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# Serum Biomarkers for Evaluating Portal Hypertension

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## Abstract

Cirrhosis represents the final stage for wide variety of chronic liver diseases, regardless of its etiology, and the development of portal hypertension is responsible for the pathogenesis of most frequent and fatal complications of cirrhosis. It is of most importance to evaluate patients newly diagnosed with cirrhosis for the presence of clinically significant portal hypertension and associated complications, which could expose the patient to fatal conditions such as variceal bleeding. The most accurate method for evaluating the presence and severity of portal hypertension is the measurement of the hepatic venous pressure gradient, which in one hand provides us valuable prognostic information but on the other hand, it represents a problematic technique, because it is invasive, costly and not available in all centers. Several alternative noninvasive techniques have been proposed to assess portal hypertension, including serum biomarkers and imaging techniques. Various serum molecules have been investigated for their ability to predict the presence of portal hypertension, some of which have showed to either correlate with the hepatic venous pressure gradient or predict clinically significant portal hypertension. This chapter will focus on the potential role of multiple serum markers of portal hypertension that could be clinically applicate to predict the presence of clinically significant portal hypertension, to stratify patients with respect to the severity of portal hypertension, to predict lethal complications such as variceal bleeding, and to monitor disease progression or treatment response without exposing patients to the risks of repeated invasive assessment.

**Keywords:** Hypertension; Cirrhosis; Patients

## Definitions of Words and Terms

**Ascites:** A term that describes the accumulation of more than 25 ml of fluid in the peritoneal cavity.

**Cholestasis:** A condition that describes an impaired bile formation and flow. The causes are classified as intrahepatic, in which there is a secretory defect of the hepatocytes and cholangiocytes, and extrahepatic characterized by obstruction of bile ducts.

**Cirrhosis:** An abnormal condition of liver characterized by development of scar tissue that replaces normal liver tissue leading to decreased in hepatocellular mass, and thus decreased liver function, and an alteration of blood flow with an increased pressure in the blood vessels that supplies the liver.

**Endothelial dysfunction:** A pathologic state of the function of endothelium, the cellular inner lining of blood vessels, in which its ability to regulate the vascular tone is decreased.

**Esophageal varices (EV):** Varices are abnormally dilated blood vessels, usually veins. In patients with cirrhosis an elevation in blood pressure in the portal vein leads to the formation of varices in multiple sites in the abdomen, but the most important is the lower third of esophagus.

**Extracellular matrix (ECM):** ECM is the non-cellular component present within all tissues and organs, composed of proteins and polysaccharides that are secreted locally, and their function is to provide support, segregate tissues from one another, and regulate intercellular communication.

**Hepatic encephalopathy (HE):** A syndrome observed in patients with liver cirrhosis, characterized by personality changes, intellectual impairment, and a depressed level of consciousness.

**Hepatorenal syndrome (HRS):** HRS is a syndrome of progressive kidney injury seen in patients with liver cirrhosis and portal hypertension, and associated with high risk of motality.

**Insulin resistance:** A condition in which the insulin, a hormone that regulates carbohydrate and lipid metabolism, has a decreased activity on its receptors in insulin-sensitive tissues such as liver, skeletal muscle and adipose tissues.

**The Model for End-stage Liver Disease (MELD):** MELD is a scoring system for assessing the severity of chronic liver disease. The score uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict three-month survival.

**Spontaneous bacterial peritonitis (SBP):** SBP is an acute bacterial infection of ascitic fluid, that complicates patients with liver cirrhosis, diagnosed when the peritoneal fluid contains excess of neutrophils of more than 250 cells per $mm^3$. SBP is associated with high rate of mortality.

**Thrombopoietin (TPO):** TPO is a hormone produced by liver, and its function is to stimulate platelet production by bone marrow.

## Introduction

Development of clinically significant portal hypertension (CSPH) is a major cornerstone in the natural history of any chronic liver disease (CLD) regardless of the etiologic cause of CLD, and it is associated with clinical decompensation and development of portal hypertension (PTH)-related complications. Portal hypertension is defined as a pathological increase in portal venous pressure between the portal vein and the inferior vena cava to higher than the normal range (≤5 mmHg).

The clinical manifestations of portal hypertension include ascites, gastroesophageal varices, hepatic encephalopathy (HE), variceal bleeding; spontaneous bacterial peritonitis (SBP), infections other than SBP, and hepato-renal syndrome (HRS). The occurrence of these complications reflects the severity of portal hypertension, and substantially worsens the prognosis of cirrhosis.

