La gestione della coagulopatia nel paziente cirrotico: dal laboratorio alla clinica

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Changing Concepts of Cirrhotic Coagulopathy

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The state of clinical art of the coagulopathy of cirrhosis changed considerably over the last decade. Until 2005, cirrhosis was considered as the epitome of the hemorrhagic coagulopathies and the abnormal hemostasis tests associated with the disease were corrected with infusion of fresh frozen plasma or platelets to minimize the risk of bleeding. Since that time, a great deal of work has been done and there is now a change of paradigm. The prothrombin time once considered as an isolated measure of bleeding risk was rejected, and cirrhosis shifted from a purely hemorrhagic construct to a mixed and thrombosis-prone paradigm. In this article we examine the interesting history of how these conceptual changes came about.

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REVIEW

Hemostasis in Cirrhosis

The Facts….(1)

- ***Cirrhosis is characterized by***

- Impaired synthesis of all clotting factors (except FVIII and VWF)
- Thrombocytopathy (??)
- Thrombocytopenia
- Hyperfibrinolysis (??)

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Hemostasis in Cirrhosis
The Facts….(2)

- *These complex defects were historically documented through the*

- PT & APTT
- Skin bleeding time
- Platelet count
- Measurement of fibrinolytic components

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Hemostasis in Cirrhosis

The Dogma…

- The causal relationship between abnormal hemostasis tests and bleeding widely accepted
- Common practice of screening patients with hemostasis tests
- Treatment to correct the identified abnormalities prior to invasive procedures

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The challenge of the Dogma

- *Rebalanced coagulation*
  - Deficiency of pro-coagulants is counterbalanced by deficiency of anti-coagulants
- *Evidence*
  - Clinical
  - Pathophysiological
  - Laboratory

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The challenge of the Dogma
Clinical evidence

- Gastrointestinal (GI) bleeding the most common hemorrhagic event
- But, PT & APTT do correlate poorly with GI bleeding
- PT/APTT do not predict transfusion requirement during liver transplantation *(Massicotte, 2008)*

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Poor Correlation between Global Conventional Hemostasis Tests and Bleeding

Review of the Literature

- Ewe K. *Dig Dis Sci 1981; 26; 388*
- Segal JB & Dzik WH. *Transfusion 2005; 45:1413*
- Boks AL, et al. *Hepatology 1986; 6: 79*
- Diaz LK &Teruya J. *New Engl J Med 2001;344:2030*
- Grabau CM et al. *Hepatology 2004;40:484*
- Terjung B et al. *Digestion 2003; 67: 138*
- Mc Gill DB et al. *Gastroenterology 1990; 99: 1396*
- Vieira da Rocha E et al.*Clin Gastroenterology and Hepatol 2009; 7: 988*

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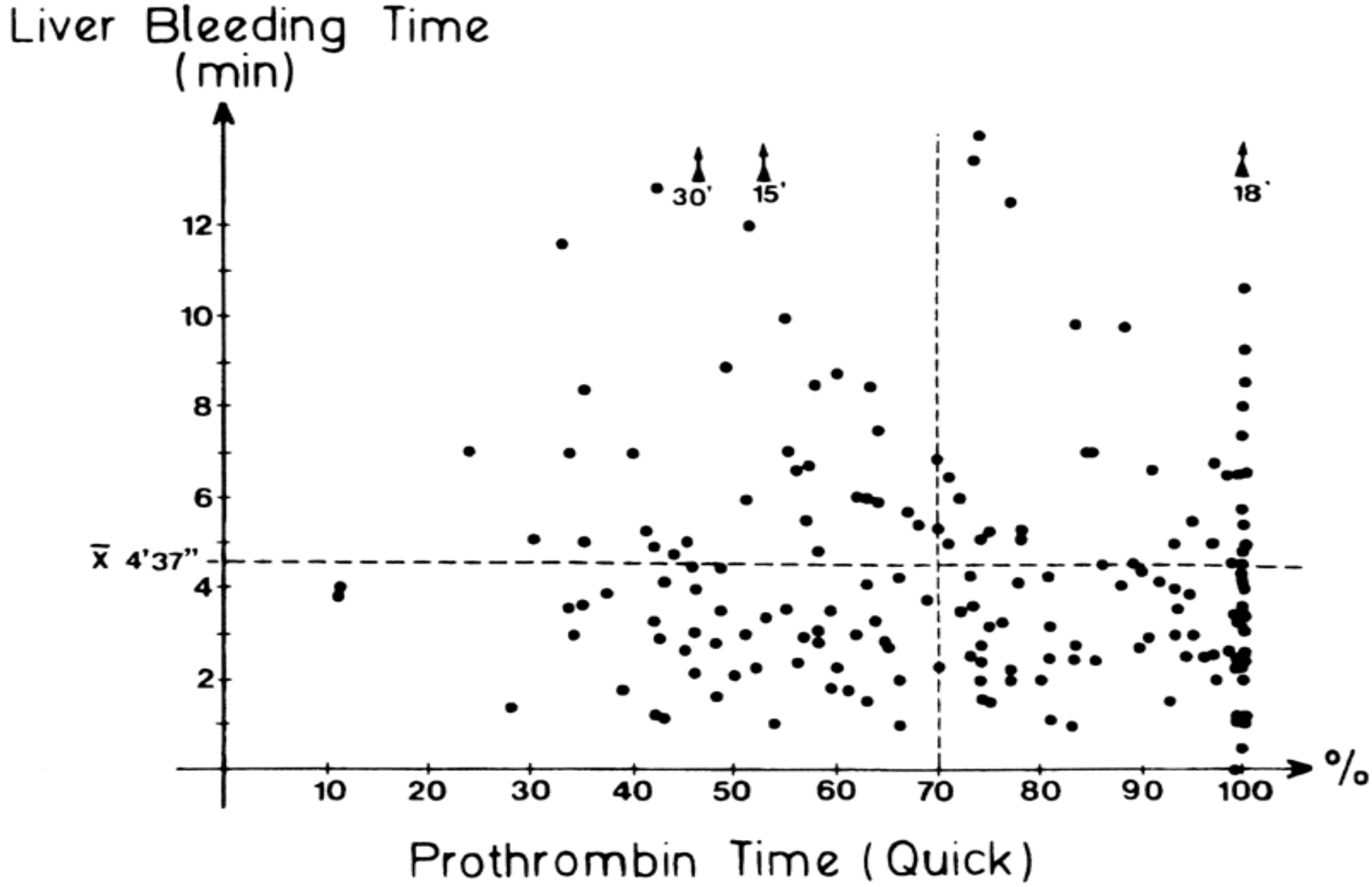

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Ewe, 1981

Why PT & APTT do not Correlate with Bleeding in Cirrhosis ?

Pathophysiological evidence

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Coagulation in Cirrhosis

Considerations on the value of PT & APTT

- *PT & APTT might be inadequate to reflect the coagulation balance as it occurs in vivo especially in cirrhosis*

- Protein C and antithrombin are reduced
- Protein C in vitro is activated to a limited extent in the absence of thrombomodulin
- Thrombomodulin located on endothelial cells, much less in plasma

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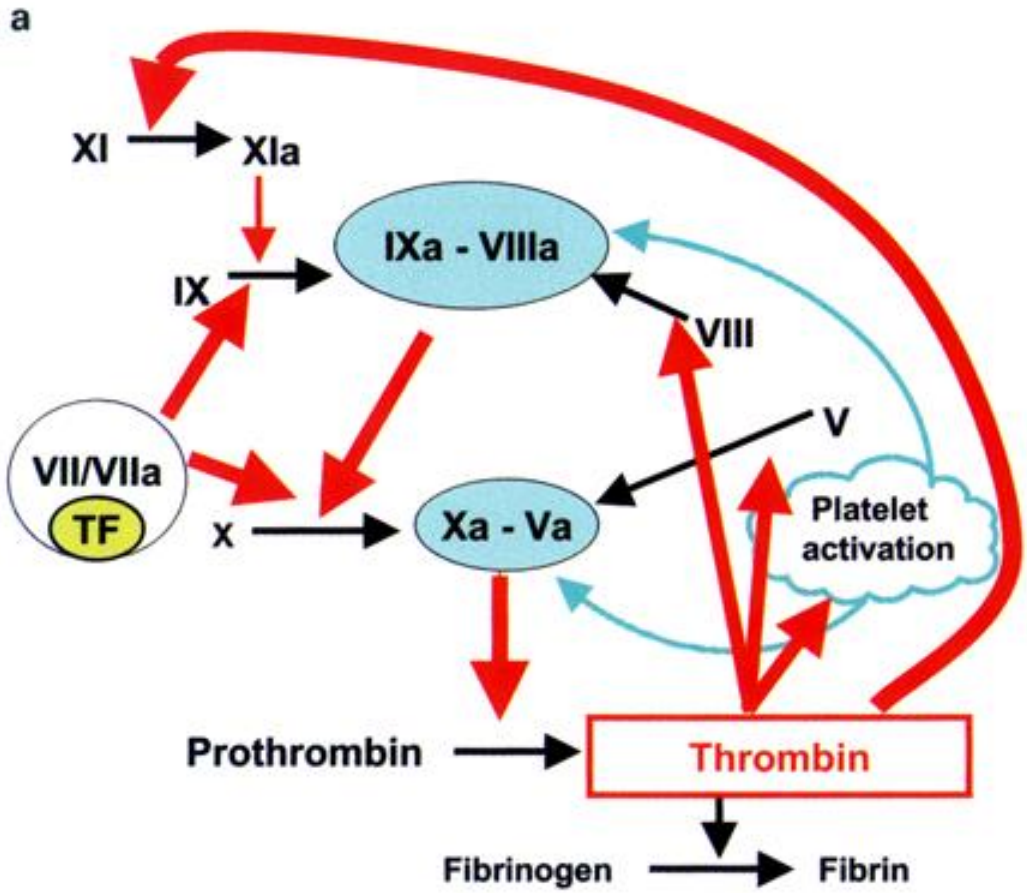

