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# Endothelial Dysfunction and Systemic Inflammation in the Pathogenesis and Progression of Portal Hypertension

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## Abstract

Hepatic and extrahepatic factors contribute to mortality related to liver cirrhosis and therefore much research is still to be done in order to understand the condition thoroughly and to possibly intervene in the process. It is considered that the currently applied prognostic scores are not ideal mortality predictors. On the other hand, recent scientific concepts have revealed the significant contributing role of endothelial dysfunction and of systemic inflammation in the pathogenesis of portal hypertension. Consequently, these concepts are inevitably leading towards proposing and validating new prognostic indicators in cirrhotic patients. Von-Willebrand factor as an indicator of endothelial dysfunction and C-reactive protein as a surrogate marker of systemic inflammation and several other parameters and biological markers have been emerging as a relevant and potentially useful prognostic indicators. Also, the coagulopathy associated to liver disease is in close relation with these entities and still an important research topic. Despite the promising data regarding their prognostic potential, additional research is needed in order to define and validate their value more precisely in clinical and prognostic settings.

**Keywords:** cirrhosis, portal hypertension, endothelial dysfunction, systemic inflammation, von-Willebrand factor, CRP, coagulopathy

## 1. Introduction

Liver cirrhosis represents the final stage of chronic liver disease which denotes reduced hepatic cell mass, formation of regenerative nodules and progressive fibrosis. The altered hepatic architecture leads to an impaired hepatic haemodynamics that manifests with portal hypertension (PH) and gradually leads to development of liver failure [1, 2]. PH is an accompanying condition of the natural course of chronic liver disease and a key factor underlying most of the complications that often determine the prognosis in these patients [3]. Although the development of PH has been mainly attributed to the elevated hydrostatic pressure due to increased vascular resistance, different perspectives have recently emerged regarding this topic. Endothelial dysfunction (ED), a state that indicates irregular function of the endothelial cell (EC), seems to have an important role in the increased vascular tone of the hepatic microcirculation [4, 5] and is an important factor involved in

the development of PH [6]. It is also considered that elevated von Willebrand factor (vWF) contributes to the presence of a subtle hypercoagulable state that worsens the PH [7]. Chronic liver disease has also been related to many complex abnormalities in all segments of the haemostatic process. Moreover, the simultaneous impairment in the procoagulant and anticoagulant activity and the increased vWF concentration transform liver cirrhosis into a condition that is characterized by a globally rebalanced hemostasis [8].

## **2. Portal hypertension: definition, diagnostic criteria, clinical and prognostic significance**

PH is an entity that indicates elevated hydrostatic pressure in the portal vein that initially occurs as a result of the structural abnormalities in the hepatic vasculature [6]. The increased vascular inflow which develops as a consequence of the splanchnic vasodilation and of the increased cardiac “output” also contribute in the progression of PH [9]. The main diagnostic criterion for PH is the presence of elevated hepatic venous pressure gradient (HVPG). HVPG denotes the pressure gradient between the so-called “wedged” pressure and the free pressure of the hepatic veins, which actually reflects the pressure gradient between the portal vein and the inferior vena cava. The HVPG value correlates with PH-related complications [10] and the HVPG measurement is used in therapeutic as well as in prognostic purposes [11]. Clinically significant portal hypertension is defined as the presence of HVPG  $\geq 10$  mmHg and it indicates an increased risk of complications and death associated with liver disease and an increased risk of hepatocellular carcinoma [12–15]. HVPG  $\geq 12$  mmHg carries an increased risk of variceal bleeding, and HVPG  $\geq 20$  mmHg is associated with poor clinical outcomes in cirrhotic patients [12–15]. The PH-related complications are often life-threatening conditions associated with high morbidity and mortality [3] and hence early diagnosis and appropriate treatment is essential for improving the prognosis in these patients [16]. Although HVPG measurement is the gold standard for determining the presence and extent of PH, this diagnostic procedure is not widely used in the everyday clinical practice. It is invasive, expensive and due to technical reasons in about 4% of patients it could be unsuccessful [17]. Consequently, these limitations also preclude the widespread use of the diagnostic and therapeutic algorithms that rely on pressure-based diagnostics. Therefore, the Baveno V Consensus for portal hypertension encourages research towards defining new, non-invasive indicators of PH with better sensitivity and specificity than the ones that are currently used [16, 18].

