Trastornos de la coagulación en la cirrosis ¿Hay que tratarlos?

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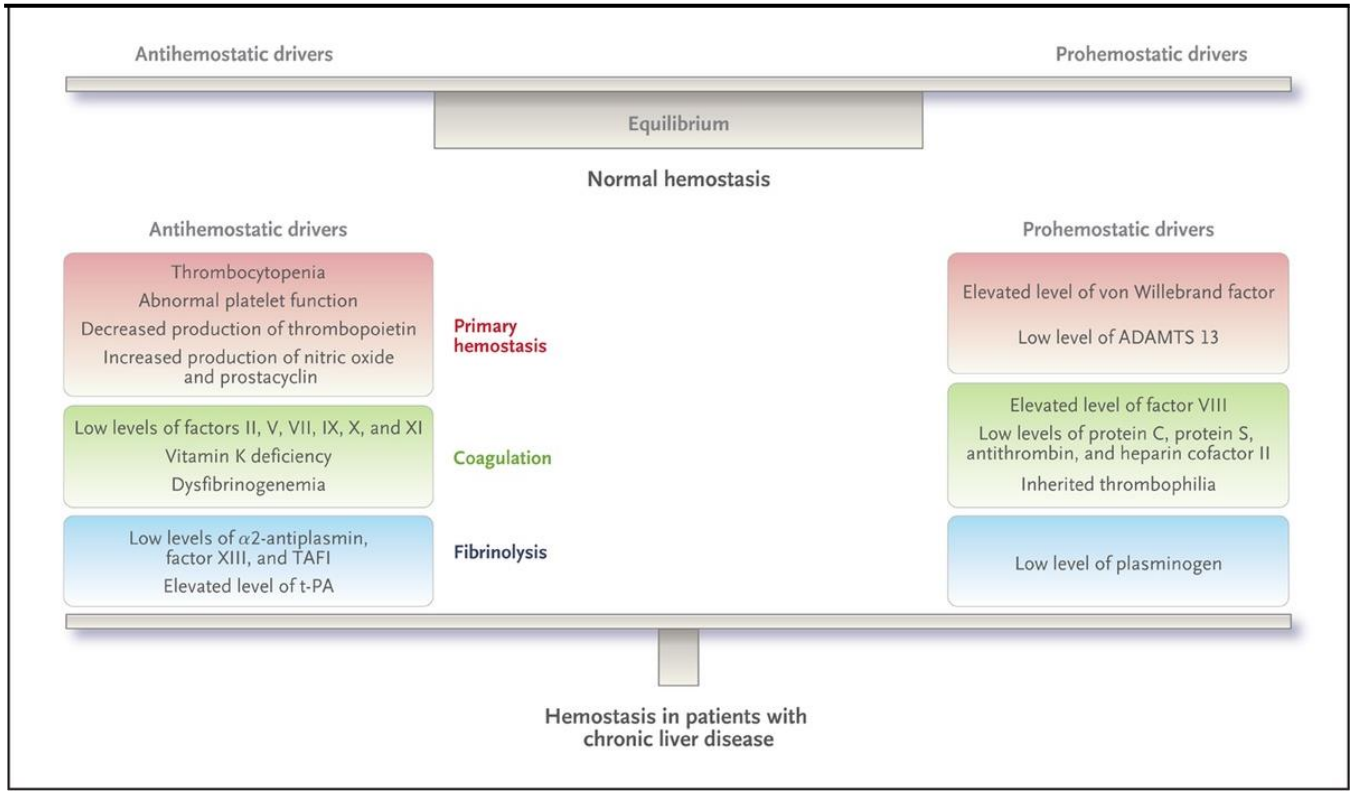
Features of Coagulation in Liver Disease Resulting in a "Rebalancing" of Hemostasis



Tripodi. N Engl J Med. 2011 Jul 14;365(2):147-56

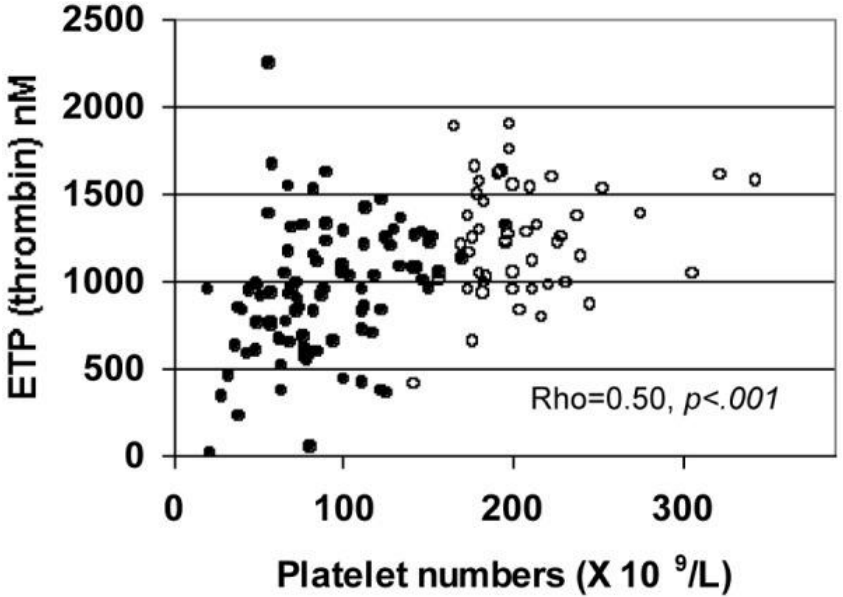
Thrombin and cirrhosis: role of platelets