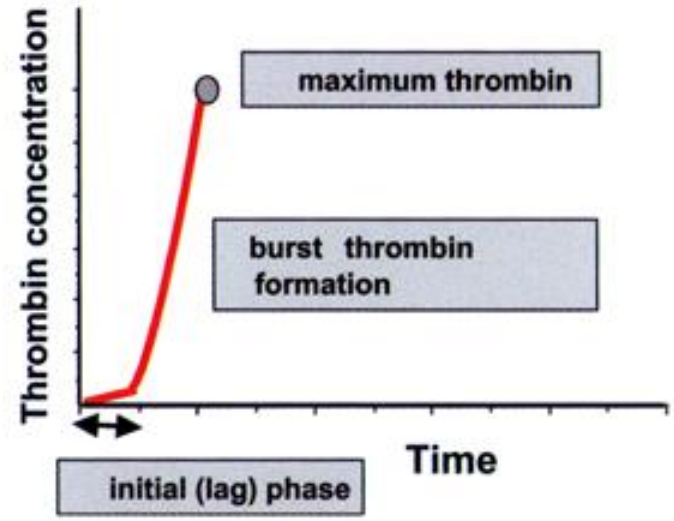

PT & APTT are responsive only to procoagulant factors

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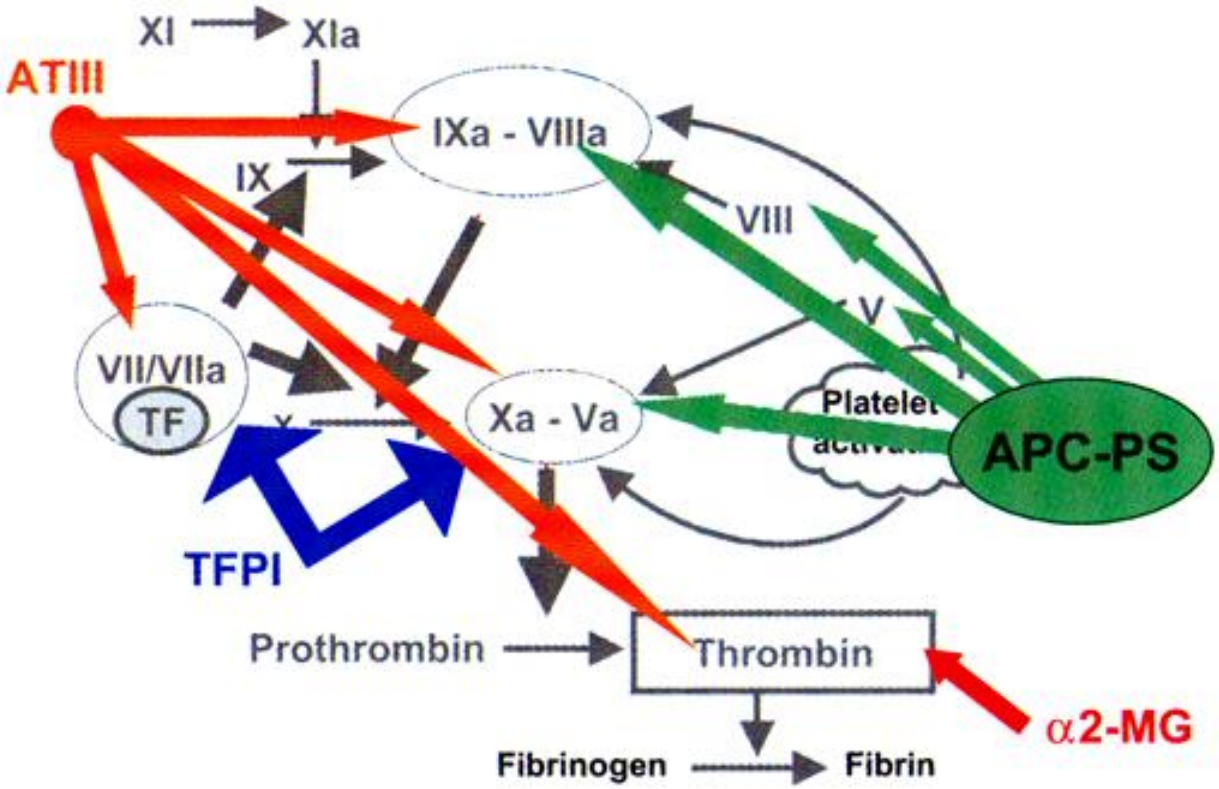

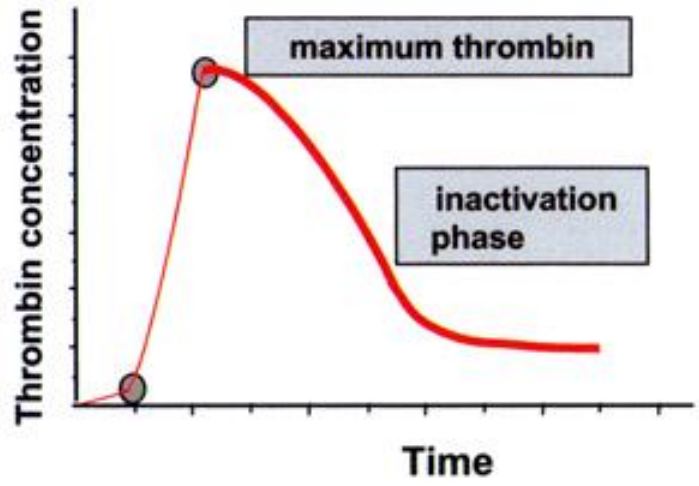

…and much less to the anticoagulant factors

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PT & APTT as Tools to Investigate the Balance of Coagulation

- PT & APTT can tell us whether a patient is deficient in one (or more) pro-coagulants *(hemophilia & allied disorders)*

- ….but not if this deficiency is counterbalanced by a parallel deficiency of the anti-coagulants (acquired coagulation disorders such as cirrhosis)

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Laboratory evidence

The thrombin generation assay (TGA)

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Hepatology 2005; 41: 553

LIVER FAILURE AND LIVER DISEASE
LIVER FAILURE

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 mech-

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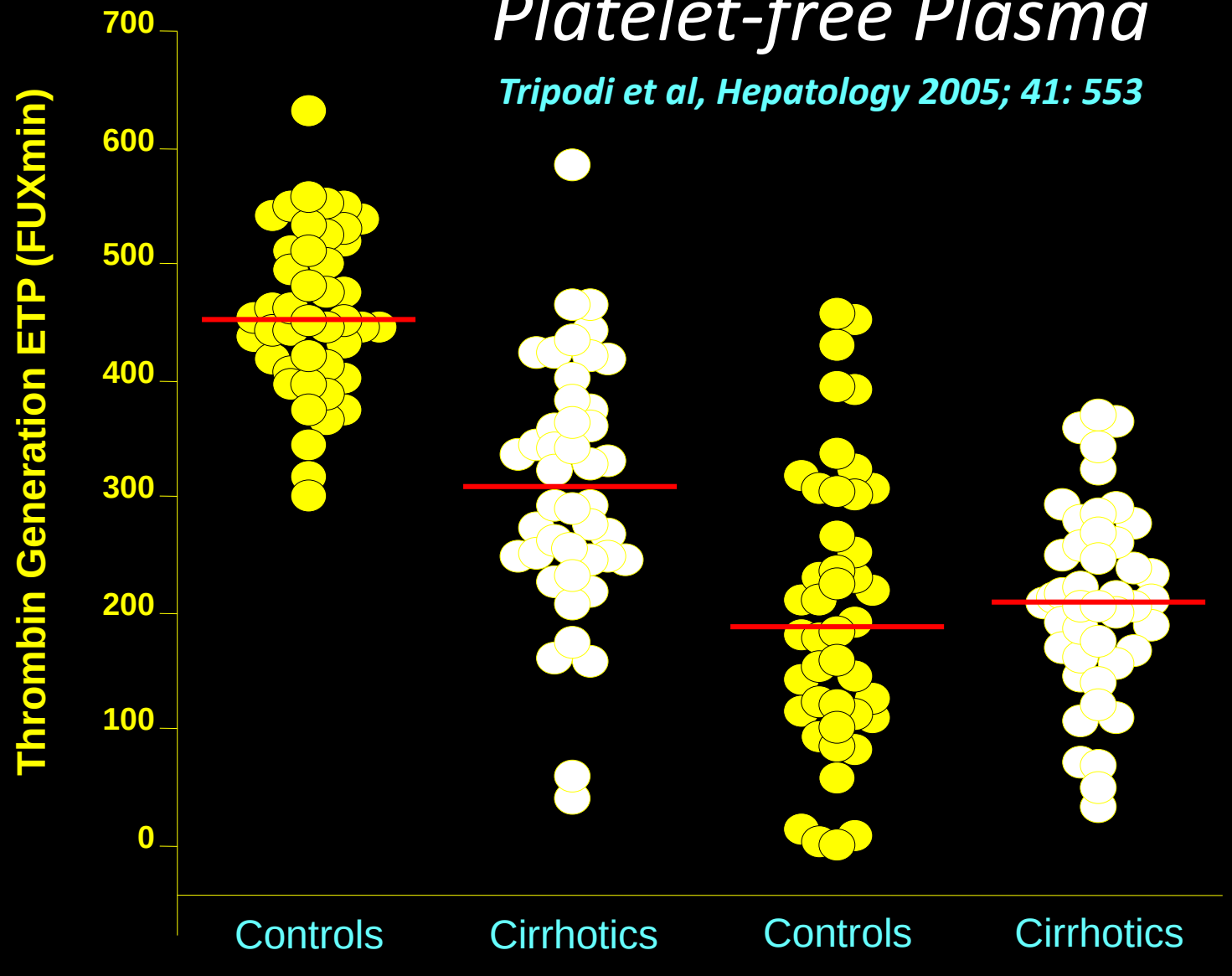
Platelet-free Plasma

