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Fibrinolysis in Patients with Liver Disease

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Abstract

Keywords

- liver disease
- coagulation
- fibrinolysis
- cirrhosis
- acute liver failure
- acute-on-chronic liver failure
- antifibrinolytic therapy
- liver transplantation

Patients with liver disease acquire complex changes in their hemostatic system. Historically, these patients were considered to have a bleeding tendency related, in part, to a hyperfibrinolytic state. However, studies using more modern fibrinolysis tests have questioned the presence of a hyperfibrinolytic state in patients with liver disease and its association with bleeding risk. It may be that the sickest patients with liver disease do have fibrinolytic abnormalities. However, the debate on the fibrinolytic state of patients with (decompensated) cirrhosis or critically ill liver disease is complicated by the fact that hypo- and hyperfibrinolysis have been poorly defined. This could, in part, be explained by the lack of reliable tests that assess a patient's fibrinolytic status. Moreover, large clinical studies on the relationship between bleeding and fibrinolysis in patients with liver disease are scarce. Here, we provide an overview of the current knowledge on fibrinolysis in various types of liver diseases and possible implications as a target for therapeutic strategies in liver disease. As antifibrinolytic therapy has been shown to be safe and effective during liver transplantation, it could potentially be of use in patients with (either laboratory-established or suspected) hyperfibrinolysis-related bleeding.

The liver plays a central role in the hemostatic system, as it is the site of synthesis of many hemostatic proteins. As a consequence, patients with liver diseases ultimately acquire complex changes in their hemostatic system.¹ Such changes include thrombocytopenia and (ill-defined) functional changes in platelets and decreases in plasma levels of pro- and anticoagulant proteins, as well as changes in proteins involved in the fibrinolytic system.² The hemostatic changes of patients with liver disease are not exclusively related to defective hepatic synthesis of hemostatic proteins. For example, chronic endothelial activation, which is likely related to a systemic inflammatory response, results in elevated levels of endothelial-derived proteins including von Willebrand factor, tissue-type plasminogen activator (tPA), and plasminogen activator inhibitor type 1 (PAI-1).^{3–5} In addition, the thrombocytopenia of liver disease is related not only to defective hepatic synthesis of thrombopoietin but

also to direct bone marrow toxicity, increased clearance, and splenomegaly.^{6,7} Finally, a consumptive process, either systemically or by activation of hemostasis within the diseased liver, likely contributes significantly to the hemostatic changes in patients with liver diseases.^{2,8}

Historically, patients with liver diseases and hemostatic changes were considered to have a hemostasis-related bleeding tendency. The observations of clinical bleeding combined with abnormalities in laboratory tests of hemostasis, such as increased prothrombin time (PT) and reduced platelet count, were seemingly consistent with a liver disease related coagulopathy. However, although bleeding in patients with chronic liver disease is frequent, bleeding complications are often unrelated to failing hemostasis, but are rather a consequence of portal hypertension (e.g., variceal bleeding) or mechanical injury, for example, inadvertent laceration of large vessels during invasive procedures.^{9,10} Interestingly, patients with

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acute liver failure (ALF), who have the most pronounced decreases in plasma levels of coagulation proteins rarely bleed,¹¹ and a proportion of patients undergoing liver transplant surgery are able to endure this lengthy and invasive procedure without the requirement for blood product transfusion despite profound intraoperative abnormalities in routine tests of hemostasis, such as the PT and platelet count.¹² These observations thus argue against the historic concept that patients with liver disease hold a (severe) bleeding tendency.

These clinical observations combined with extensive laboratory studies have led to a substantial change in the historic dogma of liver diseases such as hemostasis-related bleeding disorders. Patients with liver diseases are now considered to be in a state of rebalanced hemostasis due to simultaneous changes in pro- and antihemostatic factors (summarized in ►Fig. 1).¹³ This state of rebalanced hemostasis appears maintained even in the sickest patients, although the stability of the hemostatic status is likely decreasing with increasing severity of disease.¹⁴ This decreased stability of the hemostatic balance explains why some patients do experience hemostasis-related bleeding complications, whereas others experience thrombotic events including deep vein thrombosis, pulmonary embolism, and portal vein thrombosis.¹⁵

