The paradox of coagulopathy in cirrhosis

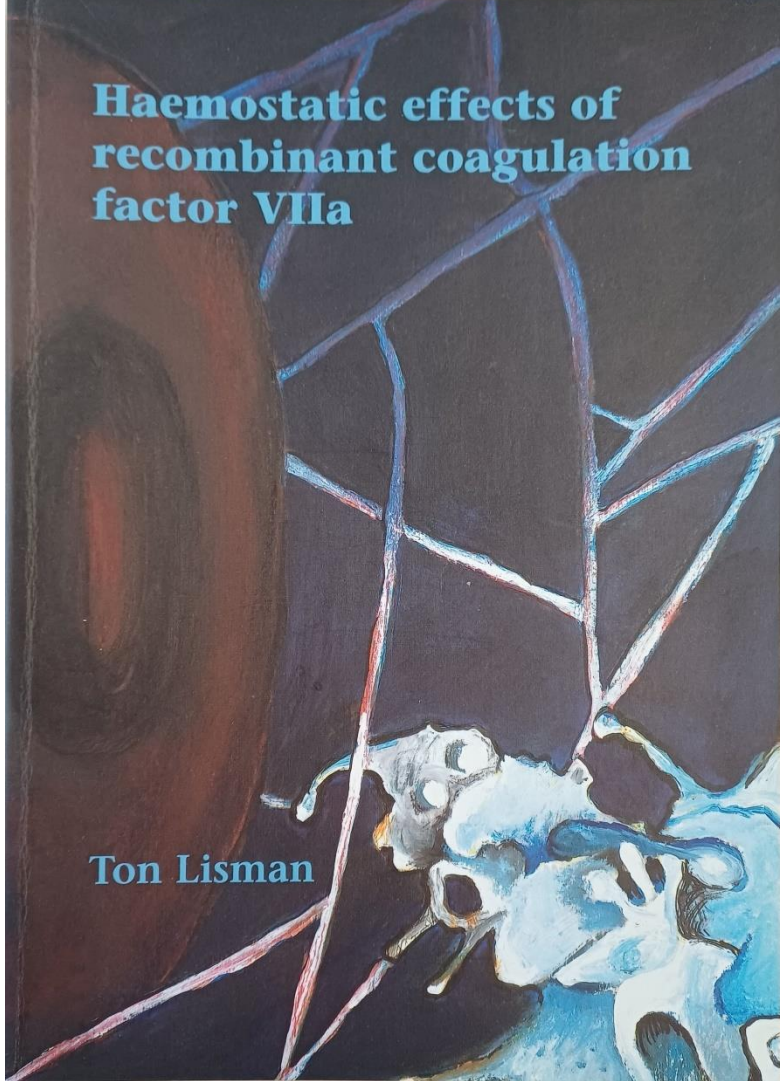
An evolving concept

Ton Lisman, Department of Surgery, UMC Groningen, The Netherlands

A tribute to Prof. Jaime Bosch

1947-2025

Haemostatic effects of recombinant coagulation factor VIIa



Ton Lisman

Blood Coagulation and Fibrinolysis 2000, **11 (suppl 1)**:S107–S111

NovoSeven® as a universal haemostatic agent

U. Hedner

Initiation of haemostasis involves the formation of a complex between tissue factor (TF) and activated factor VII (FVIIa) following injury. TF is found in the deeper layers of the vessel wall, in atherosclerotic plaques and in some types of tumour cell and is only exposed to circulating blood after tissue damage. Likewise, FVII is only enzymatically active when complexed with TF (TF/FVIIa). It has recently been shown that the administration of recombinant activated FVII (rFVIIa) in high doses (~100 μg/kg) can induce haemostasis in the absence of FVIII and FIX. In addition, from in-vitro studies it appears that rFVIIa can bind with low affinity to the activated platelet surface and, independently of TF, induce the thrombin burst needed for haemostasis. The ability of rFVIIa to compensate for FVIII/FIX deficiency has been proven clinically in haemophilia patients with life- and limb-threatening bleeds. In addition, patients with congenital FVII deficiency have been successfully treated for bleeds with rFVIIa. Recombinant FVIIa has been used in patients with platelet disorders; five patients with Glanzmann's thrombasthenia and one with Bernard-Soulier's thrombasthenia have had bleeding episodes managed effectively. Recombinant FVIIa has also been shown to normalize prothrombin time in patients with liver disease and in warfarin-treated individuals. *Blood Coagul Fibrinolysis* **11 (suppl 1)**:S107–S111 © 2000 Lippincott Williams & Wilkins.