Tripodi et al, Hepatology 2005; 41: 553



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Thrombin Generation in Platelet-free Plasma

Summary of findings and consequences

- *Findings*

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

- *Consequences*

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

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

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Poor Efficacy of rFVIIa to Stop Bleeding in Cirrhosis

- Bosch J et al, *2004 (variceal bleeding)*
- Bosch J et al, *2008 (variceal bleeding)*
- Lodge JP et al, *2005 (hepatectomy)*
- Planinsic RM et al, *2005 (hepatectomy)*

In spite of the fact that rFVIIa is effective in shortening the PT

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Is Fresh Frozen Plasmas (FFP) more effective than rFVIIa ?

Randomized clinical trials are not available

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Intern Emerg Med 2012; 7: 139-44

Intern Emerg Med
DOI 10.1007/s11739-011-0528-4

IM - ORIGINAL

Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma

Armando Tripodi · Veena Chantarangkul · Massimo Primignani · Marigrazia Clerici · Alessandra Dell'Era · Alessio Aghemo · Pier Mannuccio Mannucci

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In vitro addition of pooled normal plasma (PNP)

- PNP was added to cirrhosis plasmas and controls to mimic the infusion of FFP corresponding to 15 mL/Kg
- PT and TGA were measured before and after PNP addition

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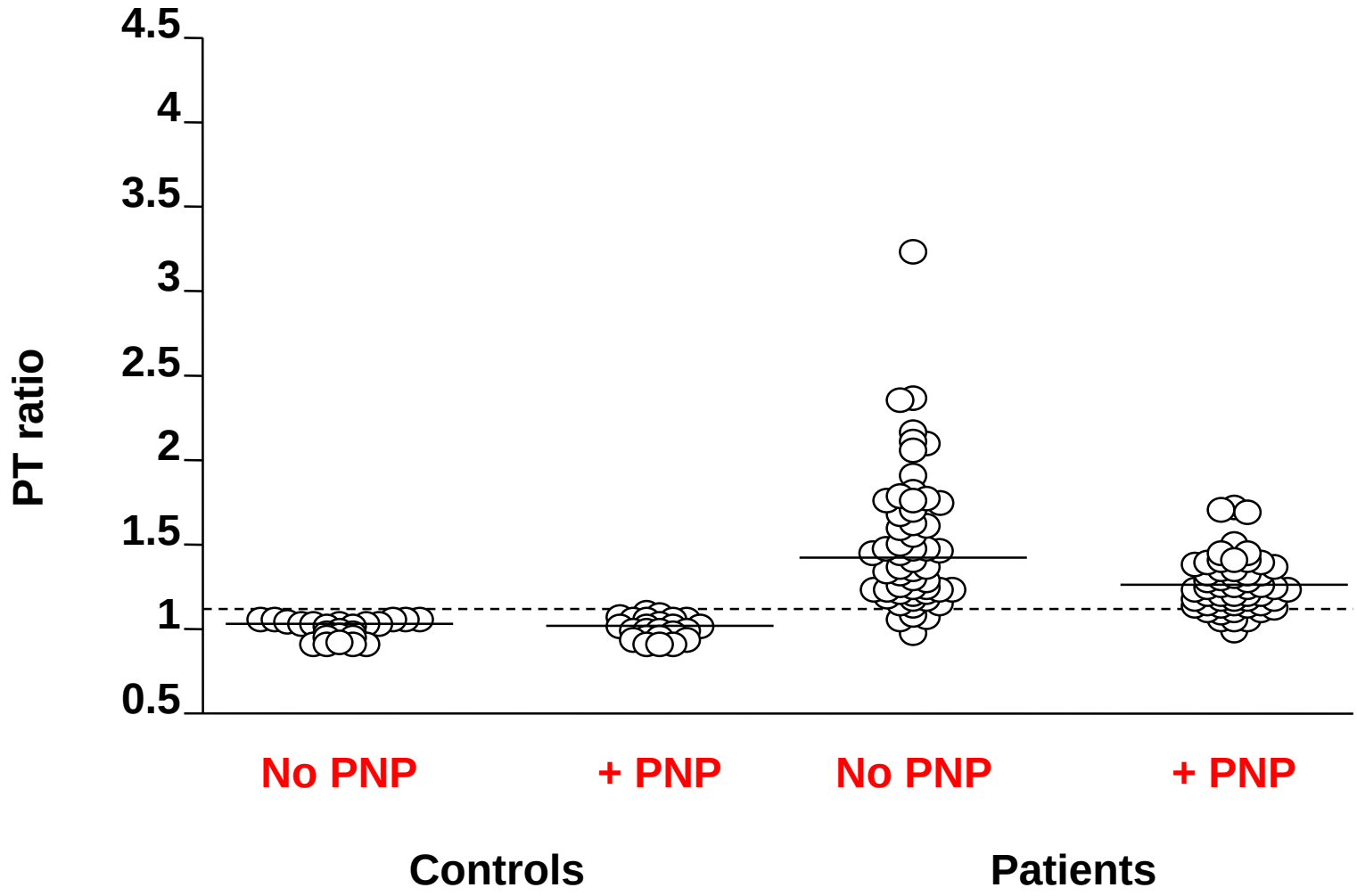

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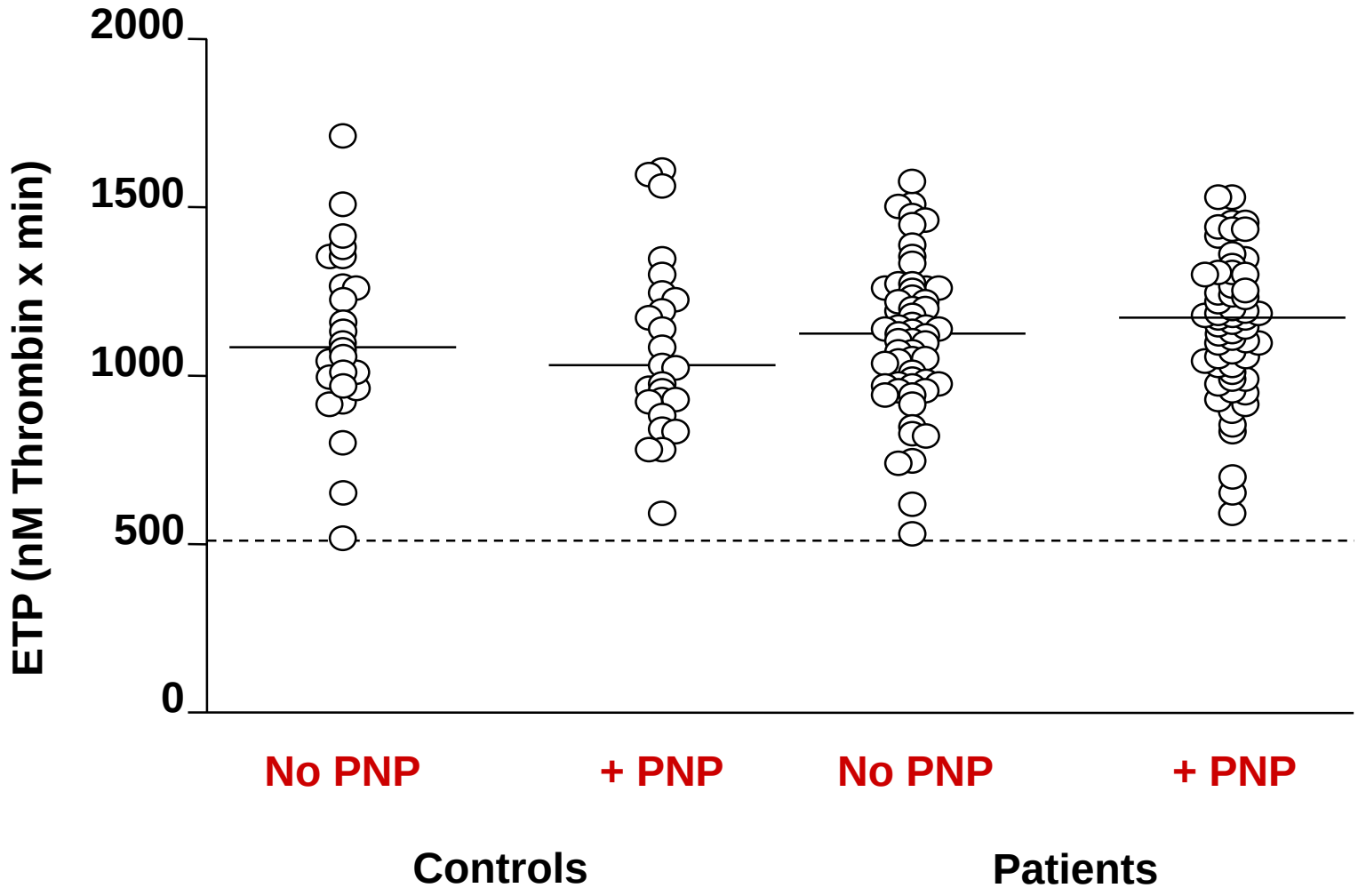
A. TRIPODI et al 2012



