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Published in:
Hepatology

DOI:
[10.1002/hep.31451](https://doi.org/10.1002/hep.31451)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Lisman, T. (2020). Hemostatic Changes of Acute Kidney Injury in Patients With Cirrhosis: What Do They Mean? *Hepatology*, 72(4), 1163-1165. <https://doi.org/10.1002/hep.31451>

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Hemostatic Changes of Acute Kidney Injury in Patients With Cirrhosis: What Do They Mean?

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Historically, patients with liver disease were considered to have a bleeding tendency that was a consequence of changes in their hemostatic system. An important consequence of this concept is the ongoing policy of prophylactic blood product transfusion prior to invasive procedures aimed at reducing bleeding risk. However, it is increasingly acknowledged that although bleeding in patients with liver diseases can be the consequence of a (temporal) hypocoagulable state, it is frequently unrelated to hemostatic failure and rather caused by portal hypertension (e.g., variceal bleeding) or inadvertent laceration of a blood vessel (e.g., during liver biopsy or paracentesis). In addition, because liver disease is associated with simultaneous changes in prohemostatic and antihemostatic pathways, hemostatic capacity appears to remain intact.⁽¹⁾ Therefore,

prohemostatic therapy by blood product transfusions or pharmacological interventions may not be required and may even be inefficient, as demonstrated by the lack of effect of fresh frozen plasma infusion on *ex vivo* indices of hemostasis.⁽²⁾

In recent years, the thrombotic tendency of patients with liver disease has been extensively studied. It appears that in at least some patients the “rebalanced” hemostatic status becomes hypercoagulable, which may increase the risk for thrombotic events such as venous thrombosis and portal vein thrombosis.⁽¹⁾ However, similar to the notion that not all bleeding events in patients with liver disease are a consequence of hypocoagulability, it is possible that not all thrombotic events are connected to hypercoagulability. For example, there is ongoing debate on the role of hypercoagulability in portal vein thrombosis, which may largely or exclusively be related to a reduction in portal flow rather than prothrombotic hemostatic changes.

Interestingly, similar changes in perspective on the hemostatic system have occurred in patients with renal failure, who were historically considered to be bleeders but are now recognized as having an increased risk of venous and arterial thrombotic events.⁽³⁾ The most notable hemostatic defect in patients with renal disease is in platelet function; however, the observation that bleeding in these patients was largely driven by anemia has questioned the relevance of platelet function as a contributor to bleeding.⁽³⁾ Interestingly, in both liver and renal failure, the acquired platelet defect appears to be compensated for by highly elevated levels of the platelet adhesive protein von Willebrand factor (VWF).^(4,5)

What happens to the hemostatic system in patients who develop renal failure during the course of their disease? Clinically, renal failure complicating liver disease appears to be associated with bleeding. For example, bleeding during liver transplantation increases with declining renal function,⁽⁶⁾ and spontaneous bleeding in patients with acute liver failure, although rare, is

Abbreviations: AKI, acute kidney injury; ETP, endogenous thrombin potential; FXIII, factor XIII; VWF, von Willebrand factor.

Received June 15, 2020; accepted June 28, 2020.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.31451

Potential conflict of interest: Nothing to report.

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more frequent in patients receiving renal replacement therapy.⁽⁷⁾ In patients with cirrhosis, acute kidney injury (AKI) has been shown to increase the risk for postparacentesis bleeding.⁽⁸⁾ Whether these observations reflect a more hypocoagulable hemostatic status or whether renal failure is simply a marker for severity of disease is uncertain.

A study by Zanetto and coworkers published in this issue of HEPATOLOGY has meticulously cataloged hemostatic changes in patients with cirrhosis and AKI to assess whether the increased bleeding risk of renal failure complicating liver disease may be attributed to abnormal hemostasis.⁽⁹⁾ A particular strength of the study is that patients with and without AKI with very similar liver function were compared and that in some of the patients, additional testing was performed after AKI was resolved.

The study showed a pronounced decrease in *ex vivo* platelet function, with no alterations in VWF levels. This decrease in platelet function was independent of the extent of thrombocytopenia, and resolution of AKI improved platelet function compared to patients with cirrhosis who did not have AKI. These findings are in line with the known platelet function defects of renal failure in patients without liver disease and suggest that platelet function defects in patients with cirrhosis and AKI contribute to bleeding. Platelet function was assessed by whole blood platelet aggregation, and although this test is clinically relevant, platelet adhesion and the role of VWF in platelet adhesion and aggregation are not explored in this particular test. Future studies of platelet adhesion and aggregation under experimental conditions in which platelet function is studied in flowing blood and studies on markers of *in vivo* platelet activation could further strengthen the hypothesis that AKI-induced platelet function in cirrhosis truly leads to defective primary hemostasis.