Keywords: haemostasis, haemophilia, recombinant activated factor VII (rFVIIa), Glanzmann's thrombasthenia, Bernard-Soulier's thrombasthenia

GASTROENTEROLOGY 2004;127:1123–1130

Recombinant Factor VIIa for Upper Gastrointestinal Bleeding in Patients With Cirrhosis: A Randomized, Double-Blind Trial

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The Coagulopathy of Cirrhosis: Myth or Reality?

See Article on Page 553

The concept that liver failure results in a profound coagulopathy is firmly established among hepatologists.[1] The origin of the coagulopathy is commonly believed to be a defective hepatic synthesis of clotting factors, which is aggravated by the thrombocytopenia caused by portal hypertension.[1] Hyperfibrinolysis may further contribute to a bleeding tendency.[2,3] In addition, many studies have shown a decreased hepatic synthesis of coagulation factors, reflected globally by the prothrombin time (PT). PT is an excellent marker of liver failure and a strong independent prognostic indicator of survival in patients with chronic liver disease.[4] As such, new and old models of prognosis for patients with advanced liver disease include PT as one of its components.[4,5]

In this issue of HEPATOLOGY, the very interesting paper by Tripodi et al.[6] challenges these concepts. Patients with cirrhosis, in spite of abnormal standard coagulation tests (PT and activated partial thromboplastin time, or APTT), may generate adequate amounts of thrombin in an *in vitro* assay (the endogenous thrombin potential, or ETP) modified by the addition of thrombomodulin. In their elegant study, Tripodi et al. show this is mainly due to the fact that these patients, in addition to the diminished hepatic synthesis of clotting factors, also have a profound deficit of natural anticoagulants, mainly of protein C (a protein synthetized by the liver), and also of antithrombin, which may counterbalance the bleeding tendency caused by the deficiency in procoagulants. Based on their findings, Tripodi et al.[6] suggest that the feared coagulopathy of cirrhosis is more a myth than a reality and that patients with cirrhosis are probably not at an increased risk of bleeding from other causes than the existence of portal hypertension and its local consequences in the gastrointestinal tract (gastroesophageal varices, portal hypertensive gastropathy, and colopathy).

In our view, although this study supports the view that the coagulopathy of cirrhosis is less important than what suggested by measuring the PT or APTT, the conclusion that the bleeding tendency in cirrhosis is merely due to the presence of portal hypertension goes beyond what is shown by their data:

(1) First, they studied a series of stable patients with cirrhosis that included only 14 patients in Child-Turcotte-Pugh class C. Thus, the number of patients with advanced liver failure (at risk of exhibiting a severe "coagulopathy") was probably too small to establish in this group whether thrombin generation was adequate or not. This is especially the case in view of the very large range of values obtained in control subjects, suggesting the need for a better standardization of the test to avoid its large variability.[7] The argument that their findings are in keeping with the fact that patients with cirrhosis do not exhibit soft-tissue hematomas and hemarthroses is not entirely correct; in fact, spontaneous hematomas or after minimal or inadvertent trauma are extremely common in patients with advanced liver failure and can be quite severe in some cases.[8]

(2) Second, the potential contribution of thrombocytopenia (and/or platelet dysfunction) and hyperfibrinolysis to such a bleeding diathesis is not commented upon, in spite of documenting a marked reduction of platelet counts and prolonged bleeding time in their patients. Thrombocytopenia in cirrhosis can be very profound, and in these cases there is an increased risk of bleeding complications in invasive procedures and surgery, even without a marked deficit of clotting factors. It should be noted in this regard that the endogenous thrombin potential was measured in platelet free plasma; as a result, possible differences caused by the platelet number or function were not evaluated. This is relevant because it has been shown in previous studies[9] that the amount of thrombin generated depends clearly on platelet count and function, both of which are frequently altered in cirrhosis.[10]

(3) Third, the possible role of these coagulation abnormalities in worsening the bleeding due to portal hypertension is not recognized, despite the clinical evidence indicating that variceal bleeding is more severe, more difficult to control, and more likely to recur in patients with more advanced liver failure (with more prolonged PT, and sometimes, but not always, with lower platelet counts) compared with those with relatively preserved liver function.[4,11]

We entirely agree with Tripodi et al. that it is very unlikely that these coagulation abnormalities play any role in initiating variceal bleeding. However, we believe they can be clinically relevant, contributing to aggravation of the portal hypertensive bleeding and facilitating recurrence. This view is compatible with the exploratory

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; ETP, endogenous thrombin potential.

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Conflict of interest: Nothing to report.