Plasma from patients with cirrhosis generates as much thrombin as plasma from controls.

Thrombin generation in vivo and in vitro is down-regulated by thrombomodulin.

Reagents that are used to measure the prothrombin time do not contain thrombomodulin

Platelet count > 50,000 is needed to preserve thrombin generation in vitro



Estimate of the platelet numbers (i.e., 56 × 10^9/L) that can generate 875 nmol/L thrombin

Tripodi et al, Hepatology. 2006 Aug;44(2):440-5.

Coagulation Tests in Cirrhosis

PT/INR	Designed for monitoring anticoagulation (warfarin) Does not help assess thrombin generation Does not help predict bleeding risk
Platelet count	Risk of spontaneous bleeding at very low levels (< 10,000) (non-cirrhotics).
Fibrinogen lev	
Bleeding time	
Fibrinolysis	
Global tests: -Thrombin gen	ch.
- Viscoelastic tests: Thromboelastometry/graphy	Global viscoelastic tests (VETs) may provide a more physiologic assessment of coagulation. Values defined in healthy subjects. Thresholds not fully validated, few data showing they can predict bleeding risk

NONE ACCOUNT FOR VARIABLES SUCH AS AKI, SEPSIS,

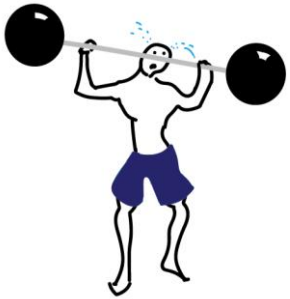
ENDOTHELIAL DYSFUNCTION, OR VOLUME STATUS

Platelet dysfunction in patients with decompensated cirrhosis and acute kidney injury (AKI)

Decompensated cirrhosis – fragile hemostatic *rebalance*

PROHEMORRHAGIC

- ↓ Platelet count
- ↓ Factor XIII
- ↓ α2-antiplasmin
- ↓ TAFI
- ↑ t-PA

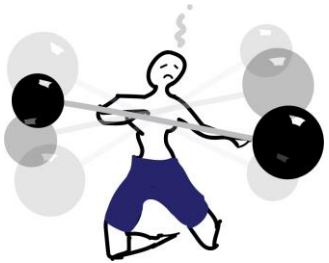


PROTHROMBOTIC

- ↑ Von Willebrand factor
- ↑ Factor VIII
- ↓ Protein C, protein S, antithrombin
- ↓ Plasminogen
- = ↑ PAI

Decompensated cirrhosis with AKI – *unstable* hemostatic balance
(may easily shift towards either hypo- or hypercoagulability)

- ↓ Platelet count
- ↓ Platelet dysfunction
- ↓ Factor XIII
- ↓ α2-antiplasmin
- ↑ t-PA



- ↑ Von Willebrand factor
- ↑ Factor VIII
- ↓ Protein C, Protein S
- ↓ Antithrombin
- ↓ Plasminogen
- ↑ TAFI-a
- ↑ PAI

