Pathogenesis, prevention, and management of bleeding and thrombosis in patients with liver diseases

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

Importance of the liver in hemostasis

Synthesis of

- Coagulation factors
- Fibrinolytic proteins
- Thrombopoietin

Hemostatic alterations in liver disease

- Thrombocytopenia and platelet function defects
- Low levels of coagulation proteins & inhibitors
- Low levels of fibrinolytic proteins
- High VWF, FVIII, tPA, PAI-1

Hemostatic alterations in liver disease

Consequences for labvalues

- Low platelet count
- Prolonged PT, APTT

Hemostatic alterations in liver disease

- Low platelet count
- Prolonged PT, APTT

Bleeding?

Bleeding complications during liver transplantation

Transfusion. 1987 May-Jun;27(3):222-5:

“During the first 5 years (1981-1985) of the liver transplantation program in Pittsburgh, a total (preoperative, intraoperative, and postoperative) of 18,668 packed red cell units, 23,627 fresh-frozen plasma units, 20,590 platelet units, and 4241 cryoprecipitate units was transfused for the procedures (626 transplants). This represents 3 to 9 percent of the total of blood products supplied by the Central Blood Bank to its 32 member hospitals.”

Classical Notions of Coagulation Revisited in Relation with Blood Losses, Transfusion Rate for 700 Consecutive Liver Transplantations

Luc Massicotte, MD[1] Lynda Thibeault, MD, MSc[2] André Roy, MD[3]

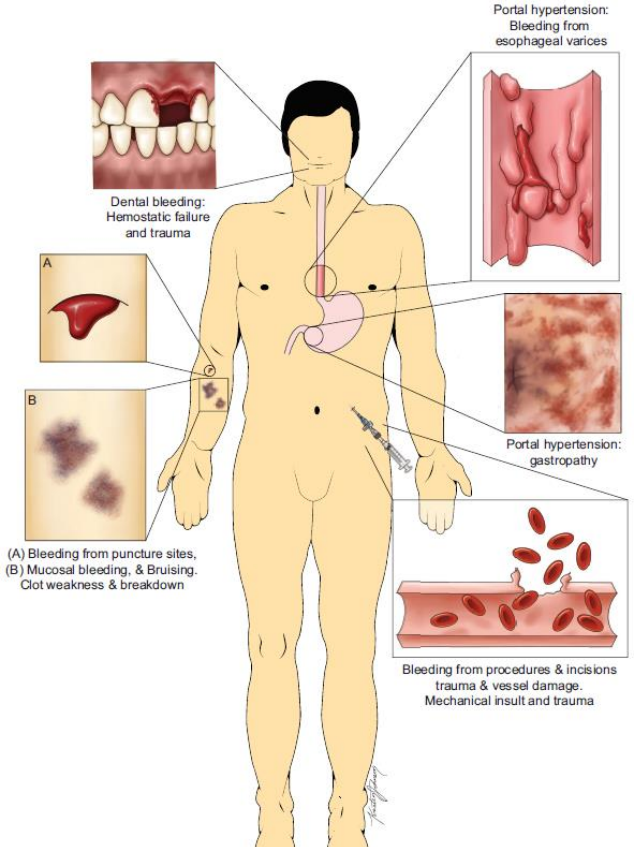
[1] Department of Anesthesiology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada
[2] Department of Public Health, University of Montreal, Montreal, Quebec, Canada
[3] Department of Hepatopancreatobilliary Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada

Address for correspondence Luc Massicotte, MD, Centre Hospitalier de l'Université de Montréal (CHUM) Hôpital St-Luc, 1058, St-Denis, Montreal, Quebec, Canada, H2X3J4 (e-mail: luc.massicotte@umontreal.ca).

Semin Thromb Hemost 2015;41:538–546.