Historically, patients with liver diseases have been described to have accelerated fibrinolysis, which was recognized as early as 1914, and it has long been generally accepted that this hyperfibrinolytic state contributes to bleeding.¹⁶ However, studies using more modern fibrinolysis tests have questioned the presence of a hyperfibrinolytic state, and the causality behind previously established links between laboratory evidence of hyperfibrinolysis and clinical bleeding has also been questioned. Specifically, studies have described hyperfibrinolysis to be linked to the risk of gastrointestinal bleeding.¹⁷ However, the most common gastrointestinal bleeding complication, variceal bleeding, is unrelated to hemostatic failure but is rather exclusively related to portal hypertension and local vascular abnormalities.^{18,19} Clinical observations support the notion that variceal bleeding is unrelated to hemostatic failure. Specifically, the severity or outcome of variceal bleeding is not different between patients who are or are not using anticoagulant drugs at the time of the bleed,²⁰ and the use of anticoagulants does not increase the risk of a future variceal bleed.²¹

This paper provides current concepts of the fibrinolytic status in various types of liver diseases and addresses in which patients antifibrinolytic therapy may be useful in treating or preventing bleeding episodes.

How to Define Fibrinolytic Status?

A key issue in previous debates on the fibrinolytic status of patients with liver disease is the definition of abnormal fibrinolysis. In contrast to a hyper- or hypocoagulable state, which is defined by a combination of laboratory abnormalities and elevated thrombotic risk or clinical bleeding, definitions of hyper- or hypofibrinolysis are much less clear. This is, in part, because we lack well-validated tests of fibrinolysis

and because the causal relationship between laboratory abnormalities in the fibrinolytic system and clinical outcome has not been firmly established.

Clinically, a hyperfibrinolytic state is obvious in patients with congenital fibrinolytic abnormalities associated with bleeding, such as antiplasmin deficiency, PAI-1 deficiency, or Quebec platelet disorder.²² The definition of a hypofibrinolytic state is already much less obvious; although one would expect that congenital plasminogen deficiency would predispose to thrombosis, in reality these patients are not at increased risk of venous or arterial thrombosis but rather present with a specific pathology of the eye (ligneous conjunctivitis).²³ Acquired hyperfibrinolytic states are defined by a combination of clinical bleeding and laboratory abnormalities. Acquired hyperfibrinolysis can be primary (such as in acute promyelocytic leukemia) or secondary to excessive activation of coagulation (such as during cardiopulmonary bypass).²⁴ That the nature of a hyperfibrinolytic state is not always clear is evidenced, for example by trauma, which has been classified as both a primary and secondary hyperfibrinolytic state.^{24,25} Acquired hypofibrinolytic states most often are related to substantially elevated PAI-1 levels. Documented conditions in which laboratory evidence of PAI-1-related hypofibrinolysis is accompanied by thrombotic risk include obesity,²⁶ aging,²⁷ thrombosis,²⁸ trauma,²⁹ and the “postoperative fibrinolytic shutdown.”³⁰

From a laboratory perspective, abnormal fibrinolysis can be defined by multiple strategies, all of which have caveats. First, global tests of fibrinolysis in whole blood, plasma, or plasma fractions have been used. Whole blood tests (such as thromboelastography [TEG] or rotational thromboelastometry [ROTEM]) are not very sensitive for mild hyperfibrinolysis.³¹ Although multiple investigators use viscoelastic tests to classify patients as hypofibrinolytic,^{32,33} it is uncertain whether regular viscoelastic tests are suitable for this purpose, again due to sensitivity issues.³⁴ Specifically, although some patient groups have decreased fibrinolysis in TEG or ROTEM compared with a comparator group, the “hypofibrinolytic” patients have lysis parameters that are still in the normal range.³⁴ Viscoelastic tests modified by addition of tPA to the reagent may be more suitable for the detection of hypofibrinolytic states.³⁵ Plasma-based tests have shown merit in detecting both hyper- and hypofibrinolysis, and although abnormal fibrinolysis detected by these tests correlate with clinical bleeding or thrombosis, these tests are limited by the lack of cellular components that are known to affect fibrinolysis.^{36,37} Tests using plasma fractions, such as the euglobulin clot lysis, have been widely used as screening tests in the past, but the issues with reproducibility and the fact that the test is only sensitive for part of the fibrinolytic proteins (as others are removed during the euglobulin precipitation) limit the usefulness of the test. Second, antigen or activity assays of individual fibrinolytic factors have been used as indicators of hyper- or hypofibrinolysis, but this approach is only useful when a single-factor deficiency (such as plasminogen, antiplasmin, or PAI-1) or excess (tPA) is present. Finally, markers of activation of fibrinolysis have been used to identify hyperfibrinolytic states. For example,

