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Effects of Inflammation on Hemostasis in Acutely Ill Patients with Liver Disease

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Abstract

Patients with liver diseases are in a rebalanced state of hemostasis, due to simultaneous decline in pro- and anticoagulant factors. This balance seems to remain even in the sickest patients, but is less stable and might destabilize when patients develop disease complications. Patients with acute decompensation of cirrhosis, acute-on-chronic liver failure, or acute liver failure often develop complications associated with changes in the hemostatic system, such as systemic inflammation. Systemic inflammation causes hemostatic alterations by adhesion and aggregation of platelets, release of von Willebrand factor (VWF), enhanced expression of tissue factor, inhibition of natural anticoagulant pathways, and inhibition of fibrinolysis. Laboratory tests of hemostasis in acutely-ill liver patients may indicate a hypocoagulable state (decreased platelet count, prolongations in prothrombin time and activated partial thromboplastin time, decreased fibrinogen levels) due to decreased synthetic liver capacity or consumption, or a hypercoagulable state (increased VWF levels, hypofibrinolysis in global tests). Whether these changes are clinically relevant and should be corrected with antithrombotic drugs or blood products is incompletely understood. Inflammation and activation of coagulation may cause local ischemia, progression of liver disease, and multiorgan failure. Anti-inflammatory treatment in acutely-ill liver patients may be of potential interest to prevent thrombotic or bleeding complications and halt progression of liver disease.

Keywords

- hemostasis
- coagulation
- inflammation
- acute-on-chronic liver failure
- acute liver failure

Liver diseases have long been considered to be associated with a hemostasis-related bleeding tendency, given that patients may bleed profoundly and often have abnormalities in routine laboratory tests of hemostasis that suggest a bleeding tendency. More recent studies based on assays that are sensitive for both pro- and anti-coagulant factors provide evidence that liver patients are in a rebalanced state of hemostasis.[1] This hemostatic rebalance appears to remain even in the sickest patients with acute or chronic liver disease.[2–4] However, patients with increasing severity of disease may develop complications such as renal failure and infection that—by themselves—are associated with changes in the hemostatic system that could destabilize the rebalanced hemostatic state. These complications often develop in cirrhotic patients with acute decompensation (AD) or acute-on-chronic liver failure (ACLF). AD and ACLF patients are acutely ill patients with disease complications such as ascites, variceal bleeding, and hepatic encephalopathy.[5] ACLF patients have additional (extrahepatic) multiorgan failures and are at particularly high risk of short-term mortality.[6] Systemic disturbances and additional disease complications may thus result in changes in the hemostatic "rebalance," resulting in a prohemorrhagic or prothrombotic state. Patients with acute liver failure (ALF), a syndrome characterized by acute loss of hepatic function without pre-existing liver disease,[7] also have rebalanced

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hemostasis despite the profoundly increased international normalized ratio (INR) of the prothrombin time.

Although acutely ill liver patients generally have a rebalanced hemostatic state, both hypo- and hypercoagulable features have been described.[2,8] Systemic inflammation has been proposed to play a central role in transition from compensated to decompensated cirrhosis,[9] and could play an important role in the hemostatic alterations.[10,11] Indeed, systemic inflammation is frequently associated with profound hemostatic changes in patients without underlying liver disease.[12]

In this narrative review, we will describe the role of systemic inflammation in disease progression in acutely ill liver patients, and will describe the interactions between inflammation and coagulation. We discuss specific alterations in primary and secondary hemostasis, fibrinogen properties, and fibrinolysis, and the role of systemic inflammation on these alterations in patients with AD, ACLF, and ALF.

Inflammation in Acutely Ill Liver Patients

Systemic inflammation plays an important role in development and progression of many pathologies,[13] including liver disease. Patients with liver diseases have increased susceptibility to primary and secondary infections, which may foster progression of liver disease and development of other complications.[14–17] Impaired intestinal barrier function facilitates bacterial translocation and endotoxemia, leading to release of pathogen-associated molecular patterns (PAMPs; for example, lipopolysaccharide [LPS]).[18] In addition, hepatic tissue injury causes the release of damage-associated molecular patterns (DAMPs; for example, extracellular matrix components like heparan sulfate or nuclear components such as histones or DNA).[13] PAMPs and DAMPs are recognized by pattern-recognition receptors such as toll-like receptors on Kupffer cells or dendritic cells. Activation of these receptors leads to production of reactive oxygen species (ROS) and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α).[19,20] ROS and cytokines stimulate a systemic inflammatory response, leading to potentially deleterious consequences including systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome, and death. In a recent review, systemic inflammation was proposed as the key mechanism in progression of compensated to decompensated cirrhosis, and was described as important precipitant in the development of encephalopathy, ascites, and renal failure.[9] Also in ALF, systemic inflammation has been described as an important contributor to multiorgan failure and disease progression.[21] It has been demonstrated that progressive encephalopathy in ALF patients may be associated with more severe SIRS and that SIRS worsens the prognosis of ALF.[17]