Patients with cirrhosis are considered high risk if they experience any episode of decompensation associated with high mortality risk such as variceal bleeding, refractory ascites, SBP, HRS, hyponatremia and HE. 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.

One of the most accurate methods for determining portal venous pressure involves the catheterization of the hepatic vein and the measurement of the hepatic venous pressure gradient (HVPG) defined as the difference between the wedged or occluded hepatic venous pressure and the free hepatic venous pressure [1], and if measured precisely, has a very low variability. Portal hypertension is considered moderate when the HVPG ranges from 5 to 10 mmHg and severe when the HVPG is greater than 10 mm Hg. HVPG correlates with both structural and functional changes that occur in cirrhosis, and it carries valuable prognostic information to stratify the mortality risk. CSPH is established when HVPG is >10 mmHg, and at this value the patient usually develops of PTH-related complications, while if HVPG is >12 mmHg, the risk of variceal bleeding increases [2]. Some meta-analyses have demonstrated that a reduction of HVPG to <12 mmHg or more than 20% of baseline significantly reduces the risk of bleeding [3-5], whereas HVPG values equal to or below 8 mmHg are expected to control refractory ascites [6]. Several studies demonstrated that HVPG has an independent predictive value on mortality in decompensated patients [7]. Ripoll et al. [8] in a series of 393 patients, mostly with previous decompensation, showed that the HVPG, independently of the model for end-stage liver disease (MELD) score, had an overall effect of 3% increase of mortality for each 1 mmHg of HVPG increase.

Despite its excellent diagnostic and prognostic value, the use of HVPG in clinical practice is limited due to several factors such as the invasiveness of the procedure, availability only in specialized centers, and excessive costs [9].

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% [10]. In acute variceal bleeding, an HVPG ≥ 20 mmHg identifies patients at high risk of early rebleeding and bleeding related mortality [11]. Upper Gastrointestinal tract endoscopy is the gold-standard technique for identifying esophageal and gastric varices and is essential for the endoscopic management of variceal hemorrhage [12]. There is consensus that it is mandatory to screen for EV by endoscopy when the diagnosis of cirrhosis is established, and the endoscopy should be repeated at 2-3 years interval in patients without varices. However, this approach has some limitations, as endscopy is an invasive procedure, the cost-effectiveness is questionable becuase only 9%-36% of patients with cirrhosis found to have varices on screening endoscopy.

Currently, there is no established noninvasive test that can predict portal pressure among patients with chronic liver disease, and the ability to predict portal pressure with a simple blood test would revolutionize clinical management of patients with chronic liver disease.

Serum biomarkers of portal hypertension can be classified to parameters that reflects liver function, markers related to complications of portal hypertension, markers related to the pathogenesis of portal hypertension, and models combining multiple parameters.

## Markers related to Liver Function

Liver functions tests can be classified into parameters related to cell lysis or inflammation (AST and ALT), parameters of cholestasis (γGT and bilirubin), and parameters that reflect hepatocyte synthetic function (PT-INR, albumin). These parameters are surrogates of inflammation and steatosis, which have a significant predictive value for the progression of fibrosis [13].

Child-Pugh score and its objective component (albumin, bilirubin, INR) correlate with HVPG [14-16] and correlate with the prevalence and grade of esophageal varices in cirrhotic patients. Interestingly this correlation is observed also in patients with compensated cirrhosis [17], suggesting that a close relationship exists between the structural changes which give onset to portal hypertension and hepatocellular dysfunction. Another model obtained by the combination of biochemical parameters, namely albumin, ALT, and INR, had an area under the curve (AUROC) of 0.952 in the prediction of CSPH [17].

# Markers related to Complications of Portal Hypertension

## Platelet count

Thrombocytopenia, defined as platelet counts<150,000 /μL, is a common complication in patients with chronic liver disease (CLD), reported in as many as 76% of cirrhotic patients [18]. The major mechanisms for thrombocytopenia in liver cirrhosis include the portal hypertension related hypersplenism leading to platelet sequestration in the spleen, and the decreased production of platelets in the bone marrow due to decreased production of thrombopoietin in the liver. The degree of thrombocytopenia also correlates with the extent of chronic hepatic injury. Studies have shown that platelet count is one of the factors that reflect the degree of liver fibrosis or the severity of liver cirrhosis [19,20]. Studies have also showed a correlation between platelet count and HVPG, and that thrombocytopenia can predict the presence of esophageal varices. one study showed that it was approximately five times more likely for large esophageal varices or gastric varices to be present if the platelet count was <88,000 and the negative predictive value for large esophageal varices was 92% [21].