The Hemostatic Balance

Fig. 1 Hemostatic balance in patients with liver disease. The hemostatic balance in healthy individuals (A) is stable. The hemostatic balance in patients with liver disease (B) is less stable and could be easily tipped over toward either bleeding or thrombosis. Concomitant changes in both pro- and anti-hemostatic pathways (table) result in a “rebalanced” hemostatic state in patients with liver disease. In the fibrinolytic system, changes including low levels of antiplasmin and elevated tPA levels often occur simultaneously with low levels of plasminogen and elevated PAI-1 levels, resulting in a rebalance of the fibrinolytic state in patients with liver disease. VWF, von Willebrand factor; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1. Image Courtesy: Warnaar et al⁸¹ (with permission from Wolters Kluwer Health).

elevated levels of plasmin–antiplasmin (PAP) complexes signal recent plasmin generation in circulation, and elevated levels of D-dimer signal recent breakdown of factor XIIIa crosslinked fibrin. Although PAP complexes may indicate recent plasmin formation, and high levels may thus indicate a hyperfibrinolytic state, under specific conditions false-positive results may be obtained. For example, high PAP complexes in patients with clinical bleeding or thrombosis may simply reflect a physiological response to fibrin formation rather than a hyperfibrinolytic state. Furthermore, in patients with liver disease, elevated PAP complexes may be a reflection of defective clearance of the complex rather than excessive production. Interpretation of elevated D-dimer levels in the context of fibrinolysis is difficult, as although elevated D-dimer may signal recent fibrinolysis, it is clinically related to (ongoing) clot formation.³⁸ Again, in patients with liver disease, D-dimer levels may be elevated because of lack of clearance. Indeed, one study showed that 100% of patients with severe cirrhosis had elevated D-dimer levels, whereas none of these patients had (macrovascular) thrombosis at the time of the D-dimer measurement.³⁹

When defining fibrinolytic status in relation to clinical outcome, a correct interpretation of both clinical features and laboratory parameters is key. Particularly in case of bleeding, it is mandatory to ascertain that the bleeding complications are likely related to hemostatic failure. Typical “hyperfibrinolytic” bleeding is delayed bleeding after surgery or trauma.⁴⁰ Bleeding complications in patients with cirrhosis such as variceal bleeding and bleeding after invasive procedures are often a result of nonhemostatic issues. For variceal bleeding, local vascular abnormalities and portal hypertension are initiators of the bleed, whereas many postprocedural bleedings are likely related to inadvertent vessel wall injury (e.g., puncture of a larger vessel during a paracentesis procedure).^{10,19} Possible relationships between fibrinolytic abnormalities and bleeding risk may not necessarily be causal but rather a reflection of severity of liver disease with increased portal hypertension, local vascular abnormalities, or more severe complications (e.g., massive ascites) that increase bleeding risk.

Also, when defining a fibrinolytic status, it is crucial to distinguish basal plasma hyperfibrinolytic activity from a fibrinolytic response to injury. The latter involves acute release of fibrinolytic activators (notably tPA), whereas basal fibrinolytic activity relies on circulating tPA. Under normal circumstances, plasma levels of circulating tPA are very low, and it is only after tPA release from endothelial cells that appreciable fibrinolytic activity commences.⁴¹ For this reason, fibrinolytic tests relying on circulating tPA (e.g., viscoelastic tests) may not provide very relevant information in patients without vessel injury, and tests that induce fibrinolysis by exogenous tPA may be more physiologically relevant.