Mechanisms of Organ Failure Caused by Systemic Inflammation

Several mechanisms have been described to link systemic inflammation and multiorgan failure. First, tissue damage is caused by ROS and cytokines released in the inflammatory response. Second, systemic inflammation causes dysregulation of vascular tone, which leads to altered blood flow and vasoconstriction in tissue vascular beds. The consequent hypoperfusion in the brain or kidneys, for example, may lead to hepatic encephalopathy or renal failure.[9,21] Third, the metabolic demand of activated innate immune cells causes a shortage of nutrients in peripheral organs and decreased mitochondrial oxygen consumption and ATP-production. This decrease in energy production in peripheral organs may lead to dysfunction and multiorgan failure.[9]

Definition of Systemic Inflammation in Acutely Ill Liver Patients

It is of importance how the inflammatory state is defined in patients with (acute) liver disease. Many studies have used biomarkers such as IL-6 and C-reactive protein to assess systemic inflammation or sepsis in liver patients. However, interpreting the levels of systemically elevated markers of inflammation might be challenging in (severe) liver disease, since massive hepatic inflammation alone can cause a sustained increase in those biomarkers. In addition, elevated levels of inflammatory biomarkers could reflect the failing liver rather than an actual inflammatory response, as the liver is responsible for clearance of many of those molecules. Simply measuring the levels of those biomarkers in peripheral blood might thus overestimate the proportion of patients with genuine systemic inflammation.[10] Evaluating the presence of SIRS components or sequential (sepsis-related) organ failure assessment may be better diagnostic tools for systemic inflammation in acutely ill liver patients.[22]

Inflammation and Coagulation

Inflammatory responses and activation of coagulation are invariably associated, as more recently emphasized in coronavirus disease 2019 (COVID-19), where the prothrombotic state is deeply sustained by enhanced release of proinflammatory mediators.[23] In vitro studies have demonstrated that activation of coagulation is initiated by most proinflammatory cytokines by activation of blood cells, resulting in expression of tissue factor (TF), and studies in human and animals have confirmed the roles of cytokines such as TNF-α and IL-6 in activation of blood coagulation.[12] Activation of blood coagulation in turn triggers various mechanisms by which it contributes to boost the inflammatory response, mediated, for example, by thrombin generation during coagulation. Inflammation and coagulation are intricately related processes, which may considerably affect each other.[24] Pathways that cause activation of coagulation upon inflammatory stimulation are summarized in ►**Fig. 1**. Proinflammatory cytokines directly activate platelets or cause endothelial cell injury, leading to release of P-selectin and von Willebrand Factor (VWF), and subsequent increased platelet adhesion and aggregation. Secondary hemostasis activation in inflammation is mainly mediated by TF. Proinflammatory stimuli activate the expression of TF, which initiates the activation of coagulation leading to thrombin generation. Thrombin is a key enzyme in hemostasis, since it converts fibrinogen to fibrin, activates platelets, and

