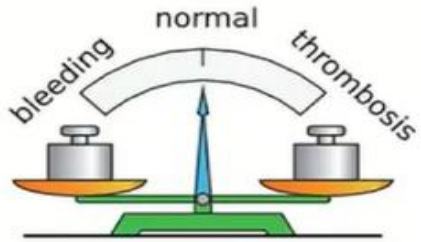
Introduction

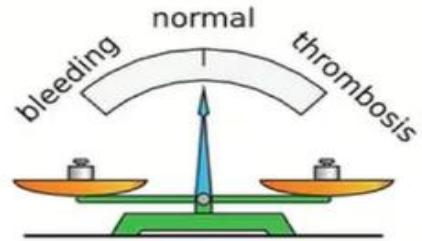
- **Prevalence of procedural related bleeding in patients with cirrhosis varies ranging from 2%-20%**
- Clinicians routinely perceive patients with cirrhosis to be higher risk to bleed and utilize coagulation testing to measure risk
- EASL guidelines recommend **AGAINST conventional lab testing** and **AGAINST bleeding prophylaxis prior to most procedures**
- These guidelines emerged in the context of a larger paradigm shift in hemostasis in liver disease

Thrombotic complications in cirrhosis

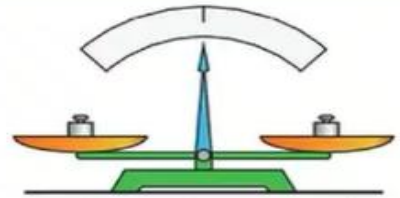
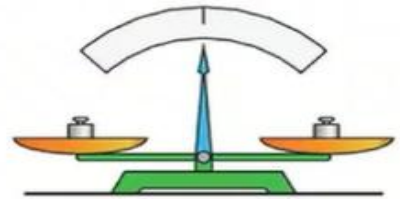
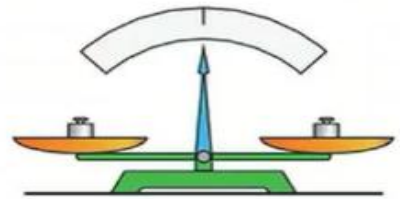
- Venous thrombosis
  - Liver diseases are a risk factor for VTE!
- Portal vein thrombosis
  - Up to 25% of patients on the transplant list
- Coronary events
- Intrahepatic thrombosis
- ……