Fibrinolysis in Stable Cirrhosis

The concept of a hyperfibrinolytic state in patients with compensated cirrhosis or outpatients that have (controlled) decompensated disease has a long history. Evidence in favor

of a hyperfibrinolytic state includes abnormalities in tests such as the euglobulin clot lysis time (CLT) or the whole blood CLT.^{42,43} The hyperfibrinolytic state as detected by these tests is at least, in part, driven by an unfavorable tPA/PAI-1 ratio in plasma,⁴⁴ which, as mentioned in the previous section, may not be that physiologically relevant. What may be physiologically relevant, but is vastly understudied, is the acute release of tPA induced by some sort of endothelial stimulation. In fibrinolysis research, venous occlusion has been frequently used to study acute fibrinolytic responses,⁴⁵ but to our knowledge, only one small study has been conducted in patients with cirrhosis, demonstrating excessive tPA release compared with healthy controls.⁴⁶ In addition, it has been demonstrated that tPA release after exercise or administration of nicotinic acid is prolonged, likely due to a reduced clearance of tPA by the diseased liver.^{47–49}

More contemporary studies have assessed fibrinolytic status in patients with liver diseases by plasma-based or whole blood assays. In the plasma-based assays, fibrinolysis is initiated by exogenous tPA, whereas the whole blood tests rely on endogenous plasminogen activators. Plasma-based clot lysis has been well validated in relation to thrombotic risk, and large epidemiological studies have shown plasma hypofibrinolysis to increase the risk of both venous and arterial thrombosis.⁵⁰ These assays, however, have not been extensively studied in the context of a bleeding tendency. Studies on fibrinolytic status in patients with relatively stable disease have been conflicting, with some finding no evidence of a hyperfibrinolytic state and others reporting hyperfibrinolysis in a proportion of patients.^{39,43,51,52} These discrepancies may be explained by subtle differences in methodology but also by differences in patient selection. Most studies have included patients with varying severity and etiologies of disease and lacked the power to perform meaningful subgroup analyses. Also, studies combined in- and outpatients or did not specify whether the patients were hospitalized or not. We have performed two studies in which we specifically stratified according to etiology. In a relatively small study comparing patients with alcoholic cirrhosis ($n = 15$) and nonalcoholic steatohepatitis (NASH) cirrhosis ($n = 22$), we found that patients with alcoholic cirrhosis had significantly decreased CLT, indicating a hyperfibrinolytic state, in comparison to patients with NASH cirrhosis and healthy controls.⁵³ In another study, we compared patients stratified according to disease etiology that all had mild cirrhosis and found that CLT was higher in patients with NASH and cholestatic liver disease.⁵⁴ Similarly, plasma levels of PAI-1 were higher in these two patients groups compared with other etiologies and healthy controls. Thus, these findings indicate that patients with NASH and cholestatic disease have a hypofibrinolytic state, which could explain the increased risk on thrombotic events that has been reported in NASH,⁵⁵ and the decreased bleeding tendency of patients with cholestatic liver disease.⁵⁶

Although there remains debate on whether a hyperfibrinolytic state is present in patients with stable cirrhosis, clinical observations largely argue against an overt

hyperfibrinolytic state, although admittedly dedicated studies on bleeding and fibrinolysis in stable cirrhosis are lacking.^{9,57} Patients with stable cirrhosis do not show typical signs of fibrinolytic bleeding, which is delayed bleeding after invasive procedures or trauma. Bleeding from mucosal tissues, which are high in fibrinolytic activity, may occur, and although these may be linked to a hyperfibrinolytic state, such bleeds are commonly self-limiting.

In patients with more advanced disease, it has been argued that a hyperfibrinolytic state is increasingly common, and the concept of accelerated intravascular coagulation and fibrinolysis has been postulated.^{58,59} The problem with this concept is that it defines accelerated activation of coagulation and activation of fibrinolysis by activation markers such as prothrombin fragment 1 + 2 (F1 + 2) and PAP complexes, which may be spuriously elevated in patients with liver disease as a consequence of defective clearance. Even if low-grade continuous activation of coagulation (either systemically or intrahepatically) is present in these patients, their fibrinolytic response may be physiological and should not necessarily be categorized as abnormal and accelerated.

In the absence of solid evidence of a hyperfibrinolytic state in a proportion of patients with stable cirrhosis, the absence of validated tests to diagnose hyperfibrinolysis, and the absence of evidence that accelerated fibrinolysis may predispose to spontaneous or procedure-related bleeding, we feel that a fibrinolytic work-up of these patients should not be clinically pursued.