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A. TRIPODI et al, 2012

Conclusions on plasma infusion

- In vitro addition of PNP (at dosage corresponding to 15 mL/Kg***)*** ***does*** shorten PT, but ***does not*** modify TGA
- Whether this occurs also after FFP infusion is unknown, but seems plausible
- The risk/benefit ratio of FFP infusion in cirrhosis should be carefully considered

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The role Platelets

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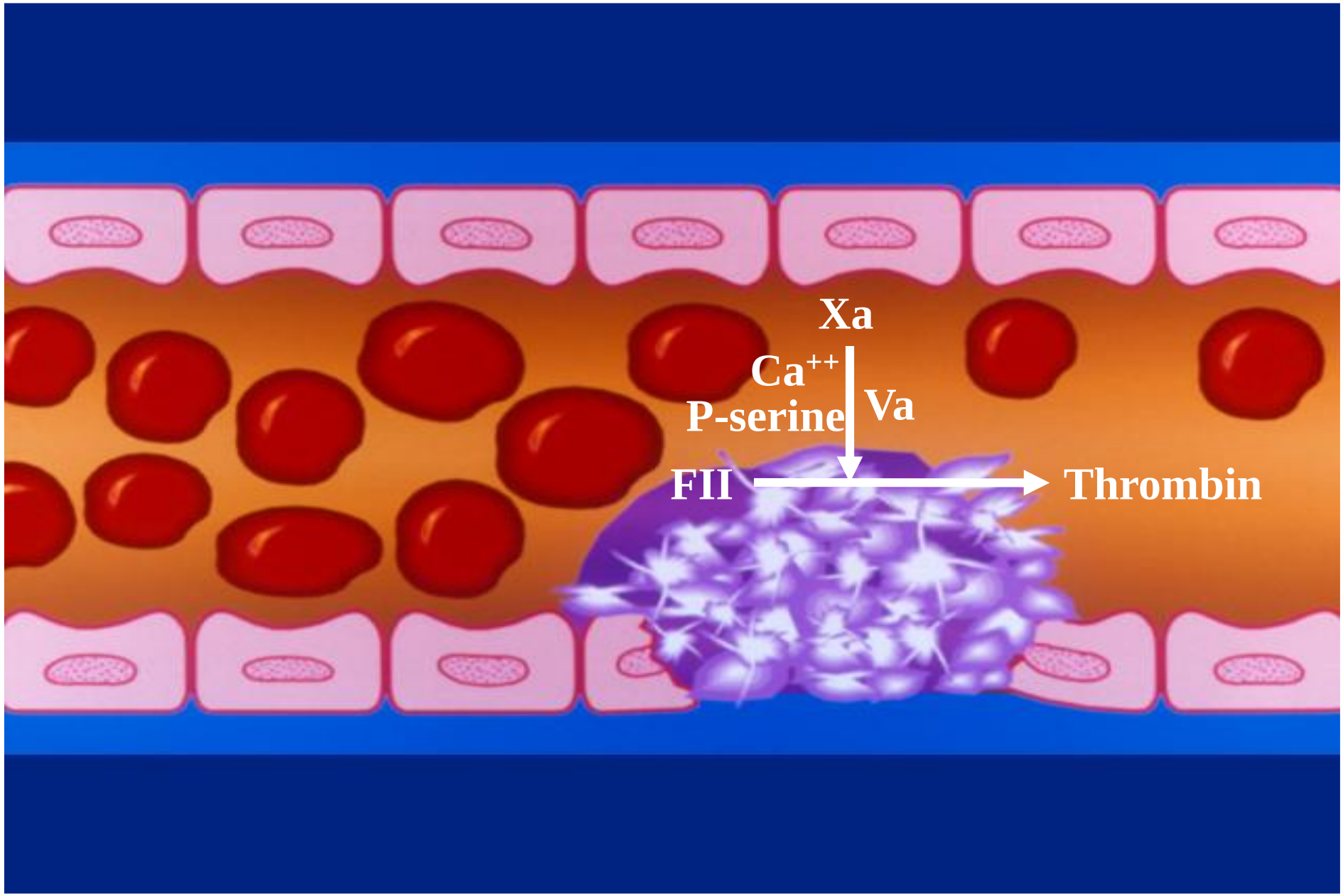

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Rebalanced Primary Hemostasis in Cirrhosis

- Increased levels of VWF counteract thrombocytopenia *(Lisman T et al 2006)*
- VWF is increased by the relatively low levels of ADAMTS-13 *(Feys HB et al 2007)*
- Serum levels CD40L and p-Selectin are increased suggesting platelet activation *(Raparelli et al 2016)*

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Do platelets from cirrhotics support normal thrombin generation ?

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Hepatology 2006; 44: 440-5

Thrombin Generation in Patients With Cirrhosis: The Role of Platelets

Armando Tripodi, Massimo Primignani, Veena Chantarangkul, Marigrazia Clerici, Alessandra Dell'Era, Federica Fabris, Francesco Salerno, and Pier Mannuccio Mannucci

Coagulation factor defects, thrombocytopenia, and thrombocytopathy are associated with cirrhosis. However, bleeding in patients who have cirrhosis does not entirely correlate with abnormal coagulation tests. Recently, it was shown that because of the concomitant abnormalities of

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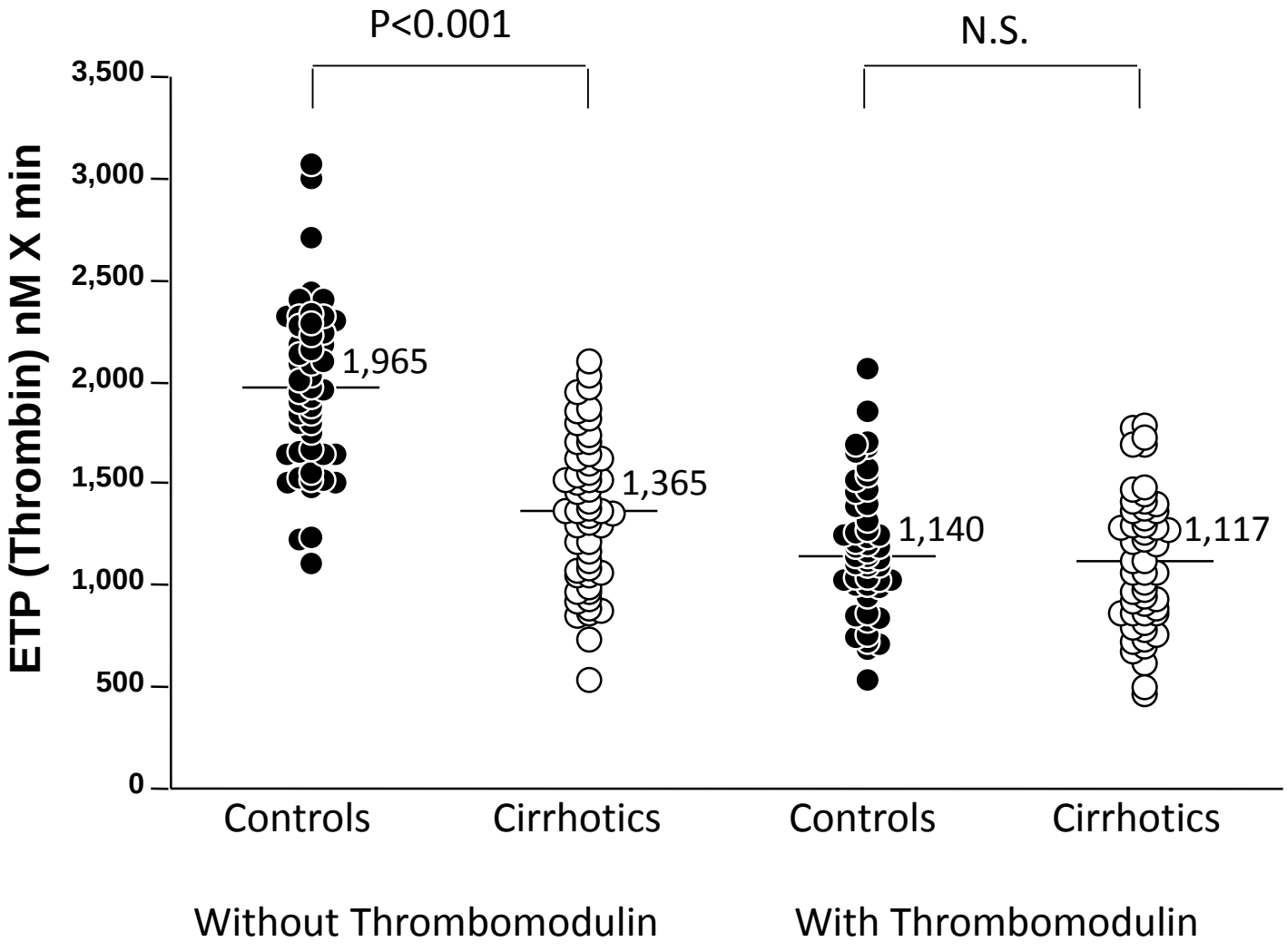
Platelet-Rich Plasma

