Overview of Plasma Von Willebrand Factor Level in Acute-on-Chronic Liver Failure Patients

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Abstract

Cirrhosis is a pathological diagnosis characterized by diffuse fibrosis, severe disruption of the intrahepatic arterial and venous flow, portal hypertension and, ultimately, liver failure. The concept of acute-on-chronic liver failure (ACLF) has been widely used in critical care hepatology to study patients who underwent artificial support therapies as a bridge to liver transplantation. Viral hepatitis, alcohol or a combination of both are the predominant causes of underlying chronic liver disease in ACLF in the world.The most commonly inherited bleeding disorder, von Willebrand disease, is caused by the deficiency of von Willebrand factor (VWF).Multiple studies showed that plasma VWF levels are useful as an independent predictor of short-term outcome in patients with sepsis and systemic inflammatory response syndrome. The imbalance of high VWF and low ADAMTS13 in sepsis/inflammatory conditions can be a predisposition to platelet microthrombi and an impedance to vital organ microcirculation, leading to multi-organ failure and death in critically ill patients. The aim of the current study to review pathophysiology of ACLF and the significant role of plasma von willebrand factor level among patients with ACLF

Keywords: Acute-on-Chronic Liver Failure; Pathophysiology; Von Willebrand Factor Level

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Introduction

Traditionally, cirrhosis has been dichotomised in compensated and decompensated, and the transition to decompensated cirrhosis happens when any of the following hallmarks occurs: presence of ascites, variceal haemorrhage and/or hepatic encephalopathy (HE). Once cirrhosis transitions from the compensated to the decompensated stage, it is associated with short-term survival (3-5 years) and evaluation for liver transplant is recommended in the absence of contraindications **(1)**.

The 2014 definition was further expanded to include 'high 28-day mortality'. Such initiative led the scientific community to identify new venues of research of a syndrome with extrahepatic organ failure (OF) associated with short-term mortality **(2)**.

Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute and severe hepatic abnormalities resulting from different types of insults, in patients with underlying

chronic liver disease or cirrhosis but, in contrast to decompensated cirrhosis, has a high short-term mortality, mimicking the prognosis of acute liver failure **(3)**.

There are multiple definitions for ACLF. Given this heterogeneity and the importance of identifying patients with ACLF for a more expedited triage and work-up, four major societies/organisations have provided working definitions **(4)**.

The main difference with all other definitions is that hepatic insults are only taken in consideration if they lead to liver failure (jaundice and HE **(3)**. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) centred their efforts to understand the factors associated with mortality in hospitalised infected patients with cirrhosis. Consequently, all other triggers were not considered and the generalisability of their findings to non-infected patients with cirrhosis is unknown **(5)**.

The European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium started a prospective, multicentre European observational study in 1,343 patients who were hospitalized for acute decompensation of cirrhosis (the CANONIC study). This study aimed to define ACLF in cirrhosis, to assess the prevalence and clinical course of the syndrome and to improve the accuracy of the prognostic scores currently available through an evidence-based pragmatic approach. The analysis of this study lead to a new definition with three major characteristics: acute decompensation of cirrhosis; the presence of organ failure (or failures, which can be either hepatic or extrahepatic); and a high probability of short-term (28-day) mortality. **(6)**.

ACLF is a major worldwide medical problem, the worldwide reported mortality of ACLF according to the EASL-CLIF Consortium definition ranges between 30% and 50% and correlates closely with the number of organ failures. In Europe, the average 28-day mortality rate without liver transplantation reported by the CANONIC study was 1.9% in patients with decompensated cirrhosis without ACLF and 32.8% in patients with ACLF (23% in patients with ACLF grade 1, 31% in patients with ACLF grade 2 and 74% in patients with ACLF grade 3) **(7)**.

A study using the North-American Consortium for the Study of End Stage Liver Disease (NACSELD) criteria reported that the 30-day mortality rate associated with infected decompensated cirrhosis without ACLF was 8% and this rate increased to 27% in patients with one, 49% in patients with two, 64% in patients with three and 77% in patients with four organ failures. In addition, in Asia, no significant reduction in mortality in patients with ACLF has been observed over the past two decades, with mortality in the nationwide sample approaching 50%. **(8)**.