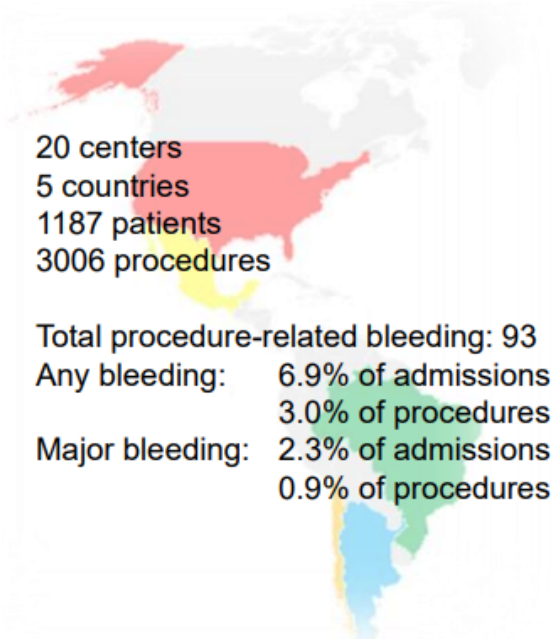
The median blood loss was 920 mL.
Overall, 77.4% of the patients did not receive any blood product and the mean RBC transfusion was 0.5 +/- 1.4 units per patient.

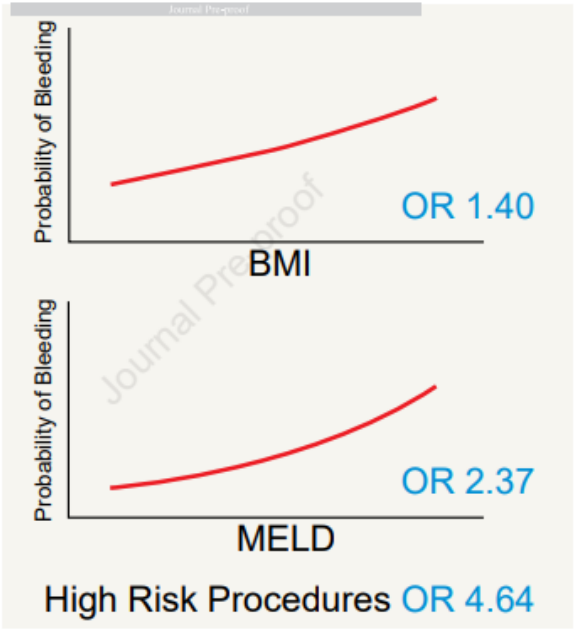
Bleeding complications in liver disease: often unrelated to hemostatic failure

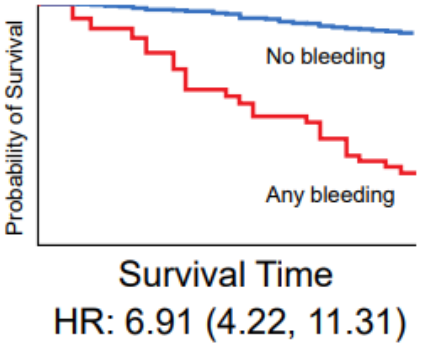


Hepatology. 2021;73(1):366-413.

Procedural bleeding in liver disease is rare







Gastroenterology

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

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

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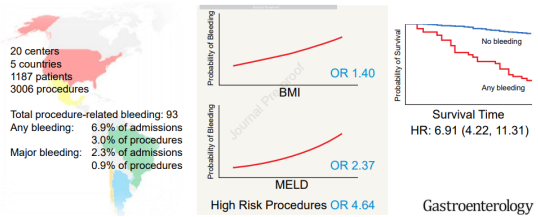
DOI: 10.1111/apt.16078

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

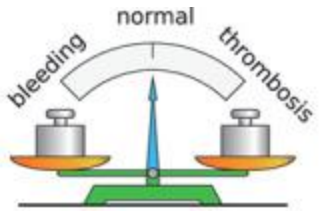
Clinical consequences (ISTH/SSC guidance)

• We suggest PT/INR, APTT, platelet count, and fibrinogen should not be routinely evaluated to predict bleeding risk prior to procedural intervention in patients with cirrhosis, even in those who are critically ill.

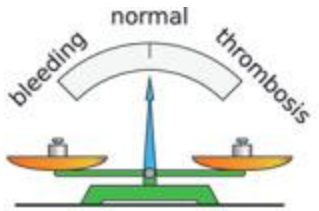
• We recommend against prophylactic correction of abnormal coagulation parameters in the periprocedural setting in the absence of vitamin K antagonist use.