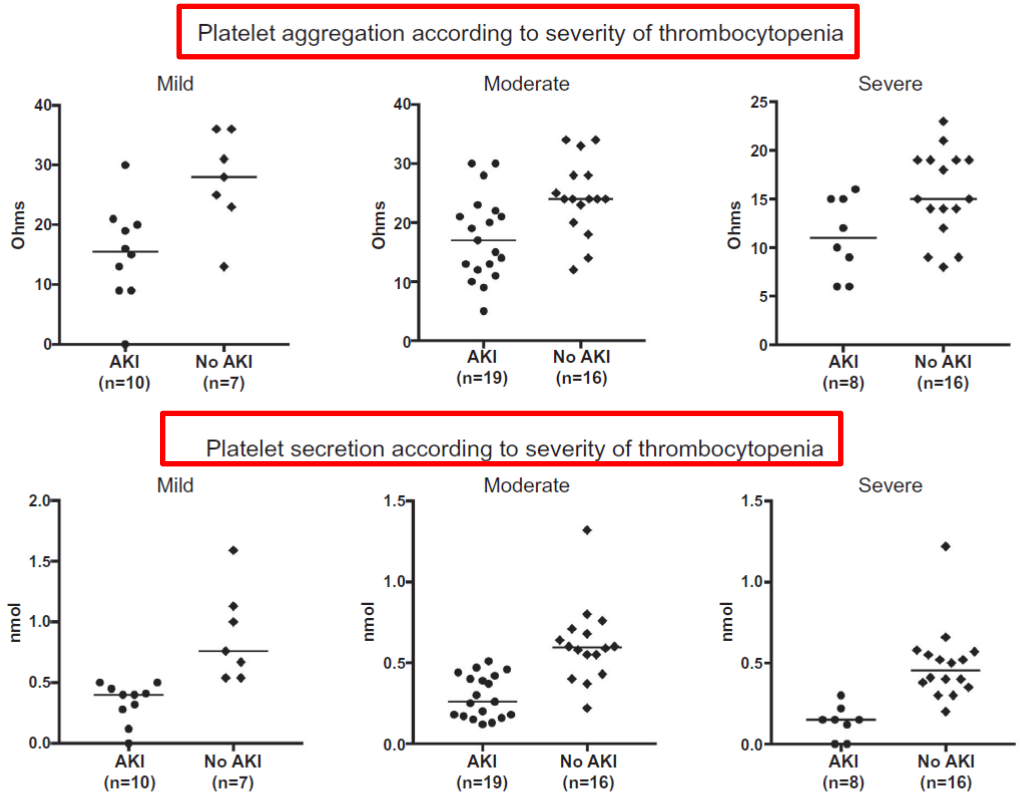
Primary hemostasis

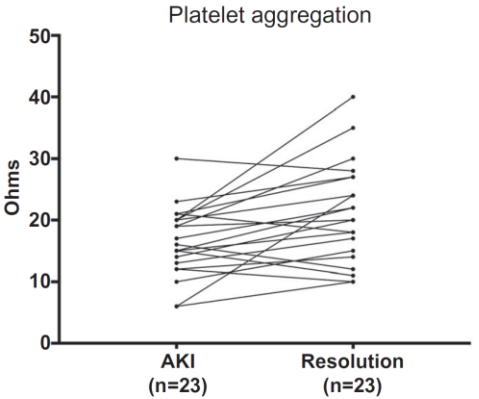
Coagulation (secondary hemostasis)

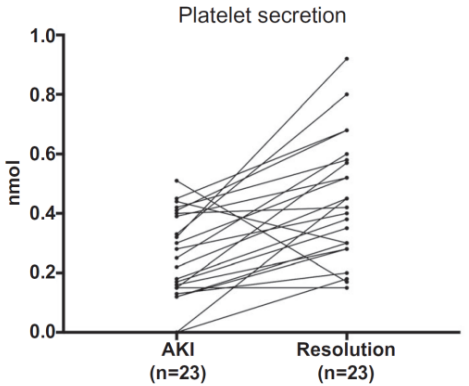
Fibrinolysis (tertiary hemostasis)

Zanetto et al. Hepatology 2020;72:1327-1340

Platelet dysfunction is present in patients with AKI, independent of severity of thrombocytopenia