Patients with AKI had lower levels of coagulation proteins, which increased following AKI resolution. Why AKI would be accompanied with a decrease in coagulation factor levels is not immediately evident. Because the synthetic capacity of the liver appears similar in patients with and without AKI, it may be that local or systemic activation of coagulation with consumption of coagulation factors explains the lower factor levels in patients with AKI. Indeed, thrombin-antithrombin levels, which reflect *in vivo* activation

of coagulation, are higher in patients with AKI. The authors interpret the changes in coagulation factor levels as “prothrombotic” and base this conclusion in part on the endogenous thrombin potential (ETP) ratio. However, the authors show *ex vivo* thrombin-generating capacity (the ETP) to be identical in patients with and without AKI, reinforcing that the ETP ratio can be misleading.⁽¹⁰⁾ My interpretation is that coagulation potential is not affected by AKI but that there is an increased *in vivo* trigger of coagulation—possibly the injured kidney. Plasma levels of factor XIII (FXIII), which crosslinks and stabilizes the fibrin clot, were decreased in patients with AKI, which the authors rightfully categorize as a hypocoagulant element. However, the fibrin clot in patients with cirrhosis has hypercoagulable properties, and these may be enhanced by AKI because isolated renal failure also leads to a prothrombotic fibrin clot structure. Future experiments should therefore assess the structural properties of the fibrin clot using established functional tests in patients with cirrhosis with and without AKI as the decreased FXIII levels might be compensated for by prothrombotic features of the fibrin clot.

Finally, the interpretation of the status of the fibrinolytic system is not straightforward from the data presented. Based on modestly higher plasmin-antiplasmin levels in patients with AKI compared to those without, the authors propose that patients with cirrhosis and AKI are in a relative hyperfibrinolytic state, which is in contrast with the well-known hypofibrinolytic state of patients with isolated renal failure. It may be that the elevated plasmin-antiplasmin levels in patients with AKI do not signal an overactive fibrinolytic system but rather reflect a physiological response to the enhanced coagulation activation (as indicated by elevated thrombin-antithrombin levels). Future studies should explore the status of the fibrinolytic system using functional assays.

In summary, Zanetto et al. have elegantly demonstrated that development of AKI in patients with cirrhosis is accompanied by additional hemostatic changes that reverse when AKI resolves. Table 1 summarizes hemostatic changes in patients with cirrhosis with and without AKI and their functional consequences and indicates current uncertainties. It remains to be studied whether the hypocoagulable

TABLE 1. Hemostatic Changes and the Functional Effects of These Changes in Patients With Cirrhosis and the Additional Changes and Functional Consequences of Superimposed AKI

Hemostatic Process	Hemostatic Changes in Cirrhosis	Functional Effects	Additional Hemostatic Changes in Cirrhosis + AKI	Functional Effects
Platelet adhesion and aggregation	Thrombocytopenia; ill-defined platelet function defects; highly elevated VWF with low levels of its regulating protease ADAMTS13	High VWF/low ADAMTS13 compensates for thrombocytopenia; anemia may contribute to an adhesion defect	Platelet activation impaired; no change in VWF but no data on ADAMTS13; exacerbation of anemia?	Platelet adhesion and aggregation defect? May contribute to bleeding
Coagulation and fibrin clot formation	Low levels of procoagulants and anticoagulants (except Factor VIII, which is elevated); low fibrinogen in advanced disease; decreased fibrin clot permeability	Enhanced thrombin-generating capacity and thrombogenic clot structure; may contribute to thrombosis	Further decreases in procoagulant and anticoagulant factors	No change in thrombin-generating capacity; enhanced <i>in vivo</i> activation of coagulation; may contribute to thrombosis
Fibrinolysis	Low levels of plasminogen, antiplasmin, TAFI, and FXII; elevated levels of tPA and PAI-1	Normal fibrinolytic potential in compensated patients; mixed pattern of hypofibrinolysis and hyperfibrinolysis in decompensated patients with hypofibrinolysis dominating ACLF	Further decreases in profibrinolytic and antifibrinolytic factors; increased tPA; increased <i>in vivo</i> TAFI activation	Unclear; elevated tPA and decreased FXII may contribute to bleeding; mixed fibrinolytic patterns likely

Abbreviations: ACLF, acute-on-chronic liver failure; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PAI-1, plasminogen activator inhibitor 1; TAFI, thrombin-activated fibrinolytic inhibitor; tPA, tissue plasminogen activator.

and hypercoagulable elements identified by the authors contribute to bleeding or thrombotic complications of patients with cirrhosis and AKI. If bleeding risk is shown to be directly related to AKI, possible interventions—besides optimization of renal function—include optimal treatment of anemia (which improves hemostasis by improving platelet function), platelet transfusion, or administration of desmopressin, which is commonly used as a prohemostatic agent in renal failure without underlying liver disease.

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