• We recommend no treatment to increase the platelet count prior to most procedures for patients with cirrhosis.

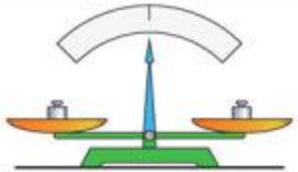
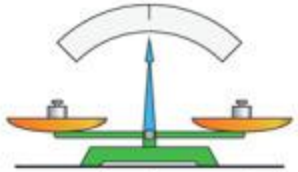
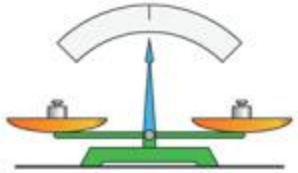
J Thromb Haemost 2022 Jan;20(1):39-47



(A) normal situation

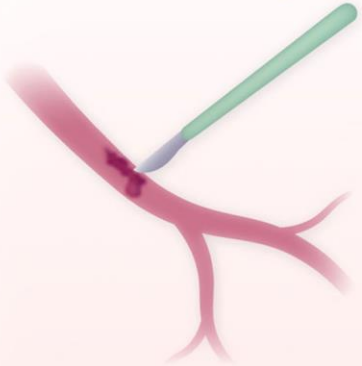


(B) situation in patient with liver disease

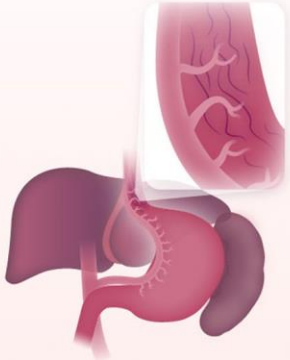
antihaemostatic changes	'rebalance'	prohaemostatic changes
- Thrombocytopaenia - Platelet function defects - Enhanced production of nitric oxide and prostacyclin	 primary haemostasis	- Elevated levels of VWF - Decreased levels of ADAMTS13 - Platelet activation by endotoxaemia
- Decreased levels of coagulation factors II, V, VII, IX, X, XI - Vitamine K deficiciency - Hypo- and dysfibrinogenaemia	 secondary haemostasis	- Elevated levels of factor VIII - Decreased levels of protein C, protein S and antithrombin - Prothrombotic fibrin clot structure
- Decreased levels of α2-antiplasmin, factor XIII and TAFI - Elevated levels of tPA	 fibrinolysis	- Decreased levels of plasminogen - Elevated levels of PAI-1

Bleeding complications in patients with liver disease

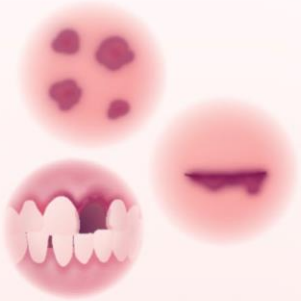
Mechanical injury



Portal hypertension



Hemostasis



Prevention

Mechanical injury

- Meticulous surgical techniques
- Imaging-guidance during invasive procedures

Portal hypertension

- Non-selective beta blockers
- Endoscopic variceal band ligation

Hemostasis

- Stop antithrombotic drugs prior to dental work
- Optimise renal function, manage infection

Treatment

Mechanical injury

- Identify bleeding source and directly treat site of rupture
- Hemostatic support only for continued bleeding

Portal hypertension

- Endoscopic variceal ligation
- Vasoactive medication
- Restrictive red cell transfusion
- Avoid FFP and platelets
- Avoid tranexamic acid

Hemostasis

- Topical measures
- Optimise renal function, manage infection
- Tranexamic acid and fibrinogen for intractable bleeds
- Avoid FFP and platelets

Thrombotic complications in cirrhosis

- Venous thrombosis
  - Liver diseases are a risk factor for VTE!
- Portal vein thrombosis
  - Up to 25% of patients on the transplant list
- Coronary events
- Intrahepatic thrombosis
- ……

Antithrombotic treatment in patients with liver disease

- VTE prevention
- Treatment of VTE
- Atrial fibrilation
- MI/stroke

Issues with antithrombotic treatment in patients with liver disease

- Which drug?
  - VKAs – difficult to dose in patients with baseline INR prolongation
  - LMWH – less suitable for long-term use
  - DOACs – no RCTs, contraindicated in the sickest patients
  - Antiplatelet agents in thrombocytopenic patients?
- Which dose?
- Which patient?
- How long?