HEPATOLOGY
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REVIEW

New Therapeutic Paradigm for Patients With Cirrhosis

Emmanuel A. Tsochatzis,[1] Jaime Bosch,[2] and Andrew K. Burroughs[1]

Cirrhosis is a major health problem, being the 5th cause of death in the U.K. and 12th in the U.S., but 4th in the 45 to 54 age group. Until recently cirrhosis was considered a single and terminal disease stage, with an inevitably poor prognosis. However, it is now clear that 1-year mortality can range from 1% in early cirrhosis to 57% in decompensated disease. As the only treatment for advanced cirrhosis is liver transplantation, what is urgently needed is strategies to prevent transition to decompensated stages. The evidence we present in this review clearly demonstrates that management of patients with cirrhosis should change from an expectant algorithm that treats complications as they occur, to preventing the advent of all complications while in the compensated phase. This requires maintaining patients in an asymptomatic phase and not significantly affecting their quality of life with minimal impairment due to the therapies themselves. This could be achieved with lifestyle changes and combinations of already licensed and low-cost drugs, similar to the paradigm of treating risk factors for cardiovascular disease. The drugs are propranolol, simvastatin, norfloxacin, and warfarin, which in combination would cost £128/patient annually—equivalent to U.S. $196/year. This treatment strategy requires randomized controlled trials to establish improvements in outcomes. In the 21st century, cirrhosis should be regarded as a potentially treatable disease with currently available and inexpensive therapies. (HEPATOLOGY 2012;56:1983-1992)

Coagulation and liver disease

- Revolutionary new concepts
- Collaboration
- Dedicated meetings

2005 – Steve Caldwell starts biannual coagulation in liver disease meetings

2021 – It’s been too long…..


EASL
EASL
EASL

Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences

Ton Lisman[1,2] and Robert J. Porte[1]

[1]Section Hepatobiliairy Surgery and Liver Transplantation and [2]Surgical Research Laboratory, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Rebalanced Hemostasis in Patients with Acute Liver Failure

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Semin Thromb Hemost 2015;41:468–473.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

The Coagulopathy of Chronic Liver Disease

Armando Tripodi, Ph.D., and Pier Mannuccio Mannucci, M.D.

ORIGINAL ARTICLE

AJT

Evidence for a rebalanced hemostatic system in pediatric liver transplantation: A prospective cohort study

Maureen J. M. Werner[1,2] | Vincent E. de Meijer[1] | Jelle Adelmeijer[2] | Ruben H. J. de Kleine[1] | René Scheenstra[3] | Sander T. H. Bontemps[4] | Koen M. E. M. Reyntjens[5] | Jan B. F. Hulscher[6] | Ton Lisman[1,2] | Robert J. Porte[1,2]

The two tales of coagulation in liver transplantation

Nienke Warnaar[a], Ton Lisman[a,b] and Robert J. Porte[a]

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Current Opinion in Organ Transplantation 2008, 13:298–303

Purpose of review
Hemostatic alterations in cirrhosis involve molecular pathways that both promote and stabilize blood clotting and pathways that mediate clot dissolution. Orthotopic liver transplantation for end-stage liver disease historically was a long and risky procedure, accompanied by substantial blood loss. The aim of this review paper is to provide an overview of recent studies and developments that have gradually changed our understanding about the hemostatic system and changes that may occur in patients undergoing liver transplantation.

Recent findings
Patients with severe liver disease not only have a deficiency of procoagulant and antifibrinolytic factors, but also have a deficiency of naturally occurring anticoagulants and profibrinolytics. Studies using modern laboratory technology have shown that thrombin generation in these patients is less abnormal than traditionally believed based on standard coagulation tests. In addition, clinical observations indicated that patients with cirrhosis are not protected against thromboembolic complications.

Summary
Hemostatic alterations in cirrhosis concern both pro- and antihemostatic pathways and the net result is a rebalancing of the hemostatic system, albeit with narrower margins. This delicate balance will become precarious when the system is heavily challenged such as during liver transplantation. The balance may than be turned to either hypocoagulation or hypercoagulation, making patients with cirrhosis both prone to bleeding as well as thromboembolic complications.

Keywords
bleeding, hemostasis, liver transplantation, thrombosis

Curr Opin Organ Transplant 13:298–303

1087-2418

Review › Acta Gastroenterol Belg. 2009 Oct-Dec;72(4):433-40.

