibility. Among them, one of the most widely used and validated is the FibroTest [27,28]. Several independent and combined analyses have demonstrated excellent diagnostic performance for the detection of histological stage F4 fibrosis [27,28]. However, it is less accurate in detecting the presence of intermediate stages of fibrosis as compared to the detection of cirrhosis [28]. There is also a significant correlation between FibroTest values and HVPG values, but this correlation is weaker in patients with cirrhosis [27]. Although the FibroTest value was significantly higher in patients with severe portal hypertension, the area under the receiver operating characteristic curve for the diagnosis of severe portal hypertension was only 0.79 [27]. Thus, other studies are needed to confirm these results, especially in patients with compensated cirrhosis [29].

Other serum markers such as laminin levels or serum hyaluronic acid concentrations have shown acceptable positive predictive value for the prediction of severe portal hypertension, but poor negative predictive val-

ue [30,31]. These markers cannot be currently used to detect the presence of severe portal hypertension [29].

Transient elastography has shown an excellent accuracy for detecting cirrhosis [32] with sensitivity and specificity values approaching 90% [33,34]. For the detection of hepatic fibrosis between stages 2–4, however, its sensitivity and specificity are markedly reduced [33, 34]. Moreover, its accuracy is diminished when obesity and narrow rib interspaces are encountered [35]. Transient elastography has also shown an excellent accuracy for detecting severe portal hypertension with an HVPG above 10 to 12 mmHg [36–38]. However, the correlation with HVPG was less strong in patients with an HVPG value above 10 or 12 mm Hg [36–38]. Transient elastography has been more accurate than serum markers for detection of cirrhosis [39]. This suggests that it may be useful for determining the presence of clinically significant portal hypertension, with risk of developing esophageal varices and decompensation.

Additional large-scale prospective studies are needed to further define the role of Transient elastography for diagnosis and management of severe portal hypertension in compensated cirrhosis.

Magnetic resonance elastography has demonstrated feasibility and diagnostic accuracy in detecting hepatic fibrosis in initial prospective studies [40,41]. As with Transient elastography, the detection of cirrhosis by magnetic resonance elastography is highly accurate with sensitivity and specificity values exceeding 90% [40,41]. This technique is not significantly affected by obesity or rib interspace width [39]. However, its correlation with the HVPG should be established.

3. Prognostic assessment in primary prophylaxis

Gastroesophageal varices are the most relevant portosystemic collaterals because their rupture results in variceal hemorrhage, the most common lethal complication of cirrhosis. Gastroesophageal varices are present in approximately 50% of patients with cirrhosis [42]. Their presence correlates with the severity of liver disease: while only 40% of Child A patients have varices, they are present in 85% of Child C patients [42,43]. Variceal hemorrhage occurs at a yearly rate of 5%–15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices [44]. Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the endoscopic presence of red wale marks [44].

In patients with cirrhosis the incidence of esophageal varices increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year [6,45,46]. Practice guidelines recommend screening for varices in all patients with cirrhosis because nonselective beta-blockers and band ligation reduce the risk of first bleeding by 50% in patients with medium or large varices [47,48]. Prognostic markers in this setting should investigate factors indicating risk of varices (or large varices) and factors indicating risk of bleeding among those with varices.

3.1. *Detection of varices and prognostic markers for varices*

At present, upper gastrointestinal endoscopy is the gold standard for determining the presence of varices [47]. This technique is uncomfortable and invasive for patients and is costly and time-consuming, and it has been shown that there is interobserver variability as high as 30% for the detection of small esophageal varices. Moreover, since the point prevalence of medium/large varices is approximately 15%–25% [42], the majority of subjects undergoing screening endoscopy either do not have varices or have varices that do not require prophylactic therapy. Taking into account these issues, numerous non-invasive methods alternatives to endoscopy have been studied for determining the presence of varices, including biochemical and ultrasound methods, computed tomography (CT) scanning, video capsule endoscopy and spleen magnetic resonance imaging. Among them, video capsule endoscopy appears to be a very promising tool for the detection of esophageal varices. Video capsule endoscopy has been compared to conventional upper endoscopy in several studies [49–53]. A significant correlation has been found between capsule and standard endoscopy for the detection of varices. The sensitivity of capsule endoscopy ranged from 68% to 100% with a specificity ranging from 88% to 100% [49–53]. For the detection of large varices, the sensitivity was 78% with a specificity of 96% [52].

Some simple non-invasive methods may have a value as first line screening for esophageal varices. The diagnostic value of platelet count has been extensively studied, and a low platelet count has been repeatedly found to be related to the presence of esophageal varices [39,46,54–56]. However, the optimal threshold varies markedly from study to study, and its diagnostic value in patients with compensated cirrhosis has been questioned [57]. Some simple serum non-invasive

markers such as the Lok index, the Forns' index or the platelet count/spleen diameter ratio have shown a good performance for diagnosis varices. Remarkably, in a recent large-scale multicenter study a combination of a Lok index (cutoff 1.5) and a Forns' index (cutoff 8.8) had a high negative predictive value for excluding presence of clinically relevant varices that would benefit from primary prophylaxis (large varices or small varices with red signs or in Child–Pugh class C patients) [58]. The platelet count/spleen diameter ratio is a promising index recently proposed, which has shown a 100% negative predictive value for excluding any grade varices [59]. However, the performance characteristics of the test in a following validation study were lower than in the original report [60]. Two small studies have also suggested that the FibroTest may be valuable for excluding presence of large varices [39,61]. Despite its excellent accuracy for detecting cirrhosis, transient elastography seems less sensitive for esophageal varices and did not perform better than serum indexes for both the detection of varices and large varices in a recent study [39].