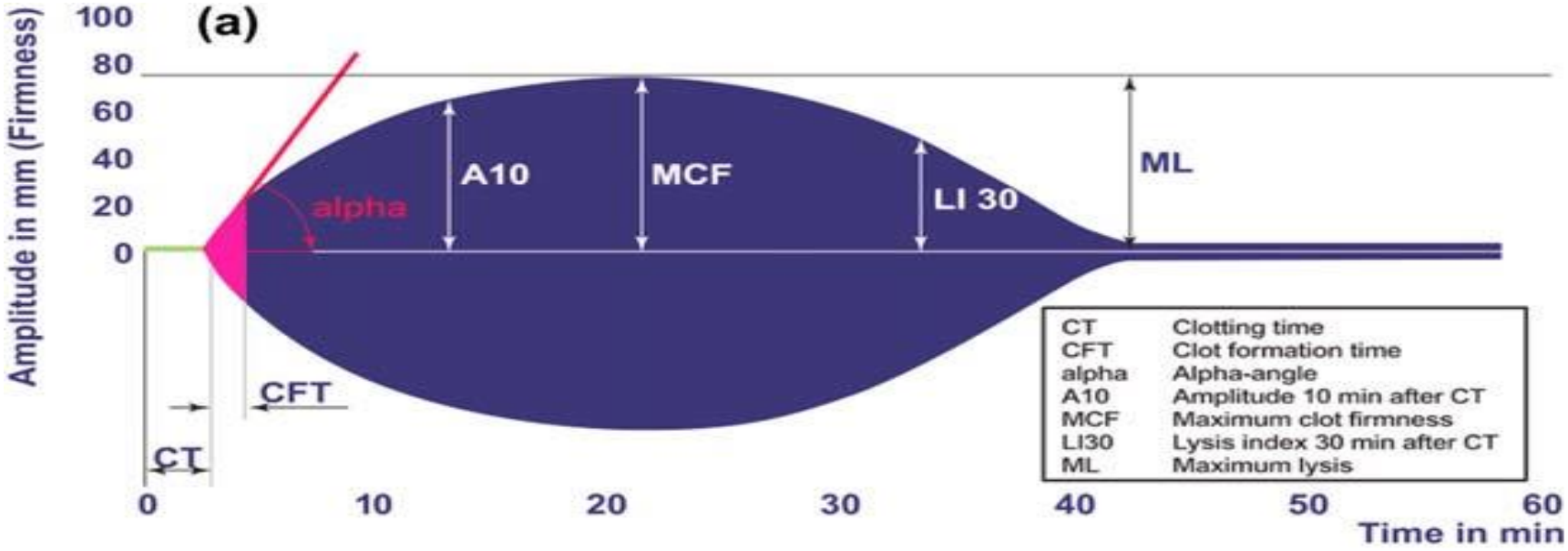




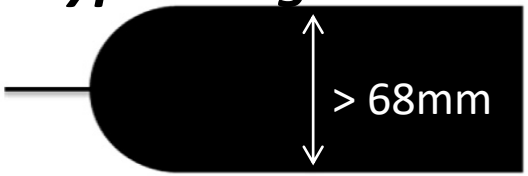
Zanetto et al. Hepatology 2020;72:1327-1340.

Thromboelastography/metry

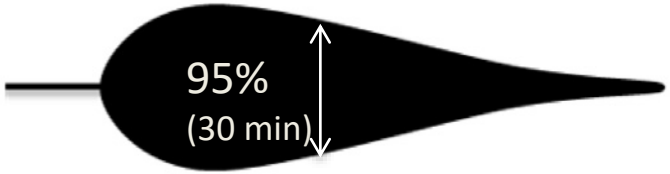
TEG and ROTEM : Point of care tests (bedside)
Measure the evolution of clot structural development and the ability of the clot to perform its basic role in promoting hemostasis.