Hemostasis in patients with liver disease

J van der Werf [1], R J Porte, T Lisman

Affiliations + expand

PMID: 20163038

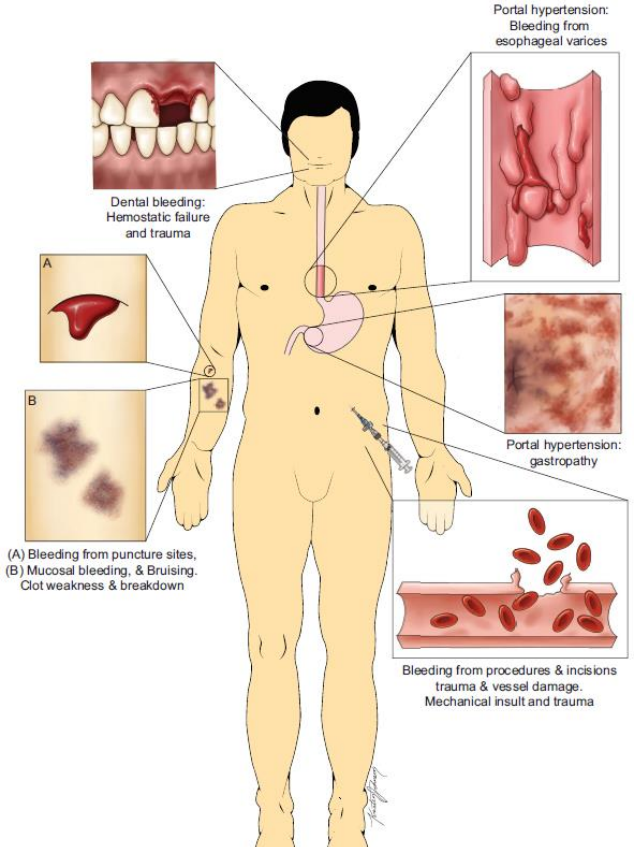
Abstract

In patients with liver disease alterations in the hemostatic system frequently occur. Although it was generally believed that these changes result in a bleeding tendency, laboratory models and clinical data have shown evidence for a rebalanced hemostasis in liver disease, as a result of a concomitant decrease in both pro- and antihemostatic systems. The rebalanced system presumably has much narrower margins as compared to healthy individuals and therefore can more easily turn to either a hypo- or hypercoagulable state. Bleeding does occur in patients with liver disease but this is frequently related to non-hematological factors, for example bleeding from ruptured esophageal varices. Further clinical data supporting the concept of rebalanced hemostasis include the lack of major blood loss in a great proportion of patients during liver transplantation and the fact that patients with liver disease are not fully protected from thromboembolic complications including venous thrombosis and thrombosis of the hepatic vessels. It is still common practice to prophylactically treat patients with liver disease prior to invasive procedures to prevent bleeding. Because of a lack of data supporting the effectiveness of this management and the proven side-effects of transfusion of blood products, we believe transfusion of blood products can and should be restricted. The most important thrombotic problem after liver transplantation is hepatic artery thrombosis, a potentially devastating complication. Since the bleeding tendency in patients with liver disease may not be primarily caused by a deranged hemostatic system, the restricted use of anticoagulant drugs in the post-transplant setting should be reconsidered.

What have we learned?

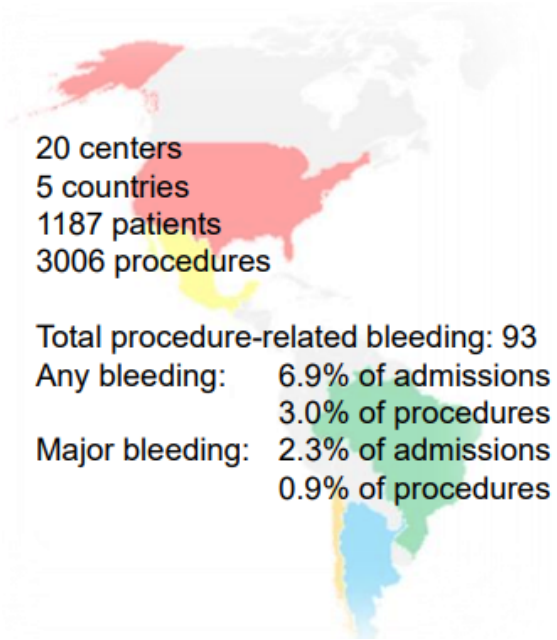
Agreements and points of discussion.

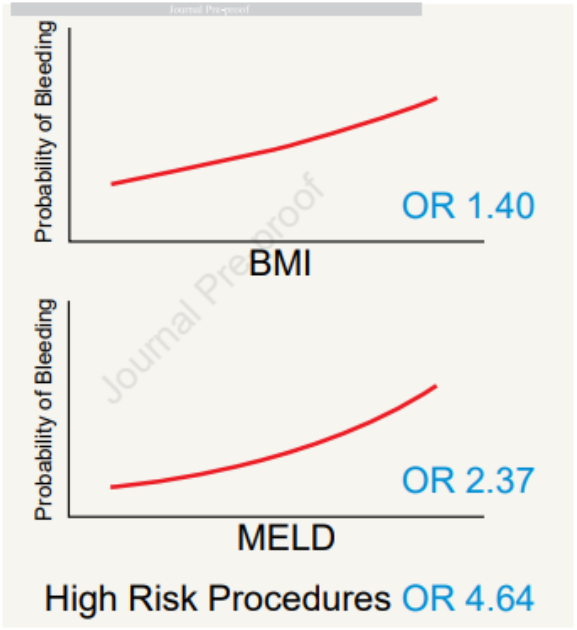
Bleeding complications in liver disease: often unrelated to hemostatic failure