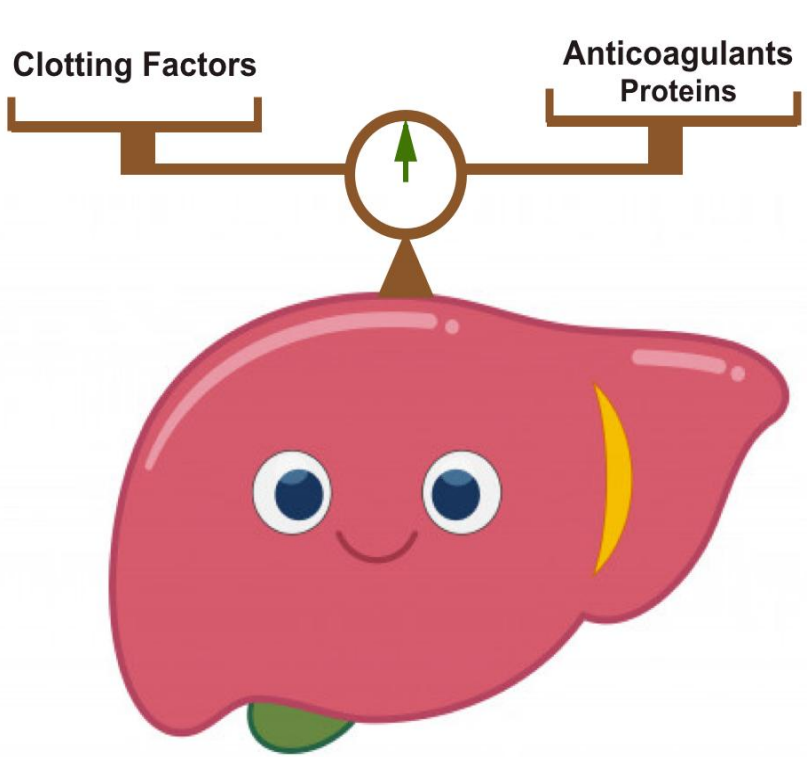


(A) normal situation

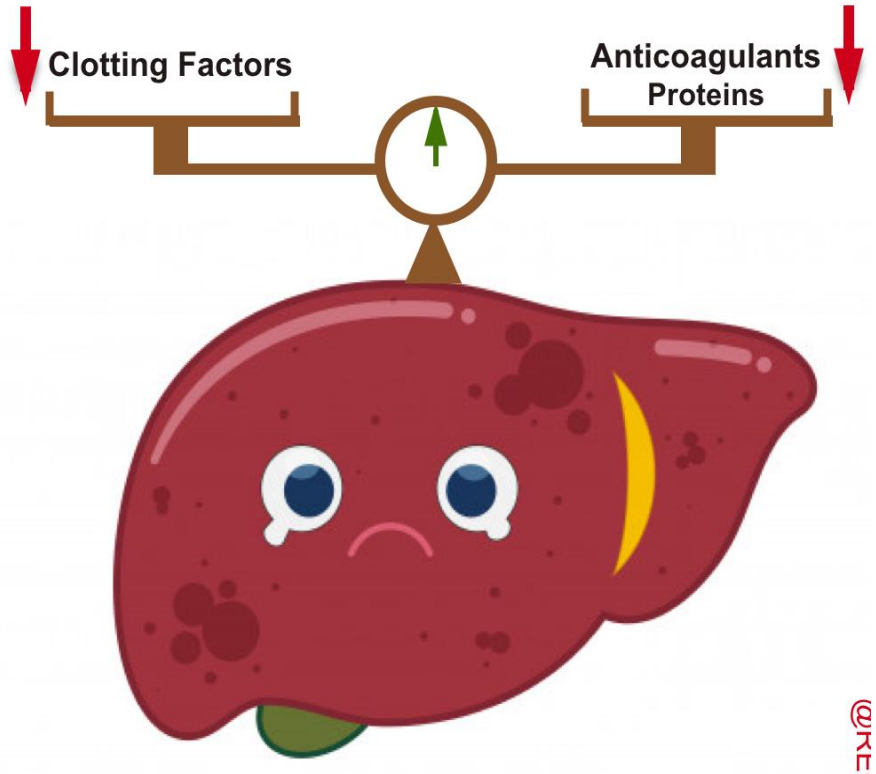


(B) situation in patient with liver disease

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



Healthy Liver



Cirrhotic Liver

Defining bleeding and risk

Defining bleeding:

1. Bleeding related to the procedure?
2. Severity?
    1. ISTH definitions[1,2]
    2. WHO grade

1Schulman et al JTH 2005; 2Kaatz et al. JTH 2015

Defining procedure risk:

EASL and AASLD guidelines use binary assessment of low/high:

1. **Low risk:** expected bleeding < 1.5% of procedures or if significant bleeding occurs easily controlled
2. **High risk:** expected bleeding >1.5% and/or bleeding not easily controlled, or minor bleeding will lead to severe consequences

Procedural bleeding risk in patients with cirrhosis

Procedure	Bleeding rate (%)
Low bleeding risk (<1.5%)	
Paracentesis	
1,100 procedures[47]	None
4,729 procedures[76]	0.2
Thoracentesis	
215 procedures[49]	None
Trans-oesophageal echocardiography	
24 procedures[77]	None
Percutaneous liver biopsy	
68,276 procedures[78];	
3,357 procedure[80]	0.06–0.69
Transjugular liver biopsy	
7,493 procedures[51]	0.07
HVPG measurement	
238 procedures[79]	None
Percutaneous ablation of liver cancer	
1,843 procedures[53]	0.5
High bleeding risk (≥1.5%)	
ERCP	
2,620 endoscopic biliary sphincterotomy[74]	3.5
581 endoscopic papillary balloon dilation	1.9
Endoscopic polypectomy	
814 procedures[54]	7.9 immediate, 1.2 delayed
Endoscopic oesophageal varices ligation	
886 procedures[56]	2.8
Dental extraction	
333 extractions[75]	6.3 intraoperative, 6.3 postoperative

ERCP, endoscopic retrograde cholangiopancreatography; HVPG, hepatic venous pressure gradient.