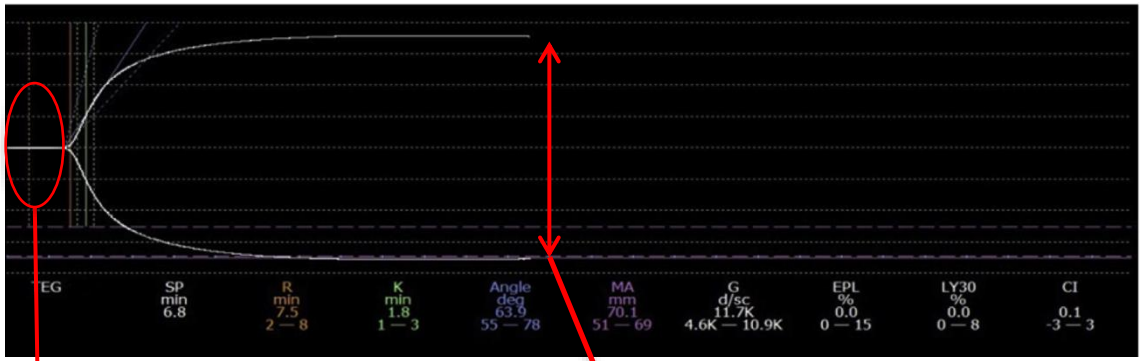


hypercoagulable



fibrinolisis





formation

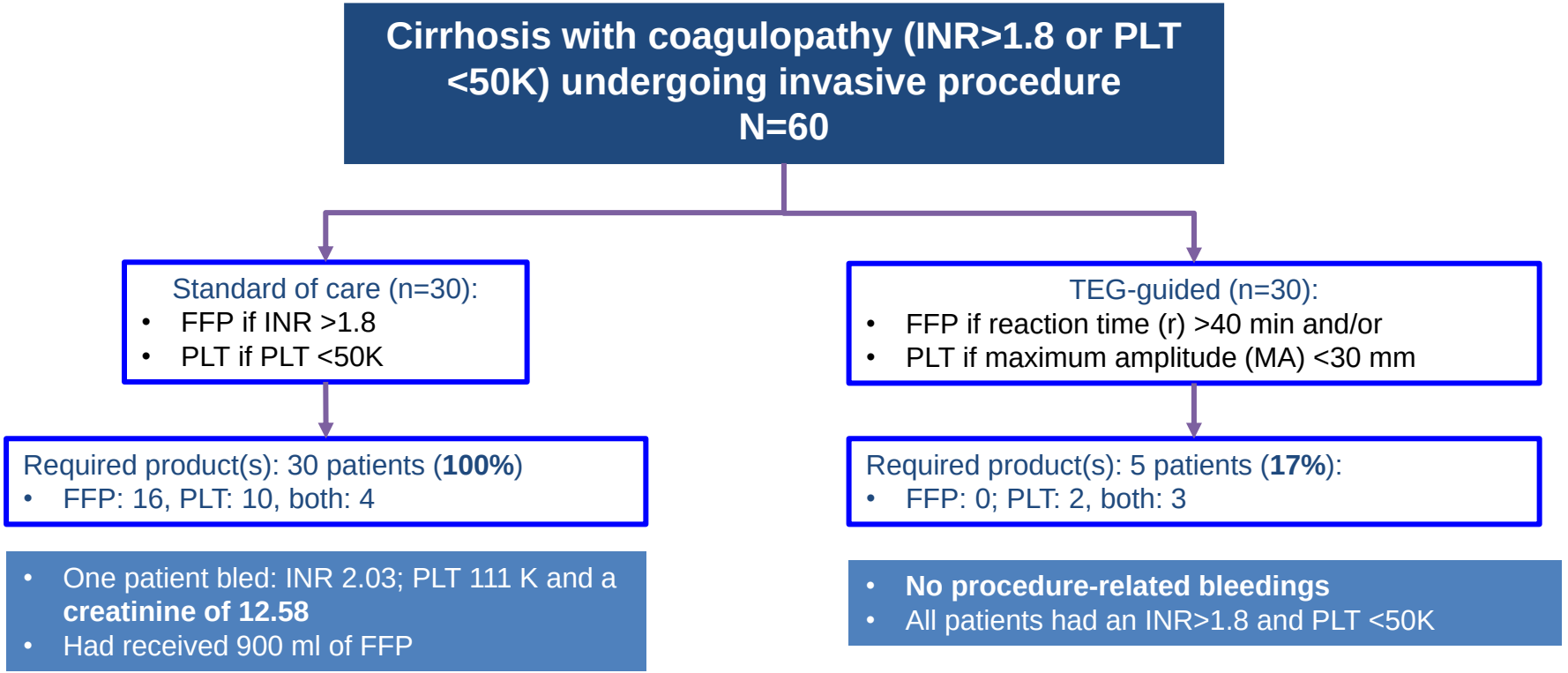
Start

CT* problem with factors (plasma)

stability

Firmness

MCF* (fibrinogen / platelets)



TEG did not predict risk for procedure-related bleeding
FFP does not correct INR or reduce bleeding events
Established cutoffs for FFP and PLT do not predict post-procedural bleeding

LVP = large-volume paracentesis

De Pietri et al. Hepatology 2016;63:566-573

Procedures and the risk of bleeding

Guidelines	INR	Platelets (x 10 ^{9})	Fibrinogen (g/dL)
AASLD, 2021	There is no specific PT-INR and/or platelet count cutoff at or above which potentially adverse bleeding can be reliably predicted		
AASLD, 2017 *PHT bleeding*	Correcting INR is not recommended	No recommendations can be given regarding platelet transfusion in patients with variceal bleeding	
AASLD, 2010 TIPS placement	INR > 5 contraindicate TIPS	< 20 contraindicate TIPS procedure	
AASLD, 2013 *Paracentesis*		ntesis should be	
AGA, 2019	by evidence.	or high-risk	For management of active bleeding or high-risk procedures, >1.2
BAVENO VI, 2015	Recomendations for management for coaguloptahy cannot be made based on current evidence		
Society of Interventional Radiology, 2019	Low risk: NA High risk: < 2.5	Low risk: > 20 High risk: > 30	Low risk: >1 High risk: > 1

Too many guidelines!
None are based on data.
Expert opinion

Invasive procedures and bleeding risk

Low-Moderate (<1.5%)	**High (≥1.5%)**
Polypectomy < 1 cm	*Mucosectomy /Polypectomy ≥1 cm*
Central line placement	*Therapeutic bronchoscopy*
Cardiac catheterization	*Enteral or biliary dilatation , biliary sphincterotomy*
Hepatic catheterization	*Lumbar puncture / CNS procedures*
Paracentesis	*Endoscopic band ligation*
Therapeutic paracentesis	*Radiofrequency, TACE of HCC*
Endoscopy and colonoscopy	*Percutaneous liver biopsy*
Diagnostic EUS	*Therapeutic coronary angiography*
Pacemaker/defibrillator placement	*EUS- FNA/FNB*
Diagnostic bronchoscopy without biopsy	*Percutaneous gastrostomy*
Diagnostic thoracentesis	*Percutaneous biopsy of extrahepatic organ*
Transesophageal echocardiogram	*All major surgery (cardiac, intra-abdominal, orthopedic) and dental extractions*
Skin biopsy	*TIPS, Transjugular liver biopsy*
Other	*Intraocular therapy*