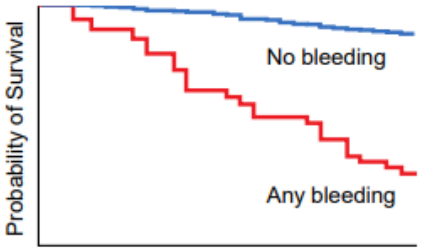


Hepatology. 2021;73(1):366-413.

Procedural bleeding in liver disease is rare







HR: 6.91 (4.22, 11.31)

Gastroenterology

Gastroenterology 2023 Sep;165(3):717-732

Bleeding liver disease is not predicted by PT/INR or platelet count

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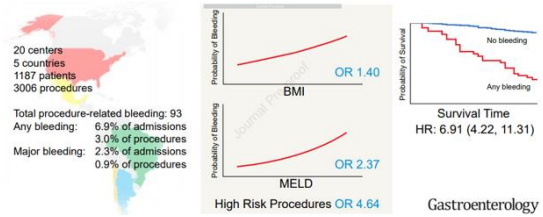
DOI: 10.1111/apt.16078

APT Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: abnormalities in the international normalised ratio do not correlate with periprocedural bleeding events among patients with cirrhosis

Alexander J. Kovalic[1] | Chaudry Nasir Majeed[2] | Naga Swetha Samji[3] | Paul J. Thuluvath[4] | Sanjaya K. Satapathy[5,6]

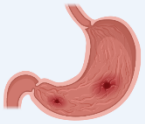


doi: https://doi.org/10.1053/j.gastro.2023.05.046

Risk factors for procedural bleeding

Patient/disease factors

Severity of liver disease



Portal hypertension

Anemia

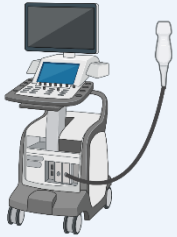
Infection

Renal impairment

Anticoagulants
Antiplatelets

Procedural factors

Procedural bleeding risk



Imaging guidance

Proceduralist experience

Review

JOURNAL
OF HEPATOLOGY

Haemostasis in cirrhosis: Understanding destabilising factors during acute decompensation

Alberto Zanetto[1,2], Patrick Northup[3], Lara Roberts[4], Marco Senzolo[1,2,*]

Summary

Hospitalised patients with decompensated cirrhosis are in a *rebalanced* haemostatic state due to a parallel decline in both pro- and anti-haemostatic pathways. However, this rebalanced haemostatic state is highly susceptible to perturbations and may easily tilt towards hypocoagulability and bleeding. Acute kidney injury, bacterial infections and sepsis, and progression from acute decompensation to acute-on-chronic liver failure are associated with additional alterations of specific haemostatic pathways and a higher risk of bleeding. Unfortunately, there is no single laboratory method that can accurately stratify an individual patient's bleeding risk and guide pre-procedural prophylaxis. A better understanding of haemostatic alterations during acute illness would lead to more rational and individualised management of hospitalised patients with decompensated cirrhosis. This review will outline the latest findings on haemostatic alterations driven by acute kidney injury, bacterial infections/sepsis, and acute-on-chronic liver failure in these difficult-to-treat patients and provide evidence supporting more tailored management of bleeding risk.

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DOI: 10.1111/liv.13712

CIRRHOSIS AND LIVER FAILURE

WILEY Liver INTERNATIONAL

Acute kidney injury, but not sepsis, is associated with higher procedure-related bleeding in patients with decompensated cirrhosis

Adelina Hung[1] | Guadalupe Garcia-Tsao[1,2]

21 patients with post-paracentesis hemoperitoneum

HEPATOLOGY

HEPATOLOGY, VOL. 72, NO. 4, 2020

LIVER FAILURE/CIRRHOSIS/PORTAL HYPERTENSION

Acute Kidney Injury in Decompensated Cirrhosis Is Associated With Both Hypo-coagulable and Hyper-coagulable Features

Alberto Zanetto [1-3], Henry M. Rinder [4,5], Elena Campello [6], Graziella Saggiorato [6], Yanhong Deng [7], Maria Ciarleglio [7], Francis P. Wilson [8], Marco Senzolo [3], Sabrina Gavasso [6], Cristiana Bulato [6], Paolo Simioni [6], and Guadalupe Garcia-Tsao [1,2]

Prevalence of Bleeding and Thrombosis in Critically Ill Patients with Chronic Liver Disease

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Thromb Haemost 2022;122:1006–1016.