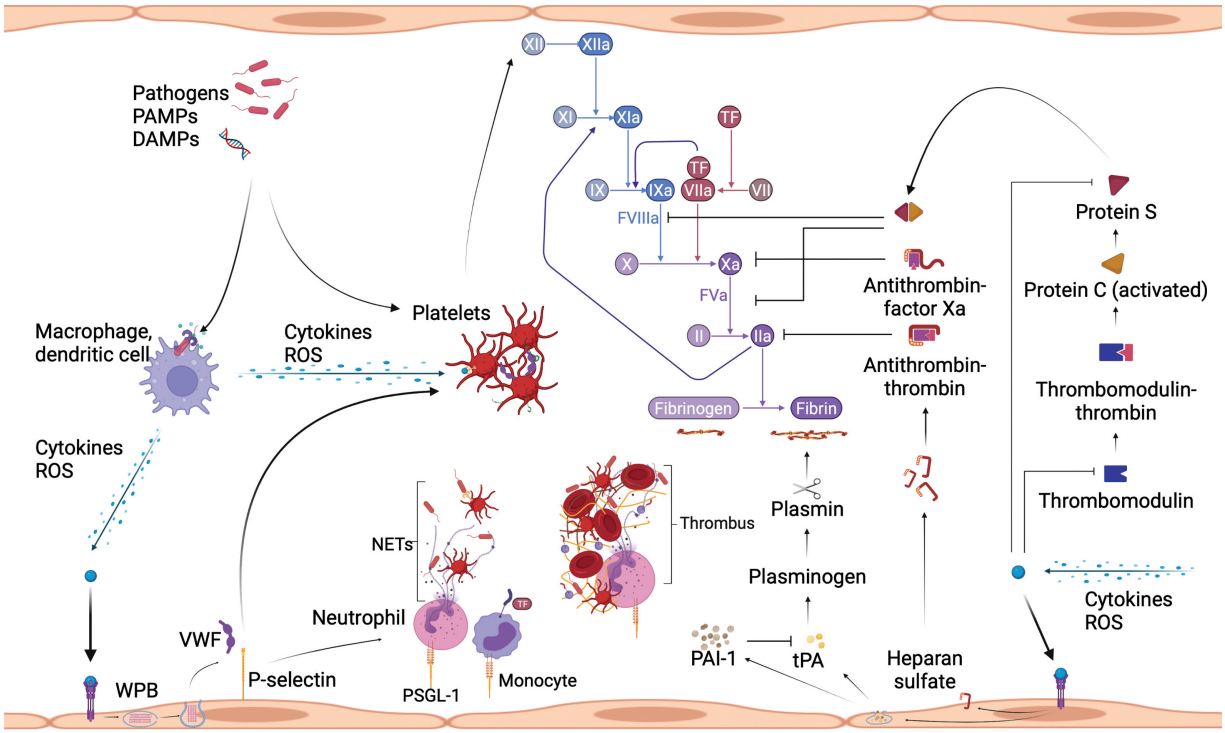

Fig. 1 Inflammation causes activation of coagulation. Proinflammatory stimuli from pathogens, PAMPs, and DAMPs cause release of cytokines and ROS from inflammatory cells. Cytokines and ROS stimulate endothelial cells to release VWF and P-selectin from WPB, resulting in platelet adhesion and aggregation. P-selectin also engages with PSGL-1 on neutrophils and monocytes that are activated to form NETs and express tissue factor, respectively. Inflammation-induced upregulation of tissue factor causes activation of the coagulation cascade, leading to thrombin generation and formation of a fibrin clot. Anticoagulant pathways are inhibited by cytokines and ROS. Inflammation activates fibrinolysis by plasmin through stimulated release of tPA, but also inhibits fibrinolysis through stimulated release of PAI-1 by endothelial cells. DAMPs, damage-associated molecular patterns; NETs, neutrophil extracellular traps; PAI-1, plasminogen-activator inhibitor-1; PAMPS, pathogen-associated molecular patterns; PSGL-1, P-selectin glycoprotein ligand-1; ROS, reactive oxygen species; tPA, tissue-type plasminogen activator; VWF, von Willebrand factor; WBP, Weibel-Palade Bodies. (Created with BioRender).

regulates coagulation and fibrinolysis by activation of multiple pro- and anticoagulant, and antifibrinolytic enzymes.[25]

Inflammation causes dysfunction of anticoagulant pathways, leading to a hypercoagulable state. Antithrombin is the main inhibitor of thrombin and activated factor X, and plasma levels are markedly reduced during inflammatory responses. In addition, glycosaminoglycans (such as heparan sulfate) at endothelial surfaces act as a physiological heparin-like cofactor of antithrombin, and are released into plasma as a consequence of inflammatory stimuli. This results in a more prothrombotic endothelial surface, but the heparin-like effect of these glycosaminoglycans may also result in a hypocoagulable state within the plasma compartment.[26] Another important anticoagulant system is the protein C pathway, which is inhibited by inflammatory cytokines, for example, due to down-regulation of thrombomodulin during systemic inflammation. Thrombomodulin forms a complex with thrombin to activate protein C under normal conditions. Activated protein C then interacts with protein S to inactivate activated factor V (FVa) and VIII (FVIIIa), which inhibits coagulation. Reduced levels of thrombomodulin thus result in a more prothrombotic state, which is enhanced by the inactivation of protein S by inflammatory cytokines.[24,27] Fibrinolysis is inhibited during inflammatory states, mainly by inflammatory stimulation of plasminogen activator inhibitor-1 (PAI-1) expression.[28] The effects of inflammation on hemostatic alterations in acutely ill liver patients will be discussed in the following sections.

Hemostatic Alterations in Acutely Ill Liver Patients

There is now abundant literature on the hemostatic changes in patients with stable cirrhosis. Most studies have been performed with patients sampled on the outpatient clinic and most studies have grouped patients with varying etiologies of disease. It has been demonstrated that in patients with mild cirrhosis, hemostatic changes were comparable between different etiologies.[29] Only in recent years, hemostatic changes of hospitalized patients with severe disease have been described, and results will be discussed in this section. ►**Table 1** summarizes hemostatic changes in patients with mild cirrhosis, those with ACLF, and those with ALF, based on work published by our group[29–33] or others.[34]

Primary Hemostasis—Platelets

Patients with liver diseases have both hyper- and hypocoagulable changes in their primary hemostatic system,[35] with one of the clearest being thrombocytopenia. Thrombocytopenia, defined as platelet counts $<150 \times 10^9$/L, is common in chronic liver disease, but rarely becomes severe (platelet counts $<50 \times 10^9$/L). Decreased platelet counts have been

Table 1 Hemostatic changes in patients with mild cirrhosis, acute-on-chronic liver failure, and acute liver failure