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PROC-BLeeD Multicenter prospective cohort

EASL CONGRESS Milan, Italy 5–8 June 2024

9.1% of procedures classified as high bleeding risk

Bleeding prophylaxis was provided before 7.8% of procedures

- Patients with bleeding with INR >1.5 or platelets < 50 **more likely to receive prophylaxis**

Predictor	Ratio	AOR (95% CI)	P value
Procedure risk	**High: Low**	**4.64 (2.44-8.84)**	**<.001**
MELD score at admission	**3rd quantile (25.9): 1st quantile (13.6)**	**2.37 (1.46-3.86)**	**<.001**
BMI	**3rd quantile (33.3): 1st quantile (24.1)**	**1.40 (1.10-1.80)**	**.007**
Ascites present	Present: Absent	1.31 (0.99-1.75)	.062
Trainee performed	Yes: No	1.56 (0.81-2.99)	.177
AKI present at admission	Present: Absent	0.72 (0.42-1.22)	.223
INR prior to procedure	3rd quantile (2.0): 1st quantile (1.3)	1.22 (0.84-1.79)	.294
Infection at admission	Present: Absent	1.26 (0.76-2.08)	.337
Antithrombotic prior to procedure	Yes: No	1.34 (0.69-2.61)	.394
Platelet level prior to procedure	3rd quantile (137.0): 1st quantile (59.0)	0.93 (0.69-2.61)	.635
Number of prior procedures	x + 1: x	1.02 (0.92-1.13)	.657
ACLF present at admission	Yes: No	1.04 (0.8-1.35)	.776
VTE prophylaxis at admission	Yes: No	1.01 (0.52-1.96)	.972

PROC-BLeeD Multicenter prospective cohort

FACTORS NOT ASSOCIATED WITH BLEEDING

- **Pre-procedure platelet and INR**
- VTE prophylaxis at admission
- Antithrombotic medication use within 24 hours of procedure
- Trainee participation
- Number of prior procedures
- **AKI at admission*, infection at admission*, and ACLF at admission***
  - *Covariation/ multicollinearity is a problem with these variables*
  - *Further study is needed*

*Zanetto A, Northup PG, Roberts L, and Senzolo, M. Haemostasis in cirrhosis: Understanding destabilising factors during acute decompensation, Journal of Hepatology. 2023.

Preventing bleeding strategies

1. **Labs prior to procedures do not predict bleeding**
2. **Assess procedure risk**
3. **Assess patient risk factors**
   - Decompensated cirrhosis with organ failures*
     - Infection and organ failure/ ACLF?
   - High BMI or other anatomical characteristics
4. **Team collaboration**
   - **<u>Take time to educate colleagues</u>**
   - Technique modification
   - Rescue strategy plan and monitoring

Correction of coagulation disorders to prevent bleeding related to dental extraction?

Anticoagulation not stopped before dental extraction (patients w/o cirrhosis): relative risk 2.8

Recommendation

- In patients with cirrhosis, antiplatelet and/or anticoagulant agents should be managed following the same guidelines as in patients without cirrhosis before invasive procedures **(LoE 4, strong recommendation).**

=> Stop ATC whenever possible

Shi, Front Pharmacol 2017; EASL CPG 2022

Correction of coagulation disorders to prevent bleeding related to dental extraction?

Thrombocytopenia inconstantly associated with bleeding

	Local heamostasis possible	Local heamostasis not possible
PLT > 50 000/mm3	NO	NO
PLT 20-50 000/mm3	NO	Case by case
PLT < 20 000 / mm3	NO	

Ward, J Oral Maxillofac Surg 2006; Perdigao J Oral Maxillofac Surg 2012; Cocero, J Oral Maxillofac Surg 2017; Medina, Int J Oral Maxillofac Surg 2018; Franco, OOOO 2022; EASL Clinical Practice Guidelines 2022

- In patients with cirrhosis, bleeding after dental extraction is not uncommon; severe bleeding is exceptional
- Prophylactic platelet transfusion is usually not needed even in patients with severe thrombocytopenia
- When bleeding occurs, local hemostasis is the 1st - and most efficient - treatment

- If dental extraction is not feasible before liver transplantation, it may be easier after liver transplantation