The natural course of chronic liver disease is characterized by two phases. The first compensated phase is followed by a rapidly progressing, decompensated phase characterized by the presence of complications of PH and/or hepatic dysfunction [1]. As the disease progresses, portal pressure increases and liver function decreases, leading to development of ascites, hypertensive gastrointestinal bleeding, encephalopathy, and jaundice [1]. The occurrence of any complication of PH defines the transition from a compensated to a decompensated phase [1]. The occurrence of ascites is the most common initial complication of PH in cirrhotic patients [19] and it is usually considered a hallmark of the decompensated phase [1]. By combining data from two large studies involving 1649 patients that analyzed the natural course of the disease [19, 20], four clinical stages of cirrhosis were defined, each with a different clinical presentation and a significantly different prognosis [1]. Stage 1 is characterized by the absence of esophageal varices and ascites (mortality rate about 1% per year); stage 2 is characterized by the presence of esophageal varices but without bleeding or ascites (mortality rate

3.4% per year); stage 3 is characterized by the presence of ascites with or without varices in a patient who has never bled (mortality rate 20% per year) and stage 4 is characterized by gastrointestinal bleeding with or without ascites (mortality rate 57% per year). Stages 1 and 2 correspond to compensated and stages 3 and 4 to decompensated cirrhosis [1]. The transition from compensated to decompensated phase occurs at a rate of 5–7% per year [21, 22] and with the onset of the first episode of decompensation the life expectancy of patients is significantly shortened [1]. Median survival is significantly shorter in patients with decompensated than in patients with compensated cirrhosis (approximately 2 years versus over 12 years) [1]. Consequently, the prognostic indicators used in both stages are different and have different prognostic significance [23, 24].

### **3. The role of endothelial dysfunction in the pathogenesis of portal hypertension**

EC has a potential for producing many different mediators that are crucial for proper regulation of the vascular homeostasis, the vasomotor tone and for many inflammatory, metabolic and hemostatic processes in the body [25]. EC regulates the vascular tone by its ability to release vasoactive substances, including vasodilators such as nitric oxide (NO) and prostacyclin and vasoconstrictors such as thromboxane A<sub>2</sub> (TXA<sub>2</sub>) [9]. Endothelial activation is a broad term implying EC function changes occurring as a response to a number of different stimuli. As a response to vascular stress, infections or hypoxia, the EC undergoes certain changes that lead to an imbalance in the release of vasoactive mediators predisposing development of a pro-inflammatory and pro-coagulant state [26–32]. As a response to chronic, continuous exposure of the EC to various physical or chemical stimuli a disturbance in the function of the EC occurs, a state defined as ED. [25]. ED is a condition of imbalanced release of vasoconstrictors and vasodilators, stimulators and inhibitors of growth, proatherogenic and antiatherogenic, and pro-coagulant and anticoagulant mediators [4, 25]. It has been established that ED is an early key event in many vascular diseases [5] and its presence is generally associated with a poor prognosis [7]. Also, ED is an early event that has been involved in the pathogenesis of PH [6]. ED as part of the liver disease occurs in the liver microcirculation and in the EC in the systemic and splanchnic circulation. Hepatic inflammation in early cirrhosis is the primary trigger that causes damage to the hepatic reticuloendothelial system and leads to intrahepatic ED [33–41]. This ED is manifested by an increased release of vasoconstrictive substances leading to impaired flow-associated endothelial-dependent vascular relaxation, i.e., to inadequate postprandial vasodilation. Intrahepatic ED is considered to be the primary disorder that leads to increased intrahepatic vascular resistance and progressive PH [4, 5, 9, 42], and later, to a consequent arterial vasodilation in the splanchnic circulation [4, 43–45]. On the contrary, in advanced disease, endotoxemia is considered to be the main factor responsible for the development of ED in the systemic circulation. The systemic ED is manifested by an increased production of vasodilator molecules, mainly NO [46, 47], a vasodilator that is secreted by the endothelial and vascular smooth muscle cells [48] and that also has certain anti-inflammatory and antithrombotic properties [7]. The increased vasodilator tone in the systemic circulation leads to increased endothelial-dependent relaxation and increased blood flow, which consequently leads to the development of hyperdynamic circulation (HC) [49–51].