(Plt.s count adjusted to 100,000/μL)



Tripodi et al,
Hepatology 2006

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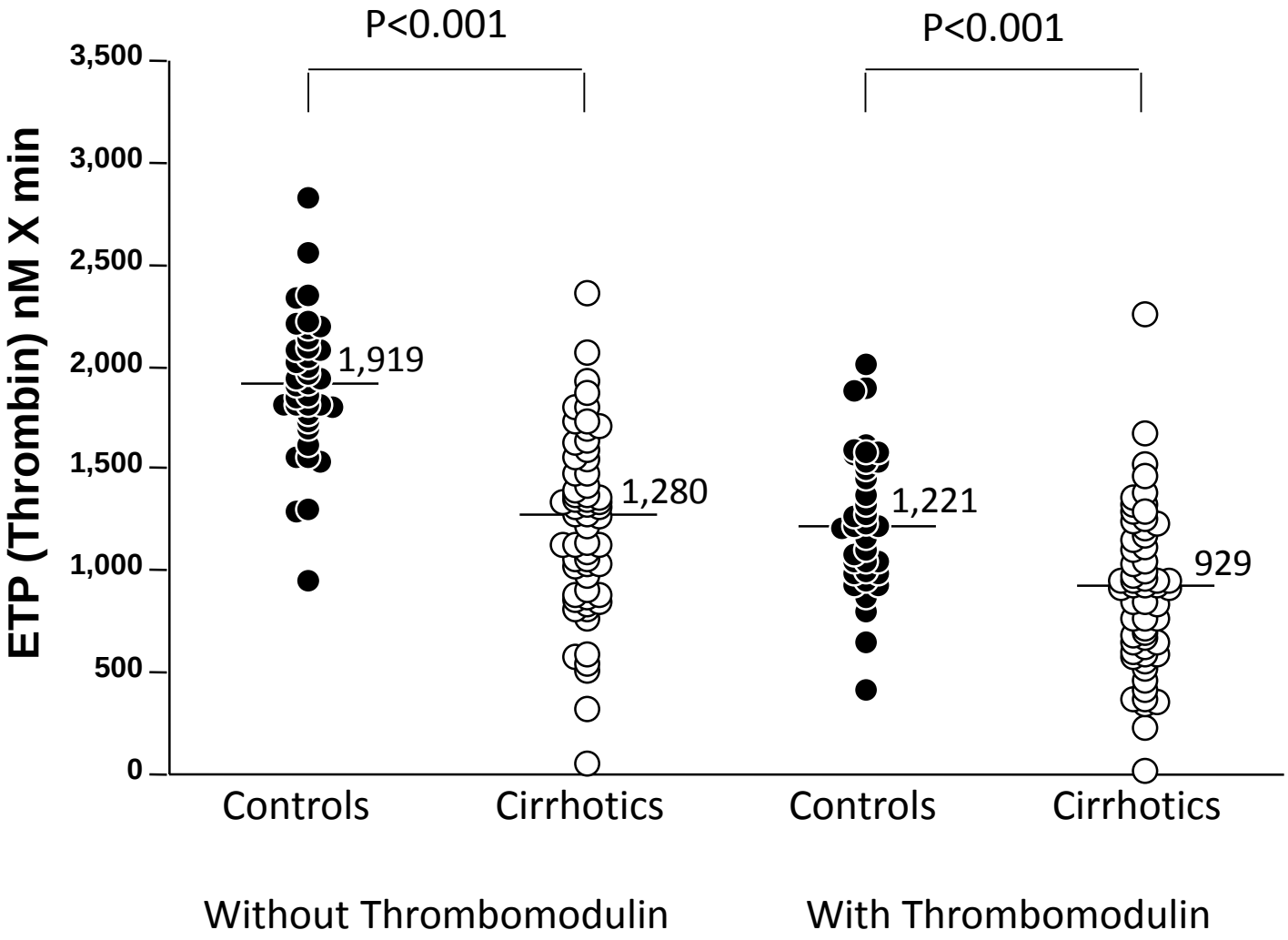
Platelet-Rich Plasma

(Plt.s adjusted to the original patient's count)



Tripodi et al, Hepatology 2006

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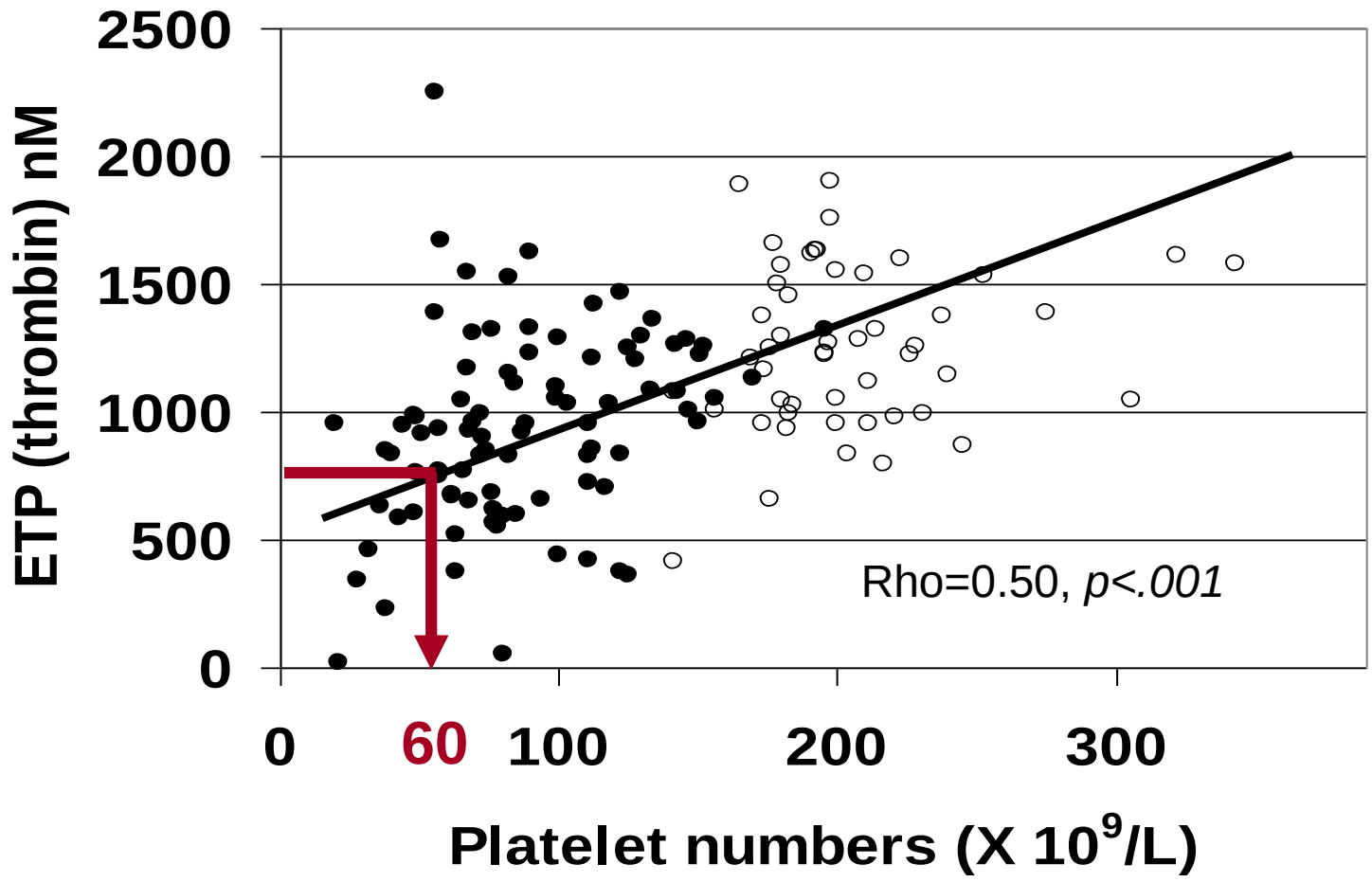
Thrombin Generation and Platelet Numbers



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Tripodi et al
Hepatology, 2006

Thrombin Generation in Platelet-Rich Plasma

Summary of Findings

- Platelets from cirrhotics are ***qualitatively*** suitable to support thrombin generation
- The ***numbers of platelets*** might be the limiting factor for thrombin generation

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….Perhaps

- Platelets transfusion may be more effective than plasma in controlling bleeding
- Randomized clinical trials are not available to substantiate this hypothesis
- Neither threshold platelet count nor lab testing are established to guide platelet transfusion

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AASLD Position Paper on Liver Biopsy

Rockey DC et al, Hepatology 2009; 49: 1017

20. Platelet transfusion should be considered when levels are less than 50,000-60,000/mL (this applies whether one is attempting biopsy transcutaneously or transvenously) (Class I, Level C).