Precipitating events of ACLF vary according to geographical areas and can be classified as hepatic or extrahepatic depending on their site of origin **(3)**. Reactivation of chronic HBV, acute hepatitis A virus or hepatitis E virus infection, acute alcoholic hepatitis and acute bacterial infection are the most frequent precipitating events of ACLF in Asia **(9)**. The most common precipitating events are active alcoholism and bacterial infections, although in a considerable proportion of patients there is no recognizable precipitating event. The potential role of drug-induced liver injury as a precipitating event in ACLF has been insufficiently explored in both the east and the west. **(10)**.

Among the different organ and system failures in ACLF, the most frequently affected organs or systems were the kidneys (55.8%), followed by the liver (43.6%), coagulation (27.7%), the brain (24.1%), circulation (16.8%) and the lungs (9.2% of patients). At first glance, it might

be surprising that not all patients with ACLF had liver failure, but there are two important issues that should be taken into account. First, the level of bilirubin used to define liver failure was very high (≥12 mg per dl) and most (if not all) patients without liver failure also had abnormal bilirubin values, which implies a variable degree of impairment of liver function in these patients. Second, it is important to note that the definition of ACLF goes beyond the classic concept of decompensation of cirrhosis and includes the consequences of cirrhosis on the function of other organs **(10)**.

- **Etiology of ACLF:**

Viral hepatitis, alcohol or a combination of both are the predominant causes of underlying chronic liver disease in ACLF in the world. The change in dietary patterns and lifestyle will likely lead to a shift on the ACLF predisposing disease and, as other areas in hepatology, it would not be surprising if non-alcoholic steatohepatitis took the lead in years to come **(11)**. The prevalence of potential triggers varies by the area of the world. Bacterial infections and alcoholism are the two major identifiable factors, Despite exhaustive examination, in 20%–45% of cases, the trigger remains unknown **(12)**.

Acute-on-chronic liver failure () can develop at any stage from compensated to decompensated cirrhosis, and can involve hepatic or extrahepatic precipitating events. A considerable proportion of patients have no identifiable triggering event. In this figure, paracentesis means 'large volume paracentesis' (>5 litres). Acute decompensation of cirrhosis defines the acute development of clinically evident ascites, hepatic encephalopathy, gastrointestinal haemorrhage or any combination of these in patients with or without prior history of these complications. Although bacterial infections are not specific complications of cirrhosis, they are considered as such in patients with prior history of ascites, haemorrhage or encephalopathy because of their high prevalence and their association with abnormalities related to cirrhosis, including bacterial translocation and impaired leukocyte function **(13)**.

- **Pathophysiology of ACLF :**

a) ACLF during the course of cirrhosis:

Cirrhosis is a progressive disease that inevitably leads to death unless the aetiological mechanism is suppressed by appropriate treatment or a liver transplantation is performed. Indeed, there is good evidence that discontinuation of alcohol ingestion in alcoholic cirrhosis, antiviral treatment in chronic HBV-related and hepatitis C virus-related cirrhosis and immunosuppressive therapy in autoimmune cirrhosis may transform decompensated cirrhosis to compensated cirrhosis or even to pre-cirrhotic phases **(14)**.

By contrast, if the aetiological mechanisms persist in patients with compensated cirrhosis, hepatic fibrosis increases progressively as a consequence of continuous liver cell necrosis and inflammation, giving rise to progressive distortion of the liver architecture, reduction in liver parenchyma cells, increase in the intrahepatic resistance to the portal venous flow, portal hypertension, liver insufficiency and acute decompensation of the disease **(15)**.