	Healthy volunteers	Mild cirrhosis	Acute-on-chronic liver failure	Acute liver failure
Platelets (x 10^9/L)	244 (188-302)	108 (81–141)	75 (48–110)	137 ± 87
Fibrinogen (g/L)	2.7 (2.5–3.0)	3.4 (2.2–4.3)	1.4 (1.2–1.5)	1.9 ± 0.8
VWF (%)	150 (106–198)	298 (140–502)	695 (385–1047)	448 ± 221
ADAMTS13 (%)	90 (79–104)	90 (31–109)	33 (17–51)	21.1 ± 23.2
AT (%)	112 (102–117)	87 (49–106)	27 (14–34)	37 ± 13
Protein C (%)	112 (101–128)	79 (40–100)	13 (12–20)[34]	5 (5–50)
INR	1.0 (0.98–1.07)	1.1 (1.16–1.4)	1.8 (1.6–2.3)	3.6 ± 1.9
TGA ETP (nM IIa, min)	420 (305–581)	607 ± 123	597 ± 292	550 ± 389
CLT (min)	64 (59–68)	59 (55–67)	67 (49–109)	143 ± 45

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AT, antithrombin; CLT, clot lysis time; ETP, endogenous thrombin potential; INR, international normalized ratio; TGA, thrombin generation assay; VWF, von Willebrand factor.
Note: Values are presented as median (interquartile range) or mean ± standard deviation. Values are based on work published by our group,[29–33] or others.[34]

associated with more advanced disease and worse prognosis.[36] However, although platelet counts may be lower in ACLF patients compared with non-ACLF cirrhotic patients,[37] even acutely ill liver patients do not often have severe thrombocytopenia.[38,39] Several reasons for thrombocytopenia in liver disease have been described, such as platelet sequestration by the spleen (i.e., hepatosplenomegaly), more rapid turnover and shorter half-life of platelets, production of antiplatelet antibodies, bone marrow suppression as a result of chronic liver disease, and reduced liver production of thrombopoietin.[40,41] Worse severity of liver disease could therefore explain the worsening of thrombocytopenia in acutely ill liver patients.

Thrombocytopenia is common in systemic inflammation and sepsis unrelated to liver disease. The main causes are decreased platelet production, enhanced platelet consumption, and immune-mediated platelet destruction.[42] Interestingly, thrombopoietin levels are upregulated during systemic inflammation,[43,44] and increased thrombopoietin levels were also found in serum samples from ALF patients taken at the second day of hospitalization.[45] This suggests that defective platelet production is not the reason for thrombocytopenia in these patients. Thrombocytopenia associated with systemic inflammation in patients with chronic and ALF may be related to inflammation-mediated platelet activation.[11,46] For example, LPS and neutrophil extracellular traps (NETs) cause activation of platelets with subsequent microparticle-release in nonliver septic patients, and is associated with thrombocytopenia and hospital mortality.[47,48] The US-based ALF Study Group showed that in patients with acute liver injury/ALF, especially those with SIRS, levels of microparticles were highly elevated and the majority of these microparticles were of platelet origin, suggesting that SIRS drives platelets to generate microparticles. These microparticles release proinflammatory cytokines, thereby aggravating the inflammatory state. The prothrombotic features of microparticles could also contribute to liver failure by intraorgan microthrombosis,[11] as platelet fragmentation and microparticle release is a well-recognized feature in sepsis as part of disseminated intravascular coagulation. This may lead to further liver injury, hypoxia, and multiorgan failure. Higher levels of microparticles were indeed associated with worse outcome in ALF patients,[49] and although no data on the role of platelet-derived microparticles exists in inflammation and disease progression in chronic liver disease, it could be hypothesized that similar mechanisms take place in those patients.

Platelet levels can be partly assessed by thromboelastography (TEG) assays that provide information on hemostatic function using whole blood. The clot firmness parameter, the maximum amplitude of the curve, is primarily a function of platelet and fibrinogen levels. TEG results from ACLF and AD patients show decreased clot firmness compared with healthy controls[39] or patients with stable cirrhosis.[50] No significant differences in maximum amplitude between ACLF patients with or without sepsis were observed.[39] In addition, patients with ALF with or without systemic inflammation do not display differences in maximum clot firmness by TEG.[51] It could be that other coagulation factors or acute phase proteins involved in inflammation and coagulation could compensate for thrombocytopenia, and therefore no difference in clot firmness is observed in the presence or absence of inflammatory responses.

Next to decreased platelet counts, alterations of platelet function are also frequently observed in patients with chronic or acute liver disease. Little is known about the mechanisms by which this occurs, and results of available studies are contradictory. Some studies suggested that platelet function is decreased in cirrhotic patients, while others suggested increased or unaltered platelet activity.[52] To the best of our knowledge, no data are currently available on specific platelet function assays in acutely ill liver patients, and this area requires more research.