Abstract

Introduction Hemorrhage and venous thromboembolism (VTE) are recognized complications of chronic liver disease (CLD), but their prevalence and risk factors in critically ill patients are uncertain.

Patients and Methods We studied a retrospective cohort of patients with CLD nonelectively admitted to a specialist intensive care unit (ICU) determining the prevalence and timing of major bleeding and VTE (early, present on admission/diagnosed within 48 hours; later, diagnosed >48 hours post-ICU admission). Associations with baseline clinical and laboratory characteristics, multiorgan failure (MOF), blood product administration, and mortality were explored. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression.

Results Of 623 patients with median age 52, bleeding (>48 hours after admission) occurred in 87 (14%) patients. Bleeding was associated with greater illness severity and increased mortality. Gastrointestinal bleeding accounted for 72% of events, secondary to portal hypertension in >90%. Procedure-related bleeding was uncommon. VTE occurred in 125 (20%) patients: early VTE in 80 (13%) and involving the portal vein in 85%. Later VTE affected 45 (7.2%) patients. Hepatocellular carcinoma (HCC) and nonalcoholic liver disease were independently associated with early VTE (OR: 2.79, 95% CI: 1.5–5.2 and OR: 2.32, 95% CI: 1.4–3.9, respectively), and HCC, sepsis, and cryoprecipitate use with late VTE (OR: 2.45, 95% CI: 1.11–5.43; OR: 2.26, 95% CI: 1.2–4.3; and OR: 2.60, 95% CI: 1.3–5.1).

Conclusion VTE was prevalent on admission to critical care and less commonly developed later. Bleeding was associated with MOF and increased mortality. Severe MOF was not associated with an increased rate of VTE which was linked with HCC, and specific etiologies of CLD.

Keywords
- liver disease
- critical care
- hemorrhage
- venous thromboembolism

Destabilising factors

- Lead to additional changes in hemostasis
- Whether these additional changes in hemostasis promote bleeding is unclear

Labvalues should be interpreted together with clinical observations

ORIGINAL ARTICLE

Whole blood thrombin generation shows a significant hypocoagulable state in patients with decompensated cirrhosis

Alberto Zanetto[1] | Elena Campello[2,3] | Cristiana Bulato[3] | Ruth Willems[4,5,6] | Joke Konings[4] | Mark Roest[4] | Sabrina Gavasso[3] | Giorgia Nuozzi[3] | Serena Toffanin[3] | Paola Zanaga[1] | Patrizia Burra[1] | Francesco Paolo Russo[1] | Marco Senzolo[1] | Bas de Laat[4] | Paolo Simioni[2,3]

"These results would challenge the current knowledge, primarily based on PPP-TG, that patients with cirrhosis have a normal to increased TG capacity independently of liver disease severity."

Labvalues should be interpreted together with clinical observations

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https://doi.org/10.1016/j.jtha.2023.11.001

JTH COMMENTARY

Thrombin generation in cirrhosis: whole blood, whole truth?

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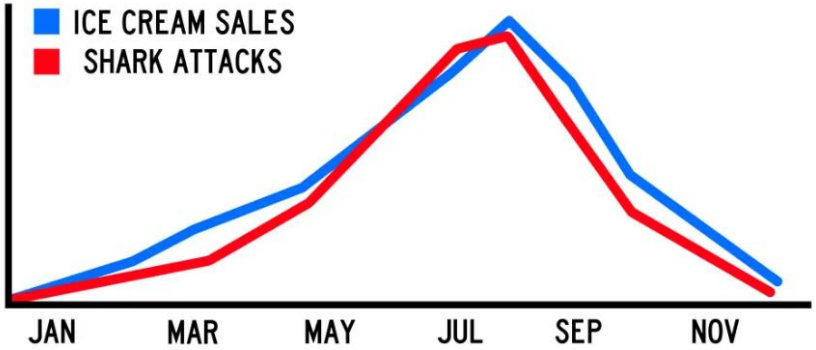
Email: mattias.mandorfer@meduniwien.ac.at

CORRELATION IS NOT CAUSATION!