As a result of the vascular stress and increased concentration of some circulatory factors such as catecholamines, estrogens, and substance P that stimulate the endothelial synthetic activity [52, 53] several typical hemodynamic disorders occur



in cirrhotic patients. The HC is one of the main and most typical hemodynamic features of patients with liver cirrhosis and PH [54–57]. It occurs as a result of a specific combination of several hemodynamic abnormalities, but the increased NO production is considered to be the major factor in the development of HC [54–57]. In this context, some studies have confirmed a significant correlation between the level of vWF and the NO production which may suggest a common activation mechanism [27]. HC is characterized by increased intrahepatic vascular resistance as a result of intrahepatic vasoconstriction and increased systemic vasodilation leading to an increased portal flow. The presence of HC in patients with liver cirrhosis is manifested by hypotension, low vascular resistance, and increased cardiac output, which develops as a compensation of the systemic vasodilation [9, 58]. Additionally, increased portal systemic shunting and reduced renal flow also occur [3, 59]. The severity of the HC has been significantly associated with the degree of PH, that is, by activating the NO synthetase, the portal pressure is an important factor that regulates the vasodilation in the splanchnic circulation [60]. Hence, in patients with liver cirrhosis, in addition to the endotoxemia, PH is thought to act as a factor of increased endothelial stress and stimulates additional NO production [52], i.e., the PH indirectly emphasizes the vasodilation in the splanchnic circulation.

#### 4. Von-willebrand factor as an indicator of endothelial dysfunction and factor of PH progression

Some mediators secreted by the activated EC such as NO, vWF, P-selectin and Isoprostran are used as indicators of ED [26, 29, 61–63]. The important role of vWF in the process of angiogenesis, inflammation, cell proliferation and tumor growth has recently been increasingly emphasized [64]. Considering the fact that liver cirrhosis is closely related to ED, vWF as an indicator of ED causes considerable attention in cirrhotic patients. Since vWF is also involved in the pathogenesis and progression of PH, its value as a prognostic indicator in these patients becomes even more important.

vWF is a large multimeric glycoprotein released by the megakaryocytes and the activated vascular EC that plays a role in the process of primary hemostasis and coagulation [65]. In a coordinated manner, the function of vWF is regulated by two platelet membrane receptors, glycoprotein Ib (GPIb/IX/V) and glycoprotein IIb/IIIa [16, 66]. During primary hemostasis, vWF participates in both platelet adhesion and platelet aggregation. In case of endothelial damage, circulating vWF binds to exposed collagen in subendothelial structures and interacts with the platelet receptor GPIb/IX/V. This transient interaction enables subsequent stable interaction between platelets and collagen through the collagen receptor  $\alpha 2\beta 1$  and glycoprotein VI [67]. This is followed by the exposure and activation of the receptor GP IIb/IIIa resulting in the release of platelet activating mediators such as *Adenosine diphosphate* (ADP) and TXA<sub>2</sub>. By binding to the GP IIb/IIIa receptor, the vWF participates in platelet aggregation and plug formation [16, 58]. Except in primary hemostasis, vWF also acts as a carrier of factor VIII protecting it from the proteolytic action of protein C and its cofactor protein S [68, 69].