The development of complications, mainly ascites and, less frequently, variceal haemorrhage or hepatic encephalopathy, marks the onset of decompensated cirrhosis. Decompensated cirrhosis is characterized by impairment in the function of the liver and extrahepatic organs and systems.ACLF may develop at any phase of the disease from compensated to early or late decompensated cirrhosis. Thus, it is not a terminal event of a long-standing decompensated cirrhosis **(16)**.

b)Inflammation in ACLF:

ACLF is associated with features of systemic inflammation. For example, white blood cell count and plasma levels of C-reactive protein and pro inflammatory cytokines and chemokines, such as IL-6, IL-1β and IL-8, are higher in patients with ACLF than in patients with cirrhosis without ACLF **(17).**

Moreover, among patients with ACLF, the higher the ACLF severity, as estimated by the number of organ failures, the higher the plasma pro-inflammatory cytokine or chemokine levels. The excessive systemic production of pro-inflammatory cytokines and chemokines or the 'cytokine storm' by the patient's immune system might cause collateral tissue damage, a process termed immunopathology **(18).**

As such, a cytokine storm might also be a prominent contributor to the development of organ failures in patients with cirrhosis. Of note, in patients with ACLF, a subset of CD14+ monocytes show overexpression of the tyrosine-protein kinase MER (encoded by *MERTK*), which results in the inhibition of the production of inflammatory cytokines by these cells, suggesting that a form of compensatory immunosuppression develops in parallel to the systemic inflammatory response **(18).**

There are two categories of ACLF: those in which the inducer (or inducers) of inflammation (for example, bacterial infection or excessive alcohol intake) are identified and those in which there is no clinically identifiable trigger (or triggers) **(17).**

c) Bacterial inducers of inflammation.

Bacterial pathogens can induce inflammation through two distinct classes of molecules: pathogen-associated molecular patterns (PAMPs) and virulence factors. PAMPs are recognized by the host via dedicated receptors called pattern recognition receptors (PRRs). The engagement of PRRs results in the stimulation of signalling cascades that activate transcription factors. PRR-activated transcription factors can induce an array of genes that encode molecules involved in inflammation, including pro-inflammatory cytokines **(18).**

The second class of bacterial inducers of inflammation includes a large number of virulence factors. Unlike PAMPs, most of these factors are generally not recognized by dedicated receptors but can be sensed by the effects of their activity (a process called functional feature recognition) **(19).**

d) Endogenous inducers of inflammation:

Endogenous inducers are released by necrotic cells or produced by extracellular matrix (ECM) breakdown in an injured tissue (such as the diseased liver in the case of ACLF) and are called damage-associated molecular patterns (DAMPs) **(6).** DAMPs can be recognized by certain receptors of the host, with this recognition resulting in 'sterile' inflammation. For example, high mobility group box 1 protein (HMGB1) engages the advanced glycosylation end product-specific receptor (RAGE), which cooperates with Toll-like receptors (TLRs; a class of PRRs) to induce an inflammatory response **(20).**

Additional factors that might also be involved in ACLF include necrotic cells, which may release members of the IL-1 family such as IL-1α and IL-33 that trigger inflammation through

their respective myeloid differentiation primary response protein 88 (MYD88)-coupled cognate receptors (21).

e) Outcomes of the inflammatory response:

The purpose of the inflammatory response to bacterial infection is to promote host resistance by reducing bacterial burden, whereas that of sterile inflammation is to promote tissue repair. However, when these two categories of inflammatory responses are excessive, they may induce tissue damage (22).

During bacterial infection, the acute phase of the inflammatory response can be excessive and can cause immunopathology. For example, effectors of the immune response, such as recruited neutrophils and inflammatory monocytes, activated T helper 1 (TH1) and TH17 cells, and cytotoxic T cells, are known to be associated with a high risk of immunopathology (23).

f) Sepsis-induced ACLF:

Organ dysfunction caused by a dysfunctional host immune response to bacterial infection defines sepsis-induced ACLF. 30% of patients with cirrhosis and ACLF have bacterial sepsis as an identifiable trigger of the syndrome. However, ACLF can also predispose to bacterial infection; indeed, a proportion of patients with ACLF develop bacterial infection during the course of the syndrome (22).

Among bacterial infections, spontaneous bacterial peritonitis (SBP), sepsis and pneumonia were more frequently associated with ACLF than other infections. In patients with cirrhosis and ascites, viable intestinal bacteria can cross the intestinal barrier and migrate to the general circulation and colonize the ascitic fluid (23).