Despite being very promising, at present, the predictive accuracy of such noninvasive markers is still unsatisfactory and additional large-scale prospective studies are needed to define the real role of these non-invasive markers for diagnosis and grading of varices. Until then these noninvasive markers should not dictate which patients should or should not be screened for esophageal varices by endoscopy [47,48]. On the other hand, it should be kept in mind that varices may appear when HVPg increases above 10 mm Hg [6,8], accordingly patients with HVPg below 10 mmHg do not need endoscopy to assess the development of varices.

3.2. *Prognostic markers of risk of bleeding in patients with varices*

Once developed, varices usually increase in size from small to large before they eventually rupture and bleed. The reported rate of progression is heterogeneous (5–30% per year) [45,62,63]. The factor that has been most consistently associated with variceal progression is liver failure, as assessed by Child–Pugh class [45,62,63]. Other factors include alcoholic aetiology of cirrhosis and presence of red wale markings at the varices [45, 62]. Changes in HVPg (either “spontaneous” or caused by therapy) are usually accompanied by parallel variations in the size of the oesophageal varices, which are significantly reduced when HVPg decreases below 12 mmHg [8].

In patients with cirrhosis the overall incidence of variceal bleeding is about 4% per year. This risk increases to 15% per year in patients with medium–large varices [64]. The most important predictive factors related to the risk of bleeding are variceal size, Child-Pugh class and presence of red signs [44]. In addition, many studies have shown that variceal bleeding only occurs if the HVPG reaches a threshold value of 12 mmHg [5,8,10]. Varices do not develop until the HVPG increases up to 10 mmHg [6], and it should be of at least 12 mmHg for the appearance of variceal bleeding [8,10]. Longitudinal studies have demonstrated that if HVPG decreases below 12 mmHg by means of treatment or spontaneously due to an improvement in liver disease, variceal bleeding is totally prevented and varices may decrease in size [8]. Even if this target is not achieved, a 20% decrease in portal pressure from baseline levels (or greater) also offers a marked protection from variceal bleeding [5,12,13].

Patients with medium to large varices should be considered for prophylactic treatment of variceal bleeding [47,48]. It is well established that “small” varices with red signs or in Child-Pugh C class patients have a bleeding risk similar to that of large varices [44]. In keeping with this, it is currently recommended that these high risk varices should also receive prophylactic treatment [47,48]. Furthermore, β -blockers may reduce the rate of progression from small to large varices, and decrease the incidence of variceal bleeding in patients with small varices [63].

Longitudinal studies have demonstrated that a decrease in HVPG to < 12 mmHg essentially eliminates the risk of bleeding and improves survival [8], while reductions > 20% from baseline or even > 10% from baseline significantly decrease the risk of first variceal bleeding [20–22]. Whether or not HVPG monitoring may be useful to guide therapy is currently under investigation.

4. Implications in future research in this area

HVPG-monitoring provides important prognostic information that can help to improve the management of compensated cirrhosis offering different therapeutic targets. In a large multicenter study β -blockers were not useful to prevent the development of varices in compensated cirrhosis with early portal hypertension (HVPG > 5 mmHg) [6]. However, whether HVPG-guided therapy may be useful to prevent decompensation of cirrhosis with clinically significant portal hy-

pertension (HVPG \geq 10 mmHg) at high risk of developing complications of portal hypertension should be investigated. Future studies should assess whether in these high-risk patients, β -blockers alone or combined with other drugs in hemodynamic non-responders to β -blockers may be useful to prevent decompensation.

In the genesis and maintenance of portal hypertension associated with cirrhosis, two mechanisms act synergistically [4]. Initially, there is an increased hepatic vascular resistance due to the disruption of liver architecture inherent to cirrhosis but also due, in part, to an increased hepatic vascular tone caused by the contraction of portal myofibroblasts and hepatic stellate cells [65]. With the progression of the disease, splanchnic vasodilatation develop and lead an increased splanchnic blood flow which maintains and aggravates portal hypertension [66]. β -blockers act on this second mechanism, decreasing portal pressure by a reduction of splanchnic blood flow as a result of drug-induced splanchnic vasoconstriction [67]. However, in early stages of portal hypertension (HVPG < 10 mmHg), intrahepatic vasoconstriction may be the main mechanism that determines portal hypertension, while splanchnic vasodilatation may not yet be fully developed, which means less potential for vasoconstrictors [68]. This suggests that hepatic vasodilators, which may reduce portal pressure by decreasing intrahepatic vascular resistance, can be more effective in early stages of cirrhosis which should also be assessed in future studies.

Whether or not non-invasive methods to detect clinically significant portal hypertension may be useful in the management of patients with compensated cirrhosis, with or without varices, should also be investigated in future studies.

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