21. The use of prophylactic or rescue strategies such as plasma, fibrinolysis inhibitors, or recombinant factors should be considered in specific situations, although their effectiveness remains to be established (Class IIa, Level C).

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Liver International 2013;33:362-7

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CIRRHOSIS AND LIVER FAILURE

Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion

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4 Scientific direction, IRCCS Cà Granda Ospedale Maggiore Foundation, Milano, Italy
5 IRCCS Cà Granda Ospedale Maggiore Foundation, Milano, Italy

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Platelet transfusion in cirrhosis

- One platelets unit was transfused to patients with platelets <$50x10^9$/L prior to invasive procedures
- TGA and thromboelastometry measured before and after transfusion

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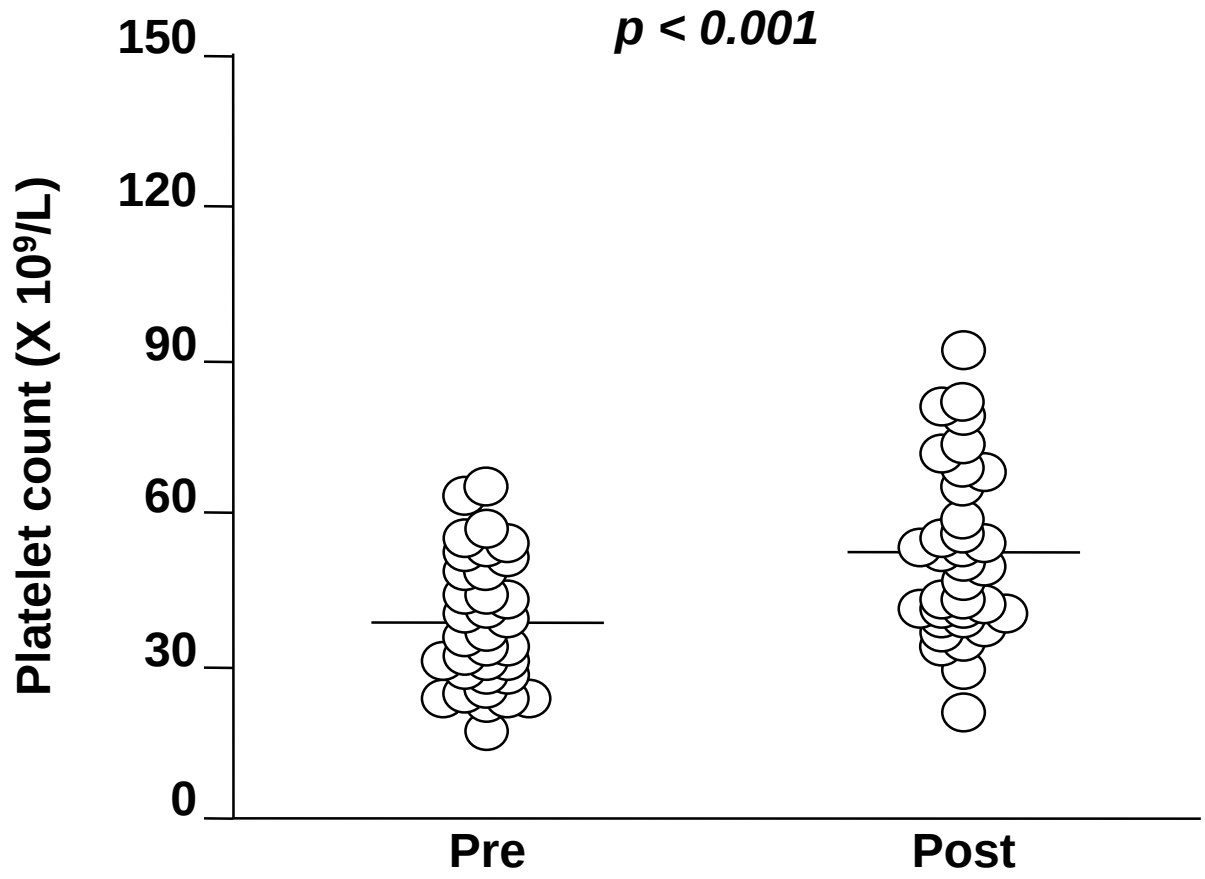

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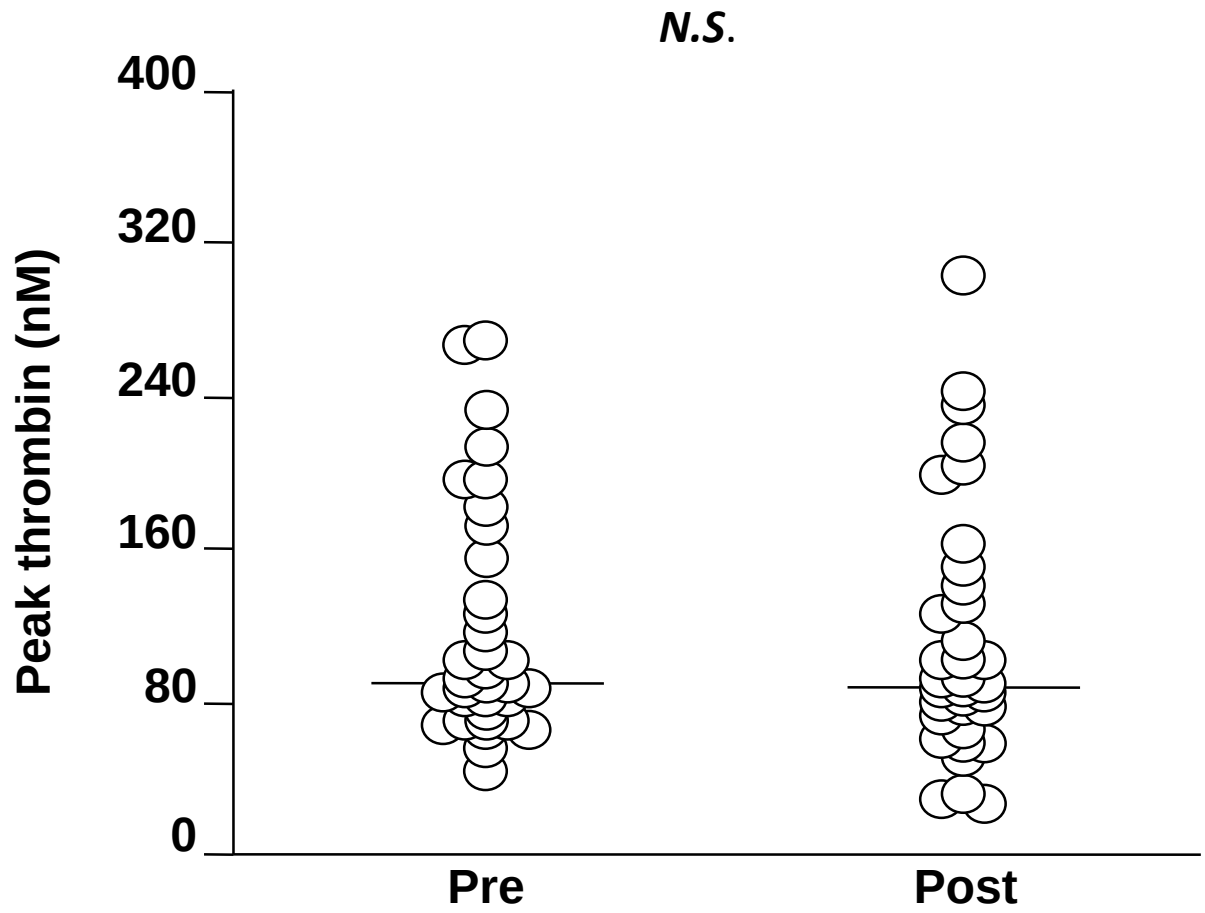
A. TRIPODI et al, 2013