Human EC has the capacity to synthesize vWF multimers with a higher molecular weight called ultra-large molecular weight multimers (ULMWM) [70]. After secretion by the EC, ULMWM usually undergo a process of fractionation to smaller vWF forms that are normally present in the circulation [70–72]. vWF is continuously secreted by the EC and megakaryocytes, while the ULMWM are stored in

the cytoplasmic granules and are released after their degranulation as a response to a significant endothelial damage [73]. Contrary to the small vWG multimers, ULMWMs are the most haemostatically active forms of vWF that have the property of spontaneous binding to platelets and subendothelial structures, and are considered prothrombotic [74]. The multimeric composition of vWF is regulated by its protease ADAMTS13 [67], a clearance metalloprotease synthesized in hepatic stellate cells [75, 76] that processes ULMWM into smaller vWF forms [67, 75, 76]. The vWF activity is strictly regulated by ADAMTS13 and the vWF reactivity towards platelets is proportional to the size of the vWF multimers [9]. Since ADAMTS13 is synthesized in the liver [77], as expected, some studies have confirmed a markedly reduced concentration of ADAMTS13 in patients with liver disease [78]. In some patients Lisman et al. also confirmed reduced ADAMTS13 concentration, but in others the concentration and activity of ADAMTS13 has been elevated [67]. This may be due to its reduced clearance of ADAMTS13 or its reduced release from platelets [79] as a consequence of platelet activation secondary to disseminated intravascular coagulation (DIC). Although in advanced liver disease the synthesis function of the hepatocytes is generally reduced, the stellate cells tend to have an increased synthetic activity [80, 81] which may also explain the increased synthesis of ADAMTS13 registered in some patients.

It has been established that intrahepatic and systemic ED is involved in the pathogenesis and progression of PH. Since vWF is an indicator of ED, vWF recently has gained an important role as a prognostic indicator in cirrhotic patients. There are many mechanisms that are related to the increased vWF production in cirrhotic patients. The intrahepatic production of vWF as a result of the intrahepatic ED has been confirmed by the positive immune staining of vWF in sinusoidal endothelial cells in these patients [82, 83]. Also, the presence of endotoxemia and bacterial products, especially in advanced diseases appear to be the most important cause of increased endothelial secretion of vWF [58, 67], which has been confirmed by the linear increase in vWF concentration with the increase of endotoxemia [58, 84]. In addition to the increased endothelial production of vWF, there are other mechanisms that contribute to the increase in vWF such as increased shear stress, bacterial infections [58, 85], neoplastic processes, physical activity, or interferon-based therapy [86, 87]. Decreased expression or activity of ADAMTS13 recorded in some cirrhotic patients may also result in reduced clearance and increased vWF concentration [79]. It is also considered that increased vWF values may be related to the hyperfibrinolysis found in some patients, but on the other hand increased vWF has been also registered in patients without evidence of an increased proteolysis [58], which means that this is probably not a dominant mechanism.

Not only vWF is an indicator of ED, but the clinical and prognostic relevance of vWF is more pronounced because vWF is involved in the progression of PH. Since vWF is a large multimeric molecule, its increased concentration along with other abnormalities that favor procoagulant tendency in cirrhotic patients often results in occurrence of thrombosis in the hepatic microcirculation. If this is a long-term and continuous process, then it progressively obliterates and increases the resistance in the portal vasculature [67, 88] that leads to additional worsening of the PH. Additionally, it is assumed that when these thrombotic events are localized in the intestinal microcirculation they favor enterocytic ischemia and consequent intestinal bacterial translocation causing endotoxemia, which is crucial for the development of the majority of PH-related complications [9]. The literature data confirm a correlation between the concentration of vWF and the HVPG values [7, 16] suggesting that vWF level reflects the degree of PH. Also, vWF level has been related to some complications of PH such as hepatopulmonary syndrome and esophageal varices [89, 90].

The presence of PH is related to most of the complications in cirrhotic patients that define the course of the disease and more importantly the prognosis in these patients. Since vWF reflects PH, recent evidence emphasizes the importance of vWF as a predictor of mortality. Most studies that have analyzed the association between vWF and chronic liver disease have reported that vWF concentration correlates with the stage of liver disease assessed by Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) score [7, 27, 91], that vWF can predict acute decompensation [16], occurrence of clinical events and PH-related complication [7, 92] and that vWF is an independent predictor of mortality that equals MELD score [7, 16, 91].