## The aspartate aminotransferase/platelet ratio index (APRI)

The APRI, Calculated as AST (U/L)/upper limit of normal × 100/platelet count (109/L), was first introduced by Wai et al. in 2003 as a simple noninvasive tool for the diagnosis of significant fibrosis and cirrhosis of various etiologies [22-24]. Subsequently many studies have shown the APRI correlates with HVPG, and an APRI of ≥1.09 had a sensitivity 66%, specificity 73%, positive predictive value 85%, negative predictive value 47%, and diagnostic accuracy 68% for predicting HVPG>12 mmHg.

## Serum ascites albumin gradient (SAAG)

SAAG, which was first proposed by Hoefs et al. [25], is calculated by subtracting the ascites albumin concentration from the serum albumin concentration. The SAAG has replaced total ascetic protein in evaluating the causal mechanism of ascites, because studies have shown that a high SAAG (≥1.1 g/dL) predicts portal hypertension with accuracy rate of 97% and sensitivity of 100%.

# Markers related to the Pathogenesis of Portal Hypertension

## Markers of endothelial function

Endothelial dysfunction is a major determinant of the increased intrahepatic vascular tone observed in cirrhosis and a number of markers reflecting this dysfunction have been identified.

Von Willebrand factor antigen (VWF-Ag) is a large adhesive protein released by activated endothelial cells and therefore represents an indicator of endothelial cell activation [26] and it is used as a surrogate marker of endothelial dysfunction [27]. Endothelial dysfunction is an early key event in many vascular diseases, and is considered a major determinant of the increased hepatic vascular tone of cirrhotic liver [28], Levels of vWF are increased in patients with cirrhosis and correlate with the grade of fibrosis and the severity of liver disease [29]. Studies have shown that VWF-Ag level correlated with HVPG and high levels of VWF-Ag is associated with CSPH, the presence of esophageal varices, and increased risk of mortality [30,31]. The AUC for the detection of CSPH using a VWF-Ag cut-off value of ≥241% is 0.85.

Recently, the The VITRO Score (the Von Willebrand factor-Ag/thrombocyte ratio) was introduced as a marker of cirrhosis and portal hypertension [32]. The VITRO score was significantly higher in patients with CSPH compared to patients with HVPG<10 mmHG (median 3.21 versus 1.29; <0.0001), it was also higher in patients with oesophageal varices (P<0.0001) and ascites (P<0.014). The diagnostic accuracy of the VITRO score for detecting CSPH shows an AUC of 0.86 (CI 0.81-0.91) with a sensitivity of 80% and a specificity of 70% at a cut-off>1.58. The correlation between CSPH and the VITRO score was independent of Child-Pugh score. This score should be validated in further studies.

Nitric oxide (NO) is an essential regulator of intrahepatic vascular tone. In cirrhosis the hepatic NO levels are significantly reduced, with associated elevated sinusoidal vascular resistance [33]. NO synthesis by endothelial nitric oxide synthase (eNOS) can be inhibited by the competitive endogenous inhibitor asymmetric dimethylarginine (ADMA). ADMA is metabolized to in the liver, thus impaired liver function is associated with increased plasma levels of ADMA. Lluch and coworkers showed that peripheral blood levels of ADMA correlated with the degree of liver failure and decompensation in patients with alcohol-related cirrhosis [34]. In a further study involving patients with compensated chronic hepatitis C cirrhosis, a positive statistically significant correlation was found between HVPG and ADMA [35].

Recently, astudy using animal model of cirrhosis and portal hypertension demonstrated that Dimethylargininedimethylaminohydrolase-1 (DDAH-1), which is the key enzyme metabolizing hepatic ADMA, is a specific molecular target for portal pressure reduction, through actions on ADMA-mediated regulation of eNOS activity [36].

Further studies are needed to define ADMA metabolism and function in Portal hypertension, and its ability to predict CSPH.

Apelin is an endogenous ligand for angiotensin-like receptor 1, and it is distributed across numerous organs, including the brain, liver, heart, spleen, kidney, and lung. In several preclinical studies with cirrhotic animal model, serum levels of apelin (s-apelin) showed close relationships with both intrahepatic fibrosis and splanchnic hemodynamics. Its clinical utility as a biomarker of portal hypertension and prognosis was recently investigated [37]. s-apelin had a direct correlation

with the degree of hepatic fibrosis and it also showed a significant linear correlation with HVPG (R2=0.356, p<0.001). The diagnostic ability of s-apelin for CSPH was also better than traditional prognosis marker Child-Pugh score and MELD score.