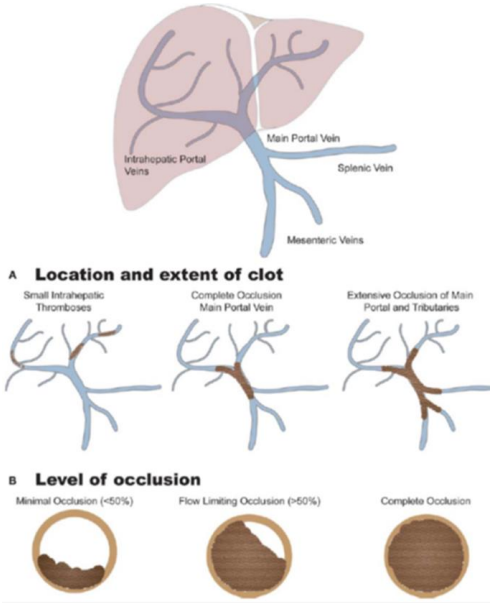
Clinical consequences (ISTH/SSC guidance)

• We recommend against the use of thrombocytopenia and/or prolongation of PT/INR as absolute contraindications to anticoagulant thromboprophylaxis in patients with cirrhosis.

• We recommend further research to refine VTE risk stratification within hospitalized patients with cirrhosis, and to establish the optimal dosing and duration of thromboprophylaxis.

J Thromb Haemost. 2022;20(10):2237-2245

Changing insights in the pathogenesis of portal vein thrombosis



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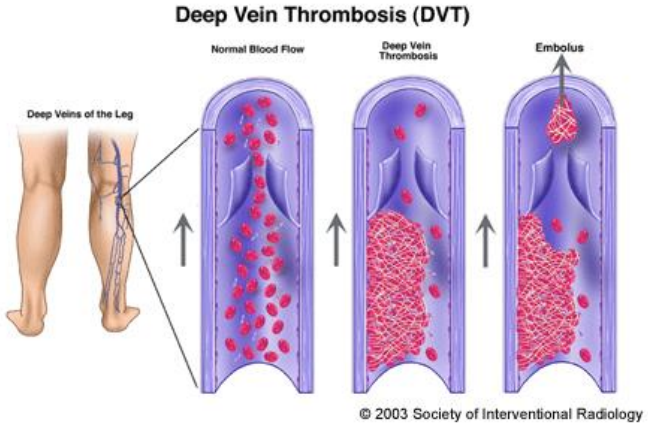
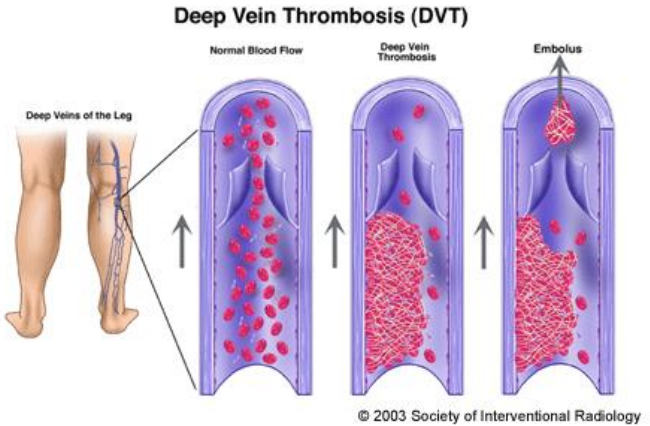