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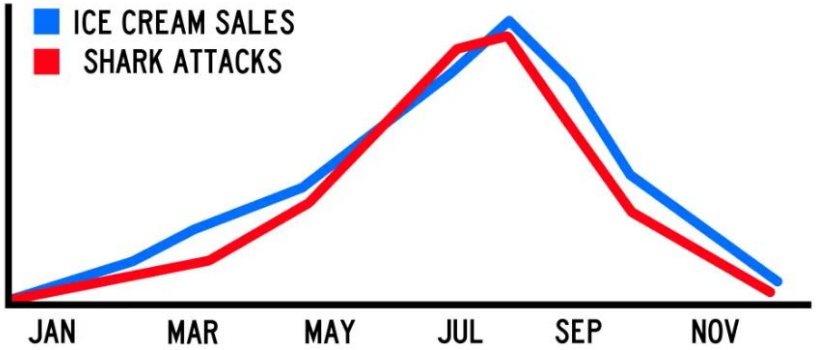


Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Impaired whole blood thrombin generation is associated with procedure-related bleeding in acutely decompensated cirrhosis

Alberto Zanetto[1,2,†], **Elena Campello**[3,4,†], Cristiana Bulato[3], Ruth Willems[5,6,7], Joke Konings[5], Mark Roest[5], Sabrina Gavasso[3], Giorgia Nuozzi[3], Serena Toffanin[3], Patrizia Burra[1,2], Francesco Paolo Russo[1,2], Marco Senzolo[2], Bas de Laat[5], Paolo Simioni[3,4,*]

Journal of Hepatology **2025**. vol. 82 | 1023–1035

Whole blood tests are as confusing as plasma-based tests

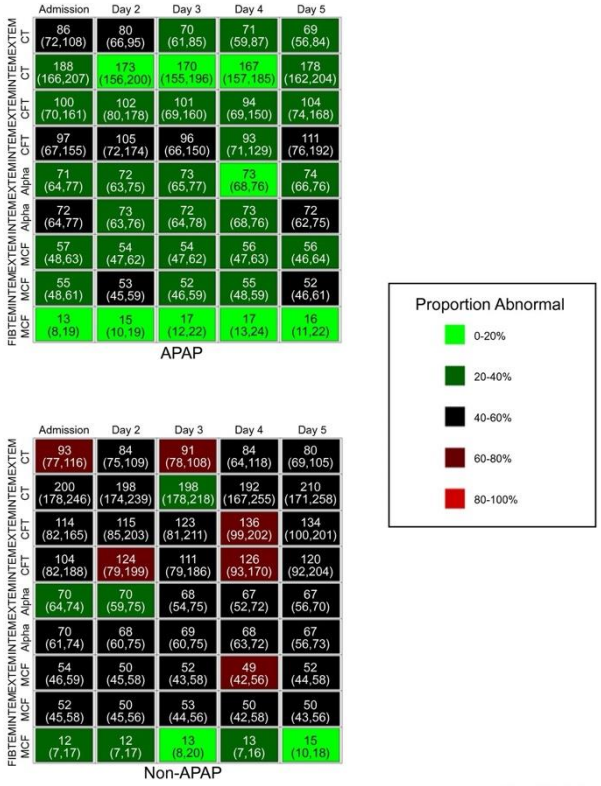
Table 3. Comparison of Standard Hemostatic Laboratory Tests and Thromboelastography (TEG) Parameters Between Patients with Acute Liver Injury (ALI)/Acute Liver Failure (ALF) and Cirrhosis

Parameter	Normal range	ALI/ALF (N=51)	Cirrhosis (N=273)	Cirrhosis INR ≥1.5 (N=48)
Standard hemostatic laboratory tests				
INR	0.9–1.1	3.4±1.7	1.3±0.3†	1.7±0.4†
Fibrinogen (mg/dL)	200–450	195±84	263±108**	179±89
Platelets (× 10^9/L)	172–440	186±95	112±79†	84±46†
TEG parameters‡				
Reaction time (min)	2.5–7.5	4.7±1.9	4.4±1.2	4.2±1.5
Kinetic time (min)	0.8–2.8	1.7 [0.8–20.0]	2.2 [0.8–16.6]	2.8 [1.2–16.6]**
α-angle (degrees)	55.2–78.4	63.7±12.2	62.6±9.3	58.1±10.8*
Maximum amplitude (mm)	50.6–69.4	55.0±10.9	51.5±10.4*	45.0±9.9†
Lysis-30 (%)	0.0–7.5	0.0 [0.0–2.1]	0.5 [0.0–5.2]†	0.25 [0.0–3.2]*

Patients with ALI/ALF have been described in detail.[32] Patients with cirrhosis and an international normalized ratio (INR) of 1.5 or greater were selected from the overall cirrhosis cohort. Normal range is for the local laboratory. Values are given as mean±standard deviation or median [range] (RT Stravitz, unpublished data).