During the first hours of bacterial infection, patients with cirrhosis have higher plasma levels of pro-inflammatory cytokines than patients without cirrhosis. This finding suggests the existence of excessive inflammation in cirrhosis. The mechanisms that underlie this excessive inflammatory response to bacterial infection are incompletely understood (24).

In fact, most of our knowledge is based on experiments investigating the innate immune response to lipopolysaccharide (LPS), a PAMP recognized by TLR4 (REFS 59–61). The response to LPS has been studied in *ex vivo* studies carried out in freshly isolated monocytes or peripheral blood mononuclear cells (PBMCs) from patients with and without cirrhosis. LPS-stimulated production of pro-inflammatory cytokines and chemokines is higher in cells from patients with cirrhosis than in control cells. (23).

The mechanisms of the LPS-induced cytokine storm associated with cirrhosis are poorly understood. *Ex vivo* experiments have shown that PBMCs or monocytes from patients with cirrhosis show defects in the following negative-feedback mechanisms of TLR4 signalling: the activation of the phosphoinositide 3-kinase (PI3K)–AKT pathway; inhibition of glycogen synthase kinase 3 activity; and the induction of IL-1 receptor-associated kinase M (IRAKM; also known as IRKA3) and of the anti-inflammatory cytokine IL-10 (25).

Following *in vivo* LPS challenge, plasma tumour necrosis factor (TNF) levels are significantly higher in cirrhotic than in non-cirrhotic patients. Moreover, in this setting, patients with, but not without, cirrhosis develop hepatocyte apoptosis and necrosis (26).

In addition, compared with normal livers, in cirrhotic livers, LPS elicits prolonged endoplasmic reticulum stress and a subsequent unfolded protein response that is responsible for sustained phosphorylation of eukaryotic translation initiation factor 2 subunit-α (eIF2α) (27).

In support of this hypothesis, normal hepatocytes exposed to high levels of TNF are protected against cell death because of the induction of NF-κB-dependent prosurvival proteins. Together, these findings led to the theory that, in cirrhosis, LPS recognition might result in severe liver damage that is due not only to an excessive innate immune response but also to the impairment of mechanisms involved in hepatocyte endoplasmic reticulum homeostasis **(28).**

g) Severe alcoholic hepatitis.

Excessive alcohol consumption alters the gut microbiota and increases intestinal permeability. In addition, chronic and excessive systemic inflammation causes damage to the intestinal barrier. These alterations might favour the translocation of bacteria into the blood-stream **(29).**

Regardless of whether these bacteria cause infection, they release PAMPs (such as LPS) that can reach the liver where they are recognized by TLRs expressed in resident macrophages (called Kupffer cells). This recognition stimulates the production of pro-inflammatory CXC chemokines, such as IL-8, that attract and activate neutrophils **(30).**

In the context of chronic alcohol consumption or after LPS challenge, ROS overproduction induces mtDNA stress. mtDNA was shown to escape to the cytosol where it engaged a cell-intrinsic response involving the innate cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS). cGAS engagement with mtDNA, in turn, mediates type I interferon (IFN) production and subsequent autocrine and paracrine induction of IFN target genes. Thus, a cell-intrinsic response to mtDNA stress might become an inflammatory response at the tissue level and thereby might contribute to liver failure. **(31).**

The inhibition of liver regeneration might be involved in liver failure associated with severe alcoholic hepatitis. Although hepatic progenitor cells are activated in livers with severe alcoholic hepatitis, these cells are committed to differentiate into cholangiocytes (epithelial cells lining the bile duct) instead of hepatocytes. Thus, it is possible that no replacement of hepatocytes that die as a result of alcoholic hepatitis occurs. Together, these findings suggest that severe alcoholic hepatitis might be caused by both immunopathology and impaired hepatocyte regeneration **(29).**

h) ACLF with no identifiable trigger:

The trigger of ACLF is unknown in approximately 40% of cases. Although these patients show features of systemic inflammation, one cannot clearly explain how the systemic inflammation is stimulated **(32).**