## **5. The relation between systemic inflammation and adverse outcomes in cirrhotic patients and the prognostic role of C-reactive protein**

It has been established that systemic inflammation (SI) is common in patients with advanced liver disease and PH [93] and that the presence of SI in these patients has been associated with adverse outcomes [94–96] and a poor prognosis [95, 97–99]. The negative impact of SI on liver disease is reflected mainly through the increase in the portal pressure and in the reduction of the hepatic blood flow i.e. through deterioration of PH and liver disease progression [100].

SI is defined as a state of persistent and inadequate stimulation of the immune system, which is manifested by the presence of elevated inflammatory cytokines and activated immune cells [101]. The presence of SI is usually assessed by the presence of systemic inflammatory response syndrome (SIRS), a set of hemodynamic alteration that develops as a response to SI. The presence of SIRS is usually confirmed by specific diagnostic criteria. Sepsis is a condition of a systemic inflammatory response to infection, which involves a characteristic range of pathological changes in many host systems. The pathophysiological sequence involves release of cytokines and endothelial and neutrophil activation, which initiates a cascade of leukocyte-endothelial interaction and adhesion. This is followed by transendothelial migration and subsequent microvascular and tissue damage, consequently leading to a multiple organ failure [102]. It has been reported that endothelial and tissue damage correlates with the intensity of the inflammatory response and leukocyte sequestration in tissues [103].

It is known that SIRS most commonly develops in the context of acute bacterial infection. In patients with liver cirrhosis acute bacterial infection (respiratory, urinary etc.) can often cause an acute deterioration of liver function, which is mainly due to the effects of the SIRS. This may be a result of some specific features of the liver sinusoidal endothelial cells (SEC) that are not typical for the endothelial cells at other locations in the body. The liver SEC are fenestrated allowing inflammatory cells to pass through easily and come into direct contact with hepatocytes [104]. Additionally, the inflammatory cytokines within SI stimulate release of vWF from the EC [105, 106] and suppress the synthesis of ADAMTS13 in the stellate cells [105, 107] which may also contribute to the vWF rise and reflect the relation between SI and ED in cirrhotic patients. It has been also established that SI is underlying many of the PH-related complications and acute events in cirrhotic patients [93]. It is considered that in critically ill patients with liver cirrhosis, these acute events are better taken into account by the use of the general prognostic scores [Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS)], which provide better short-term mortality prediction than the prognostic scores specifically designed for patients with liver cirrhosis such as CTP and MELD score [9, 108]. On the other hand, some disorders



related to liver disease, PH or HC may modify the clinical and biochemical parameters included in the SIRS scores which decreases their value as SIRS indicators [95]. Hypersplenism may mask leukocytosis or exacerbate leucopenia; subclinical encephalopathy may increase the respiratory rate and favor hypercapnia; hyperkinetic circulatory syndrome may increase the heart rate, and beta blockers may mask the tachycardia. This means that the presence of SIRS in patients with liver cirrhosis may often be underestimated by the scores and criteria for SIRS [93, 109]. Considering all the above, many researchers have focused on identifying new biological variables that would be more accurate indicators of SIRS than the currently used criteria. In this context, the value of serum C-reactive protein (CRP) as a surrogate marker of SIRS has recently been increasingly recognized [9].

CRP is an acute-phase inflammation protein that is synthesized in the liver mainly by interleukin 6. Moreover, it has been shown that CRP synthesis is preserved even in advanced liver disease [110, 111], which makes CRP a reliable SIRS indicator in this category of patients. Many researchers evaluated the predictive value of CRP in the general population and also in patients with liver cirrhosis. In the everyday clinical practice elevated CRP has been mainly used as an indicator of bacterial infection and many researchers have confirmed this relation [112–114]. Lazzarotto et al. defined that CRP value of 29.5 mg/L (sensitivity 82% and specificity 81%) is a reliable indicator of bacterial infection in cirrhotic patients [112]. Moreover, recent evidence suggests that the significant prognostic value of CRP in cirrhotic patients comes from the fact that in advanced liver cirrhosis, elevated CRP may persist after a bacterial infection has resolved [9] or it may also reflect the presence of a low grade SI that is not directly related to bacterial infection [108]. This is probably related to the endotoxemia and the bacterial products reaching systemic circulation.