## Markers of Hepatic Fibrosis

In advanced stages of fibrosis, the liver contains around six to eight times more extracellular matrix (ECM) proteins than the normal liver [38,39]. ECM mainly consists of types I, III and IV collagen, fibronectin, laminin, hyaluronan, elastin, undulin and proteoglycan [40-42]. The proteins are found in the blood and their level correlate with the development of hepatic fibrosis. These proteins were also studied as markers for predicting severe PHT. Serum laminin levels were shown to significantly correlate with HVPG values in patients with hepatic fibrosis and in patients with cirrhosis [43]. However, the prediction of severe portal hypertension or esophageal varices by laminin levels was poor with a positive predictive value of 85% and a negative predictive value of 43% [44,45].

Serum hyaluronic acid concentrations also showed correlation with HVPG [46], but as with laminin, its clinical application is limited because of low predictive value for the presence of severe PHT and EVs.

Another type of fibrosis marker was introduced and it was called Fibrotest [46]. This marker is actually a panel of biochemical markers of hepatic fibrosis, and it combines the following five serum markers, all independently related to fibrosis, as well as age and gender: alpha2-macroglobulin, haptoglobin, gamma glutamyl transferase (GGT), total bilirubin, and apolipoprotein A1. One study [47] has shown that there is significant correlation between FibroTest values and HVPG values, but this correlation was weaker in patients with cirrhosis. 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. Other studies are needed to evaluate the ability of Fibrotest to predict severe PHT, especially in patients with non-decompensated cirrhosis.

One study investigated the potential of other ECM proteins for detection of PHT [48]. The markers measured were C1M (type I-collagen), C3M and PRO-C3 (type III collagen), C4M and P4NP 7S (type IV collagen), C5M (type V collagen), C6M (type VI collagen), BGM (biglycan), ELM (elastin), CRPM (CRP). All ECM markers except for CRPM correlated significantly with HVPG. The combination of PRO-C3, C6M and ELM provided better description of PHT, and a model combining the MELD Score with PRO-C3 and ELM provided odds ratios of >100 for having clinical significant PHT.

## Inflammatory Biomarkers

The rationale for screening inflammatory serum biomarkers of portal hypertension is based on the fact that portal hypertension is pathogenically related to liver injury and fibrosis, and that in turn these are associated with the activation of inflammatory pathways [49,50]. One study found that the novel inflammatory biomarkers IL-1β, IL-1Rα, Fas-R, VCAM-1, TNFβ, and HSP-70, significantly correlated with HVPG in compensated cirrhosis [51]. By using multivariate logistic regression analysis and the composite test of TGFβ; HSP-70; status of at risk of alcohol use; and Child class B, HVPG>12 mmHg could be exclude with 86% accuracy and the sensitivity was 87.01%.

CD163 is a macrophage lineage-specific haemoglobin-haptoglobin scavenger receptor and a specific marker for macrophage activation [52]. The serum concentrations of the soluble form of CD163 (sCD163) are elevated during conditions of macrophage activation and proliferation. Elevated circulating sCD163 has been demonstrated in viral hepatitis, acute liver failure, and cirrhosis [53-55]. One study have showed a positive correlations between sCD163 and HVPG and the HVPG rose steeply to an asymptote of 22 mmHg with sCD163 up to about 5 mg/L and not to higher values with higher sCD163 [56]. sCD163>3.95 mg/L (upper normal limit) predicted HVPG ≥ 10 mmHg with a positive predictive value of 0.99.

## Metabolic Parameters

Obesity and metabolic abnormalities have been identified is an independent predictor of clinical decompensation in patients with compensated cirrhosis of various etiologies [57]. One study investigated the relationship between metabolic variables, especially insulin resistance (IR) and adipocytokines, and portal hypertension in patients with cirrhosis [58]. The IR was measured by the homeostatic model for the assessment of IR (HOMA-IR), which is calculated by multiplying fasting plasma insulin by fasting plasma glucose, then dividing by the constant 22.5. The study showed that insulin resistance (IR) and serum levels of adiponectin, an adipocyte-derived hormone, significantly correlated with HVPG, and both parameters independently predict the presence of esophageal varices, with an odds ratio of 2.01 for high HOMA-IR score, and 1.97 for high adiponectin levels. The HOMA-IR also predicted variceal bleeding, patients with MOMA<4 had a significantly higher probability of having free survival of risk of variceal bleeding than patient with HOMA>4 (97% vs 67.4%. P=0.001).