Fibrinolysis in Acutely Ill Patients with Cirrhosis

Patients with acute decompensation of cirrhosis or patients who have developed acute-on-chronic liver failure (ACLF) have additional changes in their hemostatic system. Whether the unique hemostatic profile with very low levels of hepatocyte-derived hemostatic proteins predisposes patients to hemostatic complications has been poorly studied. One study has reported an incidence of new-onset bleeding of 17% in acutely ill patients with cirrhosis and showed bleeding to be related to thrombocytopenia and hypofibrinogenemia.⁶⁰ Another study showed a 12% bleeding risk related to thrombocytopenia and sepsis.⁶¹ However, as thrombocytopenia and hypofibrinogenemia are reflections of severity of portal hypertension and severity of disease, this does not necessarily mean that hemostatic failure is directly related to bleeding risk in these patients. Indeed, in a recent study on acutely ill patients with cirrhosis, bleeding complications were more frequent in patients with increased severity of disease, but CLT did not differ between patients who bled and patients who did not or between patients who experienced portal hypertensive bleeding and other bleeding.⁶²

We have recently studied fibrinolytic status in a cohort of acutely ill patients with cirrhosis. In contrast to our studies on stable cirrhotic patients, in which we found comparable fibrinolytic status in patients and controls, we found highly variable test results in these acutely ill patients.¹⁴ A propor-

tion of patients, particularly those with acute decompensation of cirrhosis, were clearly hyperfibrinolytic. Other patients, particularly those with ACLF, showed great variation in their fibrinolytic status, ranging from severely hypofibrinolytic to hyperfibrinolytic. One explanation for this might be that the presence of sepsis in combination with ACLF results in a hypofibrinolytic state, as hypofibrinolysis is common in patients with sepsis without underlying liver disease.⁴ This is substantiated by the results of a study in a larger cohort of ACLF patients, where both sepsis and organ failure were associated with a hypofibrinolytic state.⁶² It has been postulated that this hypofibrinolytic state contributes to persistent microthrombus deposition within various organs, which may result in multiple organ failure and death. However, clinical evidence for this hypothesis remains scarce.

The variation in fibrinolytic status of acutely ill patients with cirrhosis poses challenges to their management. Whether a hypofibrinolytic state is useful as prognosticator or whether those patients with a hypofibrinolytic state would benefit from anticoagulant or profibrinolytic therapy remains to be studied.

Fibrinolysis in Acute Liver Failure

Patients with ALF have profound changes in their hemostatic status, resulting in a fragile balance between bleeding and thrombosis. We have demonstrated that patients with ALF have a profound hypofibrinolytic state, with a large proportion of patients showing no clot lysis at all within the time frame of our assay.⁶³ Moreover, results from a large cohort study by the United States ALF Study Group (676 patients) confirmed that patients with severe acute liver injury and ALF were (severely) hypofibrinolytic.⁶⁴ At variance with results from a study in patients with ACLF,⁶² a hypofibrinolytic state in ALF was not clearly associated with infection and short-term mortality. In addition, we did not find an association between decreased fibrinolytic capacity and bleeding during short-term follow-up. Although the hypofibrinolytic state in patients with ALF contributes to a prothrombotic state, which, in turn, could lead to both local (intrahepatic) and systemic increases in (micro)thrombus formation, the lack of association between hypofibrinolysis and short-term mortality suggests that this mechanism is of limited importance in humans. Clinical evidence supporting that (micro)thrombus formation contributes to progression of liver disease is limited, and experimental studies on the role of fibrin deposition and the role of fibrinolysis in liver disease progression are often contradicting. On the one hand, mouse models of acetaminophen (APAP)-induced ALF demonstrate increased fibrin deposition in the liver related to progression of disease.⁶⁵ Blocking fibrin formation by anticoagulants has been shown to decrease disease progression.^{65,66} However, using the same model for ALF, fibrinogen deficient mice showed similar liver injury as wild-type mice,⁶⁷ suggesting that it is not fibrin deposition per se that is of critical importance for the progression of liver injury in ALF. Blocking plasminogen (either by gene

knockout or administration of tranexamic acid) resulted in decreased liver injury in a mouse model of APAP-induced ALF.⁶⁷ In addition, PAI-1 deficiency resulted in increased liver injury and intrahepatic hemorrhage, and decreased high-molecular-weight fibrin(ogen) deposition in the liver.⁶⁸ Thus, although the fibrinolytic system seems involved in progression of ALF in mice, this again is not through fibrin deposition, as accelerated fibrinolysis promotes rather than inhibits progression of injury.