Modified from : 1. Intagliata et al Thromb Haemost. 2018 Aug;118(8):1491-1506
2. Northup P. Hepatology 2020 Nov 20. doi: 10.1002/hep.31646

Multicenter study of 1,472 EBL, bleeding was rare and was unrelated to INR/PLT or to transfusion of blood products

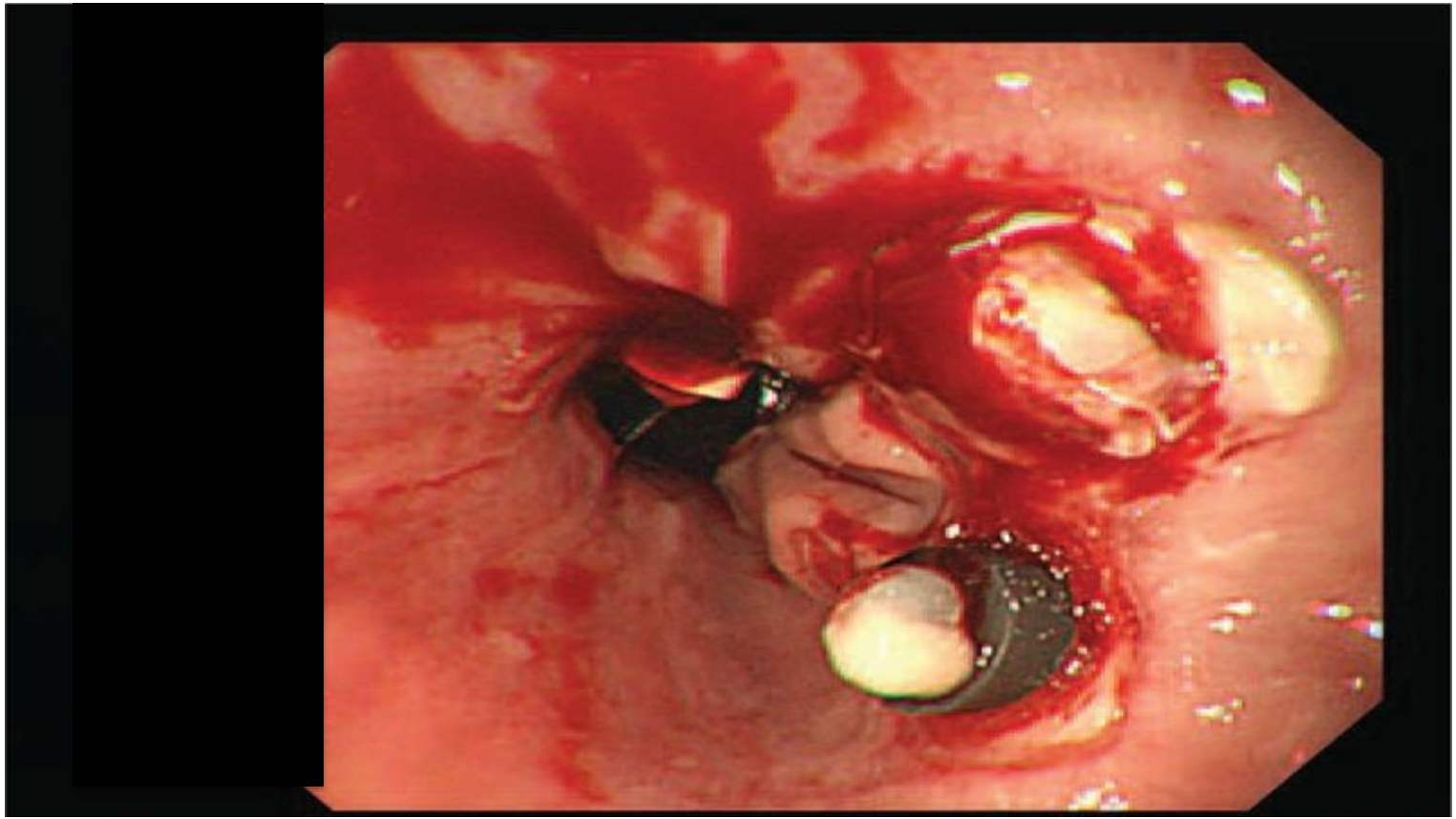
	Bled	Did not bleed
Total EVL procedures **N=1,472**	**33 (2.2%)**	**1,446**
INR >1.5 **N=108** 17 received FFP* (18%)	4 (4%) -2 had received FFP	104 - 15 had received FFP
PLT <50 **N=85** 24 received PLT** (28%)	7 (8%) - 4 had received PLT	78 - 20 had received PLT