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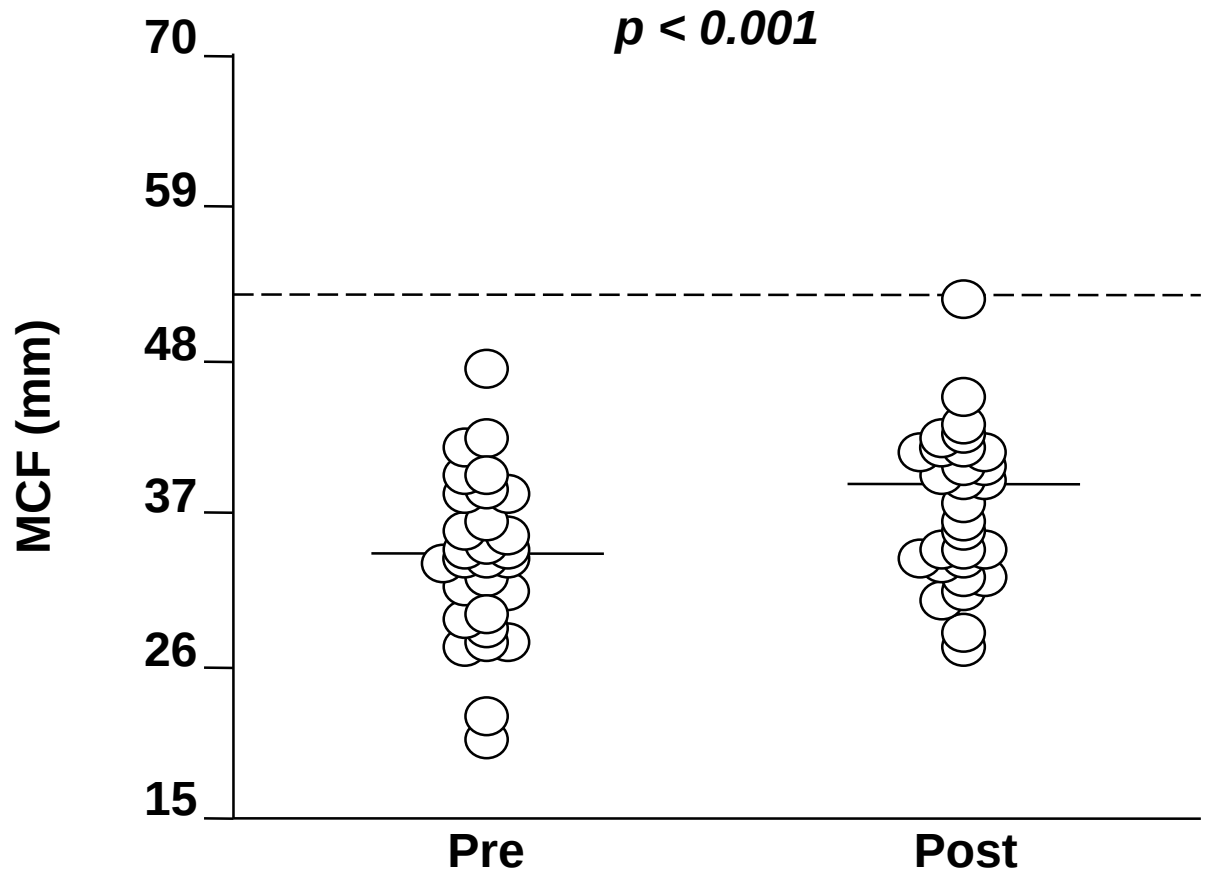

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A. TRIPODI et al 2013

Conclusions on platelet transfusion

- Infusion of one platelet unit
  - Increases marginally platelet counts
  - Does not modify TGA and thromboelastometry
- If substantial platelet increase is needed, multiple transfusion or other approaches (eltrombopag) is needed
  - The benefit of this strategy is questionable as it may increase the risk of thrombosis (Afdhal NH et al, NEJM 2012)

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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. 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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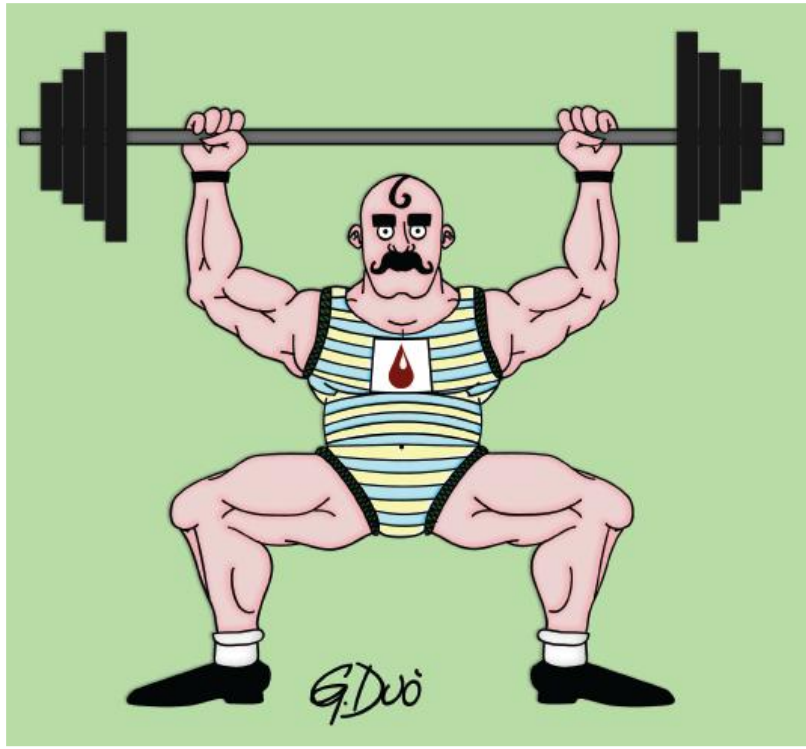
Hemostasis Balance

Healthy subject



Excess of	Procoagulants
	Anticoagulants
	Platelets

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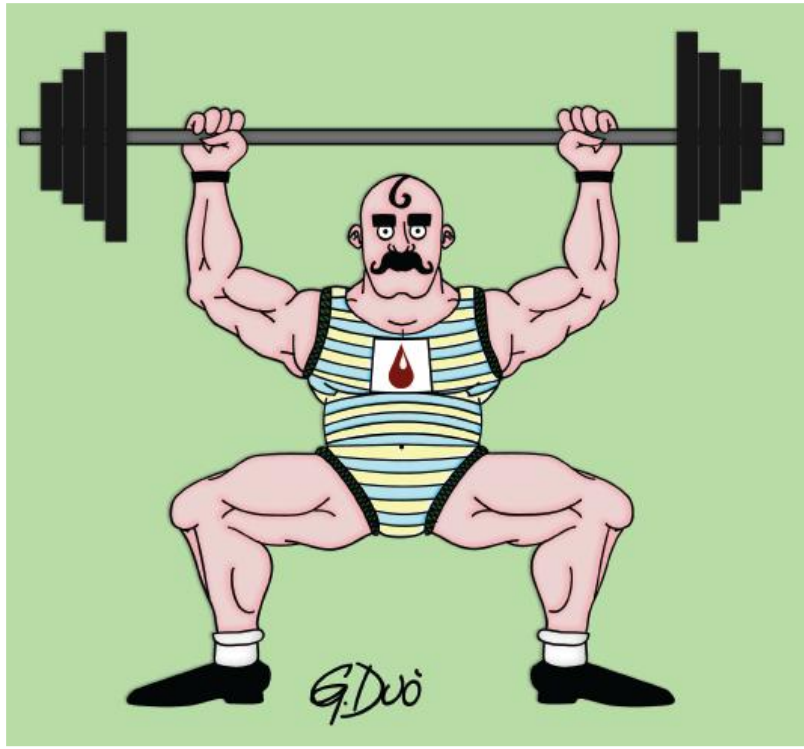
Hemostasis Balance