Unique characteristics of the portal vein

The portal vein drains blood to the liver

The portal vein lacks venous valves



Hypercoagulability and DVT

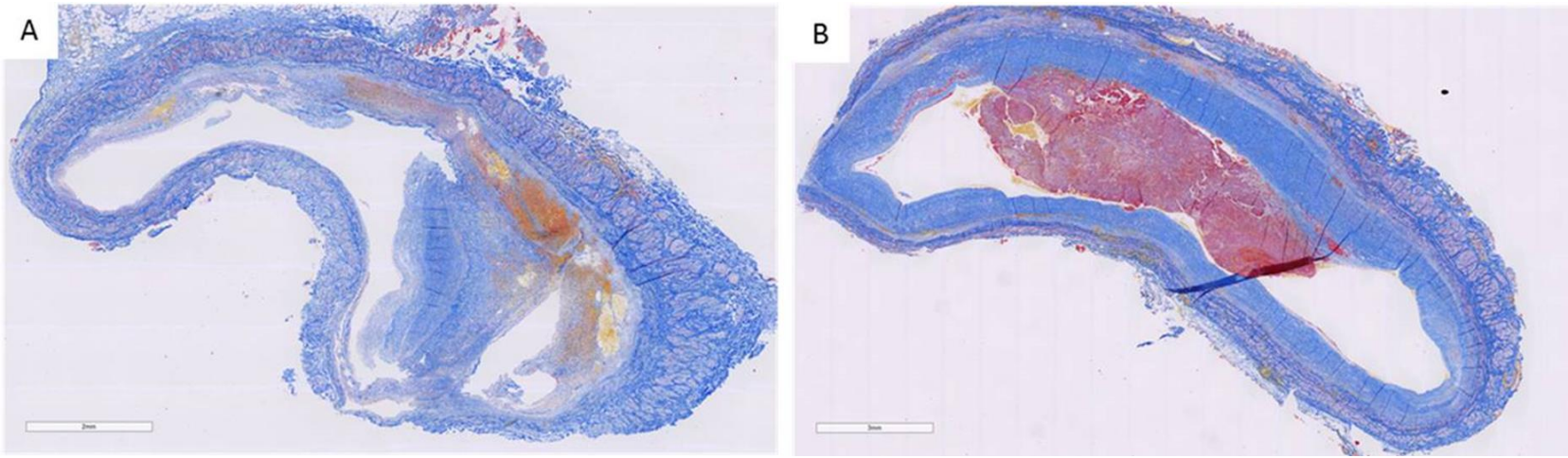
Hypercoagulability is a well-established risk factor for development of DVT

- Acquired & hereditary hypercoagulable states
  - Blood type
  - FVleiden, prothrombin G20210A, AT deficiency…..
  - High levels of coagulation factors
  - Hypofibrinolysis
  - ……