The presence of SI in cirrhotic patients has the potential to trigger several serious complications and acute events related to PH and liver disease such as encephalopathy [68], renal failure [65, 70] or infection [108] and it has been related to negative outcomes during acute [115–117] or chronic [94–96] liver failure. Also, elevated CRP has been related to the organ failure and liver disease-related mortality [93, 112, 118]. Lazzarotto et al. confirmed that in patients with liver cirrhosis higher initial CRP values were associated with death before the ninetieth day of hospitalization [112]. Cervoni et al. demonstrated that mortality in liver cirrhosis was independently associated with CRP, MELD score, and extrahepatic comorbidities. They defined a CRP cut-off value of 29 mg/L persisting for 15 days after hospitalization to have the best sensitivity and specificity for predicting mortality in cirrhotic patients [93]. By using the variables found to be independent predictors of a six-month mortality (variations in CRP, MELD score and extrahepatic comorbidities) in the previous research [93], Di Martino et al. developed a prognostic model in order to predict the three-month mortality in patients with advanced liver cirrhosis and in a subgroup of patients with acute decompensation. They found that the MELD score [HR 1.10; 95% CI, (1.05–1.14);  $P < 0.001$ ] and mean CRP above 32 mg/L at baseline or 15 days after hospitalization [HR 2.21; 95% CI (1.03–4.76),  $P = 0.042$ ] were independent predictors of the three-month mortality. Moreover, the study showed better diagnostic efficacy of the prognostic model than the diagnostic efficacy of the MELD score (AUROC, 0.789 vs. 0.734;  $P = 0.043$ ) [118]. Also, a positive correlation was registered between CRP and MELD score in the whole population, but such correlation was not registered in the subgroup of patients with end-stage liver disease. These findings suggested that the presence of SI was clinically more significant in patients with advanced liver disease, that the prognostic significance of the CRP variations as indicators of SI was greater in more severe patients and that the presence of SI could not be adequately assessed by using the



MELD score. These findings once again emphasize the significant role of CRP as a prognostic indicator in patients with liver cirrhosis, especially in advanced disease.

## **6. The relation between endothelial dysfunction, systemic inflammation and haemostatic abnormalities in chronic liver disease**

The haemostatic process is a strictly regulated system in which the process of conversion of fibrinogen into fibrin is consequently followed by its subsequent degradation [119]. Since most coagulation factors and fibrinolytic proteins are synthesized in the liver, a proper hepatic function is of particular importance for the perfectly synchronized function of the haemostatic process. Hence, acute and chronic liver conditions often have an intense influence on the process of hemostasis [120] and advanced liver disease is associated with many complex abnormalities in all three parts of the haemostatic process. In patients with liver cirrhosis the haemostatic dysfunction is related to several mechanisms, such as quantitative and qualitative platelet abnormalities, quantitative and qualitative abnormalities in the coagulation factors and fibrinolytic proteins, reduced clearance of activated coagulation factors, abnormalities in the process of fibrinolysis, as well as to the presence of intensified fibrinolysis and low grade intravascular coagulation [121–123].

The primary hemostasis reflects the interaction between the platelets and the blood vessel and it is mediated by the action of vWF. Thrombocytopenia and the variable thrombocytopathy are the two most common abnormalities in cirrhotic patients within the primary hemostasis [124]. Thrombocytopenia occurs as a result of the increased sequestration due to splenomegaly, decreased thrombopoietin level and myelosuppression, increased systemic immune activation due to portosystemic shunting, impaired intestinal barrier and increased endotoxemia, immune-mediated platelet destruction and due to the platelet consumption within low grade intravascular coagulation [125–129]. The platelet dysfunction is presented as a reduced transmembrane signaling and progressive inability for platelet activation as a response to several stimuli such as adenosine diphosphate, thrombin, collagen, epinephrine or rhizocetine. This dysfunction results in insufficient production of thromboxane and serotonin and precipitates cascade abnormalities in the process of platelet aggregation [130, 131].