In conclusion, ALF is accompanied by a hypofibrinolytic state that is not associated with increased mortality in humans. Whether there is a role for hypofibrinolysis in disease progression in ALF remains to be elucidated. Although experimental evidence suggests a role for fibrin and fibrinolysis in progression of ALF, both beneficial and detrimental roles have been described, which depended on the experimental context.

Fibrinolysis during Liver Transplantation

During liver transplantation, the preexistent hemostatic changes in patients further increase due to hemodilution, consumption, and the lack of clearance and synthesis of proteins involved in hemostasis during the anhepatic phase. Although plasminogen levels progressively decrease during transplantation, levels do not become rate-limiting, and an intraoperative hypofibrinolytic state therefore is not detected. Instead, it has been well established that tPA plasma levels are generally elevated in the anhepatic phase, and especially peak after reperfusion, when oxygen-rich blood is reintroduced after a period of ischemia.⁶⁹ These high levels are likely a consequence of a massive release of tPA from the injured endothelium of the donor liver, and accumulation as a result of the anhepatic phase. This (post-anhepatic) hyperfibrinolytic state in patients undergoing liver transplantation has been associated with increased blood loss during transplantation, as reflected by increased red blood cell and fresh frozen plasma transfusion requirements.^{69,70} Fibrinolysis during liver transplantation is in many centers assessed by TEG and ROTEM, allowing identification of patients in a hyperfibrinolytic state. These patients, especially in the presence of ongoing bleeding, are then considered for antifibrinolytic therapy. An alternative strategy is to prophylactically administer antifibrinolytic therapy to prevent hyperfibrinolysis-related bleeding. In a randomized controlled trial, patients receiving aprotinin during liver transplantation experienced up to 60% less blood loss and required up to 37% less red blood cell transfusions compared with patients receiving placebo.⁷¹ A meta-analysis demonstrated that the use of aprotinin was not associated with increased thrombotic complications during or after liver transplantation, and it was concluded that aprotinin was safe and effective in reducing blood loss in patients undergoing liver transplantation.⁷² Aprotinin was withdrawn from the market after concerns for mortality associated with its use during cardiac surgery were raised.⁷³ Importantly, discontinuing the routine prophylactic use of aprotinin during liver transplantation resulted in increased

blood loss in centers that did not switch to an alternative antifibrinolytic⁷⁴ but not in centers that did.⁷⁵ Overall, these results indicate that bleeding during liver transplantation is, in part, likely attributed to hyperfibrinolysis. As the use of antifibrinolytic therapy is safe and effective, antifibrinolytics are recommended to treat or prevent hyperfibrinolysis in patients undergoing liver transplantation.

Antifibrinolytic Therapy

Antifibrinolytic therapy could be divided into two categories based on the mode of action: specifically inhibitors of plasmin (including aprotinin) and inhibitors of plasmin generation (e.g., tranexamic acid, epsilon-aminocaproic acid). As mentioned previously, there is substantial evidence for the safe and effective use of antifibrinolytic therapy during liver transplantation. It is therefore likely that outside the context of transplantation, patients with liver disease and hyperfibrinolysis-related bleeding could also benefit from antifibrinolytic therapy. However, there is little clinical evidence for the use of antifibrinolytic therapy for other indications in patients with liver disease. Antifibrinolytics could be considered in patients with liver disease who are actively bleeding and have laboratory evidence of hyperfibrinolysis. Also, actively bleeding patients with presumed hyperfibrinolysis (without laboratory evidence) could be considered for antifibrinolytic therapy, as studies have shown the prohemostatic effect of antifibrinolytics in patients without apparent hyperfibrinolysis (such as patients with von Willebrand disease⁷⁶).