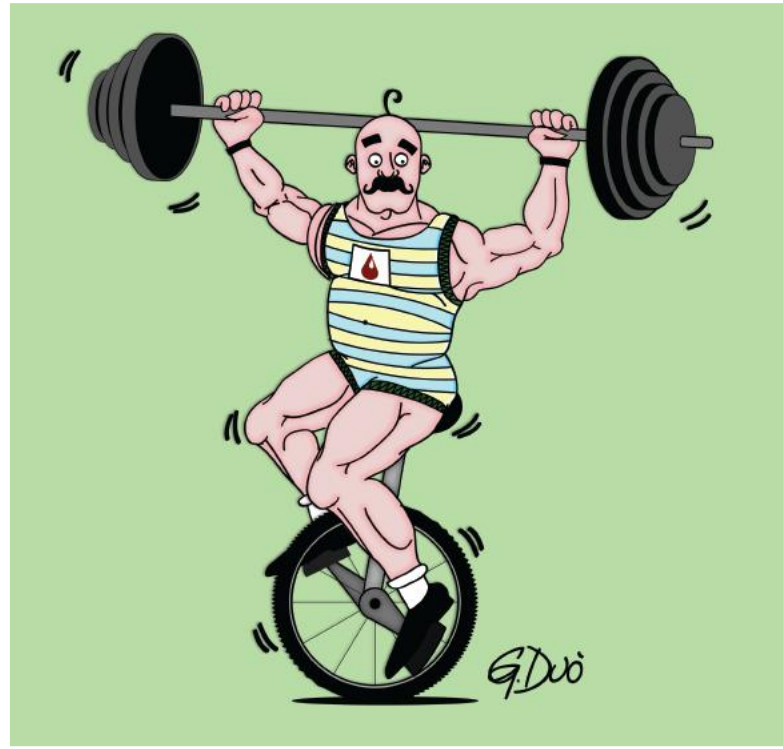
Healthy subject



Excess of

- Procoagulants
- Anticoagulants
- Platelets

Cirrhosis



Partial deficit of

- Procoagulants
- Anticoagulants
- Platelets

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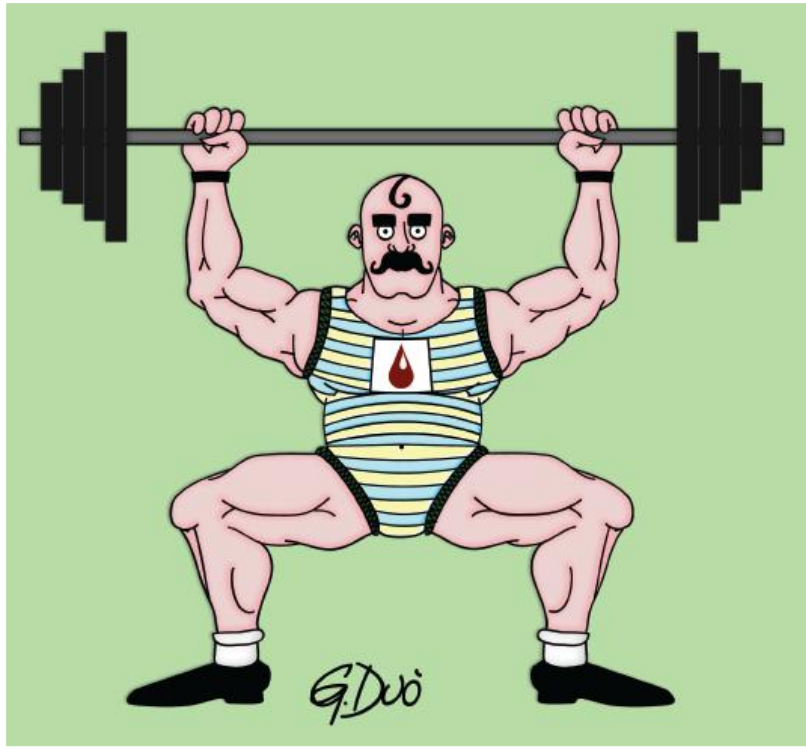
Hemostasis Balance

Healthy subject



Excess of

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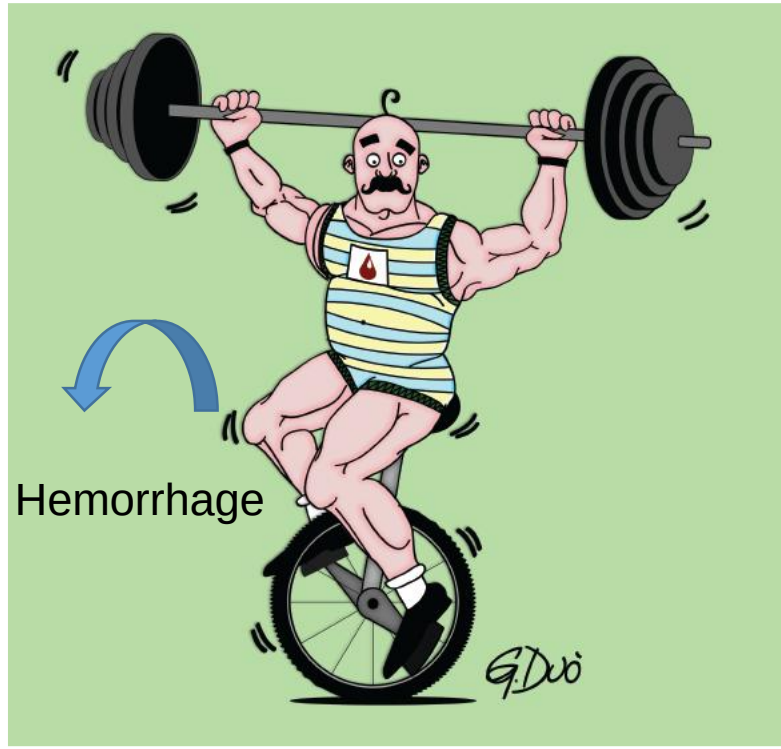
Cirrhosis



Partial deficit of

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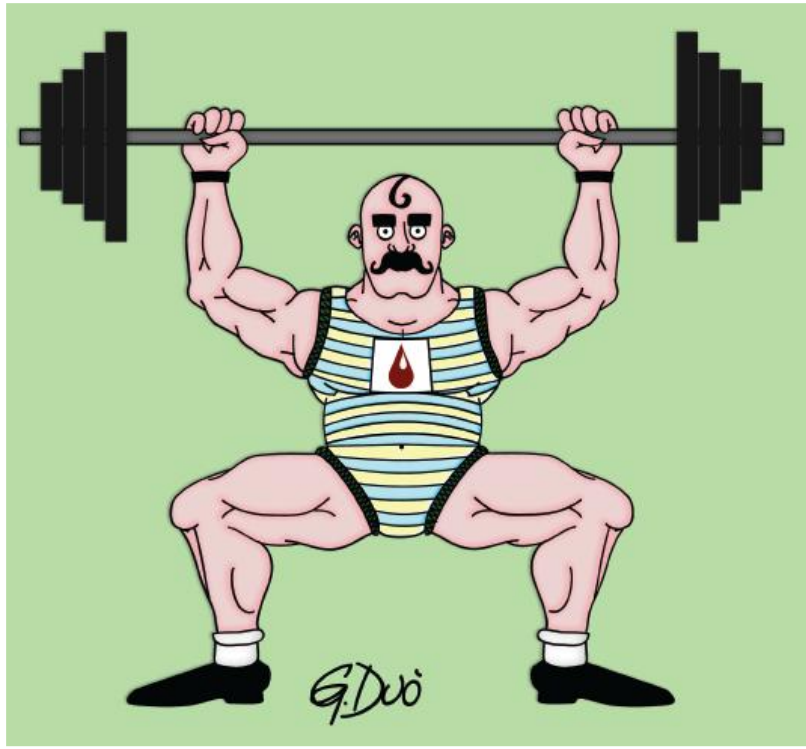
Hemostasis Balance

Healthy subject



Excess of

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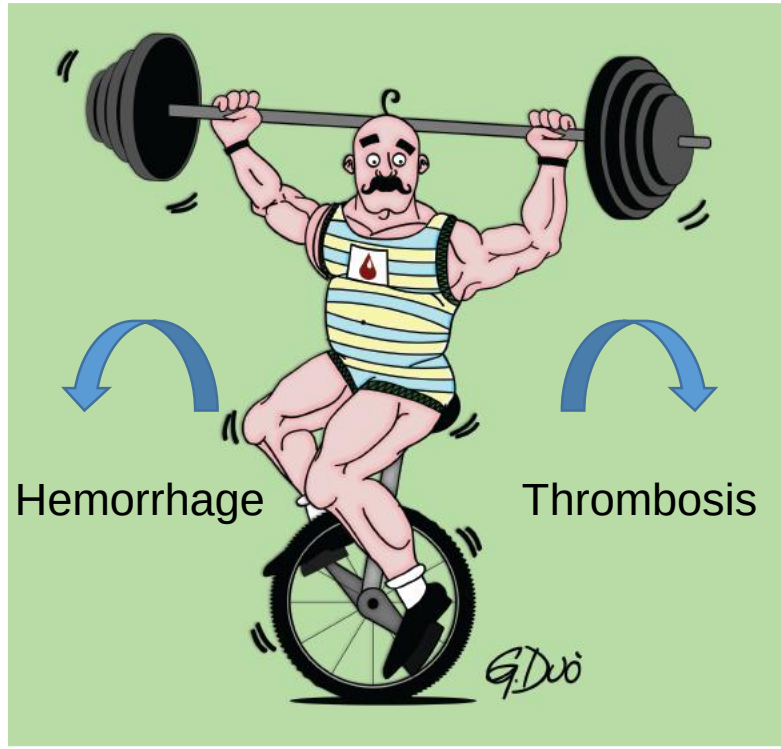
Cirrhosis



Partial deficit of

- Procoagulants
- Anticoagulants
- Platelets

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Hemostasis alterations in Cirrhosis
Overall Conclusions

- Although much more translational work is needed to cover the gap from the bench to bedside
- The hemostasis balance seems restored
- This finding questions the usefulness of:

- *PT & APTT to assess bleeding risk*
- *Indiscriminate use of pro-coagulant agents and/or platelet transfusion in controlling bleeding*

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