Primary Hemostasis—von Willebrand Factor

Another constituent of primary hemostasis is the platelet-adhesive protein VWF, which is present in four to eight times higher levels in patients with liver diseases compared with

healthy controls.[1] VWF functions through binding to collagen at vascular injury sites and binding to the glycoprotein Ib receptor on platelets, which initiates and mediates platelet adhesion and aggregation. High molecular weight multimers of VWF are the most effective in supporting interaction between collagen and platelets.[53] The largest multimers of VWF are normally cleaved by the enzyme ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), and in addition ADAMTS-13 cleaves VWF within a growing thrombus. ADAMTS-13 activity levels are markedly reduced in patients with decompensated cirrhosis.[54] Therefore, the imbalance between VWF and ADAMTS-13 appears a hypercoagulable feature in liver patients, and elevated VWF levels in liver diseases may compensate for thrombocytopenia.[55,56] The relevance of low ADAMTS-13 levels is incompletely understood. Circulating VWF in these patients lacks higher molecular weight multimers, which suggests that proteases other than ADAMTS-13 (such as plasmin, elastase, or cathepsin G) are actively cleaving VWF.[55] Conversely, it is conceivable that lack of VWF proteolysis by ADAMTS-13 within a growing thrombus is a prothrombotic feature in patients with liver disease. The VWF/ADAMTS-13 imbalance worsens from patients with stable cirrhosis to AD to ACLF, and predicts poor outcome in patients with ALF.[30,31] Inflammation in acutely ill liver patients may enhance the VWF/ADAMTS-13 imbalance, as activation of endothelial cells and subsequent cytokine release leads to VWF secretion, and function and levels of ADAMTS-13 are reduced as a result of systemic inflammation.[57] The release of ROS and myeloperoxidase causes oxidation of ADAMTS-13 protein, leading to reduced enzymatic activity.[58] In addition, disturbance of liver function will result in reduced synthesis of ADAMTS-13.

Although the VWF/ADAMTS-13 imbalance suggests a more hypercoagulable state, we recently showed in a large cohort of ALF patients that a more severe VWF/ADAMTS-13 imbalance was not associated with thrombotic, but rather with bleeding complications.[31] The paradoxical association between a hypercoagulable VWF/ADAMTS13 profile and bleeding could be explained by an enhanced inflammatory state in patients with hypercoagulable VWF/ADAMTS13 profile. Most bleeding complications in ALF patients reported in another study from the US ALF Study Group were upper gastrointestinal bleeds that are likely unrelated to hemostatic failure but rather a consequence of stress-related mucosal disease, a manifestation of critical illness characterized by intense systemic inflammation.[59,60] Whether AD and ACLF patients with systemic inflammation have these inflammatory-related bleeding complications as well remains to be investigated.

Secondary Hemostasis—Global Tests of Hemostasis

Most coagulation factors are produced by the liver, and patients with liver diseases thus have decreased levels of both pro- and anticoagulant factors. The concomitant decrease of pro- and anticoagulant factors leads to a rebalanced hemostatic state[1] that persists even in the sickest patients with AD, ACLF, and ALF.[3]

Conventional coagulation tests such as the prothrombin time or INR are often used to estimate the patients' bleeding risk, despite evidence that these tests do not have predictive value for bleeding complications,[61] because they do not consider the decreases of naturally occurring anticoagulants. Global tests of hemostasis such as thrombomodulin-modified thrombin generation assays (TGAs) are sensitive for the balance between pro- and anticoagulant factors. These tests have shown that the endogenous coagulation potential in patients with AD and ACLF is normal to increased compared with stable cirrhosis patients or healthy controls.[62] Also in patients with ALF, thrombin generation is similar to that of healthy controls.[31,63] Next to TGAs, viscoelastic tests (VETs) are also capable to measure global hemostasis. TGAs and VETs can be performed with whole blood and thus incorporate the supporting effects of blood cells in coagulation. These VETs, TEG, rotational thromboelastometry (ROTEM), and sonorheometry measure the kinetics of clot formation. Both TEG and ROTEM parameters are often normal in patients with cirrhosis, indicating rebalanced hemostasis in stable cirrhosis.[37,64–66] In AD and ACLF patients, TEG often gives normal results, but ROTEM and Sonoclot results indicate a more hypocoagulable profile in acutely ill cirrhotic patients.[8,46,67] Hypocoagulable results include delayed clot formation, longer clot formation time and decreased maximum clot firmness, and are more frequently observed in patients with systemic inflammation. Inflammation and hypocoagulable TEG and ROTEM results in ACLF patients were associated with higher 28- and 90-day mortality rates, but not with bleeding or transfusion requirements, which is explained by bleeding in these patients being unrelated to hemostatic alterations.[8,46]

TEG parameters are also often normal in patients with ALF.[51,68] For example, in a study with 50 ALF patients, two-thirds of the included patients had normal results for all the parameters of the TEG-curve. However, systemic inflammation in these patients gave more hypocoagulable reaction time, but hypercoagulable clotting time and maximum clot firmness.[51] The more hypercoagulable TEG results in ALF patients with systemic inflammation could be a reflection of increased endothelial activation, resulting in increased FVIII levels. In addition, hypercoagulable TEG results could reflect increased fibrinogen levels and platelet counts related to an inflammation-associated acute phase response. ROTEM results are more hypocoagulable in ALF patients, and are associated with more systemic complications such as SIRS.[69] Differences between VETs may be attributed to the activators that are used. As the initiating trigger in ROTEM is stronger than in TEG, the ROTEM is less sensitive to anticoagulant factors, and is therefore more often abnormal in patients with liver disease. In addition, all VETs are insensitive to VWF and the anticoagulant protein C system, and therefore VETs underestimate the true hemostatic potential in patients with liver disease.[70] Of note, all global tests of hemostasis have limitations and should be interpreted with caution. Importantly, there is no firm evidence that global tests results predict bleeding or thrombosis in patients with liver disease.[71]