Three hypotheses might explain the mechanisms that underlie inflammation in ACLF with no clinically identifiable trigger.The first hypothesis is based on the existence of dysbiosis of the gut microbiota in patients with cirrhosis. Dysbiosis associated with cirrhosis is typically characterized by a decrease in diversity, a decrease in Lachnospiraceae, Ruminococcaceae, Bacteroidaceae and Family XIV *incertae sedis* at the family level and a decrease in *Bacteroides* spp. at the genus level **(33).**

The second hypothesis is that some patients might have intestinal translocation of PAMPs, such as LPS or bacterial CpG DNA. These ligands might reach the liver and systemic circulation

and then be recognized by TLRs. Thus, TLR recognition is generally not dependent on microbial viability or invasiveness **(34).**

The third mechanism explaining inflammation in ACLF with no clinically identifiable trigger might be the release of DAMPs, for example, by necrotic hepatocytes. In patients with acute liver failure, various DAMPs, such as HMGB1, that might contribute to inflammation are released **(33).**

- **Diagnostic criteria of organ failure in ACLF:**

One of the assumptions made to define the EASL-CLIF criteria is that extrahepatic organ failure (or failures) is a major differential feature of ACLF. The CLIF-Sequential Organ Failure Assessment (CLIF-SOFA) score was the original scale used to define organ failure. It was derived from the SOFA score, a scale widely used in intensive care, which was then adapted to patients with chronic liver disease. Cut-off values were established after assessing the risk increase of 28-day mortality rates **(34).**

A simplified version of the CLIF-SOFA score, the CLIF Consortium Organ Failure (CLIF-C OF) score with identical criteria to diagnose organ failure and similar prognostic accuracy, has been developed **(35).**

Patients with decompensated cirrhosis can be stratified into four groups of severity: no ACLF or ACLF grades 1–3 on the basis of the type and the number of organ failures they have. Kidney failure is the most prevalent organ failure in ACLF grade 1. For ACLF grade 2, liver failure is the most prevalent organ failure followed by kidney, brain and coagulation failure. For ACLF grade 3, the prevalence of all organ failures is high **(34).**

- **Von willebrand factor levels in hepatic patients:**

Von Willebrand disease, is caused by the deficiency of von Willebrand factor (VWF). The VWF protein has binding sites for platelets as well as factor VIII and collagen, thus it has important roles in both primary and secondary haemostasis **(36).**

VWF was previously recognised as an endothelial activation marker in patients with cirrhosis. Recent studies document raised plasma VWF levels as a prognostic marker of outcome in patients with acute and chronic liver disease **(37).**

It is more relevant in liver disease because ADAMTS13 is produced in liver stellate cells. The level of plasma ADAMTS13 has been shown to decrease with increasing severity of liver disease. This leads to an exaggerated imbalance of primary haemostasis that favours clotting. This imbalance is probably maximised in the presinusoidal portal vein radicles (because ADAMTS13 is secreted from the stellate cells), which, in turn, explains its occurrence in pure vasculopathy in idiopathic noncirrhotic portal hypertension. This progressive imbalance may also play a part in cirrhosis disease deterioration by contributing to portal micro-occlusions and parenchymal extinction **(38).**

Plasma VWF levels are increased 2–3-fold in patients with chronic liver diseases (cirrhosis patients in the outpatient, 4.0–4.5 fold in patients with acute hepatic dysfunction (acute liver

injury and acute liver failure), and 5–7-fold in patients with ACLF, which correlated independently with organ failure and in-hospital survival **(36).**

Acute liver failure is often associated with increased release of endotoxins and cytokines, which may lead to a decrease in ADAMTS13 activity and a concomitant rise in VWF levels **(37).**

Clearance of VWF is performed by macrophages, endothelial cells, and hepatocytes via C-type lectin domain family-4 (CLEC4M) receptors, galactose-type lectin receptors, low density lipoprotein receptor related protein-1 (LRP-1),54 and Ashwell–Morell receptor **(38).**

More than 90% of tissue-resident macrophages in the body are located in the liver, known as Kupffer cells. The Kupffer cells are located in hepatic sinusoids and adhere to the hepatic sinusoidal endothelial cells. Kupffer cell population is severely decreased in acute liver failure and chronic liver injury. The cells that synthesise ADAMTS13 (hepatic stellate cells) are located in the perisinusoidal space in the liver **(39).**