Hypercoagulability and PVT

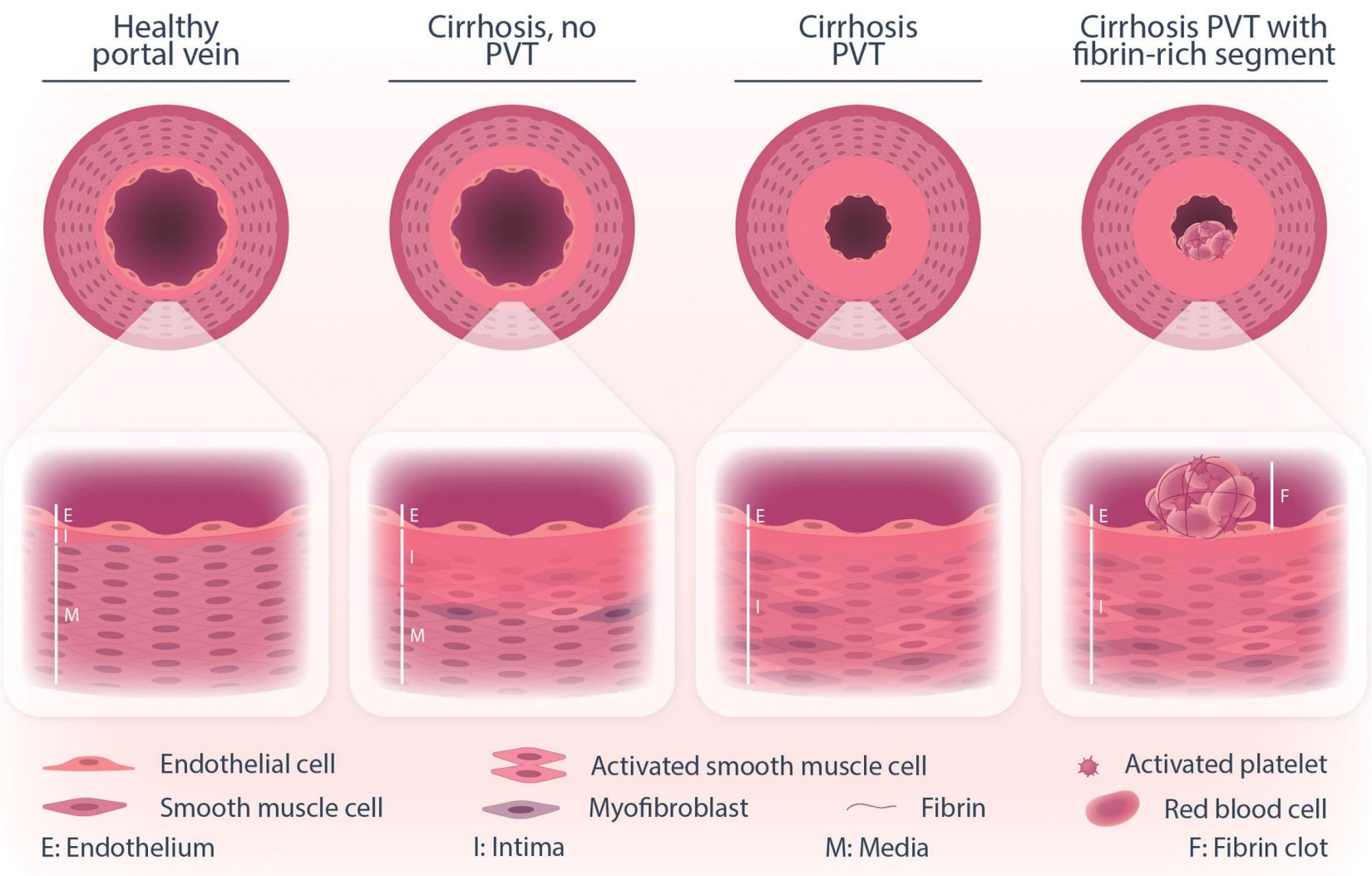
- The role of hypercoagulability in the development of PVT is unclear and challenged in a recent prospective study *(J Hepatol. 2021 Dec;75(6):1367-1376)*
- Contradictory data on FVleiden and prothrombin G20210A
- Blood type is not a risk factor for PVT development *(Liver Int. 2020;40(6):1415-1426)*

Is PVT really a thrombotic phenomenon?



MSB-stained sections. Collagen – blue; RBC’s – yellow; fibrin – orange/red

Hepatology 2022; 75(4):898-911


Healthy portal vein
Cirrhosis, no PVT
Cirrhosis PVT
Cirrhosis PVT with fibrin-rich segment
E
I
M
F
Endothelial cell
Smooth muscle cell
Activated smooth muscle cell
Myofibroblast
Fibrin
Activated platelet
Red blood cell
E: Endothelium
I: Intima
M: Media
F: Fibrin clot

Treatment of PVT

- Anticoagulants are moderately effective (~40% recanalisation without anticoagulation, ~70% with anticoagulation)
- Anticoagulant treatment is associated with a survival benefit *independently* of portal vein recanalisation (J Hepatol 2023 Jul;79(1):69-78)
- Anticoagulants have been shown to decrease intimal hyperplasia in other settings

In summary:

- The traditional concept that liver diseases are associated with a hemostasis-related bleeding tendency is no longer valid
- Bleeding in liver disease is rare, not related to abnormal hemostasis tests, and not primarily treated by prohemostatic agents
- Patients with liver disease are not ‘auto-anticoagulated’ – instead, a relative hypercoagulability may predispose to thrombosis

In summary:

- Prophylactic correction of the ‘coagulopathy’ of liver disease usually not required
- Prophylactic anticoagulation may be indicated
- Portal vein thrombosis may be a misnomer – portal vein stenosis or portal vein obstruction may be a more accurate term