A correlation between systemic inflammation and a more hypocoagulable profile could be explained by a heparin-like effect as a result of inflammation. Endogenous heparinoids are stored in mast cells, which are activated by infectious triggers (LPS, IL-1, TNF-α) during an inflammatory response.[72] In addition, mast cells are able to synthesize and release other mediators with anticoagulant activity, such as tryptase (in complex with heparin) and prostaglandins (acting as antiplatelet agents). Endothelial cells can also release heparin-like substances. In a study performed in 60 cirrhotic patients, hypocoagulable TEG results were associated with inflammatory responses, where heparinase-modified TEG analyses showed a significant heparin-like effect in patients with inflammation, whereas no heparin-like effect was detected in those without.[73] The effect disappeared after resolution of infection. This effect could be enhanced in acutely ill liver patients with inflammation, as LPS and cytokine levels are higher. However, LPS and cytokine release also causes activation of coagulation. The heparin-like effect in blood could be an initial response to inflammatory stimuli, and may be rebalanced by the procoagulant effects of inflammation on endothelial cells.

Fibrinogen Properties

Fibrinogen is a soluble protein primarily synthesized by hepatocytes, and plays a central role in clot formation and stabilization. Fibrinogen levels remain normal or are increased in patients with mild-to-moderate cirrhosis,[74] and despite its acute phase reactant character, patients with AD, ACLF, or ALF do not have increased levels. In fact, these patients often show decreased fibrinogen values, and no significant differences are found between ACLF patients with and without systemic inflammation.[3,8,51] A possible explanation for decreased fibrinogen levels in acutely ill liver patients is reduced liver synthetic capacity and fibrinogen consumption.[75] For example, in a study with 237 cirrhosis patients admitted to an intensive care unit with initial fibrinogen levels less than 1.5 g/L, severity of illness was strongly correlated with low fibrinogen levels. However, low fibrinogen levels on hospital admission were not independently associated with 30-day mortality. Treatment of low fibrinogen with cryoprecipitate also did not affect survival or bleeding complications, which suggests that fibrinogen is an additional marker of severity of illness but is not directly contributing to the pathophysiology of bleeding in acutely ill liver patients.[76]

Qualitative and functional alterations in fibrinogen and fibrin networks are a common finding in patients with liver diseases. For example, turbidity assays showed that fibrin polymerization rates of isolated fibrinogen from patients with liver diseases are reduced or delayed.[77] Delays in fibrin polymerization have been ascribed to posttranslational modifications in fibrinogen, such as oxidation, nitration, and sialylation, and are frequently observed in other settings in which inflammation or oxidative stress is prominent.[78] In a study with plasma samples from patients with cirrhosis, delayed TF and thrombin-induced clotting of plasma were observed, which could (partly) be ascribed to increased sialylation (a specific form of glycosylation) of fibrinogen in patients with cirrhosis.[78,79] Although no data are available yet on specific posttranslational protein modifications in acutely ill liver patients, systemic inflammation in these patients may cause multiple posttranslational changes and therefore change clotting and polymerization rates of fibrin. Indeed, other diseases associated with systemic inflammation showed increased glycosylation, oxidation, and nitration in fibrinogen.[78] Experiments in mice show that factor XIII (FXIII)-dependent fibrin(ogen) crosslinking within the liver of mice with ALF proceeds normally, even in the absence of effective fibrin polymerization, which is impaired in this model by oxidative modification of fibrinogen.[80] Thus, although thrombin-catalyzed fibrin polymerization is inhibited by oxidative fibrinogen modification, cross-linking and fibrinogen deposition within the liver can take place independently of thrombin, but dependent on FXIII.

In addition to clotting and polymerization rates, fibrin fiber density and fibrin network permeability may be altered by posttranslational fibrinogen protein modifications. Our group has measured the permeability of in vitro formed fibrin clots that gives information about the pore size between fibrin fibers. Despite decreased plasma levels and functional defects of fibrinogen, we showed that clot permeability was decreased in cirrhotic patients compared with healthy controls. Interestingly, no differences in fibrin density and fibrin fiber diameter were observed, and it is incompletely understood what causes the decrease in fibrin permeability.[81] Reduced permeability of the clot, even in patients with decreased fibrinogen plasma levels, may implicate a thrombotic phenotype of fibrin clots. Increased markers of inflammation have been associated with decreased clot permeability in other settings, such as chronic obstructive pulmonary disease,[82] rheumatoid arthritis,[83] and coronary artery disease.[84] We compared permeability of clots between healthy controls, ACLF patients, and nonliver sepsis patients.[3] Patients with ACLF had similar permeability compared with healthy controls, whereas the septic patients had significantly decreased permeability. These results were in line with fibrinogen levels, which were normal to slightly decreased in ACLF patients, but significantly elevated in nonliver sepsis patients. Preliminary data from our group on rheology experiments with plasma from stable cirrhosis patients, ACLF patients and nonliver septic patients, showed that clots from ACLF patients are softer and less viscous than in the other groups, independent of fibrinogen levels. Clots from ACLF patients thus have both hypo- and hypercoagulable features. The exact mechanisms underlying these divergent functional changes require further scrutiny, but it is plausible that the multiple posttranslational protein modifications may be involved.