* FFP administered at the discretion of the physician if INR was >1.5
** PLT were transfused at the discretion of the physician if platelet count <50 x 10^9/L

Patients who bled had significantly higher Child and MELD scores compared to non-bleeders

Blasi A….Cardenas A, et al. ILC 2020; J Hepatol AS105

EBL=endoscopic band ligation



Post-EBL ulcer bleed and predictors

First author (year)	N with EVL	N with bleeding	Time from EVL (days)	Deaths	Clinical predictors of bleeding
Da Rocha (2009)	150	11 (7.4 %)	9.4	-	Child C
Vanbiervliet (2010)	605	21 (3.4%)	13.5	11/21 (52%)	APRI score Prothrombin index*
Xu (2011)	342	26 (7.6)	8.0	7/26 (27%)	Ascites**
Sinclair (2015)	347	21 (2.8%)	.	5(28%)	Reflux MELD
Cho (2017)	430	33 (7.7%)	8.5+/-5.1	9(28%)	MELD
Blasi /Cardenas (2021)	1472	33 (2.2%)	10-14	3(11%)	MELD

**Child score on univariate but not entered in model*

*** endoscopic predictors were number of bands and extent of esophageal varices*

Prophylatic measures

Dig Dis Sci. 2020 May ; 65(5): 1334–1339. doi:10.1007/s10620-019-05884-0.

Clinical cirrhosis dilemmas: survey of practice from the 7th International Coagulation in Liver Disease Conference

Jonathan G Stine, MD, MSc FACP[1,2], Nicolas M. Intagliata, MD MSc[3], Neeral L. Shah, MD[3], Ton Lisman, PhD[4], Francesco Violi, MD[5], Stephen H. Caldwell, MD[3], Curtis K. Argo, MD, MSc[3]

1. Pre-procedure testing of fibrinogen and platelets is recommended for high-risk procedures and pre-procedure correction is recommended for high-risk procedures.
2. Routine prophylaxis for low or moderate risk procedures is generally not recommended.
3. Platelet transfusion prior to high-risk procedures or with active bleeding has a rational in vitro basis but lacks high level supportive data.

Intagliata et al .Thromb Haemost 2018;118:1491
Stine JG et al Dig Dis Sci.. 2020 May;65(5):1334-1339.

Plasma (INR)

- *Fresh frozen plasma (FFP) to 'correct' a prolonged INR in cirrhosis does not increase thrombin generation and can exacerbate portal hypertension*

- *Fresh frozen plasma is NOT recommended to correct any coagulation factor deficiency*

Northup P. Hepatology 2020 Nov 20. doi: 10.1002/hep.31646
O'Leary J et al. AGA CPU. Gastroenterology. 2019 Jul;157(1):34-43.e1

Received: 5 May 2020 | First decision: 3 June 2020 | Accepted: 17 August 2020
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

- 29 studies were targeted for analysis, including 13, 276 patients with cirrhosis undergoing indicated procedures (endosocpy, paracentesis, dental extraction, renal biopsy, central line, etc)
- There was no significant association between periprocedural bleeding events and pre-procedural INR [pooled odds ratio 1.52; 95% CI 0.99, 2.33; *P = 0.06*
- INR fails to serve as a significant correlate for periprocedural bleeding events among patients with cirrhosis.

Kovalic et al . Aliment Pharmacol Ther. 2020;52:1298–1310

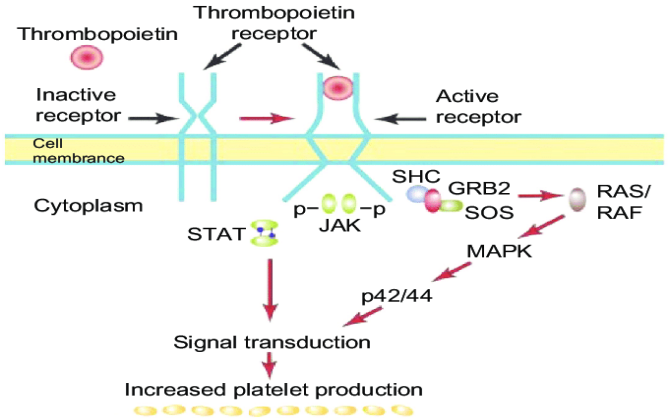
Platelets

- *Consider level > 50,000 with active bleeding*
  - *no data from randomized studies*
- *Prophylaxis used for < 50,000*
  - *no data from randomized studies*
- *Rise in platelets occurs within first hour and decreases within 48 hr.*
- *1 pool of platelets may increase the platelet count by 5-10,000.*
- *Total volume infused is ~250-500 mL of platelet-rich plasma*
- *Risk of adverse reactions (infections, lung injury, alloimmunization)*