VWF is heterogeneously expressed in endothelial cells throughout the vascular tree, with higher expression in veins compared with arteries and arterioles. However, immunostaining and messenger RNA expression studies show that VWF is not expressed on the hepatic sinusoidal endothelial cells in a healthy liver. Of note, ADAMTS is produced by hepatic stellate cells. Tissue-resident macrophages (>90% are located in hepatic sinusoidal lining) are involved in VWF clearance. Thus, in the healthy liver, hepatic sinusoidal endothelium appears to be a 'VWF-free' zone, and an important site for removing VWF from the circulation **(40).**

- **Von Willebrand factor reduction: a potential new therapeutic option in liver failure syndromes:**

Preliminary reports in and acute liver failure suggest that therapeutic plasma exchange is the most potent VWF-reducing treatment. In a small number of patients, institution of VWF-reducing treatment, as per a management protocol tailored to the degree of liver dysfunction, improved survival in patients with acute liver injury and acute liver failure, without liver transplantation **(37).**

Fresh frozen plasma contains VWF; however, the question is, is it safe to transfuse or exchange plasma in patients with acute liver injury or failure, who already have raised plasma VWF levels? It is likely that in acute liver failure patients, the plasma removed during plasma exchange has high VWF content, and is replaced by plasma obtained from healthy donors (with normal VWF content). Transfusion of fresh frozen plasma to supplement ADAMTS13, as a means to reduce VWF, appeared beneficial in patient with ADAMTS13 deficiency and portopulmonary hypertension, as well as in acute liver injury. Further studies are needed to explore the risks and benefits of plasma exchange and transfusions as a VWF-lowering strategy in patients with liver failure. **(38,41).**

- **Prevention:**

In patients with SBP, albumin is highly effective in preventing the development of type 1 hepatorenal syndrome (HRS), which is a special form of ACLF characterized by rapidly progressive renal failure. This effect is probably as a consequence of plasma volume expansion and the modulatory effect of albumin on the systemic inflammation associated with PAMPs

(such as LPS). There is no evidence that intravenous albumin is effective in other bacterial infections **(42).**

Long-term oral norfloxacin administration reduces the rate of SBP (and of other bacterial infections) and type 1 HRS in patients with decompensated cirrhosis. Norfloxacin acts by selectively reducing the Gram-negative microbiota, decreasing the permeability of the gut barrier via stimulation of IL-10 release and modulating the immune response to bacterial translocation **(43).**

Treatment of patients with severe acute alcoholic hepatitis with pentoxifylline, an inhibitor of macrophage production of TNF, or with the combination of prednisolone and intravenous N-acetylcysteine has been shown to reduce the incidence of type 1 HRS in some studies, presumably by modulating hepatic inflammation **(44).**

Finally, short-term administration of the combination of granulocyte colony-stimulating factor (G-CSF) plus darbepoetin (a synthetic analogue of erythropoietin) has been shown to improve liver function, to reduce the incidence of severe sepsis and to increase 1-year survival in comparison to placebo in patients with decompensated cirrhosis**(45).**

Conclusion:

Early diagnosis and treatment of potential precipitating events are essential in the prevention of ACLF. These all involve treating infections before they can go on to trigger ACLF and include: prompt administration of antibiotics tailored to the local epidemiological pattern of resistance in patients with suspected infections; long-term suppression of HBV infection or sustained eradication of hepatitis C virus infection in patients with compensated or decompensated cirrhosis.

Mild increases of plasma VWF levels in patients with cirrhosis, as well as a marked increase of plasma VWF levels in patients with acute and acute-on-chronic liver failure (ACLF). The raised plasma VWF levels are relatively accurate in predicting survival in patients with liver disease (cirrhosis, ACLF, and in acute liver injury and failure).

Medical management of ACLF consists of early recognition, treatment of the precipitating event and supportive care. Early treatment of the trigger is proven to reduce mortality, for example, in treatment of reactivated HBV infection with tenofovir or alcoholic hepatitis with steroids. However, most of ACLF management is focused on supportive care.

No Conflict of interest.

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