Fibrinolysis

Fibrinolysis is the enzymatic breakdown of fibrin in blood clots catalyzed by plasmin. Tissue plasminogen activator (tPA) is responsible for the activation of plasminogen to form plasmin. In patients with AD and ACLF, plasma levels of tPA are elevated, whereas plasminogen levels are

significantly decreased compared with healthy controls.[85] PAI-1 (present in elevated levels in AD and ACLF patients) and thrombin activatable fibrinolysis inhibitor (TAFI; present in decreased levels in AD and ACLF patients) are inhibitors of fibrinolysis. Most proteins involved in fibrinolysis are synthesized by the liver, except tPA and PAI-1, which are produced by endothelial cells, and may therefore be elevated in acutely ill liver patients with inflammation-related endothelial activation. Indeed, AD and ACLF patients with sepsis had higher levels of PAI-1 compared with those without.[85]

Plasma-based clot lysis time (CLT) assays provide information on the (in vitro) fibrinolytic potential. Patients with stable cirrhosis have normal to hyperfibrinolytic CLT results.[86] Patients with AD and ACLF have larger variability in their CLT values compared with healthy controls,[30,85] and median values of CLT indicated that patients with AD were more hyperfibrinolytic (lower CLT) and those with ACLF were more hypofibrinolytic (higher CLT). In particular both ACLF and sepsis patients had very high CLT values. Plasma levels of fibrinolytic proteins were only weakly correlated with CLT values, which are likely due to simultaneous up- and down-regulation of fibrinolytic proteins. This in turn is a result of reduced protein production due to liver injury and increased secretion of fibrinolytic mediators due to systemic inflammation. Elevated levels of circulating TNF-α and IL-1β lead to release of tPA and urokinase-type plasminogen activator from storage sites in endothelial cells. Although this may lead to hyperfibrinolysis, highly elevated levels of PAI-1 as a result of systemic inflammation overwhelm this increase in plasminogen activation, leading to complete inhibition of fibrinolysis.[12,87] Interestingly, although tPA release is elevated in systemic inflammation, a recent study on fibrinolysis in acutely ill liver patients showed no differences in tPA levels between patients with or without sepsis.[85] PAI-1 levels were higher and plasminogen and TAFI levels were lower in acutely ill liver patients with sepsis than those without, corresponding to prolonged CLT in the former group.[85] Inhibited fibrinolysis contributes to microvascular thrombosis and organ failure in acutely ill patients without underlying liver disease,[88] and is associated with higher severity of liver disease and 30-day mortality in acutely ill liver patients.[85]

Similar to acutely ill patients with cirrhosis, those with ALF also have increased levels of tPA and PAI-1 and decreased levels of plasminogen and TAFI.[32] CLT in ALF patients is remarkably prolonged, indicating a hypofibrinolytic state, as was shown in a large cohort of patients with ALF.[31] The hypofibrinolytic profile in patients with ALF is likely related to very high PAI-1 and very low plasminogen levels. In addition, the presence of SIRS in ALF patients was associated with hypofibrinolysis, as 75.6% of patients with SIRS had lysis time of >3 hours versus 53.4% of those without. However, no relationship between hypofibrinolysis and short-term mortality could be found in these ALF patients, which may be explained by the high rate of acetaminophen-induced ALF in the studied cohort. Patients with acetaminophen-induced ALF have higher PAI-1 levels, but also better prognosis than ALF of other etiologies.[89] The more profound hypofibrinolytic state in patients with acetaminophen-induced ALF, but better outcome compared with those with ALF of other etiologies, thus likely explains the discrepancy between hypofibrinolysis and disease severity.

Correction of Altered Hemostasis in Acutely Ill Liver Patients

The hemostatic changes described in acutely ill liver patients concern both pro- and antihemostatic pathways and result in a preserved hemostatic balance. Inflammation may cause prothrombotic or prohemorrhagic alterations (summarized in ►**Table 2**), but whether these changes are clinically relevant and should be corrected with antithrombotic drugs or blood products is incompletely understood.