## Potential Applications of Serum Biomarkers of Portal Hypertension to Prognosis, other Diseases or Conditions

For many decades, studies have been done to identify serum biomarkers that can predict the existence of portal hypertension in patients with chronic liver disease. The measurement of the HVPG is the gold standard technique for the evaluation of PHT in liver disease. In patients with cirrhosis, HVPG measurements provide independent prognostic information on survival and the risk of decompensation and complications. Variceal bleeding is the

most feared complication of portal hypertension. The appearance of varices in patients with compensated cirrhosis is associated with an increased risk of death (1.0%-3.4% per year), and the occurrence of variceal bleed significantly increases this risk, with 1-year mortality rate as high as 57%. Approximately 20% of deaths occur in the first 6 weeks of a bleeding episode. It is of most importance to do bleeding risk stratification in patients with cirrhosis. Risk factors for variceal bleeding include morphologic characteristics of varices viewed via esophagogastroduodenoscopy (large varices, red wale markings), cirrhosis severity determined by Child-Turcotte-Pugh scoring (Class B or C), and elevated HVPG. Primary prophylaxis of esophageal varices is recommended for patients at high risk for bleeding. The prophylactic options include pharmacologic agents, especially nonselective b-adrenergic blockers, such as Propranolol and nadolol, and the endoscopic prophylactic intervention variceal band ligation, and both options are effective in reducing the risk of bleeding. B-Blockers have been shown to significantly reduce portal pressure, as measured by HVPG, significantly reduce the risk of a first bleeding episode, and significantly reduce mortality [59]. HVPG has been used to evaluate the hemodynamic response to b-blockers. An HVPG reduction to less than 12 mmHg essentially eliminates the risk of bleeding and improves survival **(Tables 1 and 2)** [60].

**Table 1** This table represents a simple classification of blood test that can be used as serum biomarkers of portal hypertension, and it lists 4 groups of markers, which are widely discussed within the article body.

| **Key facts of portal hypertension** |
|---|
| The liver is a vital organ that has numerous functions in the human body, including metabolism of lipids, carbohydrates, amino acids and serum proteins, hormone production, production of bile, which is necessary to digestion, and detoxification. |
| The liver receives a dual blood supply from the portal vein and hepatic arteries. The portal system includes all veins that carry blood from the abdominal part of the alimentary tract, the spleen, pancreas and gallbladder. |
| Chronic liver disease is characterized by damage and regeneration of liver parenchyma leading to liver fibrosis and cirrhosis |
| Liver cirrhosis is characterized by two pathologic conditions, the first is loss of function of the liver, and the second is increased resistance to portal flow and elevation of the pressure in the portal system. |
| The increased resistance to portal flow is either mechanical due to the disturbed architecture and nodularity of cirrhosis or dynamic due to dysfunction of the endothelium and reduced bioavailability of nitric oxide (NO). |
| This increased pressure in the portal vein may lead to the development of large, swollen veins (varices) within the esophagus, stomach, rectum, or umbilical area. Varices can rupture and bleed, resulting in potentially life-threatening complications. |
| Causes of portal hypertension other than cirrhosis include supra-hepatic causes, such as thrombosis of inferior vena cava or hepatic vein and cardiac diseases (constrictive pericarditis for example), and infra-hepatic causes such as portal vein thrombosis. |
| The treatment of portal hypertension is mainly supportive and consists of managing portal hypertension related complicatios, and the only way to fully cure portal hypertension is liver transplantation |

**Table 2** Serum biomarkers for evaluating portal hypertension.

| **Markers related to liver function** |
|---|
| • Markers related to cell lysis or inflammation<br>• Markers of cholestasis<br>• Markers that reflect hepatocyte synthetic function |
| **Markers related to complications of portal hypertension** |
| • Parameters that represent hypersplenism<br>• Parameters defining the cause of ascites |
| **Markers related to the pathogenesis of portal hypertension** |
| • Markers of endothelial function<br>• Parameters that assess hepatic fibrosis<br>• Markers of inflammation<br>• Metabolic markers |
| Markers that represents models combining multiple parameters |

It is recommended to perform screening endoscopy at 2-3 years interval in patients without varices and at 1-2 years interval in patients with small varices to evaluate the development and/or progression of varices [61]. It was estimated that 100 screening endoscopy need to be performed to prevent 1-2 cases of variceal bleeding [62].

Identification of biomarkers of portal hypertension and esophageal varices will allow upper gastrointestinal tract endoscopy to be carried out only in selected group of patients thus avoid unnecessary intervention and at the same time not to miss patients at risk of bleeding [63]. Any surrogate biomarker of HVPG is a future candidate to be a method used for monitoring response to pharmacologic prophylaxis, either primary or secondary, without doing invasive procedures such as endoscopy and catheterization of the hepatic vein.

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