# *La Coagulopatia della Cirrosi del Fegato*


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# *The Coagulopathy of Cirrhosis: Changing Paradigm*

Up to 2004

Cirrhosis as the epitome of hemorrhagic diseases

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# *Hemostasis in Chronic Liver Disease*

## ***The Dogma…***

- The concept of a causal relationship between abnormal hemostasis tests and bleeding was widely accepted
- Common practice of screening patients with hemostasis tests
- Treating patients with abnormal values in order to correct the identified abnormalities prior to invasive procedures

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# *The Challenge of the Dogma*
## *Clinical evidence*

- Gastrointestinal (GI) bleeding is the most common hemorrhagic event in cirrhosis
- But, conventional coagulation tests do correlate poorly with GI bleeding in cirrhosis
- Coagulation defects do not predict blood product requirement during liver transplantation *(Massicotte, 2008)*

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# *Poor Correlation between Global Conventional Hemostasis Tests and Bleeding*

## ***Review of the Literature***


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- Segal JB & Dzik WH. *Transfusion 2005; 45:1413*
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- Diaz LK &Teruya J. *New Engl J Med 2001;344:2030*
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- Mc Gill DB et al. *Gastroenterology 1990; 99: 1396*
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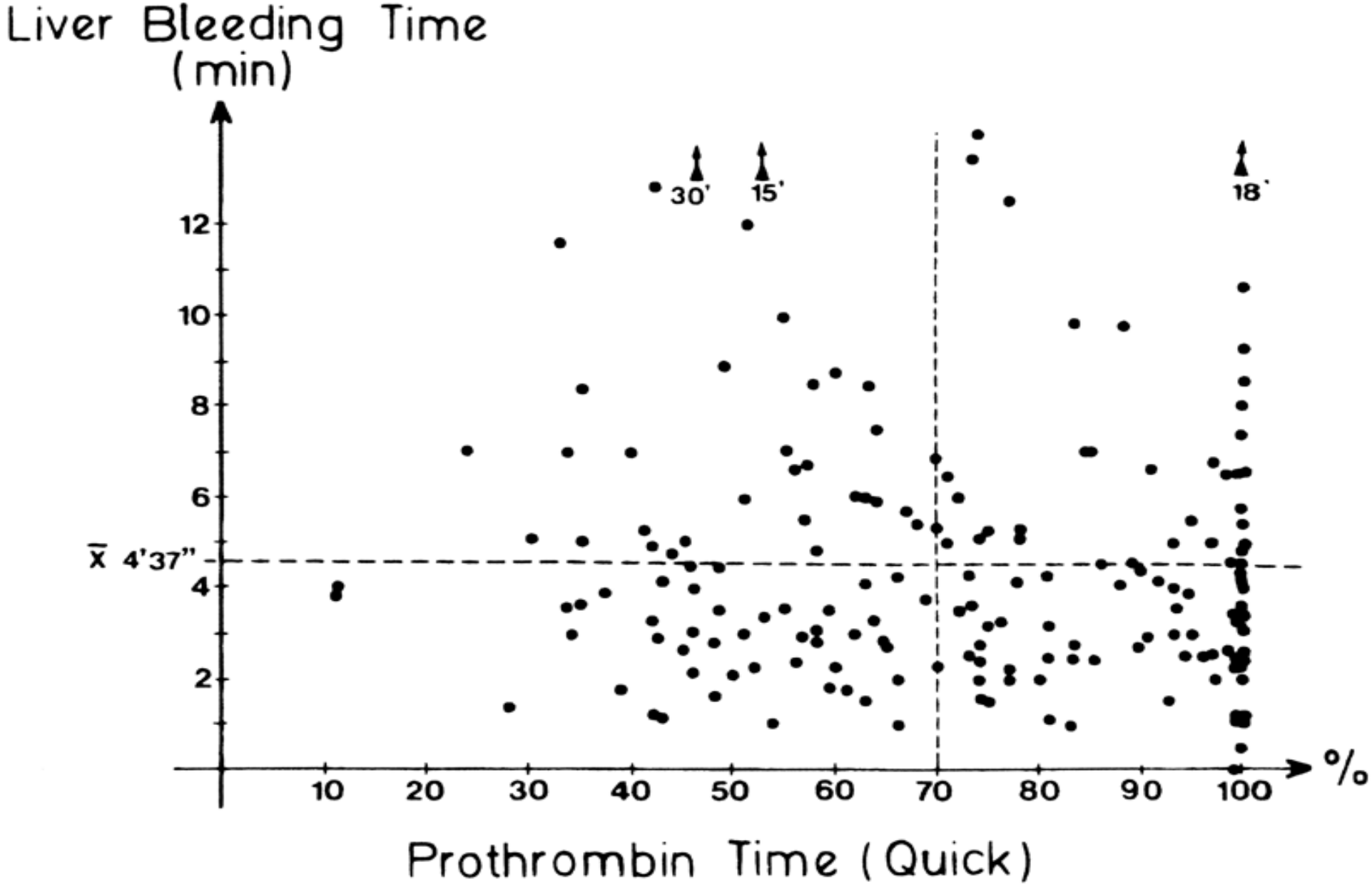


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Ewe, 1981

# *The Coagulopathy of Cirrhosis: Changing Paradigm*

Up to 2004

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2005-2009

The challenge of the dogma. Rebalanced hemostasis

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(HEPATOLOGY 2005;41:553–558.)