Prevention of Bleeding Complications

Spontaneous, portal hypertension-unrelated bleeding complications in acutely ill liver patients are rare, and mostly unrelated to the presence of hemostatic failure.[90–92] Importantly, the INR is not an indicator of the hemostatic state in these patients, and misinterpretation of its values may result in overutilization of prophylactic prohemostatic agents such as fresh-frozen plasma. Decreased platelet counts have been suggested to be merely a reflection of advanced portal hypertension or systemic inflammation,[11,59,93] and not a causative factor for bleeding. In addition, elevated levels of VWF likely compensate for thrombocytopenia in acutely ill liver patients. The observations that acutely ill liver patients have preserved thrombin generation capacity and absence of increasing bleeding complications, while the amount of blood product transfusions has declined over the past decades, also argue against the prophylactic administration of procoagulants.[59] Low levels of fibrinogen are mostly not related to bleeding complications, and are more a reflection of critical illness. Correcting fibrinogen levels that are <1 g/L before high-risk procedures could be considered in acutely ill liver patients, though specific data from use of fibrinogen concentrates in liver patients to reduce bleeding complications are still lacking.[94–96] Antifibrinolytic agents are rarely used prophylactically if the patient is not a liver transplant candidate, but are more commonly used as a rescue measure when bleeding occurs after procedures. The role of antifibrinolytics to prevent bleeding complications in acutely ill liver patients is unknown.[97]

Prevention of Thrombotic Complications

Acutely ill liver patients are at risk of thrombotic complications since the liver disease itself has been identified as a risk factor for venous thromboembolism (VTE), and hospitalization with in particular admission to a critical care unit is also a known predisposing factor for VTE. Interestingly, in a recent large retrospective study of acutely ill cirrhosis patients, venous thrombotic complications were more common than bleeding complications.[92] Of the 623 patients included, bleeding occurred in 87 (14%) patients, and VTE occurred in 125 (20%) patients. Acutely ill liver patients may benefit from thromboprophylaxis or therapeutic administration of anticoagulants to prevent development or extension of portal vein thrombosis. However, thromboprophylaxis may not result in

Table 2 Hemostatic alterations in patients with AD/ACLF or ALF and the net effect on the hemostatic state in these patients

Patients	Part of hemostasis	Hemostatic alterations	Net effect
AD/ACLF	Primary hemostasis	Thrombocytopenia VWF/ADAMTS13 imbalance	Elevated VWF levels compensate for thrombocytopenia. Inflammation may cause an overcompensation of this effect
	Secondary hemostasis	Normal thrombin generation Normal TEG Hypocoagulable ROTEM	Rebalanced hemostasis
	Fibrin(ogen) properties	Decreased fibrinogen levels Delayed fibrin crosslinking and polymerization Decreased fibrin clot permeability	Inflammation is not associated with higher levels of fibrinogen Posttranslational fibrinogen modifications as a result of inflammation could result in a more thrombotic clot phenotype
	Fibrinolysis	AD: Hyperfibrinolytic ACLF: Hypo- to hyperfibrinolytic; highly variable	Hypofibrinolysis is associated with sepsis and multi organ failure
ALF	Primary hemostasis	Thrombocytopenia VWF/ADAMTS13 imbalance	Although VWF/ADAMTS-13 imbalance is hypercoagulable, it is associated with bleeding complications (due to stress related mucosal disease)
	Secondary hemostasis	Normal thrombin generation Normal TEG Hypocoagulable ROTEM	Rebalanced hemostasis
	Fibrin(ogen) properties	Decreased fibrinogen levels Delayed fibrin polymerization	Inflammation is not associated with higher levels of fibrinogen Not related to bleeding complications
	Fibrinolysis	Increased CLT indicate a hypofibrinolytic state	Not associated with increased mortality

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALF, acute liver failure; CLT, clot lysis time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; VWF, von Willebrand factor.

sufficient anticoagulant effects in intensive care unit patients, who may be "heparin-resistant" for multiple reasons.[98] Indeed, studies with cirrhotic patients admitted to regular wards have shown that standard thromboprophylaxis did not reduce thrombosis risk.[97] Nevertheless, in a recent study performed by our group, it was shown that heparins have comparable anticoagulant effects in patients with ACLF as in those with cirrhosis or nonliver hospitalized, suggesting that the doses as currently used in patients without underlying liver disease might equally be suitable for those with ACLF.[99]

Treatment of Systemic Inflammation

Systemic inflammation likely increases the risk of thrombotic complications in acutely ill liver patients. Besides the increased risk of VTE, the inflammation-associated activation of coagulation can lead to progression of liver disease. For example, activation of coagulation causes intrahepatic fibrin and platelet deposition, as demonstrated in animal models.[100] This intrahepatic activation of coagulation leads to disease progression by inducing local ischemia, for example. Inflammation in liver disease may activate additional processes that may propagate liver injury by generating procoagulant NETs.[101] On the other hand, inflammation may increase the risk of bleeding complications as a result of release of anticoagulant endogenous heparinoids and as a complication of stress-related mucosal disease. Future studies are required to investigate the effects of specific anti-inflammatory strategies in acutely ill liver patients, as this may halt progression of liver disease and development of both thrombotic and bleeding complications.

Conclusion

Patients with liver diseases in general have rebalanced hemostasis, which remains even in the sickest patients. Systemic inflammation has profound prothrombotic effect in acutely ill liver patients, but may have some hypocoagulable effects on hemostasis tests, for example, due to consumption of components of coagulation or to heparin-like effect in plasma. Targeting inflammation in preventing liver disease progression and development of thrombotic and bleeding complications should be the focus of future studies in acutely ill liver patients.

Conflict of Interest
None declared.

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