Antifibrinolytic therapy for significant gastrointestinal bleeding has recently been studied in the Halt-IT clinical trial (NCT01658124).⁷⁷ This large, placebo-controlled randomized trial was designed to study the effects of tranexamic acid on mortality in patients with a variety of gastrointestinal bleeds. Part of the cohort had liver disease and had variceal bleeding (~45%). At variance with the beneficial effects of tranexamic acid observed in trials on bleeding associated with trauma and postpartum bleeding,^{78,79} and at variance with a meta-analysis of smaller studies in gastrointestinal bleeding,^{80,81} Halt-IT found no mortality benefit in patients with gastrointestinal bleeding. Importantly, patients receiving tranexamic acid had increased incidences of seizures and venous thromboembolic events, which suggest that antifibrinolytics may require cautious use in patients with liver disease not undergoing liver transplantation. The lack of clinical effect of tranexamic acid on variceal bleedings in patients with liver disease may be explained by the notion that these bleedings are unlikely to be related to hyperfibrinolysis but presumably attributable to portal hypertension and/or local abnormalities in vascular anatomy. In addition, it may be that patients with variceal bleeds are frequently hypofibrinolytic, as we have demonstrated in a proportion of critically ill cirrhosis patients.⁶² In conclusion, antifibrinolytic therapy can be considered in patients with liver disease with laboratory-proven or suspected hyperfibrinolysis-related bleeding. However, there is no role for the prophylactic use of antifibrinolytics or for its use in the treatment of variceal bleeding.

Table 1 Summary of fibrinolysis in various types of liver disease

Type of liver disease	Fibrinolytic state	Changes in fibrinolytic assays	Bleeding risk	Clinical implications
Stable cirrhosis	Normo- to hyperfibrinolytic	Normal to ↓ ↓ plasma-based CLT ↓ ↓ euglobulin lysis time ^{39,43,51}	Not typical (delayed) hyperfibrinolytic after invasive procedures or trauma	No fibrinolytic work-up recommended
ASH	Hyperfibrinolytic	↓ ↓ CLT ⁵³		
NASH	Hypofibrinolytic	↑ ↑ CLT ↑ ↑ PAI-1 ⁴⁹	Evidence for increased thrombotic risk ⁵⁵	
Cholestatic	Hypofibrinolytic	↑ ↑ CLT ↑ ↑ PAI-1 ⁴⁹	Decreased blood loss during liver transplantation ⁵⁶	
Acutely ill cirrhosis	Highly variable ^{14,62}		Increased, presumably related to increased severity of disease	Variation in fibrinolytic state poses challenges to the management of this patient group
Acute decompensation	Hyperfibrinolytic in a proportion of patients	Normal to ↓ ↓ CLT ^{14,62}		Role for antifibrinolytics in (suspected or established) hyperfibrinolysis-related bleeding
ACLF	Hypo - to hyperfibrinolytic (highly variable)	Profound hypofibrinolysis by CLT in 21% of 58 patients ⁶²	Not related to fibrinolytic state Hypofibrinolysis associated with sepsis and multiple organ failure	Potential role for hypofibrinolytic state as a prognosticator or therapeutic target (- profibrinolytics/anticoagulant therapy)
Acute liver failure	(Severely) Hypofibrinolytic	Profound hypofibrinolysis by CLT in 74% of 50 patients ⁶³	Little clinical evidence for relation to bleeding or (micro)thrombosis Not associated with increased mortality	Potential role for contribution to disease progression, and target for future therapeutic strategies
Liver transplantation	Hyperfibrinolytic (most profound in postanhepatic phase)	↑ ↑ tPA ⁶⁹ ↓ ↓ CLT	Increased bleeding, as reflected by increased blood product requirements ^{62,63}	Antifibrinolytics are safe and effective and thus recommended to treat or prevent hyperfibrinolysis in patients undergoing liver transplantation ^{66,69}

Abbreviations: ACLF, acute-on-chronic liver failure; ASH, alcoholic steatohepatitis; CLT, clot lysis time; NASH, nonalcoholic steatohepatitis; PAI-1, plasminogen activator inhibitor-1; tPA, tissue-type plasminogen activator.

Conclusion

Fibrinolytic defects are still poorly defined in patients with liver disease, and the fibrinolytic status of patients with various types of liver disease is a subject of debate. The current understanding of fibrinolytic profiles of various types of liver disease and their potential clinical implications are summarized in ►Table 1. When defining fibrinolytic status in relation to clinical outcome and practice, a correct interpretation of both clinical features and laboratory parameters is key. Especially in patients with (suspected) hyperfibrinolysis-related bleeding, the use of antifibrinolytic therapy may be indicated. Although tranexamic is used in some centers in patients with massive variceal bleeding (as part of a massive transfusion protocol), the results of the Halt-IT trial clearly show that the use of tranexamic acid in this setting is not indicated.

Conflict of Interest

None declared.

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