The central part of the haemostatic process is the process of coagulation, also called secondary homeostasis or thrombin generation. Most coagulation factors, such as fibrinogen, factor V, VII, VIII, IX, X, XI, XII are synthesized in the liver, which means if the liver synthetic function is impaired, their level inevitably decreases [132]. On the other hand, in patients with liver cirrhosis the synthesis of the anticoagulant proteins, such as protein C, protein S, and antithrombin is also reduced which partially compensate for the procoagulant deficiency. Despite the decreased concentration of most coagulation factors, in cirrhotic patients there is an increased concentration of factor VIII and vWF, two coagulation factors that are considered acute phase reactants [133–137]. Due to the reduced synthesis of the coagulation factors of the external pathway (mainly factor VII) prolonged prothrombin time (PT) is usually registered, while the reduced synthesis of the coagulation factors of the internal pathway results in prolongation of the activated partial thromboplastin time (aPTT). Thrombin time (TT) reflects the final step of the coagulation cascade, the conversion of fibrinogen into fibrin. TT reflects quantitative and qualitative fibrinogen abnormalities, a state called dysfibrinogenemia. Fibrinogen is also an acute phase reactant and in patients with mild or moderate liver cirrhosis it can be normal or slightly elevated [138, 139]. On the contrary, in advanced, severe cirrhosis fibrinogen concentration is usually decreased [139] resulting in prolongation of the TT. Fibrinogen is almost exclusively synthesized in

the liver and hypofibrinogenemia in these patients could be a consequence of the reduced synthetic liver capacity, the increased metabolism, the abnormal fibrinolytic activity or the consumption as part of the DIC [140].

The final phase of the haemostatic process is fibrinolysis, the process of thrombus dissolution that limits the coagulation cascade. The fibrinolytic impulse is generated by the tissue plasminogen activator (t-PA), urokinase plasminogen activator and activated factor XII. They induce the conversion of plasminogen to plasmin, which then acts on fibrin to produce the fibrin degradation products (FDP). Deviations in the fibrinolysis in cirrhotic patients occur as a result of the decreased hepatocyte function, vitamin K deficiency and presence of hyperfibrinolysis [48, 141] which has been registered in about one third of the cirrhotic patients [48, 142–144]. The presence of hyperfibrinolysis and DIC in patients with liver cirrhosis is still the subject of a wide debate [145]. According to some studies, the abnormalities in the hyperfibrinolytic process correlate with the CTP score and are more prevalent in the elderly and in patients with decompensated cirrhosis [146, 147]. Primary hyperfibrinolysis occurs due to the increased concentration of t-PA (as a consequence of impaired hepatic clearance) and decreased concentration or functionality of antiplasmin and other plasminogen activator inhibitors [148–151], which leads to an increased conversion of plasminogen to plasmin [152]. The secondary hyperfibrinolysis develops as a continuum of an emphasized coagulation, most commonly within DIC. Although DIC has been registered in a small number of patients with hyperfibrinolysis, it rarely has a significant clinical impact [152].

An important perspective of the hyperfibrinolysis in cirrhotic patients is its relation to the increased bleeding risk and to the increased incidence of portal vein thrombosis (PVT). FDP created during hyperfibrinolysis interfere with the process of fibrin polymerization by inhibiting the platelet aggregation and thus increasing the risk of bleeding. As the measurement of individual components of the fibrinolytic pathway is of little use in the assessment of this tendency, the role of hyperfibrinolysis in the pathogenesis of bleeding in patients with liver cirrhosis is still not completely clear [142]. On the other hand, the relation between elevated D-dimers and PVT in cirrhotic patients has also been evaluated. Most studies that analyzed the relation and prognostic role of D-dimers in these patients confirmed significant association between the elevated D-dimers and the occurrence of PVT [153, 154]. One study suggested that the risk of developing PVT in patients with liver cirrhosis was significantly higher in case of a significant postoperative rise in the D-dimers concentration that exceeded 16,000 ng/ml [153]. Zhang et al. confirmed significant association between the elevated D-dimers and the occurrence of PVT independent of the CTP score [154]. Additionally, a meta-analysis of 21 studies found that increased concentration of D-dimers was associated with an increased risk of PVT not related to surgery, suggesting that D-dimers could be used as a diagnostic marker for PVT in cirrhotic patients [155]. However, not all studies confirmed this relation. A retrospective observational study of 66 patients did not find any significant difference in the D-dimers level between cirrhotic patients with and without PVT [156]. Most studies suggest that elevated D-dimers in cirrhotic patients correlate with the degree of liver dysfunction which is probably related to the increased hyperfibrinolysis in advanced liver disease [144, 157, 158]. More importantly, it has also been established that in patients with liver cirrhosis elevated D-dimers were related to poor outcomes [144, 154, 157, 158] and that they were significant predictor of short-term mortality [157, 158]. These findings suggest that in critically ill cirrhotic patients or in some specific clinical settings monitoring of the D-dimers concentration may have some useful clinical and prognostic implication.