*P<.05. **P<.001. †P<.0001. All comparisons are versus ALI/ALF. ‡TEG was performed on a Thrombelastograph Haemostasis Analyzer 5000 (Haemonetics Corp., Haemoscope Division). Clotting was initiated at 37°C by the addition of kaolin to 0.34 mL of recalcified blood.

Whole blood tests are as confusing as plasma-based tests

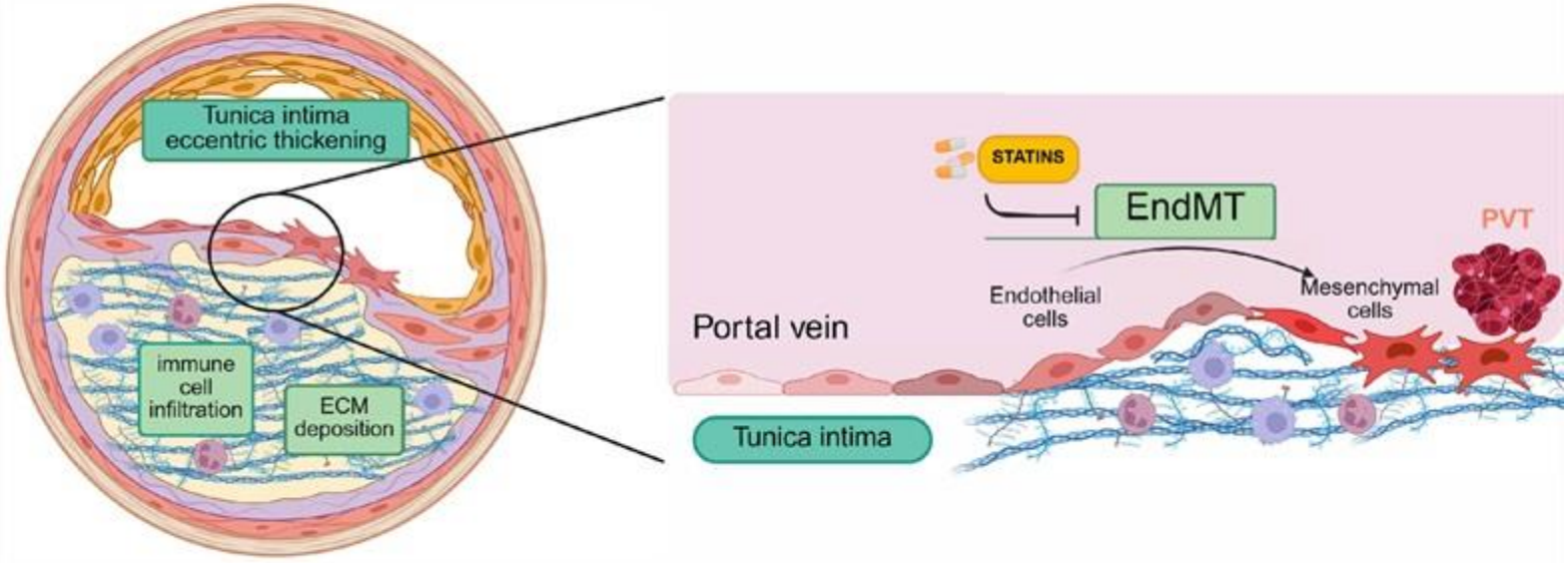


Hepatology74(2):937-949, August 2021.

Why do TEG and ROTEM give different information in liver disease?

- Trigger in TEG is weaker than in ROTEM
- More ‘chance’ for anticoagulant systems to kick in
- ROTEM more driven by procoagulants and therefore more often abnormal in liver disease (= closer to a PT than a TEG)

Portal vein during cirrhosis and PVT



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EDITORIAL

Cirrhotic portal vein thrombosis as a vascular rather than a thrombotic disorder

with PVT. This maladaptive response, including the accumulation of extracellular material and increased cellularity, leads to luminal narrowing. The fibrotic nature of the occlusive material suggests that terms like "portal vein stenosis" or "nonmalignant portal vein occlusion" that have been suggested based on previous studies could indeed be more descriptive of the underlying vascular pathology.[3]

In summary:

- Management of bleeding and thrombosis in liver disease has substantially changed in the past 25 years
- We are not there yet….
- Collaboration between institutes and between clinicians and basic scientists is key
- We need to move from confirming to innovating

“Let’s join hands to transfuse smarter in liver disease”

Principal Investigators:
- Amber Afzal (USA)
- Simon Stanworth (UK)
- Suzanne Marynad (UK)

An Internation Audit and Feedback by the ISTH SCC on “Hemostasis and Thrombosis in Liver Disease”

- 10-15 days of patient recruitment
- Up to 28 days of data collection

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