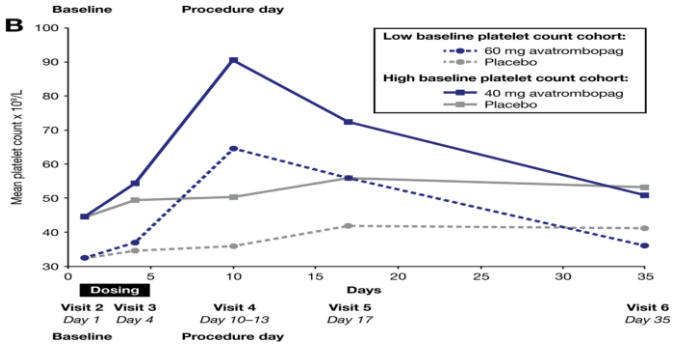
O'Leary J et al. AGA CPU. Gastroenterology. 2019 Jul;157(1):34-43.e1

TPO Agonists

- *Small molecule TPO-R agonists bind to the TPO receptors that activate the downstream signalling cascade to stimulate platelet production*



- *Eltrombopag*
- *Avatrombopag*
- *Lusotrombopag*



Peck-Radosavljevic M. Hepatology. 2019 Oct;70(4):1336-1348
Terrault N.Gastroenterology. 2018 Sep;155(3):705-718.

Fibrinogen

- *Low fibrinogen levels (< 100 mg/dL) can be associated with spontaneous & procedure related bleeding in critically ill patients with cirrhosis*

- *Cryoprecipitate can be used (volume 10-20 mL/U).*
  - *Average dose is 5-10 U (50-200mL)*

- *Experience in active bleeding during major surgery and liver transplantation but not in prophylactic bleeding in patients with cirrhosis.*

Drolz et al. Hepatology. 2016;64(2):556–68
O'Leary J et al. AGA CPU. Gastroenterology. 2019 Jul;157(1):34-43.e1

PROCEDURAL RISK & TRANSFUSION

LOW RISK PROCEDURE*

- INR – not relevant
- Fibrinogen < 100
- Platelets ≤ 30.000

- TRANSFUSE
  - *Fibrinogen*
  - *Platelets or TPO agonist*

HIGH RISK PROCEDURE *

- INR – not relevant
- Fibrinogen < 120
- Platelets ≤ 50.000

- TRANSFUSE
  - *Fibrinogen 5-10 U*
  - *Platelets or TPO agonist*

**** Take into account renal function, infection, volume status***

Blasi A, Cardenas A. Clin Liver Dis. 2021 May;25(2):461-470

ACTIVE BLEEDING AND CIRRHOSIS

ALL PATIENTS

- INR – not relevant
- HCT ≥ 25%
- Fibrinogen ≤ 120
- Platelets ≤ 50.000

TRANSFUSE :

Fibrinogen (5-10 U)
Platelets (1 pool)
RBC to achieve Hb >25%

Blasi A, Cardenas A. Clin Liver Dis. 2021 May;25(2):461-470

AASLD GUIDANCE

- **INR:**
  - INR is not an indicator of coagulopathy (and therefore is not an indicator of post-procedure bleed) and should **not** be corrected prior to any procedure

- **Platelet count (PLT):**
  - Post-procedural bleeding not related to absolute PLT cutoffs, it is related to PLT function (more altered in AKI)
  - Improving platelet count does not have a significant effect on post-procedure bleeding

- **Fibrinogen:**
  - Reasonable to administer with post-procedure bleed and if fibrinogen <100 mg/dL

It is more important to identify patients at risk of bleeding and to ensure the safety of the procedure itself

Northup et al. AASLD Vascular Disorders Guidance. Hepatology 2021;73(1):366-413

CONCLUSION

1. *There are no reliable tests that predict risk of bleeding*
2. *FFP can be deleterious (can increase portal pressure) and is NOT recommended.*
3. *Active bleeding or high-risk procedures: consider platelet and fibrinogen.*
4. *Always consider renal function, volume status and infection*
5. *Need studies comparing no transfusion vs transfusion with primary outcome of peri-procedural bleeding*

Thank you

- Unidad de Hepatología
- Unidad de Hemodinámica Hepática
- Unidad de Cuidado Intensivo
- Unidad de Trasplante Hepático
- Unidad de Endoscopia Digestiva
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- Dr. JC Reverter (Hematologia)