It is well established that the significantly reduced synthetic liver function in advanced disease is responsible for the reduced synthesis of the coagulation

factors. But, since this occurs late in the stage of the disease, several other mechanisms might be responsible for many complex abnormalities in the coagulation process in cirrhotic patients. In this context, the ED in patients with liver cirrhosis seems to be largely involved in this process through several mechanisms [48]. The process of ED by itself among other disturbances implies an imbalance in the secretion of pro-coagulants, anticoagulants, and also fibrinolytic substances, which can be responsible for some of the haemostatic abnormalities. Also, some evidence suggests that in patients with liver cirrhosis there is a direct relation between the endotoxemia and coagulation activity i.e. that endotoxemia can directly activate the coagulation and fibrinolytic pathway in patients with liver cirrhosis [159]. In this context, some researchers have demonstrated a strong association between endotoxemia and high levels of prothrombin fragments F1 + 2, which are markers of thrombin generation [159, 160], and also between endotoxemia and elevated D-dimers, which are markers of hyperfibrinolysis [159]. This is confirmed by the fact that in cirrhotic patients with elevated F1 + 2 and D-dimers a reduction in the coagulation and fibrinolytic activity has been registered after reduction of endotoxemia [159]. Some data also confirm a direct association between endotoxin and a thrombin-antithrombin complex [160]. Endothelial activation may also explain the relationship between the synchronized rise of vWF and D-dimers as part of secondary hyperfibrinolysis. Lisman et al. extensively analyzed the qualitative and quantitative deviations of vWF in patients with liver cirrhosis and found elevated levels of propeptide indicating an acute endothelial damage, presumably associated to the presence of low grade DIC [67]. It is considered that the increased plasma proteolysis in these patients leads to increased concentrations of vWF as well as highly reactive vWF multimers [161, 162]. The endotoxin also has a potential to induce increased expression of tissue factor (TF) on the surface of the macrophages and to stimulate synthesis of tumor necrotic factor (TNF), which activates the external coagulation pathway [118, 163–165]. The presence of SI in cirrhotic patients also has an influence on the coagulation process. In terms of severe inflammation, the inflammatory cytokines activate the endothelial cells, inhibit the liver synthesis of protein C [166] and can stimulate degranulation of the cytoplasmic granules and release of ULMWM [105, 107], the most prothrombotic vWF multimers. Among other complex haemostatic abnormalities in cirrhotic patients, the increased concentration of ULMWM confirmed in some patients with acute decompensation [167] is considered to be related to the increased prothrombotic tendency.

## 7. Conclusion

All the above suggests a close relation between SI, ED, and liver disease-related coagulopathy in cirrhotic patients and emphasizes their important role in the pathogenesis of majority of manifestations and complications of PH. It also explains the crucial role of endotoxemia as a central initiating factor in their pathogenesis. Elevated vWF reflecting ED and significant and prolonged CRP rise reflecting SI should be routinely used in the everyday clinical practice. Additional research is needed in order to insert more deeply into the pathogenesis of these entities and to propose new variables that would reflect their presence and significance more precisely.

## Conflict of interest

The author declares no conflict of interest.

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