# Evidence of Normal Thrombin Generation in Cirrhosis Despite Abnormal Conventional Coagulation Tests

Armando Tripodi, Francesco Salerno, Veena Chantarangkul, Marigrazia Clerici, Massimo Cazzaniga, Massimo Primignani, and Pier Mannuccio Mannucci

**The role played by coagulation defects in the occurrence of bleeding in cirrhosis is still unclear. This is partly due to the lack of tests that truly reflect the balance of procoagulant and anticoagulant factors *in vivo*. Conventional coagulation tests such as prothrombin time and activated partial thromboplastin time are inadequate to explore the physiological mechanism regulating thrombin, because they do not allow full activation of the main anticoagulant factor, protein C, whose levels are considerably reduced in cirrhosis. We used a thrombin generation test to investigate the coagulation function in patients with cirrhosis.**

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# *Thrombin Generation in Platelet-free Plasma*

## *Summary of findings and consequences*

- *Findings*

– Plasma coagulation ***is not*** abnormal in stable cirrhosis when assessed with global tests reflecting the function of both pro- and anti-coagulants

- *Consequences*

– There is little value for the PT & APTT to assess the bleeding risk in cirrhosis

– The common practice of infusing pro-hemostatic agents in cirrhosis should be reconsidered

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# *Additional Evidence Challenging the Dogma*

- Fresh frozen plasma when added to cirrhotic plasma does not modify thrombin generation (Tripodi A et al, 2012)

- Fresh frozen plasma transfusion in patients with cirrhosis does not modify thrombin generation (Rassi A, D'Amico E, Tripodi A, et al, 2020)

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# *Rebalanced Primary Hemostasis in Cirrhosis*

- Thrombocytopenia is counteracted by increased levels of the adhesive protein VWF *(Lisman T et al 2006)*
- VWF activity is increased by the relatively low levels of ADAMTS-13 *(Feys HB et al 2007)*
- Thrombin generation in platelet-rich plasma is adequate if platelet counts are >50 x $10^9$/L (Tripodi A, et al, 2006)

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# *Why do Patients with Cirrhosis Occasionally Bleed?*

- The *"**restored**"* hemostatic balance in cirrhosis may not be as stable as in healthy individuals and, therefore, slight alterations may lead to hemorrhage (or thrombosis)
- Conditions underlying bleeding

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# *Conditions Underlying Bleeding in Cirrhosis*

- Portal Hypertension
- Endothelial dysfunction
- Bacterial infections
- Hyperfibrinolysis (?)
- Renal failure

*Therapeutic interventions correcting these abnormalities might be more effective than correcting coagulopathy*

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# *The Coagulopathy of Cirrhosis: Changing Paradigm*

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2005-2009

The challenge of the dogma. Rebalanced hemostasis

2010-onward

Prothrombotic ??

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# *Pathophysiological evidence*

- *All Virchow triggers are concomitantly occurring in cirrhosis*

–Endothelial dysfunction

–Reduced blood flow

–Hypercoagulability

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CME

# Coagulopathy Does Not Fully Protect Hospitalized Cirrhosis Patients from Peripheral Venous Thromboembolism

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Am J Gastroenterol 2009; 104:96–101

# Risk of Venous Thromboembolism in Patients With Liver Disease: A Nationwide Population-Based Case–Control Study

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***Conclusions***

- Patients with cirrhosis had a relative VTE risk of 1.7 (CI 1.5-1.9)
- When the analysis was restricted to unprovoked VTE the relative risk was 2.06 (CI 1.8-2.3)

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# *Clinical evidence*

- Cirrhotics on LMWH are protected from PVT without bleeding *(Villa, 2012)*
- Patients with high ETP-ratio are at increased risk for de-novo PVT *(La Mura, 2016)*
- High VWF and procoagulant imbalance (high FVIII/PC ratio) predict outcome in cirrhotics *(Kalambokis, 2016)*
- Thrombin may trigger liver fibrosis *(Wanless, 1995)*

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# *Cirrhotics present with*

- Low protein C *(anticoagulant driver)*
- High factor VIII *(procoagulant driver)*

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GASTROENTEROLOGY 2009;137:2105–2111

# BASIC—LIVER, PANCREAS, AND BILIARY TRACT

## An Imbalance of Pro- vs Anti-Coagulation Factors in Plasma From Patients With Cirrhosis

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# *Implications of the Procoagulant Imbalance in Cirrhosis*

- Secondary prevention of VTE (VKA or LMWH) should be more extensively used
- Primary PVT prevention should be considered in patients awaiting liver transplant

  - Villa E. et al, 2012

- Other (non coagulation) thrombin effect should be considered in cirrhosis

  - Wanless et al, 1995

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# *Overall Conclusions*

- The re-assessment of hemostasis in cirrhosis questions consolidated therapeutic strategies
- ***"Correcting"*** abnormal hemostasis tests prior to surgery should be reconsidered
- While platelet transfusion may be useful, plasma, anti-fibrinolytics, or pro-coagulants should be used on individual basis
- Cirrhotics are not auto-anticoagulated
- Hyper- rather than hypo-coagulability might be the distinctive feature of cirrhosis

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